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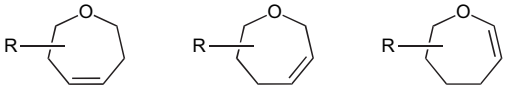
Tetrahedron

Tetrahedron Vol. 62, No. 40, 2006

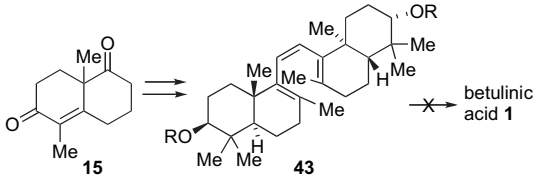
Contents

REPORT

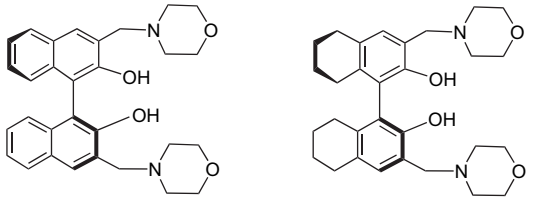


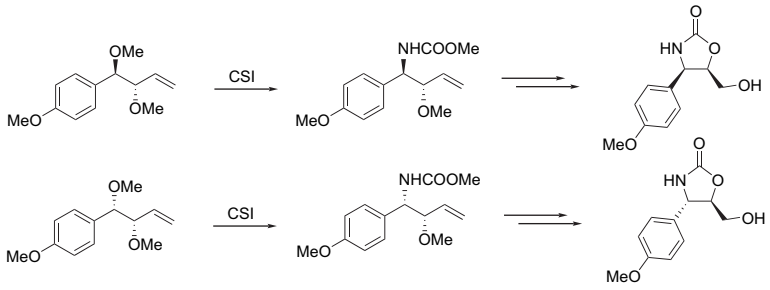
The three classes of seven-membered oxacycles shown are functionally defined as oxepines. Advances in the methods for their preparation are reviewed with 107 references.

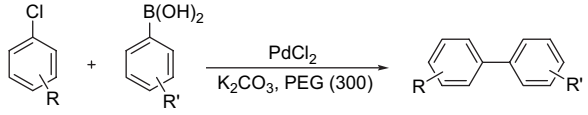
ARTICLES

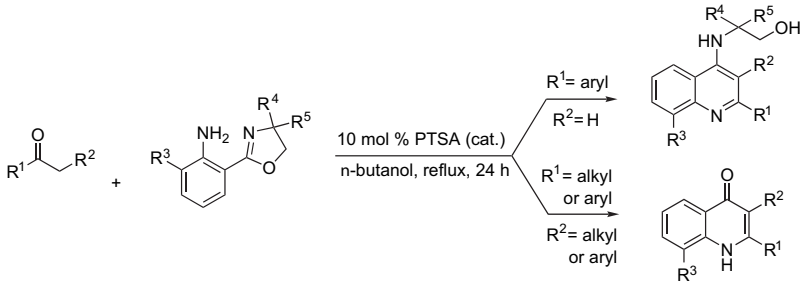


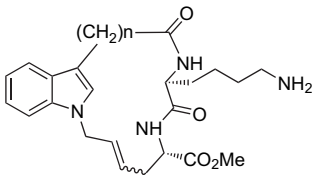
A convergent approach to the synthesis of pentacyclic triterpenes of the betulinic acid class is described.

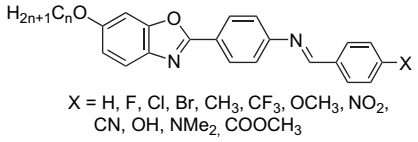


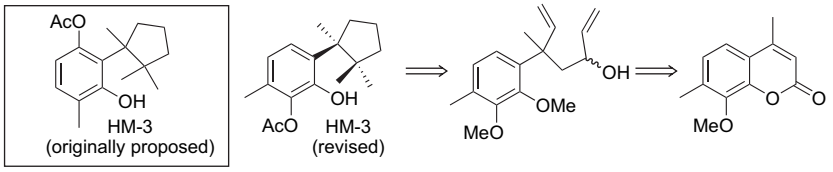


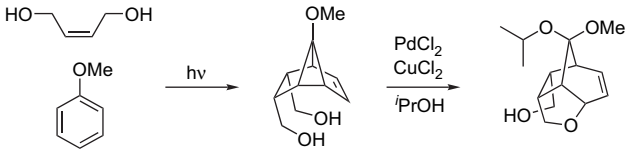


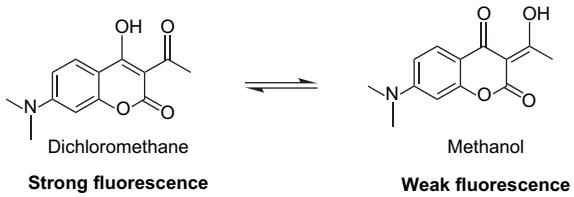




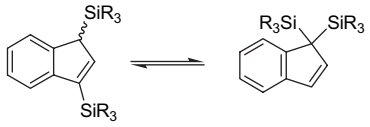


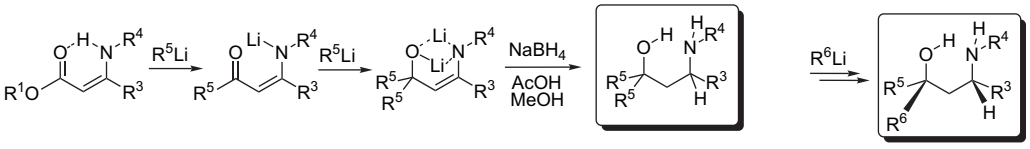


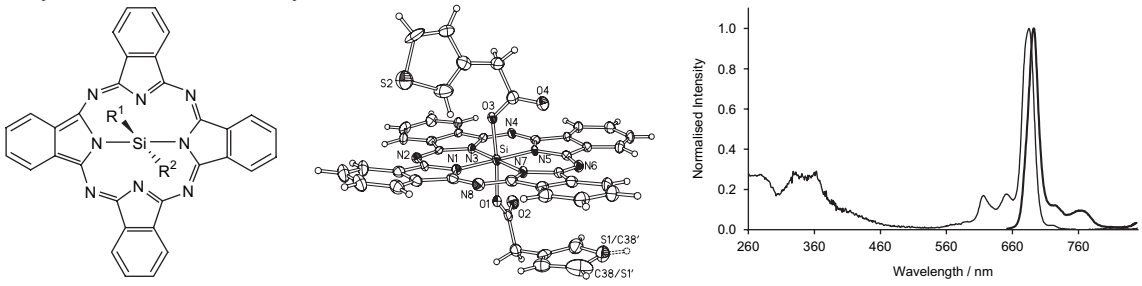


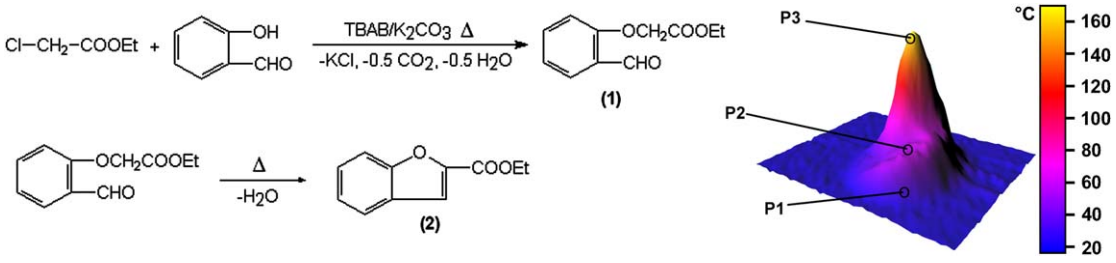


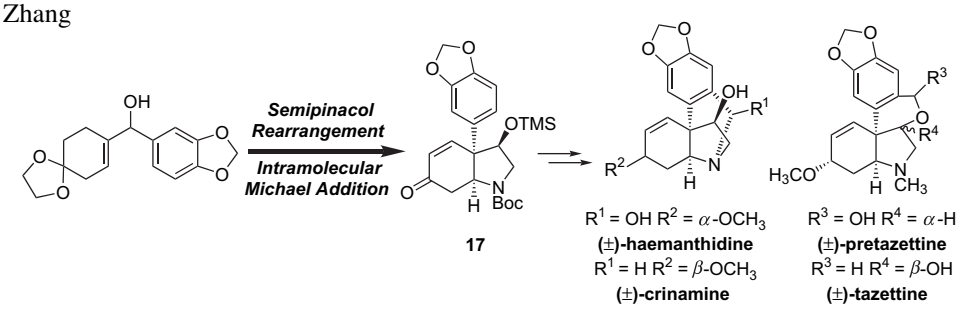
The major tautomer of several triketone derivatives in organic and aqueous solutions has been determined. Their solvent- and base-sensitive properties have been applied in the design of a polarity-sensitive fluorescent probe and an acidichromic colorant.

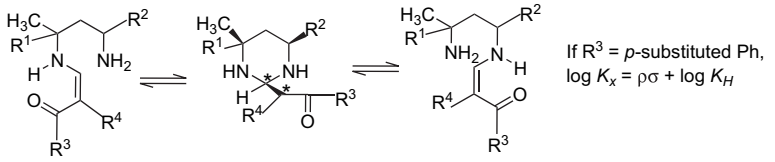


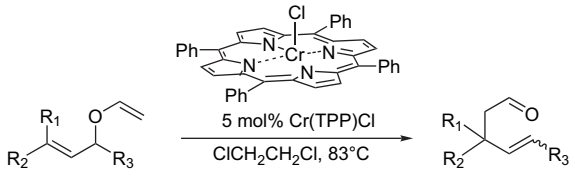


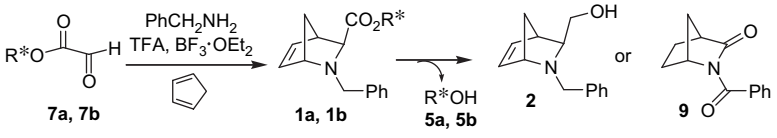


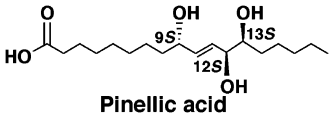












Pinellic acid

OTHER CONTENT

*Corresponding author
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Abstracted/indexed in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts. Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9301–9320

Tetrahedron report number 769

Recent developments in the synthesis of oxepines

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Received 25 June 2006
Available online 9 August 2006

Contents

1. Introduction

A remarkable diversity of natural products contains a seven-membered oxacycle in their molecular architecture (Fig. 1). Structures range from the ladder polyether neurotoxins ciguatoxin, brevetoxin, and gambierol (**1**–**3**) to the functionalized monocycles such as isolaurepinnacin (**6**) and rogioloxepane (**7**), to the spirocyclic crambescidin (**5**) and fused aryloxepine structures janoxepin, oxepinamide C, and bauhiniastatin (**10**–**12**). Notably, a majority of the natural products in Figure 1 are from marine sources. Reported pharmacological investigations on these structures showed that they have ion-channel blocking (**1**,**2**),[1] antiviral (**5**),[2] and antifungal (**8**)[3] activities.

Abbreviations: CAN, ceric ammonium nitrate; Cy, cyclohexyl; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DMAP, *N*,*N*-4-dimethylaminopyridine; DMDO, dimethyldioxirane; Eu(fod)$_3$, europium 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione; EVE, ethyl vinyl ether; IDCP, bis(2,4,6-collidine)-iodonium perchlorate; Imid, imidazole; MEM, (2-methoxyethoxy)methyl; Mes, mesityl; MPM, methoxy(phenylthio)methyl; Ms, methanesulfonyl; NaHMDS, sodium 1,1,1,3,3,3-hexamethyldisilazane; Ns, 2-nitrobenzenesulfonyl; Piv, pivaloyl; PPTS, pyridinium *p*-toluenesulfonate; TBDPS, (also BPS) *tert*-butyldiphenylsilyl; TBS, (also TBDMS) *tert*-butyldimethylsilyl; TEA, triethyl amine; TES, triethylsilyl; TFP, tris(2-furyl)phosphine; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl.

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doi:10.1016/j.tet.2006.07.021

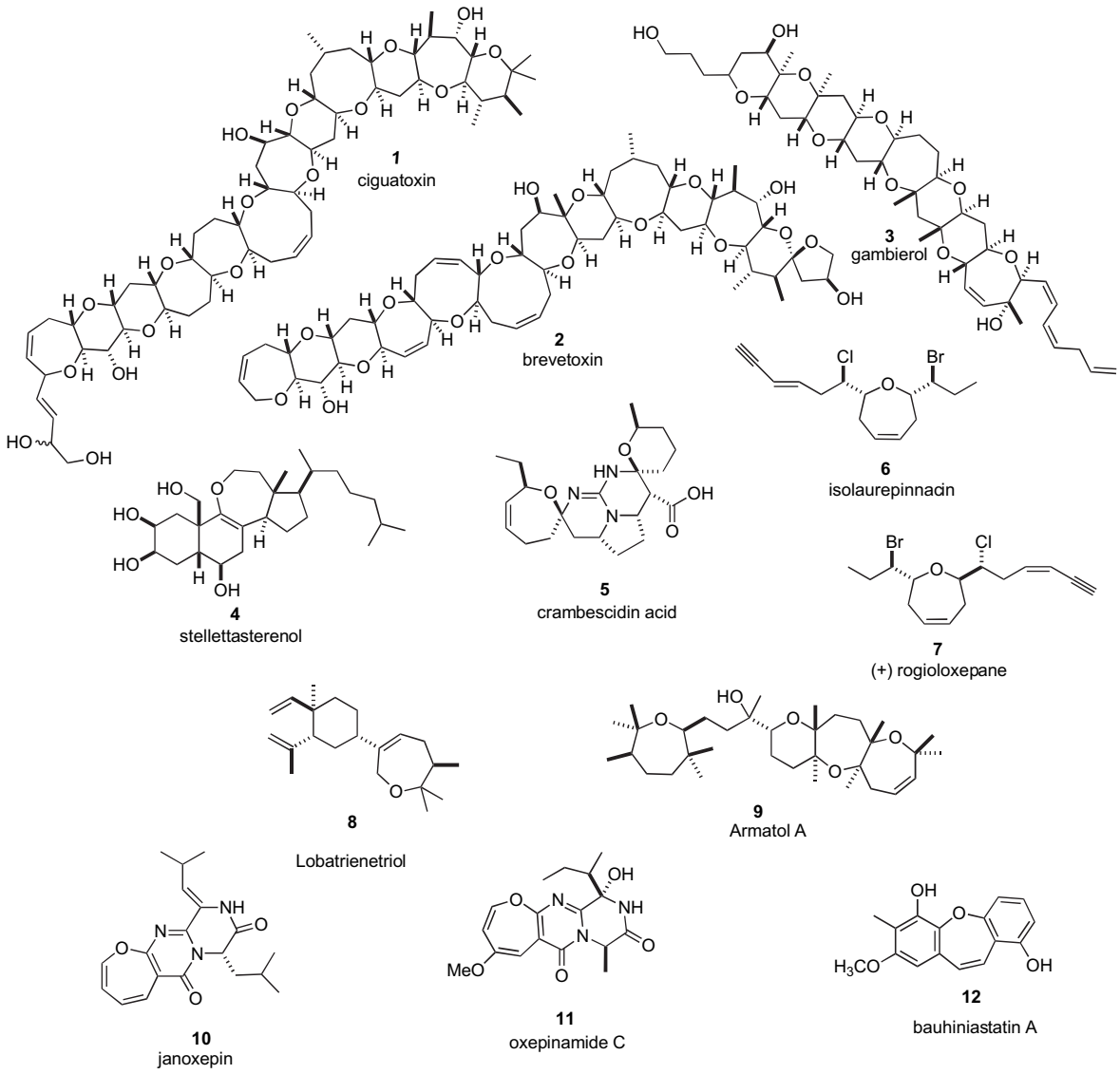
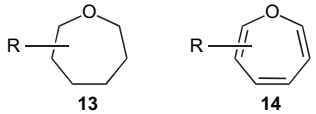


Figure 1.

From a chemical perspective, the intricacy of the structures in Figure 1 has made them the target of increased attention by synthetic chemists. The synthesis of medium ring oxacycles has been treated previously in reviews by Elliot[4] and Hoberg.[5] Here we review significant advances made in the synthesis of unsaturated seven-membered ring oxacycles. Strategies defined in the earlier reviews will be updated and new methods that have been recently reported will also be introduced. Dibenz[*b*,*f*]oxepines, which occur in natural products and synthetic pharmaceuticals will not be presented here; strategies for their synthesis have recently been reviewed.[6]

The key structural feature shared by the examples in Figure 1 is that the seven-membered oxacycle in each contains at least one carbon–carbon double bond. Following IUPAC nomenclature,[7] saturated seven-membered oxacycles are termed as oxepanes (**13**) and if the ring contains 'the maximum number of double bonds' it is an oxepine (**14**). The names of oxepine containing natural products like janoxepin (**10**) and oxepinamide (**11**) evoke the direct connection to this definition. Structures that have one double bond in the ring have been referred to as oxepanes, di-dehydro-oxepanes, oxepenes, and oxepines in the literature. Based on the prevalence of its usage, it is suggested that, in addition to **14**, the general structures in Figure 2 also be called oxepines for convenience here. Oxepines of type **15** and **16** are present in the widest variety of natural products (Fig. 1). The cyclic enol ether motif **17**, on the other hand, has only recently been identified in the unusual steroid ether stellettasterenol (**4**).[8]



13 **14**

The objective of this report is to review synthetic strategies for preparing the three classes of oxepines **15**–**17** as outlined in Figure 2. For each of the oxepine subtypes, a dashed line designates a key bond to be formed in a cyclization reaction that gives rise to that oxepine structure. Adjacent to the dashed line are listed the specific reaction types that effect

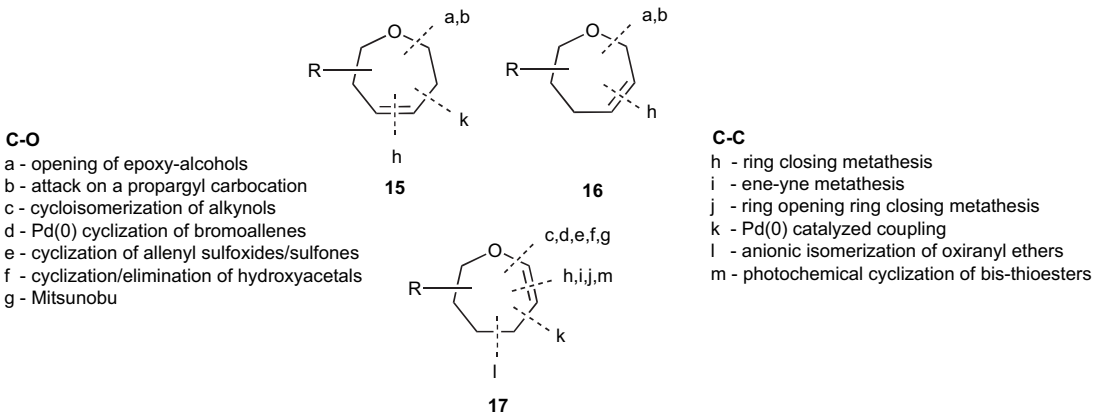


Figure 2.

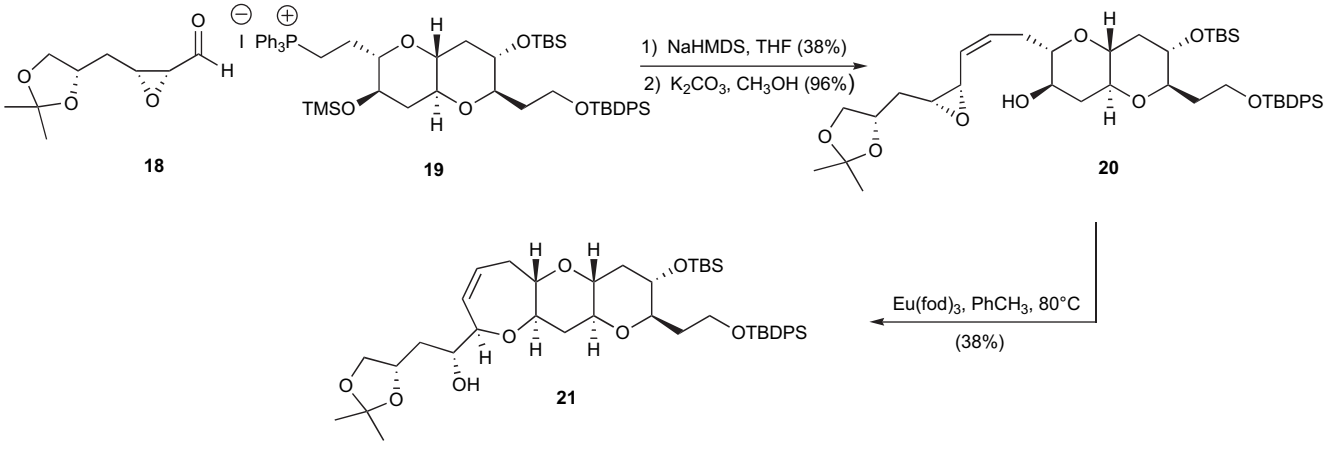
the cyclization. Reactions are broken into two classes: C–O bond forming reactions and C–C bond forming reactions. As evidenced by considering the strategies in Figure 2, the variety of new cyclization reactions that have been introduced recently for the preparation of oxepines is noteworthy. Among them, the growing focus on cyclic enol ether **17** as synthetic targets is especially interesting. Syntheses of this class of oxepine have, by and large, been characterized by the development of methods rather than being motivated by specific natural product targets. In fact, they have become attractive as intermediates en route to more complex structures. Their utility in these applications derives from the ability to functionalize the cyclic enol ether functionality (via epoxidation and nucleophilic attack, for example) under mild conditions. This strategy has been implemented in an iterative fashion for the overall synthesis of fused polycyclic ethers such as brevetoxin (**2**) and gambierol (**3**).[9–11] In total, progress in the synthesis of the oxepines reviewed here should provide a perspective on the breadth of current methods and the opportunities for development that they represent.

2. Cyclization via C–O bond formation

Formation of oxepines via C–O bond formation takes advantage of the inherent nucleophilicity of oxygen onto an electrophilic carbon species. Strategies such as cyclization of diols,[12] iodoetherification,[13] and lactonization followed by derivatization to oxepines[14] are all noteworthy, but have been discussed in previous reviews without significant new developments. Advancements on two established approaches, the intramolecular attack by a hydroxyl group on an epoxide or on a propargyl cation, are discussed first. The remainder of the methods for oxepine synthesis in this section has been introduced recently. Transformations involving cyclizations through attack at the central carbon of various allenes (metal, bromo, sulfuryl/sulfonyl) constitute the major focus. The cyclization–elimination of hydroxy-acetals and a novel Mitsunobu approach to aryl-oxepines will also be presented.

2.1. Lewis acid-mediated opening of epoxy-alcohols

Cyclization by the intramolecular attack of a hydroxyl group onto a Lewis acid-coordinated epoxide is an established method for the formation of tetrahydropyrans and oxepanes.[15] Epoxy-alcohols containing a double bond can give oxepines such as **15** or **16**. This strategy is attractive because the epoxide can often be formed enantioselectively and gives rise to a new chiral hydroxy group upon ring opening. An illustrative example comes from the synthesis of the ABC ring system of ciguatoxin (**1**) (Scheme 1).[16] Aldehyde **18** was derived from Sharpless epoxidation of the corresponding allylic alcohol followed by oxidation. Wittig coupling of **18** with phosphonium salt **19** and removal of TMS group gives the cyclization precursor **20**. After evaluating a variety



Scheme 1.

of conditions (base, protic acid, Lewis acid), the cyclization was found to be of only modest efficiency, giving oxepine **21** in 38% yield using $Eu(fod)_3$ as a Lewis acid promoter of cyclization. An alternative set of conditions where treatment of the starting material with $(Bu_3Sn)_2O$ followed by $Eu(fod)_3$ gave a similar yield for the cyclization (36%).

Recent examples of the epoxy-alcohol cyclization are taken from the formal total synthesis of (+)-isolaurepinnacin A (**6**)[17] and the total synthesis of (+)-rogioloxepane A (**7**).[18] The key difference between these two natural products, aside from the difference in the olefin geometry of the C8–C9 bond (*E* vs *Z*), is the disposition of the substituents adjacent to the ring oxygen of the oxepine. For **6** they are cis and for **7** they are trans.

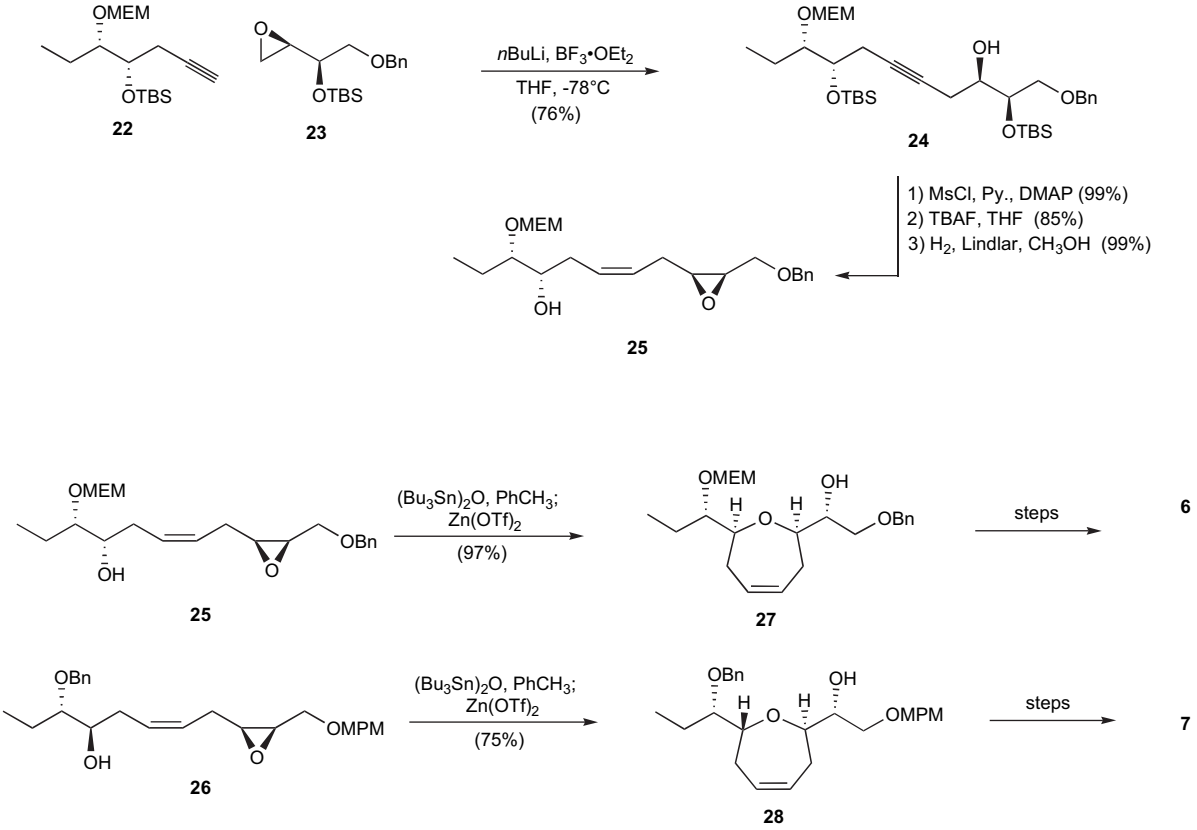
In the following examples (Scheme 2), the stereocenter of the nucleophilic oxygen determines the cis/trans stereochemistry.[19] Epoxy-alcohol precursors **25** and **26** were prepared in a similar fashion; the route is illustrated here for **25**. The anion derived from alkyne **22** is coupled with epoxide **23** to give homo-propargyl alcohol **24**. Reduction of the triple bond followed by epoxidation and nucleophilic displacement gives **25**. In the cyclization reactions the acyclic epoxy-alcohols **25** and **26** are first treated with $(Bu_3Sn)_2O$ followed by the Lewis acid $Zn(OTf)_2$ to form oxepines **27** and **28** in 97 and 75% yields, respectively.[20] The $(Bu_3Sn)_2O$ in the reactions allows the pre-formation of alkyl tin-ethers, which are argued to increase the nucleophilicity of the oxygen, presumably due to the longer Sn–O bond length relative to H–O.

Despite nearly identical reaction conditions, the cyclization of **25** and **26** to form **27** and **28** appears to be significantly more efficient than in the ciguatoxin A-ring (**20** to **21**, Scheme 1). According to the authors, the poor yield for cyclization of **20** was based on inefficient formation of the tin-ether and a ground state conformation where the nucleophilic hydroxyl group was in closer proximity to the alkene rather than the epoxide functionality. In contrast, the acyclic precursors **25** and **26** were presumably efficient in the formation of tin ethers and subsequently cyclized using $Zn(OTf)_2$ as Lewis acid.

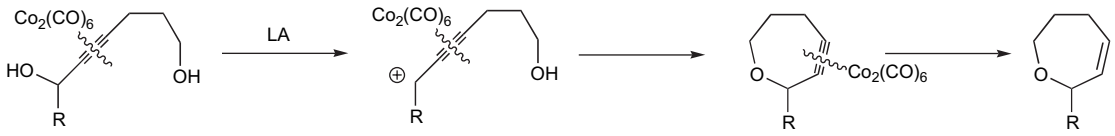
2.2. Attack on a propargyl cation

Carbocations adjacent to an alkynyl-dicobalt unit are relatively stable species that can be attacked by nucleophiles (Nicholas reaction).[21] If the propargyl carbocation is linked covalently to an alcohol, intramolecular attack will provide an oxepine. The position of the carbocation relative to the oxygen nucleophile can be on the opposite side of the $Co_2(CO)_6$ complexed alkyne (Scheme 3) or on the same side (Scheme 4). This relationship determines whether the alkyne complex is included in the developing ring or is on its periphery. Decomplexation of $Co_2(CO)_6$ using reducing conditions (H_2/$RhCl(PPh_3)_3$ or Bu_3SnH) is most common when the complex is part of the ring. Ceric ammonium nitrate (CAN) as a decomplexing agent regenerates the alkyne.

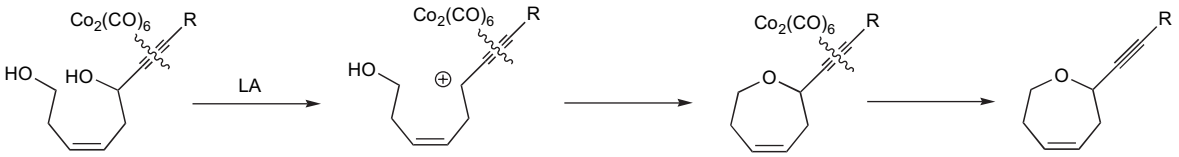
Isobe and co-workers originally reported the intracyclic approach (Scheme 5) in the synthesis of the AB ring system of ciguatoxin (**1**).[22] Cobalt complex **29** is cyclized using



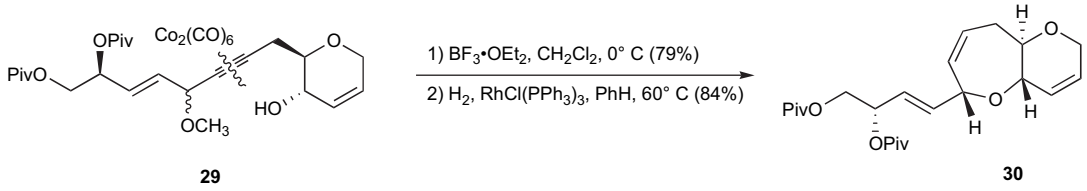
Scheme 2.



Scheme 3.



Scheme 4.

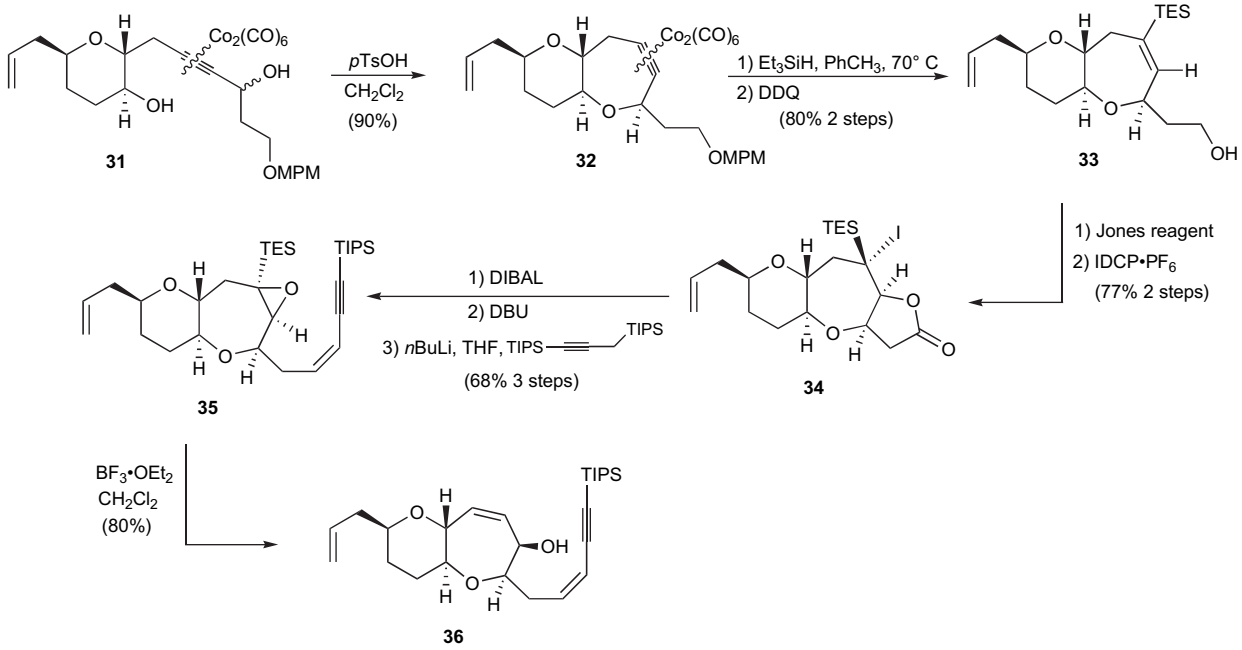


Scheme 5.

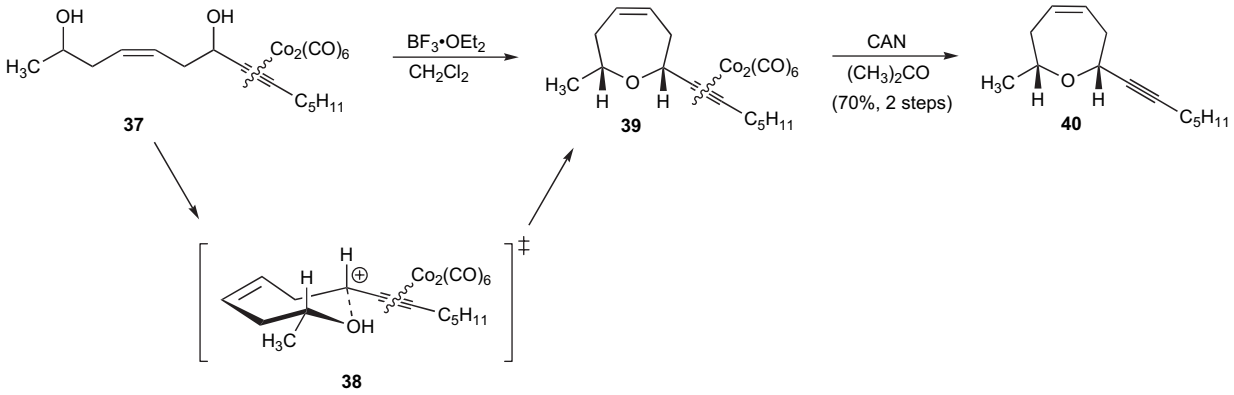
$BF_3 \cdot OEt_2$ as a Lewis acid promoter to give, after reductive decomplexation, oxepine **30** in good yield (66%, two steps). Albeit it is a different precursor, the efficiency of cyclization of the ciguatoxin A ring by this method is markedly better than in the case of the epoxy-alcohol **20** mentioned earlier. An illustration of the combination of the cyclization of a propargyl cation followed by transposition of the double bond after cyclization via a multi-step sequence is given in Scheme 6. Isobe and co-workers have made significant progress on the application of this strategy to cyclizations of the other oxepanes in the ciguatoxin (**1**) structure.[23–25]

In addition to the A ring, synthesis of the D, E, and the nine-membered F ring have also been possible using this approach.

An interesting innovation that has been added in these later treatments is that in place of the usual reductive decomplexation conditions. A reductive hydrosilylation was developed to generate a vinyl silane **33**.[26] The resulting vinyl silane serves two purposes: first, it allows further functionalization of the fused-ring system; second, it promotes migration of the double bond within the ring to its desired position.



Scheme 6.



Scheme 7.

The process is nicely illustrated in the synthesis of the (D)EF rings of ciguatoxin shown in Scheme 6.[23] Lewis acid-promoted cyclization of cobalt complex **31** cleanly provides **32**. Reductive decomplexation of the Co_2CO_6 using triethylsilane and deprotection of the MPM group gives vinyl silane **33**. Oxidation of the alcohol in **33** then sets up an iodolactonization to give **34**. Reduction of the lactone, epoxidation, and addition to the aldehyde gives epoxide **35**. Lewis acid-mediated epoxide opening and elimination provided oxepine **36** where the double bond has migrated to the adjacent carbons relative to the original (vinyl silane) oxepine.

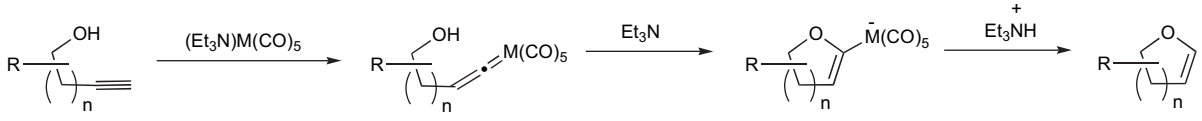
Cyclization where the cobalt complex is exocyclic to the oxepine ring formed has been utilized by Martín in the synthesis of 2,7-disubstituted oxepines similar to isolaurepinnacin (**6**).[27,28] Diol cobalt complex **37** was cyclized in the usual fashion using $BF_3 \cdot OEt_2$ as Lewis acid to give oxepine **39** as shown in Scheme 7. This was followed by removal of the Co_2CO_6 moiety using CAN to deliver the 2,7-disubstituted oxepine **40**. The diol precursor **37** in the sequence was racemic and leads to racemic mixture of oxepines **40**. There was, however, high cis diastereoselectivity in the cyclization step. This selectivity is argued to arise from the reduced transannular interactions experienced when the 2 and 7 substituents are placed in a pseudo-equatorial orientation in the transition state (**38**) to cyclization of the propargyl carbocation.[29]

2.3. Metal-mediated cyclizations by C–O bond formation

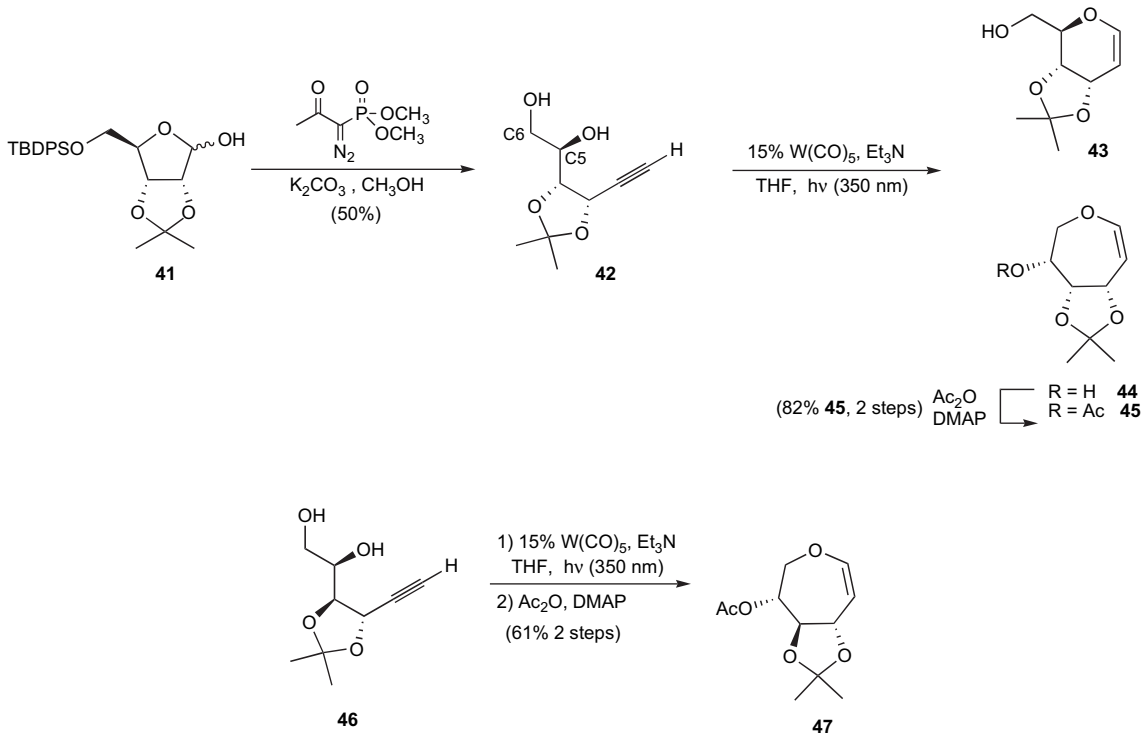
2.3.1. Cycloisomerization of alkynols. The transition metal-mediated isomerization of alkynols in the formation of five- and six-membered ring cyclic enol ethers has proven to be a rapid and effective way for preparing these useful materials.[30–32] The initial step in these reactions is the formation of a metal (ruthenium, rhodium, molybdenum, tungsten) vinylidene species[33] that undergoes intramolecular cyclization by an oxygen nucleophile. Under anaerobic conditions, formation of the metal vinylidene ensures *endo* attack on the erstwhile alkyne in forming a metal oxacarbene, which reductively eliminates to form the corresponding cyclic enol ether (Scheme 8).

This cycloisomerization strategy was recently extended to the preparation of oxepines from furanose-derived alkynols.[34] The synthesis of the alkynol precursor and the cyclization are shown in Scheme 9. Furanose lactol **41** was converted to the alkynol **42** via a modified Seyferth–Gilbert homologation;[35] the TBDPS group was removed under these reaction conditions. Cycloisomerization of **42** was originally expected to deliver a glycal such as **43** based on the rationale that 6-*endo* attack (at C5) would be preferred. However, a preference for the 7-*endo* (at C6) product **44** was observed. The hydroxy-oxepine was routinely acetylated in this study as it was found to be more stable and amenable to purification. The yield for the two-step sequence of cycloisomerization and acetylation was 82%. The acetonide protecting group on the C3 and C4 hydroxyls was shown to be necessary for cyclization to be observed. It likely contributes to the preorganization of the starting alkynol in a way that is favorable to cyclization. A subtle dependence on the orientation of the C3/C4 acetonide where the trans disposition leads to slightly lower yield (61% for conversion of **46** to **47**, Scheme 9) relative to the *cis*-oriented acetonides was noted.

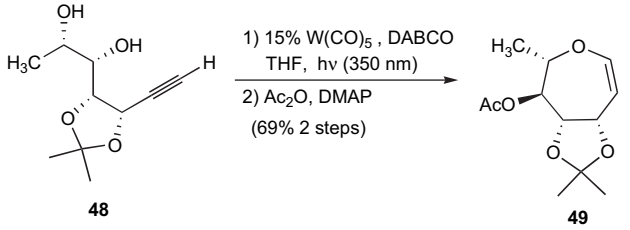
Additionally, the authors demonstrated that oxepine formation was not merely due to the greater nucleophilicity of the primary hydroxyl group (C6) over the secondary hydroxyl group (C5). This was shown by efficiently converting **48** to **49** under essentially the same reaction conditions (Scheme 10). For cyclization precursor **48**, both the hydroxyls giving rise to the 6-*endo* product and the 7-*endo* product were secondary alcohols, but cyclization occurred to preferentially form the oxepine **49** (61%).



Scheme 8.



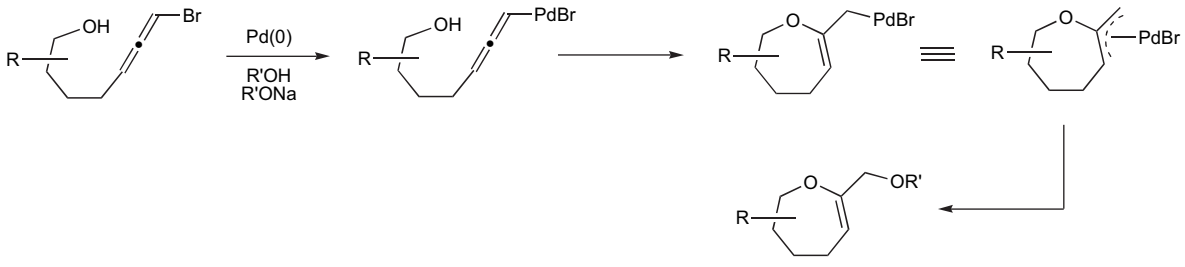
Scheme 9.



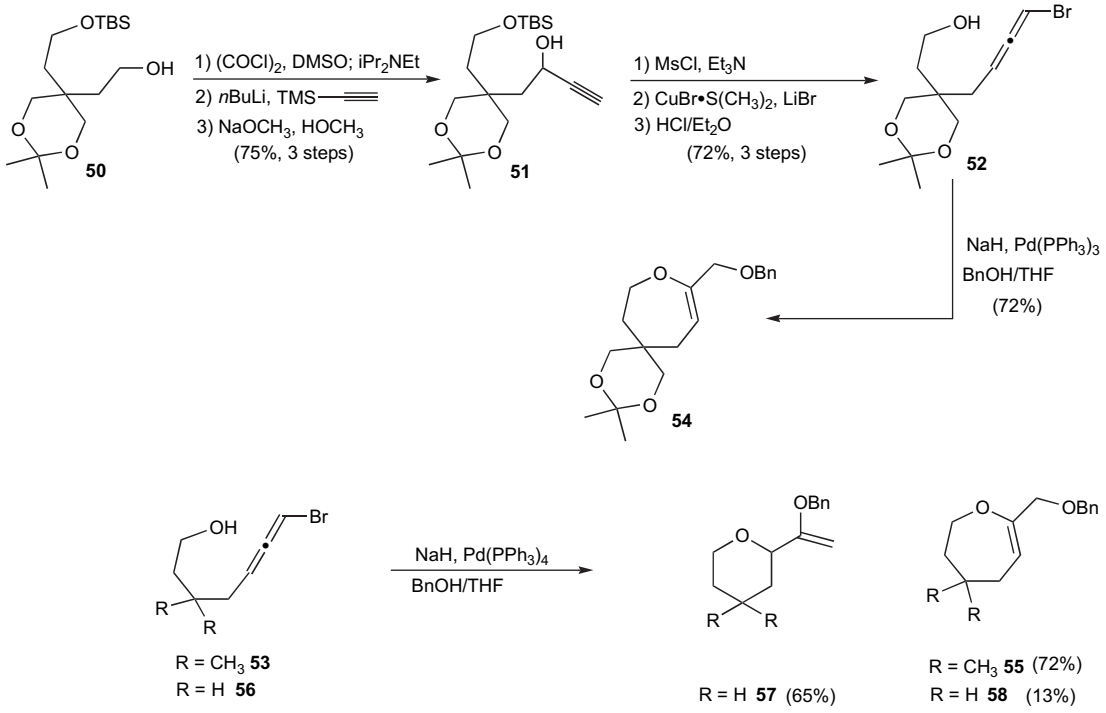
Scheme 10.

2.3.2. Pd(0) cyclization of bromoallenes. The palladium(0)-mediated allylic substitution reaction (Tsuji–Trost) is a versatile method for the formation of carbon–carbon and carbon–heteroatom bonds. Formation of a cationic π-allyl palladium complex is a key intermediate in these reactions; the π-allyl palladium species, therefore, can be considered to be functionally equivalent to an allyl cation because it is susceptible to nucleophilic attack. Palladium(0)-mediated reactions of bromoallenes[36,37] have been shown to have reactivity that is equivalent to allyl dications (Scheme 11). That is, they can be attacked sequentially by two nucleophiles to give a substituted allylic product rather than by one nucleophile as is the case in the allylic systems. Attack on the central carbon of the allene moiety occurs first to give a π-allyl palladium complex, which is then attacked by the second nucleophile to give the substituted allylic system. As shown in Scheme 11, the inclusion of an intramolecular nucleophile (the first nucleophile in this case) allows for cyclization to occur.

Bromoallene **52** (Scheme 12) was accessed through a five-step sequence from alcohol **50**. Swern oxidation of **50** followed by trimethylsilyl acetylene addition and removal of the TMS group gave propargyl alcohol **51**. Sulfonation, formation of the bromoallene functionality, and TBS deprotection gave cyclization precursor **52**. Using the same sequence, the related bromoallene **53** was also prepared. Treating **52** or **53** to reaction conditions of NaH and benzyl alcohol in the presence of $Pd(PPh_3)_4$ gave the substituted methyleneoxy oxepines **54** and **55** in 72% yield in both cases.[38] The ordering of nucleophiles in this reaction follows that outlined in Scheme 11. That is, intramolecular attack of the hydroxyl group is first, which forms the intermediate cyclic π-allyl palladium complex. Subsequent intermolecular attack by benzyl oxide on the π-allyl palladium complex provides the benzyloxymethyl substituted oxepine products.



Scheme 11.



Scheme 12.

The product distribution in this reaction depended on the substitution of the tether between the nucleophile and the bromoallene. In contrast to substituted bromoallenes **52** and **53**, precursor **56** preferentially formed dihydropyran **57** (65%) over the oxepine **58** (13%). The dihydropyran arises because intermolecular attack by benzyl oxide to form an acyclic π-allyl palladium complex predominates over intramolecular attack by the internal hydroxyl group. While a rationale to explain these results is currently incomplete, preorganization of the acyclic bromoallene precursors is presumably a key factor for oxepine formation by this route. Nonetheless, the potential for application of this strategy in the preparation of related oxepines is apparent.

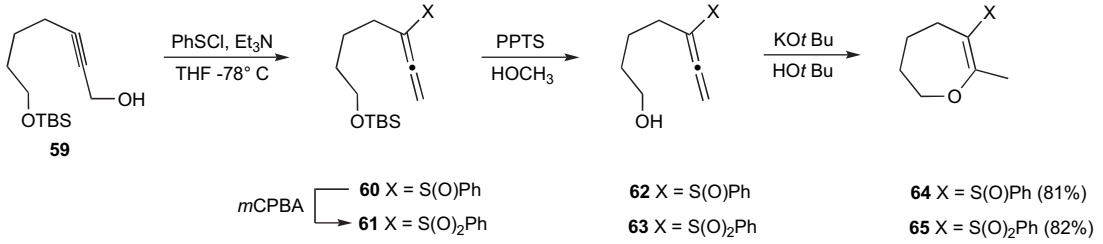
2.4. Cyclization of allenyl sulfoxides and sulfones

The reported cyclization of allenyl sulfoxides **62** and sulfones **63** shown in Scheme 13 is a cycloisomerization that is mechanistically related to the palladium-mediated cyclization of bromoallenes just discussed.[39] A [2,3]-sigmatropic rearrangement of the phenylsulfenyl ether derived from TBS protected 2-octyn-diol (**59**) and phenylsulfenyl chloride gave allenyl sulfoxide **60**. Removal of the TBS group under acidic conditions gave **62**. The allenyl sulfone precursor **63** for cyclization was prepared from sulfoxide **60** via oxidation with *m*CPBA to give **61** followed by desilylation. Under basic conditions, intramolecular attack on the central carbon of activated allenes **62** and **63** cleanly delivered the 1-methyl-2-sulfinyl oxepine **64** (81%) or 1-methyl-2-sulfonyl oxepine **65** (85%) in good yields. Formation of the related five-, six-, and eight-membered cyclic enol ethers using this strategy were also presented in the report.

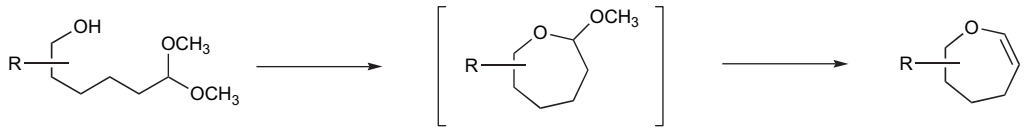
2.5. Cyclization and elimination of hydroxy-acetals

Formation of a mixed, seven-membered ring acetal from an acyclic hydroxy-acetal followed by elimination of a second equivalent of alcohol gives rise to a cyclic enol ether oxepine (Scheme 14).[40] As mentioned previously, a sequence of cyclic enol ether formation, epoxidation, and nucleophilic attack has been successfully utilized by Rainier and coworkers in the synthesis of fused polycyclic ethers.[9] The sequence is especially attractive because it can be conducted in an iterative fashion to construct ladder toxin structures.

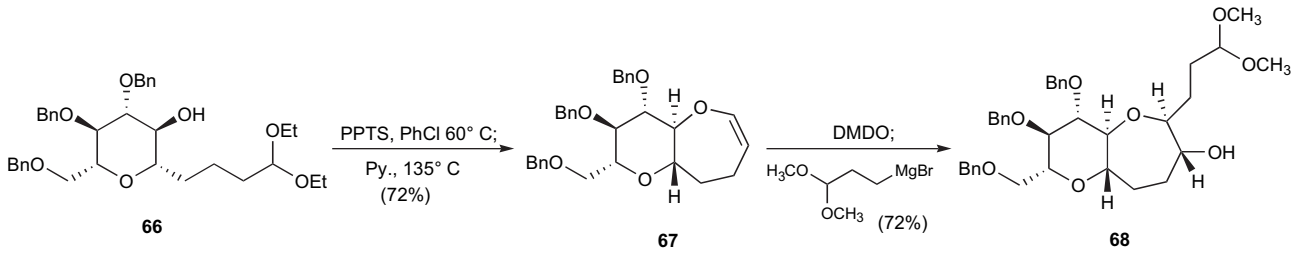
Both the cyclization–elimination strategy for oxepine formation and the iterative assembly of fused polycyclic ethers are illustrated using the model system depicted in Scheme 15.[10]



Scheme 13.



Scheme 14.



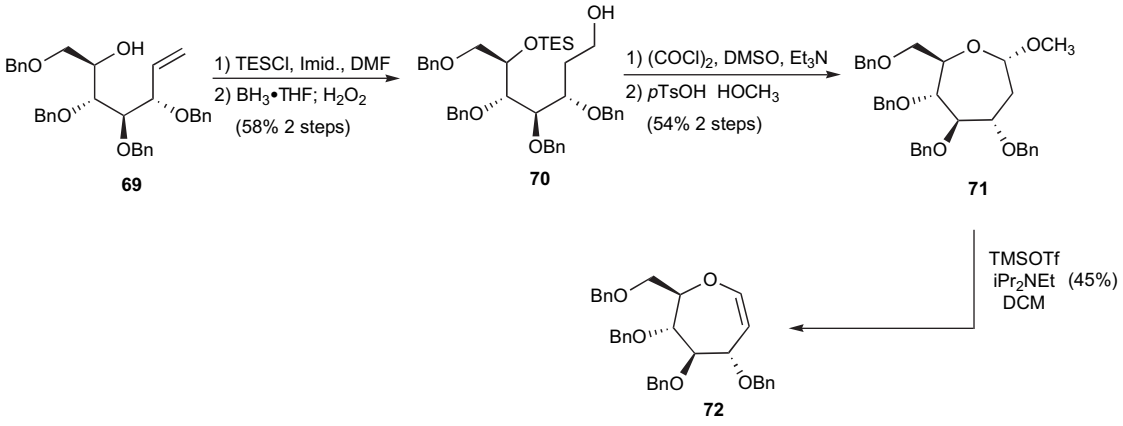
Scheme 15.

Diethyl-acetal **66** was prepared by cuprate addition to the 1,2-anhydro-sugar derivative from benzyl glucal. Cyclization of **66** occurred using PPTS in chlorobenzene; the product of this reaction is a cyclic mixed acetal analogous to the intermediate structure shown in Scheme 14. Elimination of this mixed acetal is accomplished by addition of pyridine and by increasing the temperature of the reaction. Oxepine **67** is formed in 72% yield over this two-step, one pot sequence. The product oxepine can then be functionalized in a similar manner giving rise to the iterative nature of the approach. Treatment of **67** with dimethyldioxirane (DMDO) followed by the attack of Grignard reagent delivers another hydroxy-acetal **68**, which can then undergo subsequent cyclization.

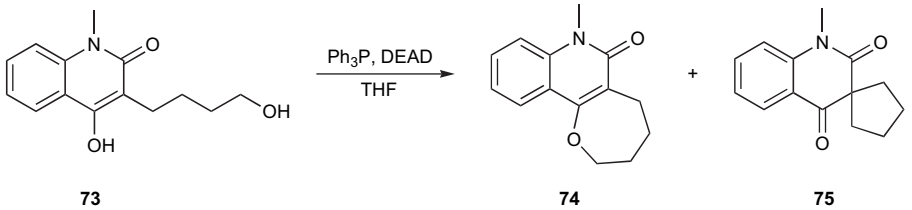
Peczuh and Castro have utilized the same strategy but in a stepwise approach for the formation of carbohydrate-based oxepines (Scheme 16).[41] Heptenitol **69**, prepared from tetra-benzyl glucose via Wittig olefination, was used to prepare glucose-based oxepine **72** in a five-step process. The C6 hydroxyl group of **69** was protected as the TES ether, and then the alkene was converted to alcohol **70** by hydroboration and oxidation. This alcohol was then oxidized to the aldehyde and treated to tosic acid in methanol. The sequence provided the cyclic mixed acetal **71** directly (54%, two steps) along with the acyclic hydroxy-acetal (11%). Mixed acetal was then converted to oxepine **72** by elimination under Gassman conditions in modest (45%) yield. The sequence is of somewhat limited scope based on the nature of the starting heptenitol (or the corresponding pyranose), but it has the advantage of being easily scalable.

2.6. Mitsunobu approach to aryl-oxepines

A Mitsunobu based cyclization has recently been reported in the synthesis of a quinolinone-fused oxepine (Scheme 17).[42]



Scheme 16.



Scheme 17.

Starting from the substituted quinolinone **73**, oxepine **74** formation (23%) competed with a spirocyclization through the α-carbon to form **75** (31%). It is unclear whether this result is from the pK_as of the respective oxygen and carbon moieties, the size of the ring formed, or a combination of these factors. The route may be applicable to other β-keto fused oxepines, making it an attractive disconnection in the preparation of aryl-oxepines such as janoxepin (**10**) and oxepinamide (**11**).

3. Cyclization via C–C bond formation

As may be expected, ring closing metathesis dominates the C–C bond forming annulation strategies to be presented. Included in this treatment will be the recent advances with ene–yne and ring rearrangement metatheses reactions. New approaches for the preparation of oxepines such as palladium-catalyzed inter- and intramolecular couplings and the anionic cyclization of glycidyl ethers will also be presented. A number of important strategies that include intramolecular Wittig[43] and Horner–Wadsworth–Emmons olefinations,[44] acetal–alkene (Prins),[45] and alkyne[46] cyclizations, and sigmatropic rearrangements[47] have been discussed in previous reviews without significant new developments.

3.1. Metal-mediated cyclizations

3.1.1. Ring closing metathesis (RCM). Recent progress in the development of organometallic catalysts for ring closing metathesis (RCM) has provided researchers with a new and convenient tool for the synthesis of medium-sized rings. The power of the RCM approach for the synthesis of oxepines, or rings containing a double bond generally, is that the disconnection is simple. It quickly defines an acyclic target structure that will provide the desired oxepine. On top of this strategic facility is the proven reactivity of a number of RCM catalysts in systems with complex functionality. These factors weigh heavily in the continued utilization of RCM as a method for the preparation of all rings including oxepines. It is worth noting that RCM is the only method that has been used to generate all three types of oxepines **15**–**17**.

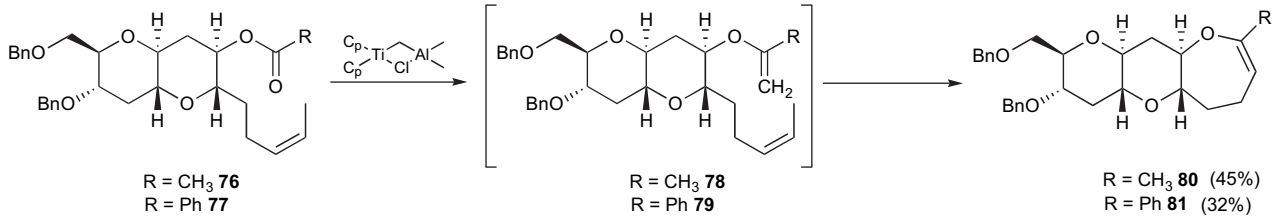
One of the first preparations of substituted oxepines of type **17** (Fig. 2) was reported by Nicolaou and co-workers.[48] These structures were inspired by the complex polyether frameworks of ciguatoxin (**1**) and brevetoxin (**2**). Olefinic esters such as **76** and **77** were subjected to methylenation using Tebbe reagent ($(Cp)_2TiCH_2ClAl(CH_3)_2$) (Scheme 18) to produce the corresponding vinyl ethers **78** and **79**. The vinyl ether intermediates were not isolated, but reacted with a second equivalent of Tebbe reagent in situ to provide oxepines **80** and **81** in 45 and 32% yields, respectively. The titanium-mediated metathesis is a key for this tandem transformation. The approach is attractive because of the ability to vary the alkyl group attached at C1 of the oxepine in the acylation step. A number of different substrates with various substituents were employed to construct six- and seven-membered ring cyclic enol ethers showing the utility of this methodology.

As presented previously, the formation of cyclic enol ethers (including oxepines) followed by epoxidation and nucleophilic attack sets up a sequence for the building of polycyclic ethers such as **1**–**3** in an iterative fashion.[11] Access to cyclic enol ether oxepines **17** in Section 2.5 was through the cyclization and elimination of hydroxy-acetals. Rainier and co-workers[10,49] have also developed an RCM approach for the synthesis of substituted cyclic enol ethers that could be used to prepare the fused polycyclic ethers. This methodology was used to prepare *C*-glycosides that could serve as the asymmetric ring junctures of the ladder polyether structures of brevetoxin (**2**) and gambierol (**3**).

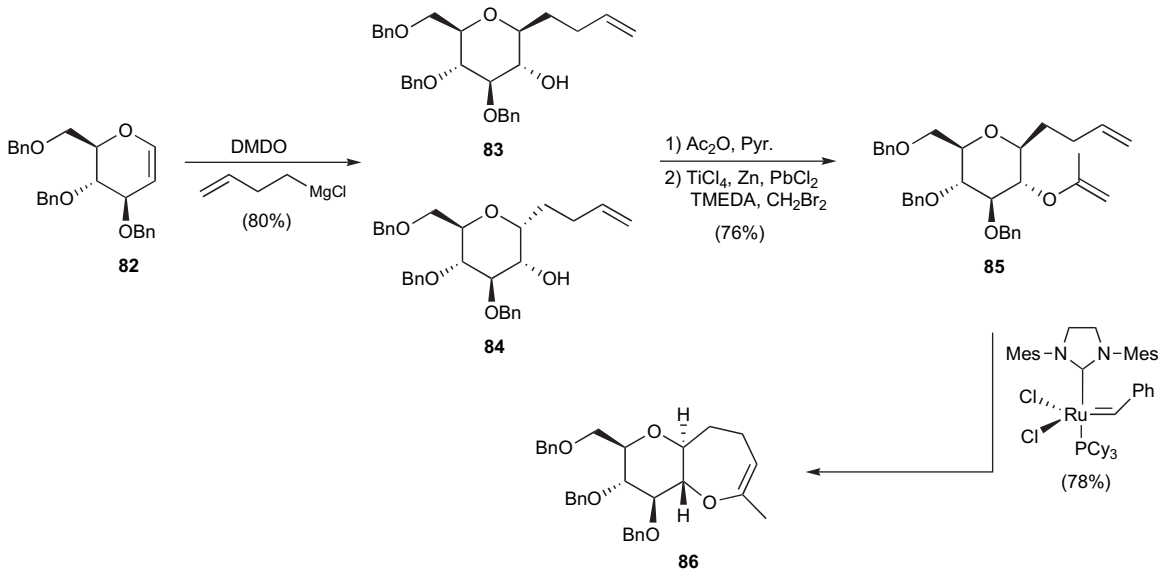
An example of this strategy is outlined in Scheme 19. Epoxidation of tri-*O*-benzyl-D-glucal (**82**) with DMDO, followed by subsequent addition of homoallylmagnesium chloride provided a 1:1 ratio of *C*-glycosides **83** and **84** in 80% yield. Acetylation of the free hydroxyl group of **83**, followed by methylenation using the Takai protocol provided metathesis precursor **85**. Ring closing metathesis of **85** using Grubbs' second generation catalyst gave the corresponding oxepine **86** in 78% yield. Note that the bicyclic oxepine **86** is now prepared for a subsequent iteration of epoxidation, nucleophilic attack, and cyclization to continue the growth of the fused polycyclic ether.

A route to unsubstituted cyclic enol ether **88** using Grubbs' first generation catalyst was recently reported by Cossy and co-workers.[44c] The authors first described the synthesis of diene **87** from 1,4-butane diol in 15 steps. Diene **87** was then subjected to ring closing metathesis using Grubbs' first generation catalyst to afford the enol ether oxepine **88** in 70% yield (Scheme 20). A related oxepine bearing a THP group in place of the TBDPS group of **88** was a key intermediate in an earlier synthesis of zoapatanol (**90**).[50] Attempts of hydroboration–oxidation followed by oxidation of the resulting alcohol under conditions that were reported in the earlier system failed to produce oxepanone **89**. The utility of oxepines as intermediates in the synthesis of complex natural (and unnatural) products is still apparent, however, from this strategy.

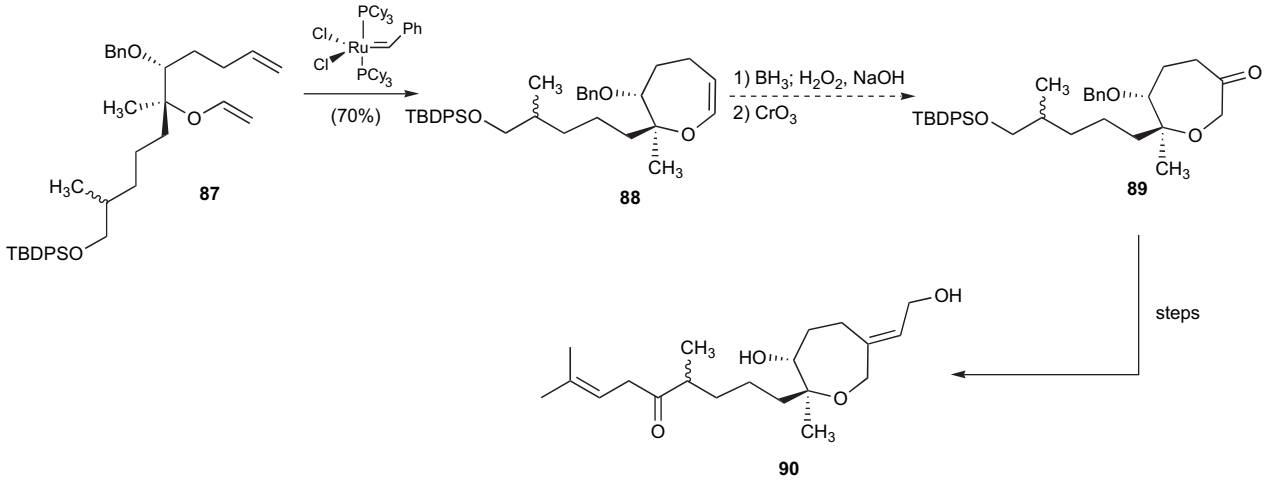
Peczuh[51] reported a ring closing metathesis method for synthesizing carbohydrate-based oxepines with functional equivalence to glycals. Glycals are unsubstituted cyclic enol ethers that are known to serve as glycosyl donors in



Scheme 18.

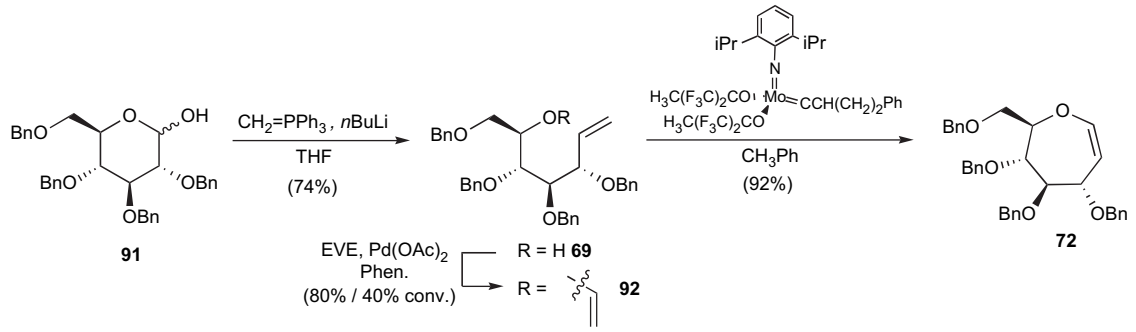


Scheme 19.



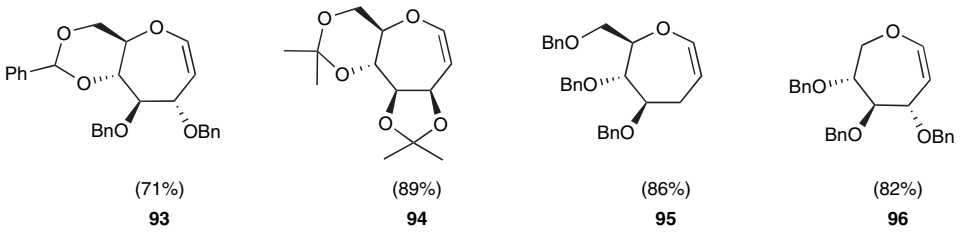
Scheme 20.

a number of glycosylation reactions[52] and can be selectively substituted through a number of processes to afford 2-oxo, 2-amino, and 2-iodo sugars with various groups positioned at the anomeric carbon C-1. Scheme 21 illustrates the three-step synthesis using readily available 2,3,4,5-tetra-*O*-benzyl-D-glucose (**91**). Wittig olefination of **91** revealed the C5 hydroxyl group of **69** and made it available for further functionalization. Vinyl ether formation using conditions involving Pd(II) in the presence of phenanthroline and ethyl vinyl ether provided enol ether **92**. Enol ether **92** was then subjected to ring closing metathesis conditions using Schrock catalyst to give oxepine **72** in 92% yield.



Scheme 21.

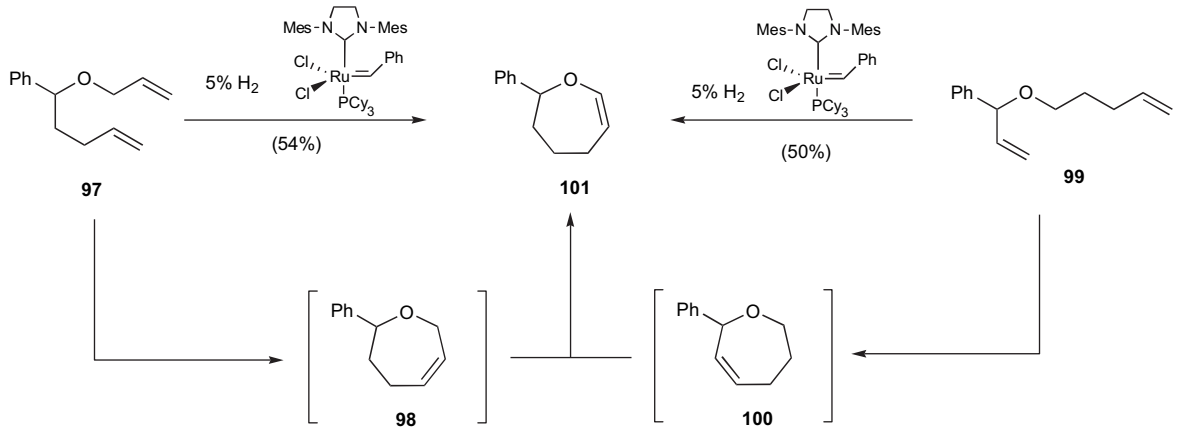
A number of carbohydrate-based oxepines with various protecting groups and sites of deoxygenation proved amenable to this approach, giving RCM yields using Schrock catalyst of 71–92%. These seven-membered ring cyclic enol ethers were derived from readily available 4,6-*O*-benzylidiene-2,3-di-*O*-benzyl-D-glucose **93**, 2,3:4,6 diacetonide-D-mannose **94**, 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucose **95**, and 2,3,4-tri-*O*-benzyl-D-xylose **96** pyranosides and have been used to access a number of important septanosides.[53] Unlike the previous examples (Schemes 19 and 20), oxepine formation using either of the Grubbs' catalysts from the carbohydrate-based dienes gave consistently poor results (yields ranged from 0 to 25% for **72**, **93**–**96**). The low yields were explained based on steric and electronic arguments.[51,54,55] Reaction of the ruthenium catalysts with the enol ether forms a relatively unreactive ruthenium alkylidene. For dienes such as **85** and **87**, the alkene double bond is sterically accessible; this allows loading of the ruthenium on the alkene carbon followed by subsequent cyclization to form the enol ether oxepines. Rigidified diene precursors, afforded by benzylidene or acetonide protecting groups, showed improved RCM yields using ruthenium catalysts.



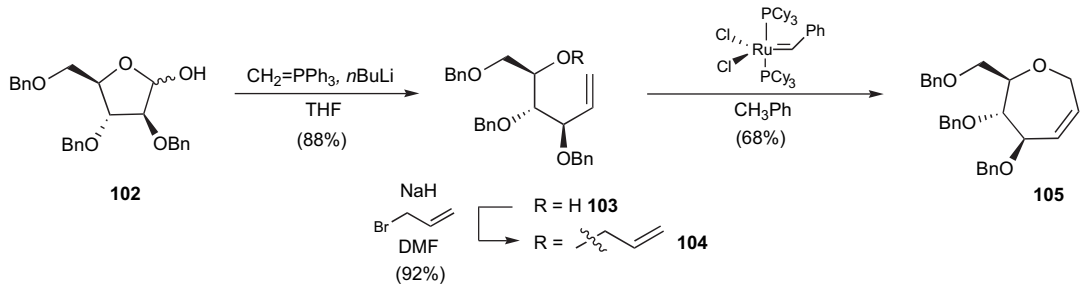
In the previous examples of enol ether oxepine (**17**) synthesis, the diene precursor consisted of an alkene and a vinyl ether. An alternative approach toward the synthesis of cyclic enol ethers has been reported by Snapper and co-workers. It entails a tandem reaction where RCM of two alkenes followed by ruthenium hydride-mediated double bond migration forms the cyclic enol ether.[56] Scheme 22 outlines the preparation of oxepine **101** via two different dienes, **97** and **99**. The reaction utilized Grubbs' second generation catalyst in the presence of 5% H_2. The H_2 facilitated the formation of a ruthenium hydride species, which is essential for double bond migration. Diene **97** initially formed oxepine **98** while **99** formed oxepine **100**. Both **98** and **100** isomerized to form the less substituted oxepine **101** under the reaction conditions in 54 and 50% overall yields, respectively. The trisubstituted oxepine (with C1 having the phenyl substituent) was not observed; the authors suggested that this product was disfavored based on sterics.

van Boom and co-workers[57] utilized one of the first ring closing metathesis routes to access carbohydrate-based oxepines of type **16** (Fig. 2). Wittig olefination of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**102**) produced the corresponding olefin **103** and revealed C4 for further functionalization (Scheme 23). Allylation of the free hydroxyl using allyl bromide to give **104** followed by ring closing metathesis using Grubbs' first generation catalyst produced oxepine **105** in 68% yield. In order to show the utility of this technique, furanose derivatives were designed that varied both the stereochemistry and electronics of the functional groups. These molecules were subjected to similar reaction conditions to obtain oxepines derived from 2,3,5,6-di-*O*-isopropylidene-D-mannofuranoside and 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribofuranose in 99 and 85% RCM yields, respectively. The authors planned to apply the methodology toward the synthesis of oxepane-containing natural products and higher carbon sugars.[58] Sturino and co-workers[59] were also able to prepare a number of carbohydrate-based oxepines using this approach.

Jenkins and Ghosh[60] used a ring closing metathesis approach to produce enantiomerically pure annulated carbohydrate derivatives that could be used as templates to prepare a number of complex natural products via the chiron approach.



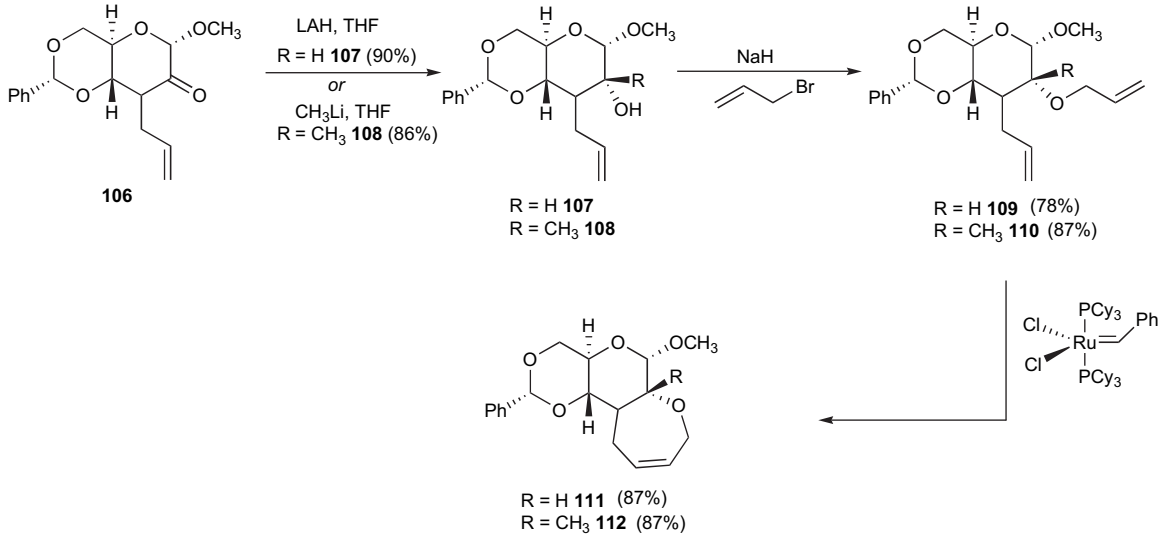
Scheme 22.



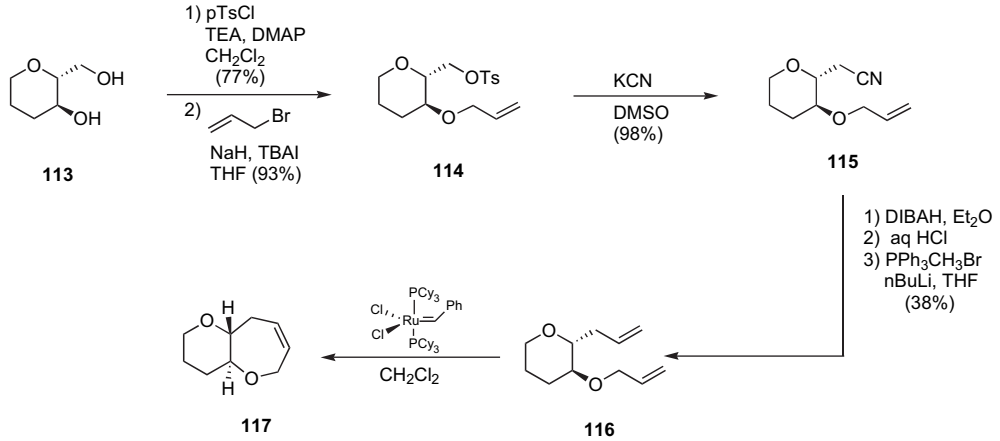
Scheme 23.

The chiron approach employs carbohydrates as chiral starting materials in the stereoselective synthesis of target molecules.[61] Their synthesis involved the addition of lithium aluminum hydride or methyl lithium to ketone **106**, which produced alcohols **107** and **108** in 90 and 86% yield, respectively (Scheme 24). Deprotonation of the alcohols using sodium hydride followed by addition of allyl bromide afforded dienes **109** and **110** in 78 and 87% yield. Upon exposure to Grubbs' first generation catalyst, dienes **109** and **110** readily cyclized to afford oxepines **111** and **112** in 87% yield. The route exemplifies the rapid access to complex 'natural product-like' structures that are afforded by RCM. Additional reactions on **111** and **112** could lead to other distinct carbon skeletons.

Martin and Delgado[62] reported the ring closing metathesis of medium-sized oxacycles in the preparation of trans-fused polyoxygenated macrocycles such as those found in ciguatoxin (**1**) and brevetoxin (**2**). As shown in Scheme 25, treatment of **116**, prepared in five steps from (2*R*,3*S*)-2-(hydroxymethyl)-tetrahydropyran-3-ol (**113**), with a catalytic amount of Grubbs' first generation catalyst resulted in the formation



Scheme 24.



Scheme 25.

of oxepine **117** in greater than 95% yield. The authors' attempts to assay the scope and limitations of this methodology revealed that the ruthenium-catalyzed ring closing metathesis was more efficient for the preparation of seven- and eight-membered ring oxacycles in comparison to larger ring systems. This observation is presumably related to the increased energy required for preorganization of larger diene species prior to ring closing metathesis. The authors also noted that the cyclization for seven- and eight-membered ring oxacycles was highly effective regardless of the position of the reacting olefin. Treatment of **120**, prepared in six steps from (2*R*,3*S*)-2-(hydroxymethyl)-tetrahydropyran-3-ol (**113**), with a catalytic amount of Grubbs' first generation catalyst resulted in the formation of oxepine **121** in greater than 95% yield (Scheme 26). It is important to note that the preparation of cyclic enol ethers, where the position of the olefin is adjacent to the oxygen in the ring, was not attempted using this methodology.

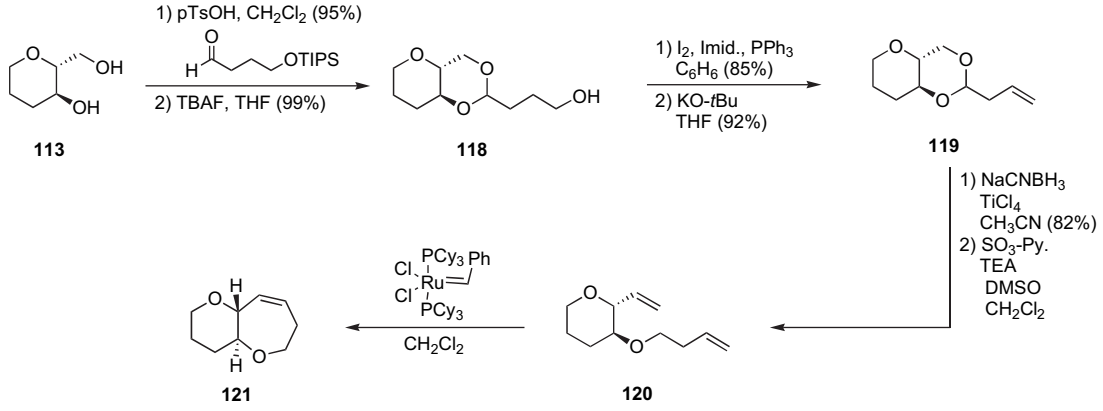
Ring closing metathesis reactions have also been used to produce oxepines of type **15**. Recently, Crimmins and DeBaillie reported the successful enantioselective total synthesis of rogioloxepane.[63] One of the key steps in their total synthesis required the cyclization of diene **123** via ruthenium-catalyzed RCM to produce the desired oxacyclic skeleton **124**. As shown in Scheme 27, production of diene **123** from racemic 1,5-hexadien-3-ol (**122**) over eight steps followed by ring closing metathesis using Grubbs' first generation catalyst gave the desired oxepine **124** in 95% yield. Rogioloxepane (**7**) was prepared from **124** in 12 additional steps.

3.1.2. Ene–yne metathesis. Clark and co-workers[64] reported one of the first successful ring closing ene–yne metathesis reactions of alkynyl ethers to form oxepines in an effort toward the preparation of gambieric acid and gambierol (**3**). Deprotonation of alcohol **125**, prepared from (*R*)-2,3-*O*-isopropylidene glyceraldehyde, followed by nucleophilic addition of the corresponding alkoxide onto 1,1,2-trichloroethene provided the corresponding enol ether **126** (Scheme 28). Base-catalyzed elimination of **126** gave the corresponding alkynyl ether **127** in good yield. Ring closing ene–yne metathesis of the alkynyl ether **127** using Grubbs' second generation catalyst provided the corresponding vinyl substituted cyclic enol ether oxepine **128** in 70% yield.

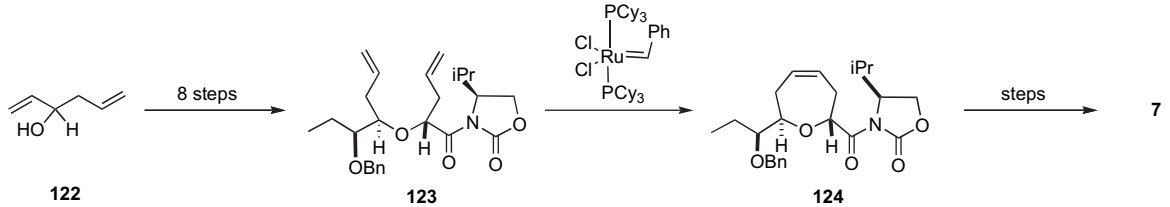
The authors also noted that the success of the ene–yne metathesis depended on the size of the group at the terminus of the alkyne. Cyclization precursor **129** showed efficient conversion to the product oxepine **131** (72%). The larger TMS substituted precursor **130**, however, failed to undergo ring closing metathesis to produce oxepine **132** using either catalyst (Grubbs' first generation or second generation catalyst) due to the inaccessibility of the alkynyl ether.

The ene–yne methodology was recently utilized by Majumdar and co-workers[65] to prepare a number of tricyclic 1,8-naphthyridinones. Examples of their synthesis are shown in Scheme 29. 3-Allyl-4-hydroxy-1,8-naphthyridinone **133**, prepared from readily available 4-allyloxy-1,8-naphthyridinone in two steps, was alkylated using propargyl bromide/chloride derivatives to provide the corresponding ene–ynes **134** and **135** (50–55%). Ring closing metathesis of **134** and **135** using Grubbs' first generation catalyst gave oxepine derivatives **135** and **136** in yields equal to or above 90%. The CH_2-*O*-aryl substitution on the alkyne in **135** in this system apparently does not inhibit cyclization; in comparison to the examples in Scheme 28, this observation suggests that the substitution on the alkyne in **135** is more like the methyl (**129**) rather than the TMS (**130**) group.

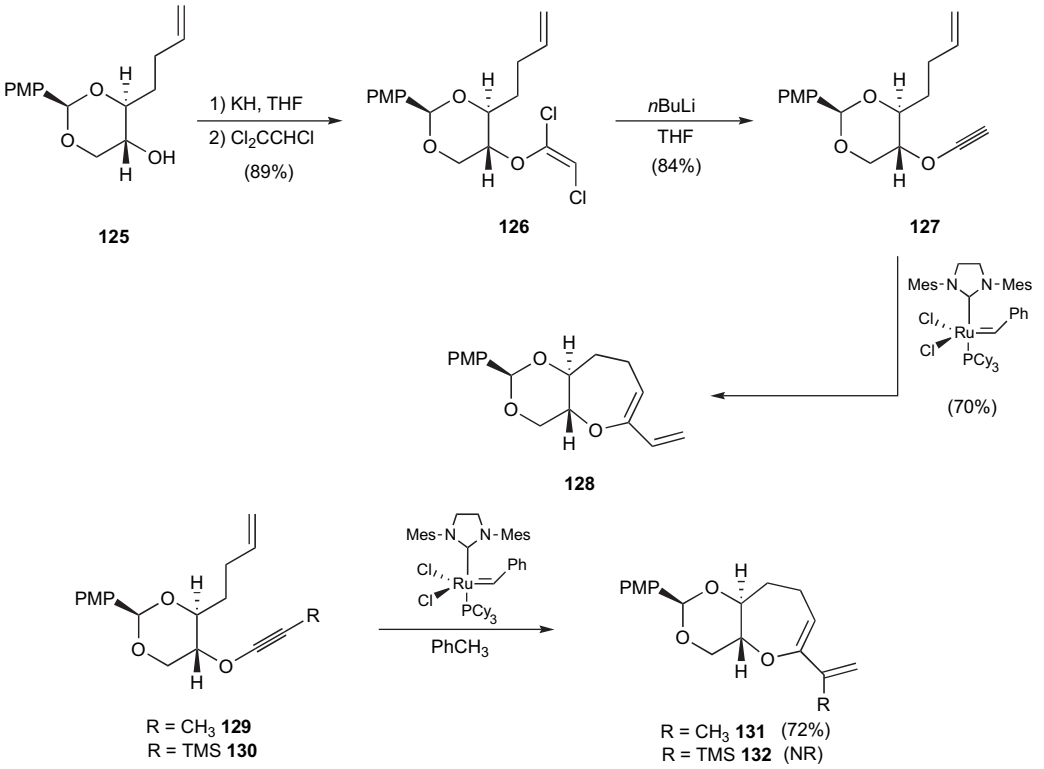
3.1.3. Ring rearrangement (ring opening–ring closing) metathesis. The first ruthenium-mediated ring rearrangement metathesis route (RRM) used to prepare oxepines



Scheme 26.



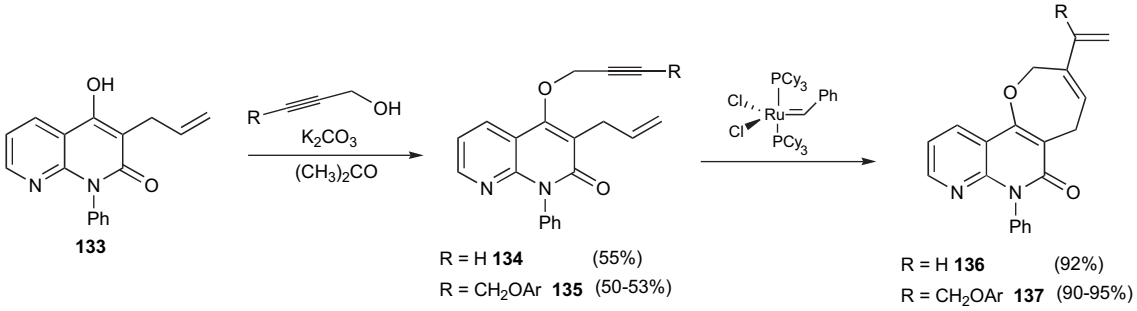
Scheme 27.



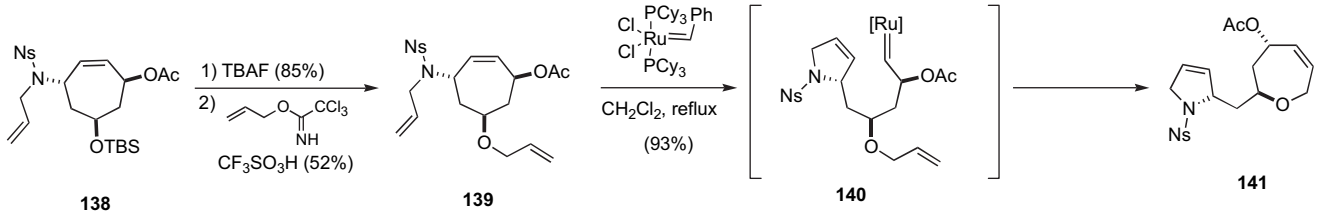
Scheme 28.

was reported by van Boom and co-workers (Scheme 30).[66] Removal of TBS protecting group of **138** with TBAF and allylation using allyl trichloroacetimidate gave the cyclization precursor **139**. The initial coordination of Grubbs' first generation catalyst to the more activated *N*-allyl alkene was followed by ring opening metathesis to give the substituted 2,5-dihydro-1*H*-pyrrole **140**. This set up the molecule for subsequent ring closing metathesis to produce the desired oxepine ring **141**. The two-step RCM process gave a yield of 93%. The authors theorized that the combined ring rearrangement metathesis reaction, which involves the liberation of ethylene as part of the reaction process, provides an additional thermodynamic sink shifting the equilibrium toward formation of the desired oxepine.

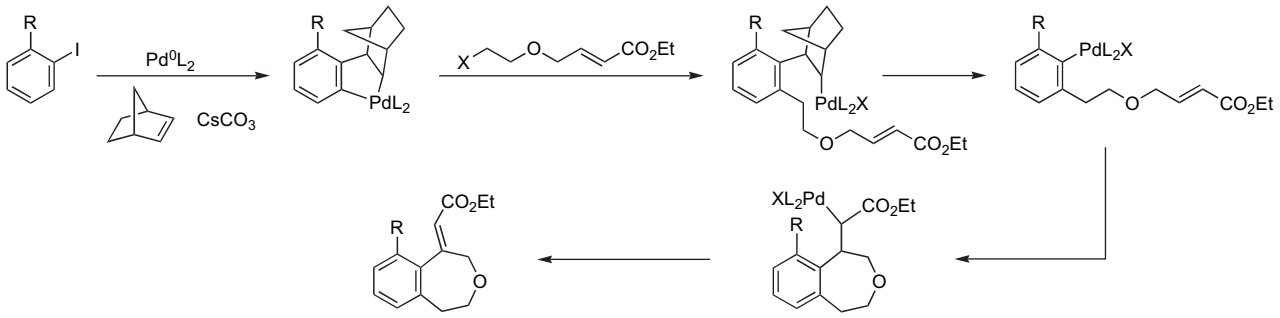
3.1.4. Palladium-catalyzed couplings. Benzoxepines have been prepared by palladium-mediated coupling of the aryl halides with activated allylic species. Although this method



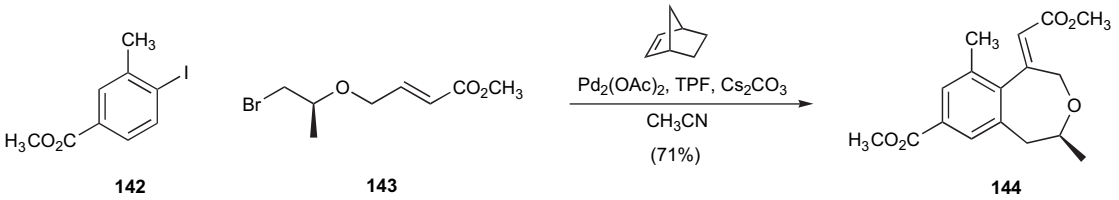
Scheme 29.



Scheme 30.



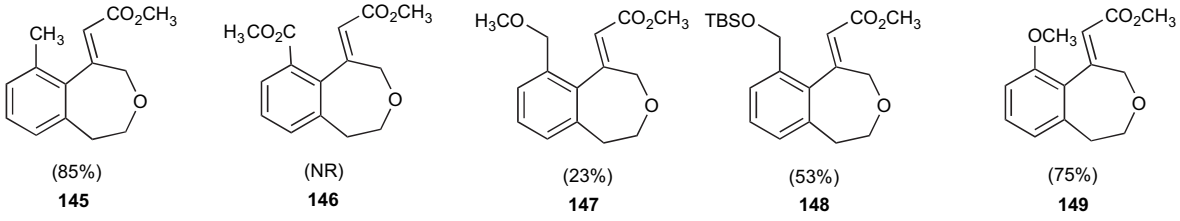
Scheme 31.



Scheme 32.

is for the preparation of 4-benzoxepines, it is added here because of its novelty and with the appreciation that the strategy could be extended to form oxepines such as **15**. The process is a palladium-mediated alkylation followed by an intramolecular alkenylation, which also constitutes the cyclization step. Scheme 31 outlines the mechanism for the transformation.[67] Oxidative addition to the aryl halide, carbopalladation of norbornene, and aryl C–H activation gives the palladacyclic species as shown. A second oxidative addition to an allyl-substituted haloethanol is followed by expulsion of norbornene to give an aryl palladium species. 1,4-Attack on the α,β-unsaturated ester and reductive elimination gives the product benzoxepine.

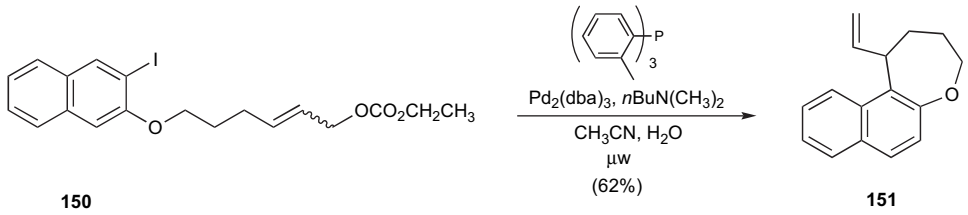
Palladium-catalyzed one pot sequential alkylation–alkenylation reactions were first reported by Lautens and co-workers in their synthesis of 2-substituted-4-benzoxepines.[68] An example of their synthesis is shown in Scheme 32. Palladium(II) acetate, trifurylphosphine, norbornene, and cesium carbonate were combined with aryl iodide **142** and ethyl bromoenoate **143** to give benzoxepine **144** in 71% yield. The effect of the 2-substituent (substituent *ortho* to iodide) in the aryl ring of the starting material was examined to evaluate the scope and limitation of this reaction. The authors noted a dramatic reduction in benzoxepine formation when the corresponding starting material was substituted with a group that could complex palladium in the intermediate aryl palladium species. This complexation inhibits further reaction through the catalytic cycle. Product benzoxepine **145**, where the 2-substituent is a methyl group serves as a reference, was formed in 85% yield. Formation of the acyl benzoxepine **146** was not observed; similarly the alkoxymethyl-substituted **147** was produced in only 23% yield. This effect was attenuated by changing the methyl group of the alkoxy group to a sterically bulkier TBS group, which disfavored complexation and gave a higher yield (53%) of the corresponding benzoxepine product **148**. The methoxy-substituted material was formed with efficiency similar to that of the original system.



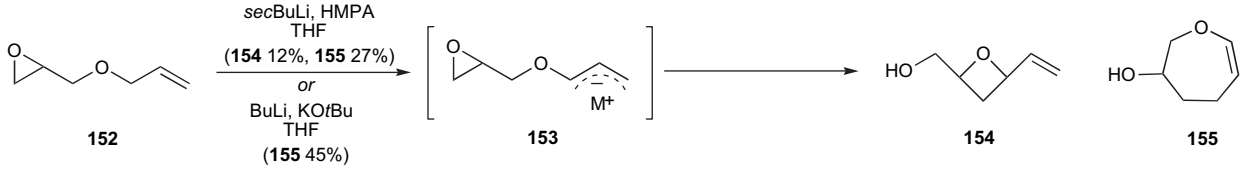
More recently, Lautens and co-workers[69] used a related palladium-catalyzed intramolecular coupling approach, coupling of aryl iodides with allyl carbonates to form five-, six-, and seven-membered ring unsaturated oxacycles with the unit of unsaturation adjacent to the ring oxygen. Seven-membered ring precursor **150** (Scheme 33) was subjected to either refluxing conditions or microwave irradiation in the presence of $Pd_2(dba)_3$, tri-*ortho*-toluyl phosphine, and *N*,*N*-dibutylmethylamine in an acetonitrile–water mixture (10:1). The resulting product **151** was prepared in 72% yield when microwave conditions were used. Refluxing provided only a 49% yield of the desired product. The authors also studied the formation of five- and six-membered ring substrates using the same reaction conditions, noting interestingly that the yields increased as the size of the ring formation increased from five- to seven-membered ring oxacycles.

3.2. Anionic isomerization of oxiranyl ethers

The base (*sec*-butyl lithium) mediated isomerization of glycidyl ether **152** to form oxetane **154** and oxepine **155** in 12

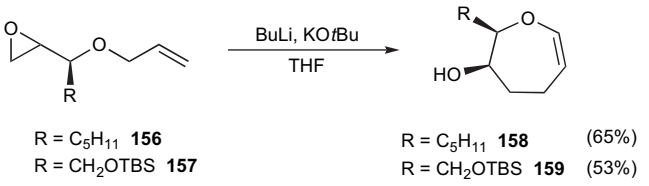


Scheme 33.



Scheme 34.

and 27% yields was reported by Ichikawa and co-workers (Scheme 34).[70] The reaction illustrates the ability of the tethered allyl anion intermediate **153**, generated via deprotonation of the allylic proton, to react at either ends of the epoxide. Attack by the interior carbon of the allylic anion on the more substituted carbon gives oxetane **154** while attack of the terminal allylic carbon on the less substituted epoxide carbon gives oxepine **155**. By switching the base in the reaction to BuLi–KO*t*Bu mixture (Schlosser's base) the formation of oxepine **155** can become the dominant mode of reaction.[71] This was attributed to the preference of the allyl potassium species (**153** where M^+ is K^+) to react at the terminal position.

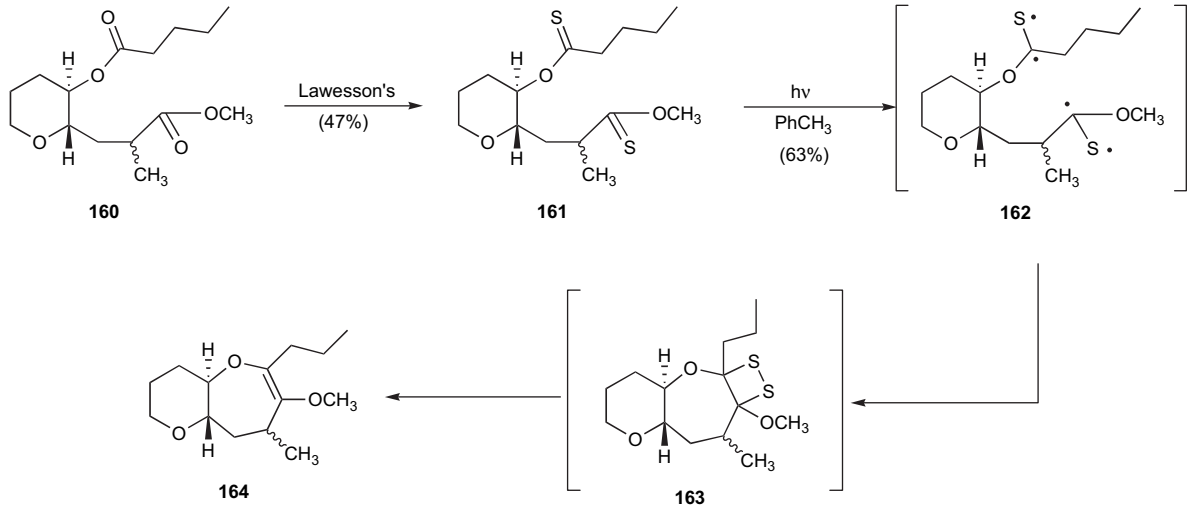


Scheme 35.

Improved yields for oxepine formation under Schlosser's base conditions from the substituted glycidyl ethers **156** and **157** were also noted. As shown in Scheme 35, cyclizations gave the corresponding oxepines **158** and **159** as the major products of the reaction in yields ranging from 53 to 65%. Glycidyl ethers **156** and **157** are homochiral and give rise to *cis*-isomers upon cyclization. However, the authors noted that the oxepines were not configurationally stable and produced a mixture of *cis*- and *trans*-isomers in deuterated chloroform.

3.3. Photochemical cyclization of bis-thioesters

Nicolaou and co-workers[72] have used the photochemical coupling of bis-thioesters to prepare oxepine intermediates in the synthesis of brevetoxin **2**. The strategy was especially attractive because one could envision it being used as a late stage connection of two complex fragments in the synthesis of the natural product. Linkage of fragments through facile ester linkages could be followed by functionalization of the thioesters and subsequent cyclization. For example, oxepine **164**, shown in Scheme 36, was prepared as a model of the D ring of brevetoxin. Diester **160** was thionated using



Scheme 36.

Lawesson's reagent to produce the dithiono system **161**. Upon exposure to UV light (450 W), **161** presumably generated the diradical **162**, which coupled to form the dithietane **163**. The dithietane expels S_2 under the reaction conditions to provide oxepine **164** in 47% yield.

4. Conclusions

The number and variety of new strategies for oxepine synthesis collected here demonstrate an increased interest in this motif as an intermediate to other oxepane or oxepine targets by synthetic chemists. The majority of these new methods give access to enol ether oxepines such as **17**. Among these, the reactions involving allenes (metal, bromo, sulfonyl) and the anionic isomerization of oxiranyl ethers provide specific examples to general themes. First, the transformations are validated by the examples given. Second, while the generality of the strategies in terms of functional group compatibility and molecular architecture has been demonstrated, careful consideration of the reaction conditions and their mechanisms may give insight into their optimization and application in a more complex setting. With increased examples of biologically active oxepines and oxepanes, and the challenge to synthesize these novel structures, it should be anticipated that the field should be active for the foreseeable future.

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Biographical sketch

Mark W. Peczuh became interested in chemistry while growing up in Carbon County, UT. In 1993, he graduated with a B.S. degree in biochemistry from Boston College. He earned his Ph.D. from Yale University in 1999 under the guidance of Andrew D. Hamilton, investigating the molecular recognition of α-helical peptides by designed receptors. After an NIH post-doctoral stint in the lab of Dan Kahne at Princeton from 1999–2001, Peczuh started his independent career at the University of Connecticut. His research group is interested in the synthesis and characterization of ring-expanded carbohydrate analogs.

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Tetrahedron 62 (2006) 9321–9334

Synthetic approach to analogues of betulinic acid

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Received 28 April 2006; revised 3 July 2006; accepted 7 July 2006
Available online 14 August 2006

Abstract—2-Methylcyclohexane-1,3-dione **14** was converted via the Wieland–Miescher analogue **15** into the 6-silyloxy-2,5,5,8a-tetramethyldecalin-1-one **21** by an efficient process. Several routes were examined to transform this compound into the pentacyclic triterpene skeleton of betulinic acid and its structural analogues. For example, the iodide **39**, easily prepared from **21**, was converted via a Sonogashira-hydroboration–Suzuki process into the *E*-triene **45**. Photolysis of **45** using a benzanthrone sensitizer afforded the *Z*-triene **43**. However, all attempts at effecting the cyclization of this triene **43** to the cyclohexadiene **47** (electrocyclic via photochemical or thermal means, metal-catalyzed processes, oxidative and radical cyclizations) failed to produce the key pentacyclic material.

1. Introduction

Betulinic acid (**1**, Fig. 1) was first isolated in 1948 from the bark of the London plane tree (*Platanus acerifolia*) by Bruckner.[1] However, betulinic acid was a known derivative of betulin (**2**, Fig. 1), which was isolated by Löwitz[2] in 1788 from the bark of the white birch (*Betula alba*). The first structural assignment of betulin and its derivatives was made by Ruzicka in 1941.[3] Betulin is one of the most plentiful triterpenes, comprising up to 24% of the outer bark of the white birch and as much as 35% of the outer bark of the Manchurian white birch (*Betula platyphylla*).[4]

Derivatives of betulinic acid **1** and betulin **2** have shown promise as HIV therapeutics by inhibiting viral growth in a manner different from that of current HIV drugs.[5–9] Although betulinic acid and betulin themselves exhibited only weak activity against HIV replication in H9 lymphocytes (**1**, EC_{50} 1.4 μM, TI 9.3 and **2**, EC_{50} 23 μM, TI 1.9), their corresponding mono and diester derivatives **3** and **4**, respectively, have been shown to be very potent inhibitors (**3**, $EC_{50}<3.5\times10^{-4}$ μM, TI>20,000 and **4**, $EC_{50}<6.6\times10^{-4}$ μM, TI>21,515, Fig. 2).[7,8] Thus, **3** and **4** are more potent and less toxic than the well-known drug AZT (EC_{50} 1.5 μM, TI 12,000). The most current data suggest that the compounds are inhibitors of virion formation, disrupting a late step in Gag processing involving conversion of the capsid precursor (p25) to the mature capsid protein (p24).[10]

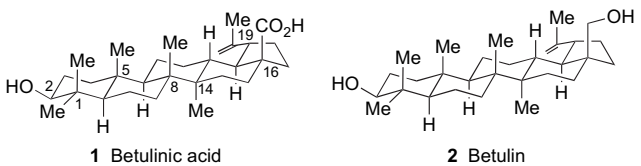

Figure 1.

In addition to the anti-HIV activity of betulinic acid and its derivatives, these compounds also exhibit anti-cancer activity in a wide variety of cell lines via selective cytotoxicity of tumor cells. Various C16 amino acid derivatives exhibit anti-melanoma/carcinoma activity with ED_{50}'s ranging from 1.5 to >20 μg/mL.[11]

Since all known derivatives have been made starting from natural materials, we chose to focus on the construction of the pentacyclic core with the two *anti*-quaternary methyl groups in the C ring. Due to the high steric demand of the β-face of the core structure in the environment around these methyl groups, their installation was seen to be quite challenging. Also, we wanted to develop a convergent synthesis where two highly functionalized portions of the ultimate core system could be joined late in the synthesis, with C ring formation as the key step. Such a strategy would allow for the facile synthesis of analogues by simply altering the construction of either of the components.

We envisioned the 11α-hydroxy betulinic acid derivative **5** to arise from dissolving metal reduction of the enone **6**,

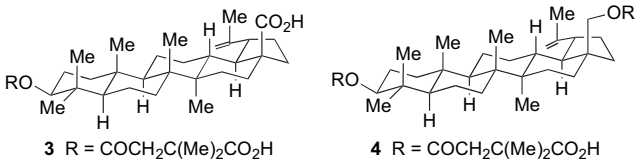

Figure 2.

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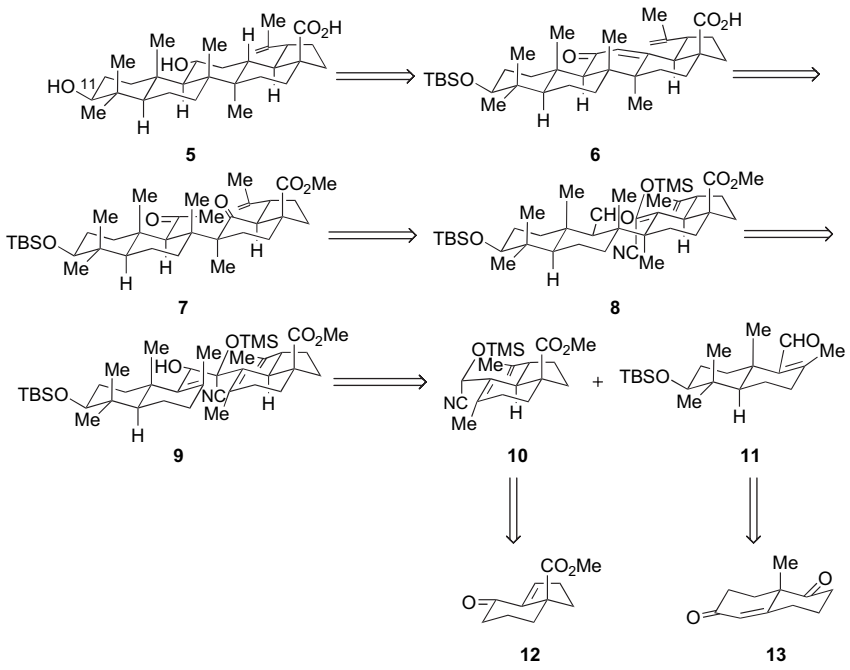
doi:10.1016/j.tet.2006.07.023



Scheme 1.

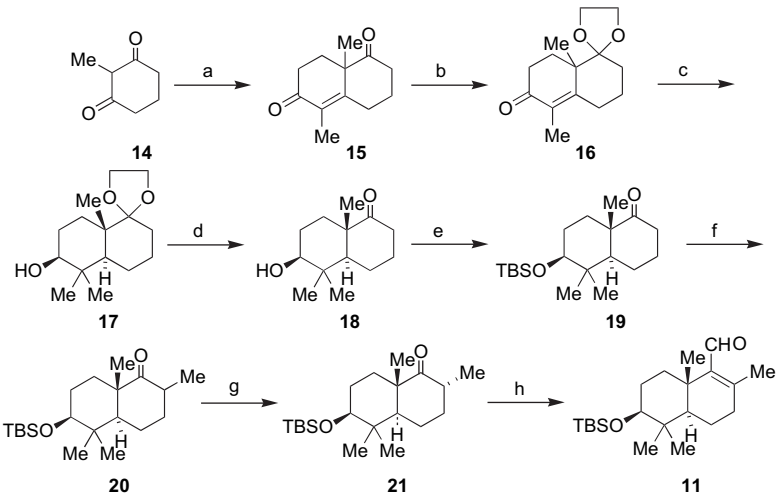
which in turn would be the product of an intramolecular aldol condensation of the diketone **7** (Scheme 1). The diketone **7** would be prepared from conversion of the aldehyde to the corresponding methyl ketone, dihydroxylation, and subsequent glycolytic cleavage of the silyl cyanohydrin of the aldehyde **8**. The aldehyde **8** would be formed via an anionic oxy-Cope rearrangement of the diene **9**, which would arise from nucleophilic addition of the acyl anion equivalent **10** to the α,β-unsaturated aldehyde **11**. The acyl anion equivalent **10** would be easily prepared from the known optically active enone ester **12**.[12] The α,β-unsaturated aldehyde **11** would be derived from the known Wieland–Miescher ketone **13**.[13] We report herein the full details of this approach, namely the facile synthesis of several advanced intermediates and our attempts to convert them into betulinic acid analogues.

2. Results and discussion

The synthesis of the DE ring system **12** was readily accomplished according to the literature method of Cossy.[12] We began synthesis of the AB ring system by converting 2-methyl-1,3-cyclohexanedione **14** into the 1-methyl analogue of the Wieland–Miescher ketone by treatment with ethyl vinyl ketone (EVK) in the presence of potassium hydroxide in methanol (Scheme 2). Subsequent reflux in benzene in the presence of catalytic pyrrolidine afforded the enone **15** in 61% yield. Selective protection of the ketone over the enone with ethylene glycol and *p*-toluenesulfonic acid in the presence of 4 Å molecular sieves provided the enone **16** in 98% yield. Reductive alkylation (Li/NH_3; MeI, THF) of the enone proceeded smoothly. The ketone was reduced in situ with additional lithium wire after the reductive alkylation was complete and then quenched with methanol to produce only the equatorial alcohol **17** in 54% yield. The ketal group of **17** was then hydrolyzed (TsOH, acetone/H_2O) to the ketone **18** and the alcohol protected (TBSOTf, pyridine, dichloromethane) as the TBS ether **19** in 83% yield. The TBS ether **19** was then treated with LDA followed by methyl iodide to furnish in 97% yield the methylated ketone **20**, as a mixture of diastereomers at the methyl stereocenter. The mixture of α-keto diastereomers was subjected to sodium methoxide in methanol to epimerize the mixture to give only the ketone **21** with the methyl group in the equatorial position in quantitative yield.

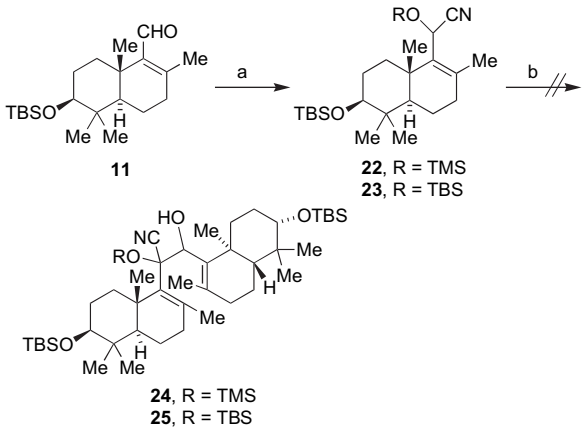
A method was then pursued that allowed direct conversion of the ketone **21** to the desired aldehyde **11**.[14] The procedure utilized dichloromethyllithium generated in situ from dichloromethane and LDA at −95 °C followed by warming to 23 °C and eventual reflux in THF. The solvents were removed and the newly generated α-chloro epoxide was then subjected to treatment with HMPA, lithium perchlorate, and calcium carbonate while being warmed to 130 °C, effecting conversion to the aldehyde **11** in 45% yield.

It was decided to work out the chemistry of the silyl cyanohydrin formation and the nucleophilic addition to the aldehyde **11** in a dimeric manner due the relative abundance of the aldehyde **11** over the enone **12**, which had not been converted to the corresponding aldehyde requisite for the synthesis. With the aldehyde **11** in hand, the trimethylsilyl cyanohydrin **22** of the aldehyde was prepared in 96% yield (TMSCN, ZnI_2, CH_2Cl_2) (Scheme 3) and the *tert*-butyl-dimethylsilyl (TBS) analogue **23** in 48% yield (TBSCN, ZnI_2, dichloromethane). In both cases, addition of the lithiate of the silyl cyanohydrin to the aldehyde **11** gave no reaction. A variety of temperatures ranging from −78 °C to reflux was used but no addition was ever seen. The addition of HMPA to the reaction mixture also had no effect on the reaction. Due to the stabilizing effect of the neighboring nitrile group as well as the sheer size of the nucleophile generated, it was believed that we would need a smaller and



Scheme 2. Reagents and conditions: (a) KOH, MeOH, EVK; pyrrol., PhH, reflux, 61%; (b) $HO(CH_2)_2OH$, TsOH, 4 Å MS, 98%; (c) Li/NH_3; MeI, THF; Li^0/NH_3; MeOH, 54%; (d) TsOH, acetone/H_2O, quant.; (e) TBSOTf, pyr., CH_2Cl_2, 0–23 °C, 83%; (f) LDA, THF, −78 °C; MeI, −78 to 23 °C, 97%; (g) NaOMe, MeOH, 23 °C, quant.; (h) LDA, −95 °C; CH_2Cl_2, **21**, −95 to −20 °C to reflux; HMPA, $LiClO_4$, $CaCO_3$, 130 °C, 45%.

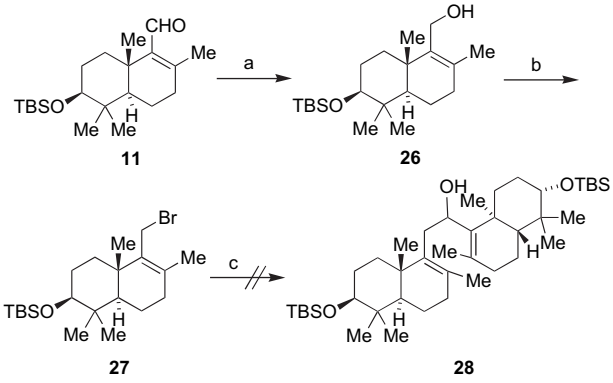
much more reactive nucleophile to be able to add to the very sterically hindered aldehyde **11**.



Scheme 3. Reagents and conditions: (a) TMSCN/TBSCN, ZnI_2, CH_2Cl_2, 0–23 °C, 96%/48% (**22**/**23**); (b) LDA, THF, −78 °C; **11**, −78 °C to reflux, 0%.

Despite reaching the requisite acyl anion equivalent of the silyl cyanohydrin and synthesizing the AB ring system as planned, the lack of reactivity of our nucleophile toward the aldehyde **11** would not allow us to prepare the substrate required to demonstrate our anionic oxy-Cope methodology for the construction of the *anti*-quaternary methyl groups in the C ring of betulinic acid **1**. Therefore, a smaller, stronger nucleophile was required to add to our very sterically hindered aldehyde in order to be able to test the validity of our anionic oxy-Cope methodology. Thus, we moved to other nucleophile sources for addition to the aldehyde **11** and the eventual construction of the ring system.

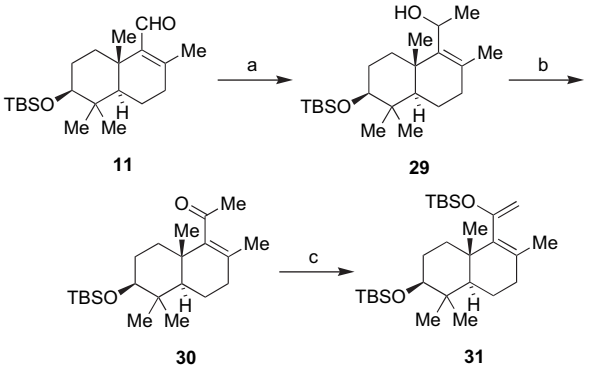
The aldehyde **11** was reduced in 98% yield to the corresponding alcohol **26** ($NaBH_4$, EtOH), which was readily converted into the bromide **27** in 48% yield (CBr_4, PPh_3, DCM) (Scheme 4). However, upon treatment of the bromide **27** with magnesium metal, even in the presence of iodine to activate the surface of the metal, and addition of the aldehyde **11**, there was no evidence of Grignard addition to form **28**.



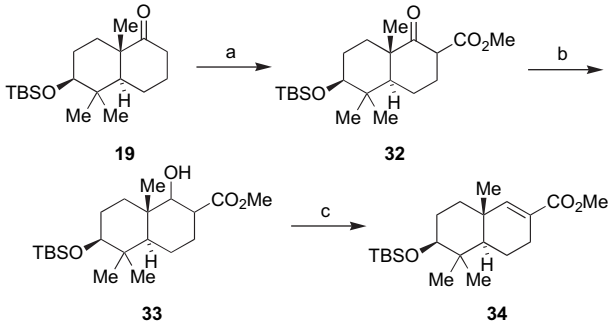
Scheme 4. Reagents and conditions: (a) $NaBH_4$, EtOH, 23 °C, 70%; (b) CBr_4, PPh_3, CH_2Cl_2, 0–23 °C, 48%; (c) Mg, Et_2O, reflux; **11**, 23 °C to reflux.

Since nucleophilic additions to the aldehyde **11** were unsuccessful, we concluded that using an anionic oxy-Cope as the key step to set the *anti*-quaternary methyl groups and ultimately close the C ring as originally designed was not viable. Starting from the aldehyde **11**, we devised a new synthetic strategy that would assemble the C ring with the *anti*-quaternary methyl groups through the use of a Diels–Alder reaction. The synthesis of the AB ring component began with methylation of the aldehyde **11** (MeLi, Et_2O) to give in 95% yield the allylic alcohol **29**, which was subsequently oxidized to the corresponding enone **30** in 80% yield (Dess–Martin periodinane, DMP, dichloromethane) (Scheme 5). The enone **30** was then converted into the kinetic silyl enol ether **31** in 99% yield (TBSOTf, TEA, dichloromethane). A possible dienophile **34** was synthesized by a three-step procedure starting from the ketone **19** by first forming the β-keto ester **32** with potassium hydride and dimethyl carbonate (Scheme 6). The ketone of **32** was then reduced to the alcohol **33** ($NaBH_4$, MeOH), and the alcohol eliminated ($POCl_3$, pyr., 80 °C) to form the α,β-unsaturated ester **34** in an overall unoptimized yield of 22%. The diene **31** and the dienophile **34** were reacted with a catalytic amount of a 5:1 mixture of aluminum tribromide and trimethylaluminum (Scheme 7), conditions proven to work in our laboratories[15] for highly hindered Diels–Alder reactions. However, these

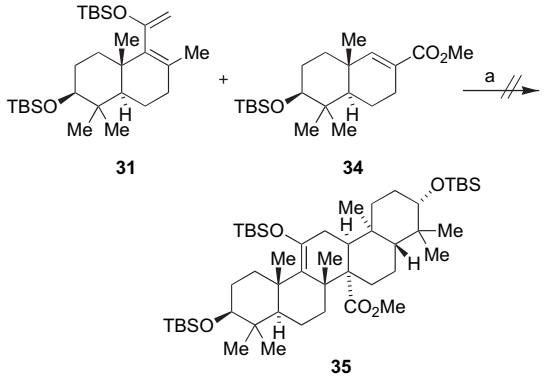
conditions failed to give the desired Diels–Alder adduct **35**. Despite the strength of the Lewis acid, only starting material was obtained. This outcome was undoubtedly due to the severe steric demand of both **31** and **34**.



Scheme 5. Reagents and conditions: (a) MeLi, Et_2O, 0–23 °C, 95%; (b) DMP, CH_2Cl_2, 23 °C, 80%; (c) TBSOTf, TEA, CH_2Cl_2, 0–23 °C, 99%.



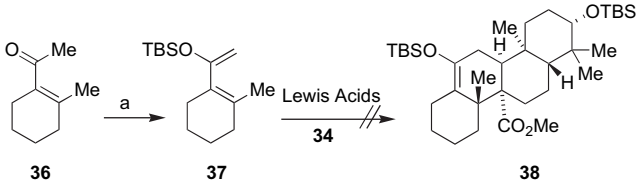
Scheme 6. Reagents and conditions: (a) KH/NaH, THF, Me_2CO_3, reflux; (b) $NaBH_4$, MeOH, 23 °C; (c) $POCl_3$, pyr., 80 °C, 22% (three steps).



Scheme 7. Reagents and conditions: (a) 5:1 $AlBr_3/AlMe_3$, $PhMe/CH_2Cl_2$, −9 to 23 °C.

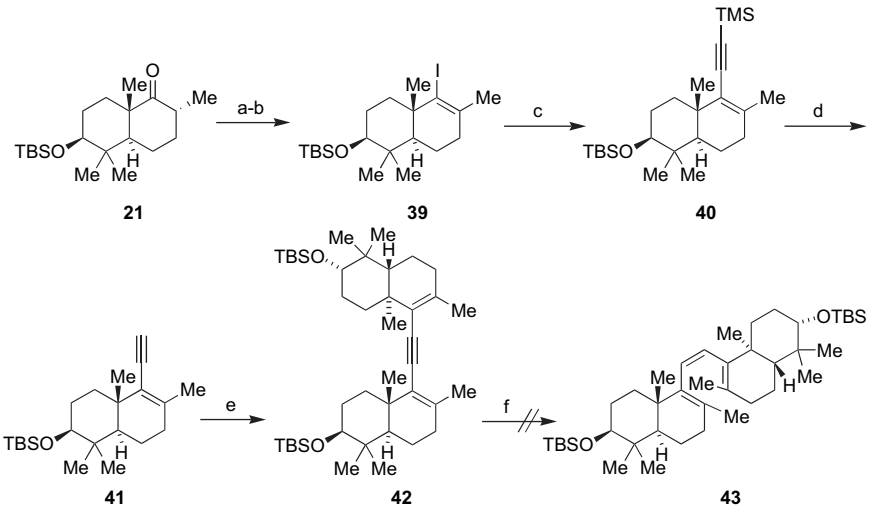
A variety of other Lewis acids were then screened in this system in hopes of finding a viable catalyst to furnish the Diels–Alder adduct **35**, but were ultimately unsuccessful. The reaction time and the variety and strength of Lewis acid catalysts should have been sufficient to see at least some formation of the Diels–Alder adduct **35**. At this point, we believed the diene was probably not cis-coplanar due to steric interaction between the silyloxy group and the adjacent quaternary center, thereby rendering the Diels–Alder reaction impossible due to poor orbital overlap. The high steric demand of the AB ring system in the environment of the silyl enol ether with its large TBS group could very easily twist the silyl enol ether out of planarity with the olefin in the B ring. Although we lacked evidence for this hypothesis other than a lack of reactivity of the diene and dienophile, we decided to test the hypothesis by eliminating the A ring and working with a smaller model system. Without the A ring present there would be no reason for the silyl enol ether to twist out of planarity.

With this hypothesis in mind, the known compound 2-methyl-1-acetyl-1-cyclohexene[16] **36** was converted into the corresponding TBS enol ether **37** (TBSOTf, TEA, dichloromethane, 0 °C) and reacted with the ester **34** using the same set of Lewis acids previously screened (Scheme 8). Once again only starting material or hydrolysis of the silyl enol ether was observed. Therefore, a rotation out of planarity was probably not the key issue since a substrate that could not even undergo this rotation also failed to produce a Diels–Alder adduct. Since the diene **37** has been successfully used in other hindered Diels–Alder reactions,[15a] the most likely explanation is that the ester **34** is just too poor a dienophile to participate. It is well known that esters are quite poor activators of alkenes as dienophiles.[15b]



Scheme 8. Reagents and conditions: (a) TBSOTf, TEA, CH_2Cl_2, 0–23 °C, quant.

Once again seeking a convergent strategy that would enable the mild coupling of two fully elaborated pieces followed by a key cyclization, we developed an organometallic coupling approach, namely a double Sonogashira sequence. Utilizing the advanced ketone **21**, we sought to install a vinyl iodide via the Barton vinyl iodide procedure (Scheme 9).[17] Following formation of the hydrazone of the ketone **21** in 75% yield (H_2NNH_2, AcOH, EtOH, reflux), nitrogen gas was eliminated by treatment with iodine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in diethyl ether followed by refluxing with DBU in benzene to afford the vinyl iodide **39** in 76% yield. Treatment of the vinyl iodide **39** with trimethylsilyl acetylene in the presence of palladium(II) [$PdCl_2(PPh_3)_2$], copper(I) iodide, and triethylamine at 23 °C effected a Sonogashira reaction to afford the silyl enyne **40**.[18] The first attempts at deprotection of the enyne under basic conditions (K_2CO_3 or KOH in MeOH) were unsuccessful. However, when fluoride ion (TBAF) was used, the enyne **41** was obtained. A second Sonogashira reaction mixture was then conducted using another equivalent of the vinyl iodide **39**, furnishing the dienyne **42** in 14% overall yield from **39** over three steps. With the dienyne in hand, several attempts were made at reduction of the alkyne to the *Z*-alkene **43**, including hydrogenation using Lindlar's catalyst as well as hydroboration ($BH_3\cdot DMS$; $BH_3\cdot THF$). Each of the reagents provided only starting material, even at extended reaction times of up to one week. We realized that if a molecule as small as borane was not reacting with

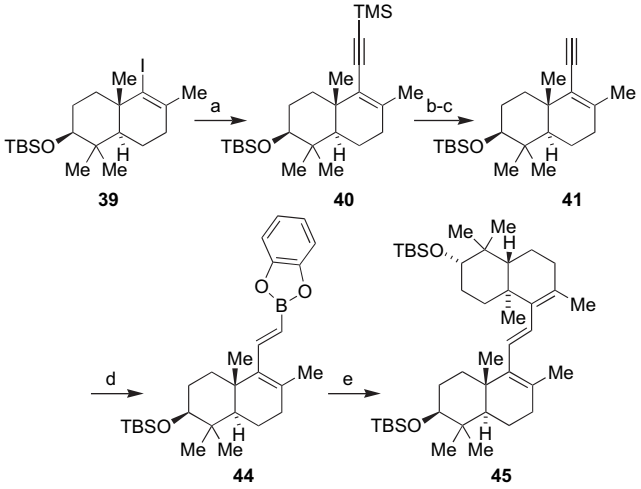


Scheme 9. Reagents and conditions: (a) NH_2NH_2, EtOH, AcOH, reflux, 75%; (b) I_2, DBU, Et_2O, 23 °C, then DBU, PhH, reflux, 76%; (c) TMS–acetylene, $PdCl_2(PPh_3)_2$, CuI, TEA, 23 °C; (d) TBAF, THF, 23 °C; (e) **39**, $PdCl_2(PPh_3)_2$, CuI, TEA, 23 °C, 14% (three steps); (f) H_2, Lindlar's cat. or BH_3.

the dienyne, it was not likely that anything else would either. Although the molecule seems not very sterically hindered, the lack of these reactions indicated that the steric environment surrounding the alkyne was heavily congested.

Even though we were unable to effect reduction to the requisite *Z*-alkene **43** for the cyclization to occur, we viewed this problem as a minor setback. All that was required to overcome this problem was a change in the type of coupling utilized. Therefore, we decided to investigate a new method of joining the two halves of the ring system that would avoid the sterically challenging alkyne reduction. By converting the enyne into a vinyl boron species, which could undergo a Suzuki reaction with another equivalent of the vinyl iodide, such as **39**, we would arrive at an *E*-triene intermediate suitable for cyclization.

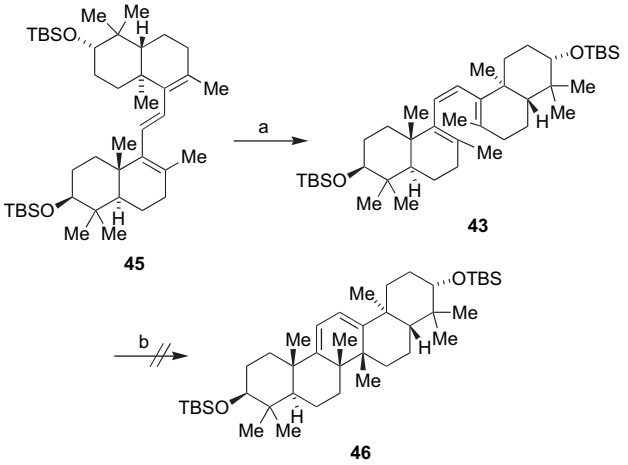
Before we subjected the enyne **41** to catecholborane, we decided to first optimize the synthesis of the enyne (Scheme 10).



Scheme 10. Reagents and conditions: (a) TMS–acetylene, $Pd(dba)_2$, CuI, PPh_3, TEA, 70 °C; (b) excess TBAF, THF, 23 °C; (c) TBSOTf, TEA, CH_2Cl_2, 0–23 °C, 75% (three steps); (d) $Cp_2Zr(H)Cl$, catecholborane, CH_2Cl_2, 96%; (e) **39**, $PdCl_2(dppf)$, 2 M NaOH, THF, 60 °C, 68%.

First, superior conditions for performing the Sonogashira reaction ($Pd(dba)_2$, CuI, PPh_3, triethylamine, 70 °C)[19] were discovered, resulting in a much better crude yield of the silyl enyne. A global desilylation was effected with excess TBAF. The resulting alcohol could then be reprotected with TBSOTf in the presence of triethylamine in dichloromethane at 0 °C to arrive at the enyne **41** in a much improved 75% yield for the three-step sequence. Treatment of the enyne **41** with bis-(cyclopentadienyl)-zirconium chloride hydride (Schwartz's reagent) to effect hydrozirconation followed by addition of catecholborane to transmetallate to the desired vinyl boronate **44** proceeded smoothly and in excellent yield. Suzuki coupling of the vinyl boronate **44** to the vinyl iodide **39** ($PdCl_2(dppf)$, 2 M NaOH, THF, 60 °C)[20] was carried out to afford the *E*-triene **45** in 68% yield.

With the *E*-triene **45** in hand, photoisomerization with a mercury lamp in the presence of a photosensitizer (benzanthrone) in a quartz tube was performed (Scheme 11). The *Z*-triene **43** was obtained in quantitative yield. Even though we ultimately wanted the *Z*-triene **43** to undergo a

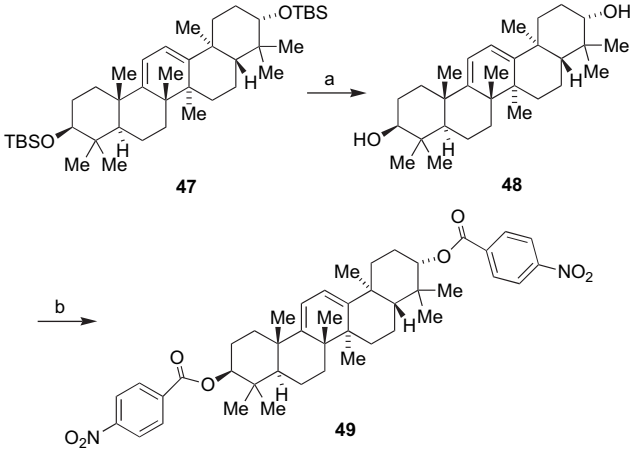


Scheme 11. Reagents and conditions: (a) hν (quartz), THF, benzanthrone, 84%; (b) DMF/1,2-$C_6H_4Cl_2$, sealed tube, 250 °C.

conrotatory six electron cyclization to achieve the desired *anti*-quaternary methyl groups in the C ring, we first tried thermal methods of disrotatory ring closure due to the reasonably similar precedent of Trost.[21] In his case, a less sterically hindered triene was able to cyclize under high heat. However, the initial attempt at heating **43** in *ortho*-dichlorobenzene and DMF (250 °C, sealed tube) gave a mixture of starting material and decomposition products arising from the HCl liberated in the breakdown of *ortho*-dichlorobenzene under the extreme heat instead of the desired diene **46**.

After this initial failure, a variety of other thermal experiments were conducted in an effort to prepare the diene **46** (Table 1). Microwave heating (entries 2–5) was investigated with solvents that had stable heating profiles, good solubility with the triene, and that facilitated monitoring the reaction by NMR. However, none of the runs furnished the diene **46**. Flash vacuum pyrolysis (FVP) was then utilized to try and effect triene cyclization (entries 6–10). Various vacuum strengths were explored at extreme temperatures to try to create as much intimate contact between the substrate and the hot tube as possible after injection of a solution of the triene **43** in diethyl ether. However, once again no cyclization was seen.

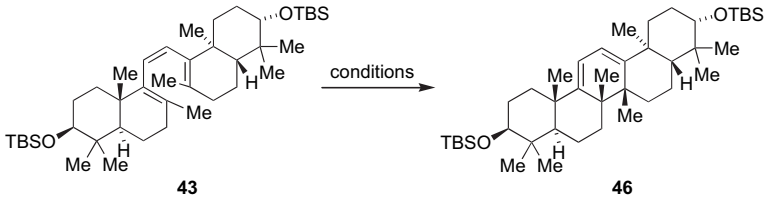
Since the thermal methods did not afford any of the cyclized substrate, we decided to switch to photochemical methods. A conrotatory photochemical cyclization was ultimately necessary to arrive at the *anti*-quaternary methyl groups, and it was thought that perhaps the excitation of the triene chromophore would more easily facilitate our sterically challenging cyclization where the thermal methods failed. Upon excitation of the triene **43**, a compound that appeared to be the desired C_2-symmetric pentacycle **47** by NMR and HRMS was isolated in 47% yield. However, the UV–vis spectrum of the isolated compound did not show absorbance typical of a *s*-cis diene in a ring, absorbing only up to about 245 nm. Therefore, it was necessary to obtain a crystal structure of the compound for structural verification. Deprotection of the TBS groups was effected with *p*-toluenesulfonic acid in 1:1 acetone/water, to afford what appeared to be the C_2-symmetric diol **48**. The corresponding bis-(*para*-nitrobenzoate) **49** (*p*-NO_2–C_6H_4COCl, pyr., DMAP, dichloromethane, 23 °C) was then prepared in good yield (Scheme 12). After much experimentation, very thin plate crystals of **49** were finally obtained from a 9:1 acetonitrile/hexanes solution. X-ray crystallographic analysis of the bis-(*p*-nitrobenzoate) **49** unambiguously showed that the triene **43** had cleaved by an unknown mechanism to give the simple olefin **50** (X-ray analysis performed on **51**) (Fig. 3).



Scheme 12. Reagents and conditions: (a) TsOH, 1:1 H_2O/acetone, 23 °C, 64%; (b) *p*-NO_2–C_6H_4COCl, pyr., DMAP, CH_2Cl_2, 23 °C, 93%.

At this point it was likely that enough energy was available to initiate photochemical transformations, but we wanted to temper the amount of energy to which the triene **43** was being exposed. Thus, a borosilicate NMR tube was used as the photolysis vessel as a thin filter against shorter wave UV and deuterobenzene (C_6D_6) was used as an internal filter as well (Table 2, entry 2). The consequence of this reaction was evidence of [1,5]-hydrogen shifts in a complex mixture of products. The identification of [1,5]-hydrogen shifts was confirmed by the similar findings of Parra[22] in his photochemical work toward the synthesis of oleanolic and maslinic acids. Looking more closely at the UV–vis spectrum of the triene, we decided to use filters to try and block out all wavelengths of light below the tail end of the absorbance

Table 1



Entry	Method	Conditions	Result
1	Sealed tube	DMF/1,2-$C_6H_4Cl_2$, 250 °C	SM+decomp.
2	μ-Wave	Hexanes, ~250 °C	SM+decomp.
3	μ-Wave	$CDCl_3$, ~250 °C	Complex mixture
4	μ-Wave	$CDCl_3$, ~200 °C	SM+decomp.
5	μ-Wave	C_7D_8, ~250 °C	SM
6	FVP (Et_2O carrier)	600 °C, <0.1 Torr	SM
7	FVP (Et_2O carrier)	600 °C, 30 Torr	SM
8	FVP (Et_2O carrier)	600 °C, 50 Torr	SM
9	FVP (Et_2O carrier)	600 °C, 100 Torr	SM
10	FVP (Et_2O carrier)	600 °C, 100 Torr, 6″ path of glass beads	SM

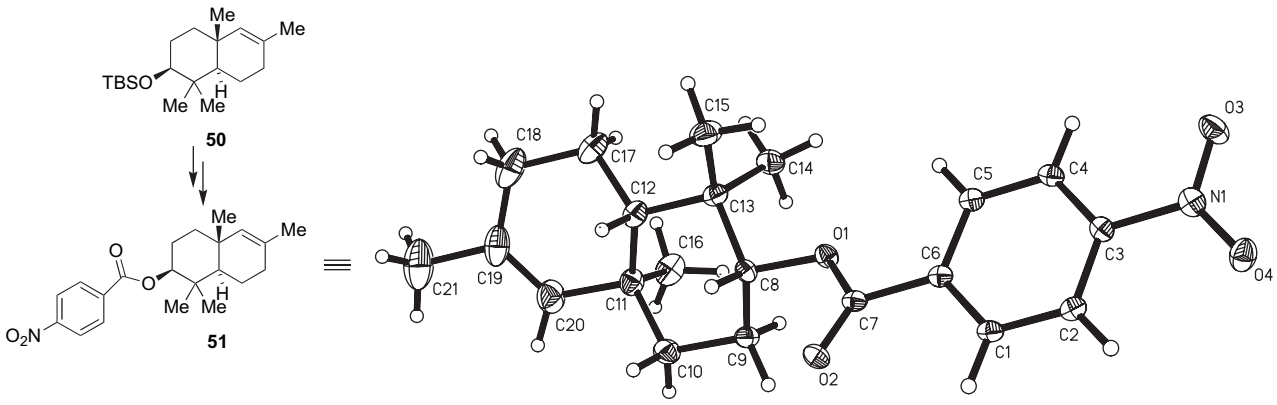
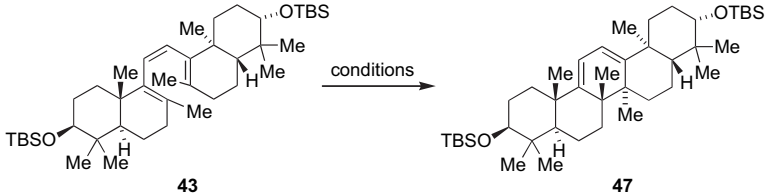


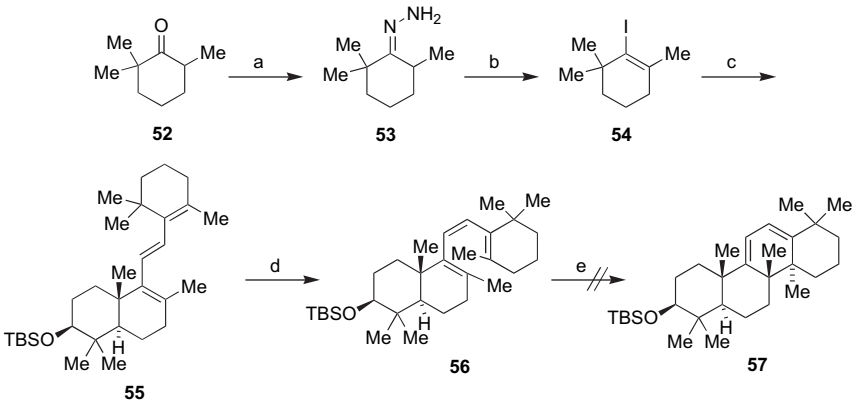
Figure 3.

Table 2



Entry	Method	Conditions	Result
1	Photolysis	THF, quartz tube	47% Cleavage product
2	Photolysis	C_6D_6, NMR tube, 3 h	[1,5]-Hydrogen shifts
3	Photolysis	C_6D_6, NMR tube, <330 nm filter, 4 h	SM
4	Photolysis	C_6D_6, NMR tube, <330 nm filter, 12 h	[1,5]-Hydrogen shifts
5	Photolysis	CD_3OD, NMR tube, <330 nm filter, 4 h	SM
6	Photolysis	CD_3OD, NMR tube, <330 nm filter, 12 h	SM
7	Photolysis	C_6D_6, 9,10-dicyanoanthracene, NMR tube, 12 h	SM
8	Reflux	PhSSPh, AIBN, PhH	SM
9	Reflux	DDQ, CH_2Cl_2	Complex mixture
10	70 °C	$Pd_2(dba)_3$, PPh_3, AcOH, PhH	SM
11	110 °C	$Pd(OAc)_2$, PhMe	SM
12	−78 to 23 °C	Cp_2ZrCl_2, *n*BuLi, THF	SM
13	60 °C	$Ni(COD)_2$, PPh_3, PhMe	SM

(entries 3–6). With the filters in place, no reaction was observed, except in the case of prolonged photolysis in C_6D_6, in which some [1,5]-hydrogen shifts had begun to take place. In hopes of activating the triene with a photooxidant, 9,10-dicyanoanthracene was employed (entry 7), but once again only starting material was obtained. Attempts were made to induce a radical cyclization through the use of diphenyl disulfide (entry 8) and a oxidative cyclization with DDQ (entry 9); however, both reactions failed. Several organometallic reagents were also employed that have been known



Scheme 13. Reagents and conditions: (a) H_2NNH_2, TEA, EtOH, reflux; (b) DBU, I_2, Et_2O, 23 °C; DBU, PhH, reflux, 76% (two steps); (c) **44**, $PdCl_2$(dppf), 2 M NaOH, THF, 60 °C, 72%; (d) hν, benzanthrone, THF, 82%; (e) hν, C_6D_6, 0%.

to promote metal-mediated oxidative cyclizations but all were unsuccessful.[23–26]

Although conditions to induce the desired cyclization were exhaustively attempted, we decided to perform the cyclization on a smaller analogue of the triene **43** to completely rule out steric complications from the larger analogue as the reason for the failure of the cyclization (Scheme 13). Repeating the same synthetic scheme as before, commercially available 2,2,6-trimethylcyclohexanone **52** was treated with hydrazine and triethylamine in refluxing ethanol to give the hydrazone **53**, which was then converted into the vinyl iodide **54** with DBU and iodine in 76% yield over the two steps. The vinyl iodide **54** was then coupled to the vinyl boronate **44** via a Suzuki reaction ($PdCl_2$(dppf), 2 M NaOH, THF, 60 °C) to give the *E*-triene **55** in 72% yield. This triene was then photolyzed in the presence of benzanthrone to effect isomerization to the *Z*-triene **56**. However, using the same photochemical conditions employed in Table 2 (entries 3–7), no cyclization of **56** to the diene **57** was observed. Consequently, we decided to abandon all work in this area, one step away from completing the synthesis of the pentacyclic core.

3. Conclusion

In conclusion, we have shown that the advanced bicyclic aldehyde **11**, the iodide **39**, and the silyl diene **31** can all be readily prepared in good overall yield and have proven to be very amenable to transformation into key compounds for a variety of synthetic pathways. Although Suzuki coupling of the advanced intermediates could be accomplished as well as photoisomerization to the potentially reactive *Z*-triene, final cyclization could not be achieved, despite extensive use of thermal, photochemical, and chemical means. The heavy steric interactions in the vicinity of the methyl groups on the olefins as well as the number of 1,3-diaxial interactions in the ring system all worked against the cyclization and formation of the *anti*-quaternary methyl groups.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether were both distilled from sodium benzophenone-ketyl. Dichloromethane, benzene, and toluene were all distilled from calcium hydride. Methanol was distilled from magnesium. Pyridine and triethylamine were both distilled from calcium hydride and diisopropylamine from NaOH. All reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise stated. Flash chromatography was performed using ACS certified solvents and Merck silica gel 60, mesh 230–400. Proton and carbon NMR spectra were obtained using a Brüker Avance 500 MHz, a Brüker ARX 400 MHz, or a Brüker ARX 500 MHz spectrometer. The signals are reported in parts per million relative to $CDCl_3$. The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in Hertz (Hz) using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. When the signals are broad, the designation 'b' is placed before the multiplicity. FT-IR spectra were obtained using either a Nicolet 510p or Nicolet Avatar 370 FT-IR spectrometer using liquid films (neat) on NaCl plates. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on a VG Analytical Autospec double focusing instrument using electron impact (EI) or chemical ionization (CI) techniques. The X-ray crystal structure was elucidated by Dr. Saeed Khan on a Brüker Smart 1000 CCD diffractometer equipped with a low temperature device from Oxford Cryosystems Model 600.

4.1.1. 3,4,8,8a-Tetrahydro-5,8a-dimethylnaphthalen-1(2*H*),6(7*H*)-dione (15). To a stirring solution of commercially available 2-methyl-1,3-cyclohexanedione **14** (5 g, 39.6 mmol), methanol (18 mL), and two pellets of KOH was added commercially available ethyl vinyl ketone (6.3 mL, 63.4 mmol) and the mixture heated to 40 °C. After 5 h, the solvent was removed in vacuo and excess water was removed azeotropically with three washings of benzene. To the crude residue was added benzene (21 mL) and pyrrolidine (0.37 mL, 4.4 mmol), and the mixture was heated to reflux overnight with a Dean–Stark trap. The solvent was removed in vacuo and the residue diluted with ether. The organic extract was washed once with a solution of 5% aqueous HCl, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo and the residue vacuum distilled (154–157 °C, <1 mmHg) to yield the diketone **15** as a pale yellow oil (4.6 g, 61%). The spectral data matched that of the compound reported in the literature.[13] IR (neat) 2953, 2872, 1711, 1686, 1611, 1455, 1421, 1356, 1308, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.80 (ddd, J=15.9, 4.9, 4.9 Hz, 1H), 2.61 (m, 1H), 1.91–2.52 (m, 8H), 1.73 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 197.7, 158.3, 130.7, 50.6, 33.7, 33.3, 29.4, 27.3, 23.4, 21.5, 11.3.

4.1.2. (±)-3′,4′,8′,8′a-Tetrahydro-5′,8′a-dimethylspiro-[1,3-dioxolane-2,1′-naphthalen]-6′(7′*H*)-one (16). A solution of the diketone **15** (1.67 g, 8.7 mmol), *p*-toluenesulfonic acid (1.7 g, 9 mmol), ethylene glycol (51 mL), and 4 Å MS was stirred at 23 °C overnight. The reaction mixture was poured into a solution of ice and saturated $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to afford the ketal **16** as a pale yellow oil (2.01 g, 98%). The spectral data matched that of the compound reported in the literature.[27] IR (neat) 2950, 2878, 1734, 1665, 1181, 1092, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87–3.98 (m, 4H), 2.70 (br d, J=19.6 Hz, 1H), 1.53–2.65 (m, 9H), 1.75 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 160.3, 130.1, 112.8, 65.3, 65.1, 45.3, 33.7, 29.7, 26.5, 26.4, 21.4, 20.9, 11.4; HRMS (EI) m/e (M^+) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1420.

4.1.3. (±)-(4′a*S*,6′*S*,8′a*S*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-5′,5′,8′′-trimethylspiro[1,3-dioxolane-2,1′-naphthalen]-6′-ol (17). A solution of the ketal **16** (7.6 g, 32.2 mmol) in THF (140 mL) was slowly added to a stirring solution of lithium metal (1.47 g, 209 mmol) in NH_3 (500 mL), and the resulting anion allowed to stir for 45 min. A solution of methyl iodide (30.1 mL, 483 mmol) in THF (60 mL) was added via syringe

to the reaction, and the resulting mixture allowed to stir for 45 min. To the white slurry was added lithium metal (6.3 g, 900 mmol) and the solution allowed to stir for 30 min. Methanol (50 mL) was added followed by 200 mL of ether, and the system was opened to the atmosphere overnight. A solution of 10% aqueous HCl was slowly added to the slurry before extracting three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvents were removed in vacuo and the resulting residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to yield the alcohol **17** as a clear, colorless oil (4.43 g, 54%). The spectral data matched that of the compound reported in the literature.[27] IR (neat) 3428 (br s), 2943, 2872, 1451, 1175, 1105, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79–3.94 (m, 4H), 3.24 (bdd, J=11.1, 4.3 Hz, 1H), 1.25–1.72 (m, 11H), 1.05 (s, 3H), 0.98 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 78.7, 65.3, 64.8, 48.2, 43.1, 38.8, 30.4, 28.7, 28.0, 27.1, 23.1, 20.6, 16.5, 15.4; HRMS (EI) *m/e* (M^+) calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1867.

4.1.4. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-5,5,8a-trimethylnaphthalen-1(2*H*)-one (18). A solution of the alcohol **17** (697 mg, 2.74 mmol), *p*-toluenesulfonic acid (521 mg, 2.74 mmol), and 1:1 acetone/water (14 mL) was stirred together at 23 °C overnight. The solution was poured into a solution of ice and saturated $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvents were removed in vacuo to yield the ketone **18** as a clear, colorless oil (576 mg, 100%). The spectral data matched that of the compound reported in the literature.[27] IR (neat) 3447 (br s), 2940, 2869, 1701, 1458, 1113, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (m, 1H), 2.54 (ddd, J=14.0, 14.0, 7.0 Hz, 1H), 2.17 (br d, J=14.0 Hz, 1H), 2.02–2.10 (m, 1H), 1.42–1.79 (m, 8H), 1.12 (s, 3H), 0.99 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 78.1, 52.6, 48.6, 37.4, 31.2, 30.9, 27.8, 26.9, 26.2, 20.7, 18.6, 15.8; HRMS (EI) *m/e* (M^+) calcd for $C_{13}H_{22}O_2$ 210.1612, found 210.1613.

4.1.5. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-5,5,8a-trimethylnaphthalen-1(2*H*)-one (19). To a stirring solution of the ketone **18** (3.3 g, 15.7 mmol), pyridine (5.08 mL, 62.8 mmol), and dichloromethane (27 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.61 mL, 15.7 mmol). The solution was allowed to warm to 23 °C and stirred overnight. The solvent was removed in vacuo and the residue taken up in ether and a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed once with a solution of 10% aqueous $CuSO_4$, once with brine, and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to afford the TBS ether **19** as an oily, white solid (4.2 g, 83%). The spectral data matched that of the compound reported in the literature.[28] IR (neat) 2934, 2855, 1703, 1462, 1250, 1100, 1076, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.15 (m, 1H), 2.56 (ddd, J=14.0, 14.0, 7.0 Hz, 1H), 2.18 (br d, J=14.0 Hz, 1H), 2.03–2.09 (m, 1H), 1.47–1.80 (m, 8H), 1.14 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.86 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 78.7, 52.7, 48.6, 40.3, 37.5, 31.1, 28.4, 27.3, 26.4, 25.9, 21.0, 18.7, 18.1, 16.3, −3.8, −5.0; HRMS (EI) *m/e* (M^+) calcd for $C_{19}H_{36}O_2Si$ 324.2485, found 324.2493.

4.1.6. (±)-(2*R*,4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1(2*H*)-one (21). To a stirring solution of diisopropylamine (3.7 mL, 26.2 mmol) in THF (40 mL) cooled to 0 °C was added *n*-butyllithium (11.2 mL, 14.4 mmol, 1.28 M in hexanes). The solution was allowed to warm to 23 °C and stirred for 30 min before being cooled to −78 °C. A solution of the TBS ether **19** (4.25 g, 13.1 mmol) in THF (5 mL) was then added dropwise at −78 °C and the resulting solution allowed to warm to 23 °C and stirred for 45 min. The solution was then cooled to −78 °C and methyl iodide (8.2 mL, 131 mmol) was added and the solution allowed to warm to 23 °C and stirred for 3 h. The reaction was quenched with a saturated solution of $Na_2S_2O_3$ and extracted three times with ether. The combined organic extracts were washed once with a solution of 10% aqueous $CuSO_4$, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo to yield both diastereomers of the ketone **20** as a crude, orange-brown oil (4.43 g, 100%).

To a stirring solution of methanol (225 mL) and sodium metal (3 g, 131 mmol) at 23 °C was added a solution of the ketone **20** (4.43 g, 13.1 mmol) in methanol (25 mL) and the resulting mixture was allowed to stir overnight. The solvent was removed in vacuo and the crude residue diluted with ether and water and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to yield the ketone **21** as an oily, white solid (4.3 g, 97%). IR (neat) 2851, 1703, 1674, 1470, 1388, 1250, 1070, 1026, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.07 (dd, J=10.0, 5.1 Hz, 1H), 2.57 (ddq, J=13.0, 6.5, 6.5 Hz, 1H), 2.02 (m, 1H), 1.40–1.70 (m, 8H), 1.04 (s, 3H), 0.92 (d, J=6.5 Hz, 3H), 0.83 (s, 3H), 0.81 (s, 9H), 0.80 (s, 3H), −0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 78.6, 53.2, 48.1, 40.1, 39.6, 35.6, 31.1, 28.1, 27.2, 25.7, 21.1, 18.6, 17.9, 16.1, 14.8, −4.0, −5.2; HRMS (EI) *m/e* (M^+) calcd for $C_{20}H_{38}O_2Si$ 338.2641, found 338.2647.

4.1.7. (±)-(6*S*,4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (11). To a stirring solution of diisopropylamine (2.5 mL, 17.9 mmol) and THF (9 mL) cooled to 0 °C was added *n*-butyllithium (5.6 mL, 8.9 mmol, 1.6 M in hexanes). The solution was allowed to stir for 30 min before being cooled to −95 °C. A solution of the ketone **21** in dichloromethane (9 mL) was added dropwise to the mixture and it was allowed to gradually warm to −20 °C over 2 h. The reaction mixture was then refluxed for 1 h, cooled to 0 °C, and the solvents removed in vacuo. To the crude residue was added hexamethylphosphoramide (17 mL), lithium perchlorate (951 mg, 8.9 mmol), calcium carbonate (1.12 g, 11.2 mmol), and the mixture was heated with stirring to 130 °C for 1.5 h. After the reaction mixture cooled, it was diluted with water and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was

removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to yield the aldehyde **11** as a brownish yellow oil (634 mg, 45%). IR (neat) 2945, 2856, 1676, 1472, 1389, 1253, 1105, 836, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.2 (s, 1H), 3.19 (dd, J=11.4, 4.7 Hz, 1H), 2.57 (ddd, J=13.4, 3.6, 3.6 Hz, 1H), 2.26 (m, 1H), 2.02 (s, 3H), 0.74–1.73 (m, 7H), 1.14 (s, 3H), 0.94 (s, 3H), 0.88 (s, 9H), 0.78 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 154.2, 143.4, 79.1, 51.0, 39.5, 37.3, 36.8, 34.2, 28.6, 28.0, 25.9, 20.1, 19.0, 18.3, 18.1, 16.0, −3.7, −5.0; HRMS (EI) *m/e* (M−H) calcd for $C_{21}H_{37}O_2Si$ 349.2563, found 349.2568.

4.1.8. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-α-(trimethylsilyloxy)-2,5,5,8a-tetramethylnaphthalene-1-acetonitrile (22). To a stirring solution of the aldehyde **11** (95.8 mg, 0.27 mmol), zinc iodide (4 mg, 0.016 mmol), and dichloromethane (0.5 mL) at 23 °C was added trimethylsilyl cyanide (43 μL, 0.32 mmol). The mixture was allowed to stir for 24 h. The reaction was quenched with pH 7 buffer and extracted three times with dichloromethane. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to yield the TMS cyanohydrin **22** as a light brown oil (118 mg, 96%). IR (neat) 2956, 2857, 2231, 1641, 1472, 1362, 1254, 1106, 842, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.21 (m, 1H), 2.10 (m, 1H), 1.85 (s, 3H), 1.49–1.80 (m, 8H), 1.01 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.76 (s, 3H), 0.26 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

4.1.9. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-α-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-acetonitrile (23). To a stirring solution of the aldehyde **11** (125 mg, 0.35 mmol), zinc iodide (4 mg, 0.016 mmol), and dichloromethane (0.6 mL) at 23 °C was added *tert*-butyldimethylsilyl cyanide (59 mg, 0.42 mmol). The mixture was allowed to stir for 24 h. The reaction was quenched with pH 7 buffer and extracted three times with dichloromethane. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to yield the TBS cyanohydrin **23** as a colorless oil (84 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 3.22 (m, 1H), 2.10 (m, 1H), 1.83 (s, 3H), 1.22–1.71 (m, 8H), 1.03 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 120.6, 79.0, 58.5, 50.9, 50.8, 39.4, 38.6, 34.8, 34.1, 32.4, 28.5, 27.9, 25.9, 22.5, 20.1, 19.2, 18.6, 18.1, 16.0, −2.9, −3.5, −5.0, −5.2.

4.1.10. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-methanol (26). A mixture of the aldehyde **11** (117 mg, 0.33 mmol), sodium borohydride (6.5 mg, 0.17 mmol), and ethanol (3.3 mL) was stirred together at 23 °C overnight. The reaction mixture was poured into water and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to afford the alcohol **26** as a colorless oil (80 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (d, J=11.4 Hz, 1H), 4.01 (d, J=11.4 Hz, 1H), 3.20 (dd, J=10.9, 5.1 Hz, 1H), 2.05 (m, 2H), 1.85 (dt, J=12.9, 3.3 Hz, 1H), 1.70 (s, 3H), 1.35–1.67 (m, 6H), 0.95 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 132.5, 79.3, 58.2, 50.9, 39.3, 37.7, 34.9, 34.0, 28.5, 28.0, 25.9, 20.7, 19.2, 18.8, 18.1, 15.9, −3.8, −5.0. HRMS (EI) *m/e* (M+Na) calcd for $C_{21}H_{42}O_2SiNa$ 375.2690, found 375.2685.

4.1.11. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-1-Bromomethyl-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (27). To a stirring solution of the allylic alcohol **26** (193 mg, 0.55 mmol) and carbon tetrabromide (202 mg, 0.61 mmol) in dichloromethane (5.5 mL) cooled to 0 °C was added triphenylphosphine (160 mg, 0.61 mmol). The reaction was allowed to warm to 23 °C and stirred for 2.5 h. Celite was added to the reaction mixture and the solvent was removed in vacuo. The solid mixture was purified by flash chromatography on a very short column of silica gel (90% hexanes/ethyl acetate) to afford the bromide **27** as a colorless oil (109 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (1H, d, J=10.0 Hz), 3.97 (1H, d, J=10.0 Hz), 3.20 (1H, m), 2.12 (2H, m), 1.39–1.90 (7H, m), 1.72 (3H, s), 1.00 (3H, s), 0.97 (3H, s), 0.90 (9H, s), 0.78 (3H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 126.7, 79.3, 50.7, 48.1, 39.8, 37.5, 36.9, 35.8, 28.1, 25.9, 24.1, 21.2, 20.8, 18.1, 15.9, −3.7, −4.9.

4.1.12. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-α,2,5,5,8a-pentamethylnaphthalene-1-methanol (29). To a stirring solution of the aldehyde **11** (141 mg, 0.40 mmol) in ether (1.4 mL) cooled to 0 °C was added methyllithium (0.57 mL, 0.80 mmol, 1.4 M in ether). The solution was allowed to warm to 23 °C and stirred for 1 h. The reaction was quenched with a solution of 15% aqueous NH_4Cl and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was removed in vacuo to yield a diastereomeric mixture of the two alcohols **29** as a colorless oil (139 mg, 95%). ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (q, J=6.7 Hz, 1H), 4.60 (q, J=6.8 Hz, 1H), 3.24 (m, 2H), 2.06 (m, 4H), 1.87 (s, 3H), 1.85 (s, 3H), 1.52–1.76 (m, 9H), 1.45 (d, J=6.8 Hz, 3H), 1.43 (d, J=6.7 Hz, 3H), 1.05–1.38 (m, 5H), 0.98 (s, 3H), 0.96 (s, 3H), 0.93 (s, 9H), 0.80 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 143.5, 130.7, 129.3, 79.1, 79.0, 66.1, 65.7, 51.5, 50.9, 39.3, 38.6, 35.4, 34.9, 28.6, 28.1, 25.8, 23.8, 20.5, 20.1, 18.7, 18.0, 16.0, −3.9, −5.1. HRMS (EI) *m/e* (M+Na) calcd for $C_{22}H_{42}O_2SiNa$ 389.2846, found 389.2840.

4.1.13. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-ethanone (30). To a stirring solution of Dess–Martin periodinane (208 mg, 0.49 mmol) in dichloromethane (3 mL) at 23 °C was added the alcohol **29** (139 mg, 0.38 mmol) in dichloromethane (1 mL). The mixture was allowed to stir for 1 h, poured into a 1:1 mixture of a saturated solution of $NaHCO_3$ and a solution of 10%

aqueous $NaHSO_3$, and extracted three times with dichloromethane. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to afford the enone **30** as a colorless oil (110 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (dd, J=11.3, 4.7 Hz, 1H), 2.23 (s, 3H), 2.04 (m, 2H), 1.52 (s, 3H), 1.50–1.74 (m, 5H), 1.45 (dd, J=13.0, 3.6, 3.6 Hz, 1H), 1.36 (dd, J=13.0, 13.0, 3.6 Hz, 1H), 1.20 (s, 3H), 0.91 (s, 3H), 0.86 (s, 9H), 0.76 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4, 146.4, 127.4, 79.1, 49.8, 39.4, 36.8, 35.2, 33.7, 32.1, 28.3, 27.7, 25.8, 20.5, 20.1, 18.4, 18.0, 15.7, −3.9, −5.1. HRMS (EI) *m/e* (M+H) calcd for $C_{22}H_{41}O_2Si$ 365.2870, found 365.2879.

4.1.14. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-1-(1-[(1,1-dimethylethyl)dimethylsilyloxy]ethenyl)-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (31). To a stirring solution of the enone **30** (94 mg, 0.26 mmol), triethylamine (0.11 mL, 0.78 mmol), and dichloromethane (2.6 mL) cooled to 0 °C was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.09 mL, 0.39 mmol). The solution was allowed to warm to 23 °C and stirred for 2.5 h. The solvents were removed in vacuo and the residue taken up in ether and extracted three times from a saturated solution of $NaHCO_3$. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate with 2% triethylamine buffer) to afford the silyl enol ether **31** as a colorless oil (122 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 1H), 3.91 (s, 1H), 3.26 (dd, J=11.2, 4.6 Hz, 1H), 2.10 (m, 2H), 1.70 (s, 3H), 1.32–1.74 (m, 5H), 1.10–1.15 (m, 2H), 0.98 (s, 3H), 0.97 (s, 9H), 0.95 (s, 3H), 0.93 (s, 9H), 0.84 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 141.7, 128.5, 125.0, 79.7, 50.3, 39.4, 35.5, 32.4, 31.5, 28.5, 28.2, 25.6 (2 C's), 22.5, 20.9, 18.6, 17.9, 15.8, 14.0, −3.1, −3.9, −4.7, −5.1.

4.1.15. Methyl (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-5,5,8a-trimethylnaphthalene-2-carboxylate (34). To a freshly washed slurry of NaH (1.4 g, 31.12 mmol, 55% w/w) and KH (five drops, 35% w/w) in THF (97 mL) was added dimethyl carbonate (2 mL, 23.3 mmol). A solution of the ketone **19** (2.5 g, 7.78 mmol) in THF (5 mL) was then added and the combined solution heated to reflux overnight. The solution was cooled to 0 °C and quenched with a solution of 15% aqueous ammonium chloride and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to afford the β-keto ester **32** as a crude, brown oil. The crude β-keto ester **32** was dissolved in methanol (78 mL), cooled to 0 °C, and sodium borohydride (194 mg, 5.13 mmol) was added. The reaction mixture was stirred at 0 °C for 6 h and quenched with a saturated solution of ammonium chloride and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo to furnish the β-hydroxy ester **33** as a crude, brown oil. The crude β-hydroxy ester **33** was dissolved in pyridine (78 mL) and stirred at 23 °C before phosphorus oxychloride (2.2 mL, 23.3 mmol) was added and the mixture heated to 80 °C for 4 h. The solvent was then removed in vacuo and the crude residue dissolved in ether and a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with a solution of 10% aqueous $CuSO_4$, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (95% hexanes/ethyl acetate) to afford the α,β-unsaturated ester **34** as a clear, colorless oil (610.7 mg, 22%, three steps). IR (neat) 2951, 2855, 1747, 1717, 1472, 1389, 1250, 1106, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 1H), 3.70 (s, 3H), 3.20 (dd, J=11.3, 6.6 Hz, 1H), 1.25–1.78 (m, 9H), 0.98 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.76 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 150.7, 126.6, 79.3, 51.5, 49.2, 39.2, 36.5, 35.6, 28.2, 27.9, 26.1, 25.9, 20.5, 18.3, 18.1, 15.9, −3.8, −5.0; HRMS (EI) *m/e* (M^+) calcd for $C_{21}H_{38}O_3Si$ 366.2590, found 366.2593.

4.1.16. 1-(1-[(1,1-Dimethylethyl)dimethylsilyloxy]-ethenyl)-2-methylcyclohexene (37). To a stirring solution of the enone **36** (424 mg, 3.07 mmol), prepared according to the literature,[16] and triethylamine (1.3 mL, 9.2 mmol) in dichloromethane (15 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.06 mL, 4.6 mmol). The solution was allowed to warm to 23 °C and stirred for 2 h. The reaction mixture was diluted with ether and quenched with a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to afford the silyl enol ether **37** as a crude, pale yellow oil (774 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (d, J=2.9 Hz, 1H), 4.10 (d, J=2.9 Hz, 1H), 2.11 (m, 2H), 1.98 (m, 2H), 1.76 (s, 3H), 1.58–1.65 (m, 4H), 0.92 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 136.1, 128.5, 94.1, 31.8, 28.0, 25.7, 22.9, 21.4, 18.2, 18.1, −3.0. HRMS (EI) *m/e* (M+H) calcd for $C_{15}H_{29}OSi$ 253.1982, found 253.1982.

4.1.17. (±)-(2*S*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-5-iodo-2-[(1,1-dimethylethyl)dimethylsilyloxy]-1,1,4a,6-tetramethylnaphthalene (39). A stirring solution of the ketone **21** (474 mg, 1.4 mmol), hydrazine (2.2 mL, 70 mmol), acetic acid (0.4 mL, 7 mmol), and ethanol (5 mL) was refluxed overnight. The mixture was cooled to 23 °C, diluted with ether and water, and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to afford the hydrazone as an oily, white solid (377 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (br s, 2H), 3.16 (dd, J=10.0, 5.5 Hz, 1H), 3.00 (m, 1H), 1.85 (ddd, J=13.5, 3.3, 3.3 Hz, 1H), 1.37–1.69 (m, 8H), 1.16 (d, J=5.5 Hz, 3H), 1.12 (s, 3H), 0.91 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 79.2, 52.4, 42.1, 39.8, 34.8, 32.6, 28.5, 27.7, 25.9, 21.7, 18.4, 18.1, 17.6, 16.1, 14.1, −3.8, −4.9. To a stirring solution of the hydrazone (79.4 mg, 0.22 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.66 mL, 4.4 mmol) in ether (3 mL) at 23 °C was added iodine (122 mg,

0.48 mmol). The solution was allowed to stir for 30 min before being quenched with a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvents were removed in vacuo and the crude residue dissolved in toluene (3 mL) and DBU (0.16 mL, 1.1 mmol). The solution was then heated at 85–90 °C for 5 h before the solvent was removed in vacuo. The residue was dissolved in ether and washed once with a saturated solution of $Na_2S_2O_3$, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to afford the iodide **39** as an oily, white solid (76.3 mg, 76%). IR (neat): 2950, 2855, 2708, 2646, 1709, 1631, 1472, 1252, 1105, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (m, 1H), 2.17–2.26 (m, 1H), 1.85 (s, 3H), 1.45–1.86 (m, 5H), 1.30 (dd, J=12.4, 1.8 Hz, 1H), 1.14–1.27 (m, 2H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 120.7, 79.3, 51.3, 42.7, 42.1, 39.5, 35.1, 30.6, 28.6, 28.4, 26.0, 19.9, 18.9, 18.1, 15.9, −3.7, −4.9; HRMS (EI) *m/e* (M^+) calcd for $C_{20}H_{37}OISi$ 448.1658, found 448.1641.

4.1.18. (±)-(4a*S*,6*S*,8a*S*)-1-Ethynyl-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (41). To a stirring solution of the vinyl iodide **39** (1.96 g, 4.36 mmol), bis(dibenzylideneacetone)palladium(II) (50 mg, 0.087 mmol), copper(I) iodide (33 mg, 0.17 mmol), triphenylphosphine (114 mg, 0.44 mmol), and triethylamine (87 mL) was added (trimethylsilyl)acetylene (0.62 mL, 4.36 mmol). After the mixture was heated to 70 °C overnight, it was filtered through Celite with ether and the solvents removed in vacuo to afford the TMS enyne **40** as a crude, black oil. The crude TMS enyne **40** was dissolved in THF (44 mL) and tetrabutylammonium fluoride (5.2 mL, 5.2 mmol, 1 M in THF) was added with stirring at 23 °C. The reaction mixture was stirred overnight and the mixture was poured into a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford a crude, brown oil. The crude oil was dissolved in dichloromethane (15 mL) and triethylamine (1.8 mL, 13 mmol) and cooled to 0 °C before *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.99 mL, 4.33 mmol) was added. The reaction was allowed to warm to 23 °C and stirred for 3 h, diluted with ether and a saturated solution of sodium bicarbonate, and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford the enyne **41** as an oily, white solid (1.12 g, 75%, three steps). IR (neat) 3311, 2950, 2856, 2087, 1472, 1361, 1255, 1105, 1070, 883, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.26 (dd, J=10.8, 5.3 Hz, 1H), 3.07 (s, 1H), 2.09–2.22 (m, 2H), 2.05 (ddd, J=13.4, 3.5, 3.5 Hz, 1H), 1.89 (s, 3H), 1.59–1.79 (m, 4H), 1.51 (dddd, J=12.5, 11.4, 11.4, 6.7 Hz, 1H), 1.32 (ddd, J=13.4, 13.4, 4.6 Hz, 1H), 1.11 (s, 3H), 0.97 (s, 3H), 0.94 (s, 9H), 0.82 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 126.2, 81.7, 80.3, 79.2, 49.8, 39.3, 36.5, 36.1, 33.1, 28.3, 28.1, 25.8, 21.9, 20.4, 18.3, 18.0, 15.7, −3.9, −5.1; HRMS (EI) *m/e* (M^+) calcd for $C_{22}H_{38}OSi$ 346.2692, found 346.2702.

4.1.19. Bis-(±)-[(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1-yl]ethyne (42). To a stirring solution of the enyne **41** (61.5 mg, 0.14 mmol), copper(I) iodide (8 mg, 0.04 mmol), bis(triphenylphosphine)palladium(II) chloride (14 mg, 0.02 mmol), and triethylamine (4 mL) at 23 °C was added a solution of the vinyl iodide **39** (46 mg, 0.20 mmol) in triethylamine (1 mL). The resulting solution was allowed to stir overnight. The reaction mixture was filtered through a plug of silica gel with ethyl acetate and the solvents removed in vacuo. The crude residue was purified by flash chromatography on silica gel (100% hexanes) to afford the dienyne **42** as an oily, white solid (11 mg, 14%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.20 (m, 2H), 2.14 (m, 4H), 1.98 (ddd, J=13.4, 3.1, 3.1 Hz, 2H), 1.86 (s, 3H), 1.85 (s, 3H), 1.19–1.75 (m, 12H), 1.06 (s, 6H), 0.92 (s, 6H), 0.89 (s, 18H), 0.76 (s, 6H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 126.9, 79.9, 79.4, 77.6, 50.0, 39.4, 37.3, 36.4, 28.4, 28.2, 25.9, 22.4, 21.0, 18.1, 15.9, −3.8, −4.9; HRMS (EI) *m/e* (M^+) calcd for $C_{42}H_{74}O_2Si_2$ 666.5227, found 666.5231.

4.1.20. (±)-*E*-(4a*S*,6*S*,8a*S*)-1-[2-(1,3-Benzodioxaborolyl)-ethenyl]-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (44). To a stirring solution of the enyne **41** (268 mg, 0.77 mmol), Schwartz's reagent (119 mg, 0.46 mmol), and dichloromethane (8 mL) at 23 °C in the dark was added catecholborane (0.13 mL, 1.2 mmol) dropwise. The solution was allowed to stir overnight in the dark. The reaction mixture was diluted with ether and a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to furnish the boronate **44** as a clear, colorless oil (345 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=18.6 Hz, 1H), 7.22 (dd, J=5.9, 3.3 Hz, 2H), 7.07 (dd, J=5.9, 3.3 Hz, 2H), 5.71 (d, J=18.6 Hz, 1H), 3.22 (dd, J=11.2, 4.8 Hz, 1H), 2.14 (m, 2H), 1.77 (ddd, J=13.1, 3.4, 3.4 Hz, 1H), 1.72 (s, 3H), 1.20–1.65 (m, 5H), 1.15 (dd, J=12.5, 1.9 Hz, 1H), 1.10 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.3, 122.5, 121.2, 115.5, 112.2, 79.3, 50.4, 39.6, 37.6, 36.4, 34.0, 28.4, 28.1, 25.9, 21.2, 20.4, 18.7, 18.1, 15.9, −3.8, −4.9 (one downfield carbon not observed).

4.1.21. (±)-*E*-Bis-1,2-[(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1-yl]ethylene (45). A solution of the vinyl boronate **44** (247 mg, 0.53 mmol), the vinyl iodide **39** (260 mg, 0.58 mmol), dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) (22 mg, 0.027 mmol), 2 M NaOH (0.27 mL, 0.53 mmol), and THF (6 mL) was stirred together at 23 °C for 1 h before being heated to 60 °C overnight. The solution was diluted with a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined

organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford the *E*-triene **45** as an oily, white solid (282 mg, 80%, two steps, tiny amount of *Z*-**43** present). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H) (*E*), 5.05 (s, 1H) (*Z*), 3.21 (m, 2H), 1.84 (s, 6H), 1.27–2.25 (m, 18H), 1.01 (s, 6H), 0.94 (s, 3H), 0.93 (s, 3H), 0.89 (s, 18H), 0.77 (s, 6H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (2 C's), 135.2 (2 C's), 126.6 (*E*), 120.7 (*Z*), 79.4, 79.3, 51.3 (2 C's), 42.7 (2 C's), 39.5, 35.1 (2 C's), 31.6 (2 C's), 30.6 (2 C's), 28.4 (2 C's), 25.9 (2 C's), 22.7 (2 C's), 21.8, 19.8 (2 C's), 18.1 (2 C's), 15.9 (2 C's), 14.1 (2 C's), −3.8 (2 C's), −4.9 (2 C's).

4.1.22. (±)-*Z*-Bis-1,2-[(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1-yl]ethylene (43). A stirring solution of the *E*-triene **45** (282 mg, 0.42 mmol), benzanthrone (145 mg, 0.63 mmol), and THF (42 mL) was photolyzed with a medium pressure Hanovia mercury arc lamp in a Pyrex immersion well at ≥290 nm for 24 h. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to furnish the *Z*-triene **43** as an oily, white solid (236 mg, 84%). IR (neat) 2936, 2855, 1472, 1462, 1389, 1253, 1105, 1071, 883, 885, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 2H), 3.21 (m, 2H), 1.94–2.23 (m, 3H), 1.84 (s, 6H), 1.21–1.72 (m, 15H), 1.06 (s, 6H), 0.94 (s, 6H), 0.89 (s, 18H), 0.78 (s, 6H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (all 2 C's) 136.6, 135.2, 120.7, 79.3, 51.3, 42.7, 42.1, 39.5, 35.1, 30.6, 28.6, 25.9, 21.6, 19.8, 18.9, 18.1, 15.9, −3.8, −4.9; HRMS (EI) *m*/*e* (M^+) calcd for $C_{42}H_{76}O_2Si_2$ 668.5384, found 668.5379.

4.1.23. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-6-(4-nitrobenzoyloxy)-naphthalene (51). A solution of the *Z*-triene **43** (42.8 mg, 0.064 mmol) in THF (6.4 mL) was degassed with Ar for 20 min and photolyzed in a quartz tube with a medium pressure Hanovia mercury arc lamp in a quartz immersion well at ≥200 nm for 24 h. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford the silyl ether as an oily, white solid (20.1 mg, 47%). IR (neat) 2930, 2855, 1472, 1389, 1252, 1103, 1070, 882, 836, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (m, 1H), 3.21 (dd, *J*=11.3, 4.8 Hz, 1H), 1.95 (m, 2H), 1.58 (s, 3H), 1.37–1.71 (m, 5H), 1.18–1.26 (m, 2H), 0.91 (s, 6H), 0.89 (s, 9H), 0.76 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 130.1, 79.8, 50.1, 39.1, 37.9, 34.8, 31.9, 28.4 (2 C's), 25.9, 23.1, 21.6, 19.0, 18.1, 15.8, −3.7, −4.9. To a stirring solution of the silyl ether (85 mg, 0.13 mmol) in 1:1 acetone/water (1.5 mL) at 23 °C was added *p*-toluenesulfonic acid (72 mg, 0.38 mmol). The solution was stirred overnight, quenched with a saturated solution of sodium bicarbonate, and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo to afford a colorless residue. The residue (45.9 mg, 0.1 mmol) was dissolved in dichloromethane (1 mL) with 4-(*N*,*N*-dimethylamino)pyridine (6 mg, 0.05 mmol) and pyridine (40 μL, 0.5 mmol) at 23 °C. To the mixture was added 4-nitrobenzoyl chloride (56 mg, 0.3 mmol) and stirring was continued for 24 h. The reaction mixture was diluted with ether, quenched with a saturated solution of sodium bicarbonate, and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to furnish the ester **51** as colorless plates (71.4 mg, 93%). Crystals were obtained by slow evaporation of a solution in 9:1 acetonitrile/hexanes, which led to the determination of the X-ray crystal structure shown in Figure 3. IR (neat) 3405 (br s), 2961, 2912, 1711, 1609, 1531, 1351, 1291, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J*=10.8 Hz, 2H), 8.21 (d, *J*=10.8 Hz, 2H), 5.08 (s, 1H), 4.81 (dd, *J*=11.5, 5.0 Hz, 1H), 1.60 (s, 3H), 1.40–2.02 (m, 9H), 1.03 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 150.5, 136.3, 134.4, 130.6, 130.5, 123.5, 83.2, 50.2, 38.0, 37.4, 34.8, 31.7, 28.1, 24.3, 23.2, 23.1, 18.7, 16.7.

4.1.24. 1-Iodo-2,6,6-trimethylcyclohexene (54). A stirring solution of commercially available 2,2,6-trimethylcyclohexanone **52** (60 mg, 0.43 mmol), hydrazine (0.28 mL, 9.03 mmol), triethylamine (0.94 mL, 6.7 mmol), and ethyl alcohol (0.72 mL) was refluxed for 3 h. The solution was then diluted with water and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to furnish the hydrazone **53** as a white solid (66 mg, 100%). To a stirring solution of the hydrazone **53** (102.4 mg, 0.66 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 mL, 13.2 mmol) in ether (6 mL) at 23 °C was added iodine (381 mg, 1.5 mmol). The viscous orange-brown mixture was stirred for 30 min. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed twice with brine and dried (K_2CO_3). The solvents were removed in vacuo to afford a thick brown oil. The oil was then dissolved in benzene (8.3 mL) and DBU (0.49 mL, 3.3 mmol) was added before heating to reflux for 3 h. The solvents were removed in vacuo and the crude residue dissolved in ether and washed once with a saturated solution of sodium sulfite, twice with brine, and dried (K_2CO_3). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (80% hexanes/ethyl acetate) to afford the known vinyl iodide **54** as an oily, white solid (126.7 mg, 76%).[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (t, *J*=6.0 Hz, 2H), 1.87 (s, 3H), 1.61–1.70 (m, 4H), 1.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 117.4, 39.6, 37.9, 33.7, 31.6, 31.1, 19.4.

4.1.25. (±)-*E*-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-1-[2-(2,6,6-trimethylcyclohexen-1-yl)ethenyl]-naphthalene (55). A stirring solution of the vinyl boronate **44** (829 mg, 1.78 mmol), the vinyl iodide **54** (423 mg, 1.69 mmol), dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) (73 mg, 0.09 mmol), and 2 M NaOH (1.1 mL, 2.1 mmol) in THF (18 mL) was heated to 60 °C overnight. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed

in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to yield the *E*-triene **55** as an oily, white solid (601.6 mg, 72%). IR (neat) 2933, 2856, 1667, 1472, 1361, 1253, 1106, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, J=17.1 Hz, 1H), 5.70 (d, J=17.1 Hz, 1H), 3.21 (dd, J=11.0, 4.8 Hz, 1H), 2.14 (m, 3H), 1.99 (m, 2H), 1.74 (s, 3H), 1.73 (s, 3H), 1.47–1.71 (m, 7H), 1.28 (m, 3H), 1.09 (s, 3H), 1.02 (s, 6H), 0.93 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 138.4, 132.3, 130.9, 127.8, 126.5, 79.4, 50.6, 39.6, 39.5, 38.0, 37.9, 34.1, 34.0, 33.0, 32.8, 31.6, 28.9, 28.5, 25.9, 22.0, 21.5, 20.2, 19.4, 18.5, 18.1, 15.9, −4.3, −4.9; HRMS (EI) *m/e* (M^+) calcd for $C_{31}H_{54}OSi$ 470.3944, found 470.3937.

4.1.26. (±)-*Z*-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-1-[2-(2,6,6-trimethylcyclohexen-1-yl)ethenyl]-naphthalene (56). A stirring solution of the *E*-triene **55** (305.2 mg, 0.65 mmol), benzanthrone (255 mg, 0.98 mmol), and THF (65 mL) was photolyzed with a mercury lamp at 290 nm for 24 h. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to furnish the *Z*-triene **56** as an oily, white solid (250.5 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J=11.0 Hz, 1H), 5.84 (d, J=11.0 Hz, 1H), 3.15 (dd, J=9.1, 3.6 Hz, 1H), 1.95–2.12 (m, 4H), 1.44–1.72 (m, 11H), 1.41 (s, 3H), 1.35 (s, 3H), 1.09 (s, 3H), 1.02 (s, 6H), 0.93 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.5, 132.1, 131.2, 130.1, 127.8, 79.3, 50.6, 40.0, 39.5, 37.5, 36.0, 35.7, 33.4, 33.3, 31.5, 29.3, 28.5, 28.0, 25.8, 23.0, 22.2, 20.9, 19.2, 18.7, 18.0, 15.8, −3.9, −5.0.

Acknowledgements

We thank Professor Miguel Garcia-Garibay of the University of California, Los Angeles for the use of his photochemical equipment and expertise. Support of this work from the National Science Foundation (CHE 0314591) is gratefully acknowledged.

Supplementary data

Proton and carbon NMR data for all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.023.

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Synthesis of the bifunctional BINOL ligands and their applications in the asymmetric additions to carbonyl compounds

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Received 26 April 2006; revised 13 June 2006; accepted 14 June 2006
Available online 14 August 2006

Abstract—Efficient one-step syntheses of the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** have been developed from the reaction of BINOL and H_8BINOL with morpholinomethanol, respectively. The X-ray analyses of these compounds have revealed their structural similarity and difference. The bifunctional H_8BINOL (*S*)-**8** is found to be highly enantioselective for the reaction of diphenylzinc with many aliphatic and aromatic aldehydes and especially is the most enantioselective catalyst for linear aliphatic aldehydes. Unlike other catalysts developed for the diphenylzinc addition which often require the addition of a significant amount of *diethylzinc* with cooling (or heating) the reaction mixture in order to achieve high enantioselectivity, using (*S*)-**8** needs no additive and gives excellent results at room temperature. (*S*)-**8** in combination with diethylzinc and $Ti(O^iPr)_4$ can catalyze the highly enantioselective phenylacetylene addition to aromatic aldehydes. It can also promote the phenylacetylene addition to acetophenone at room temperature though the enantioselectivity is not very high yet. Without using $Ti(O^iPr)_4$ and a Lewis base additive, (*S*)-**8** in combination with diethylzinc can catalyze the reaction of methyl propiolate with an aldehyde to form the highly functional γ-hydroxy-α,β-acetylenic esters except that the enantioselectivity is low at this stage. The bifunctional BINOL ligand (*S*)-**6** in combination with Me_2AlCl is found to be a highly enantioselective catalyst for the addition of TMSCN to both aromatic and aliphatic aldehydes.

1. Introduction

Development of catalysts containing both Lewis acidic sites and Lewis basic sites has attracted significant attention in the field of asymmetric catalysis.[1] Such bifunctional chiral catalysts can simultaneously activate both the electrophile and nucleophile in a chemical reaction and control the stereochemistry of the reaction course to provide efficient chiral induction. We are particularly interested in the study of the 1,1′-bi-2-naphthol (BINOL)-based bifunctional catalysts. The chiral Lewis acid catalysts prepared from the combination of BINOL with a metal complex have been used in many asymmetric organic reactions.[2] Recently, additional Lewis basic functional groups are also incorporated into BINOL to construct various bifunctional BINOL ligands for asymmetric catalysis.[3] Figure 1 gives a few examples of the bifunctional BINOL ligands. The aluminum complexes of the chiral ligands **1**[4] and **2**[5] have been used to catalyze the enantioselective reaction of aldehydes with trimethylsilylcyanide (TMSCN) to generate the synthetically useful chiral cyanohydrins. The zinc complexes of **3**[6] and **4**[7] were used to carry out the alkyne addition to aldehydes and the Simmons–Smith reaction, respectively. Ligand **5** catalyzed the aza-Morita–Baylis–Hillman reaction in the absence of a metal.[8] These ligands have exhibited high enantioselectivity in the corresponding reactions.

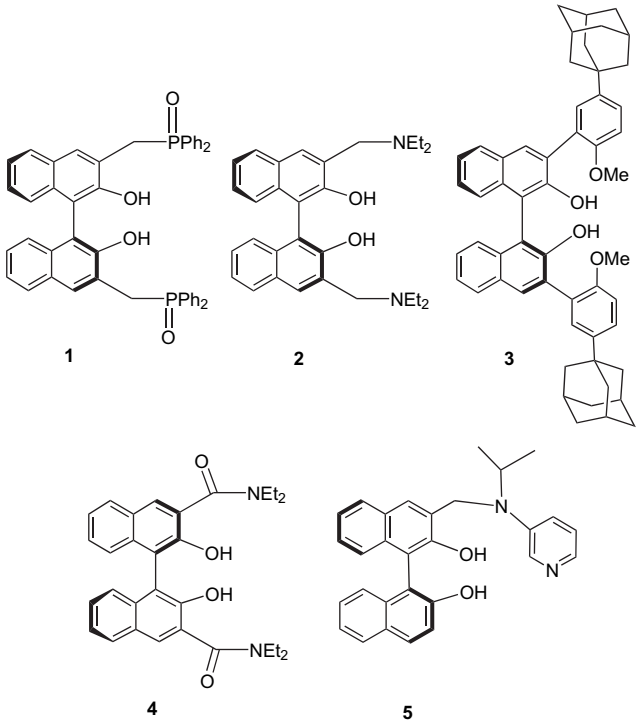

Figure 1. Examples of the bifunctional BINOL ligands.

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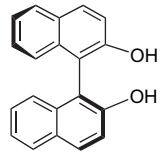
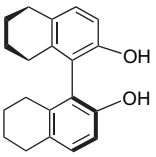
0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.06.049

Since the bifunctional BINOL ligands often require a significant number of steps to prepare, we are interested in developing more efficient synthetic methods in order to make these ligands more practically applicable. We have conducted the one-step Mannich-type reaction of BINOL or its partially hydrogenated compound H_8BINOL to synthesize the 3,3′-amino methyl substituted BINOL derivatives.[9] Herein, we report our detailed study of the synthesis of these ligands and their use in the asymmetric organozinc and TMSCN additions to aldehydes and ketones.



(*S*)-BINOL

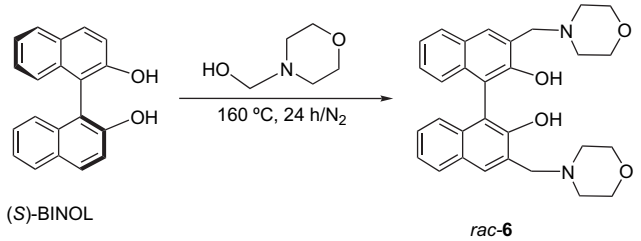


(*S*)-H_8BINOL

2. Results and discussion

2.1. One-step synthesis of the 3,3′-bismorpholinomethyl substituted BINOL and H_8BINOL compounds

2.1.1. Reaction of BINOL. Previously, Cram reported the reaction of racemic BINOL with α-alkoxyamines at 160 °C to prepare the 3,3′-bisaminomethyl substituted BINOLs.[10] We examined this reaction by using the optically pure (*S*)-BINOL to react with the in situ generated morpholinomethanol at 160 °C under nitrogen (Scheme 1). The resulting **6** was converted to its diacetate, and the subsequent analysis by using HPLC Chiralcel-OD column showed a racemic product. Thus, a complete racemization took place during this reaction.



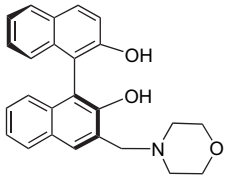
(*S*)-BINOL

rac-**6**

>90% yield, 0% ee

Scheme 1. Reaction of (*S*)-BINOL with morpholinomethanol at 160 °C.

When the reaction of (*S*)-BINOL with morpholinomethanol was conducted at 95–100 °C, the mono-morpholinomethyl substituted compound (*S*)-**7** was obtained in 3 d as the major product in 60% yield and >99% ee. The specific optical rotation of (*S*)-**7** was $[\alpha]_D$ −35.1 (*c* 1.0, CH_2Cl_2). The optically pure (*S*)-**6** was isolated only in 5% yield.



(*S*)-**7**

We further explored the reaction conditions and the results are summarized in Table 1. At 90 °C, various additives such as $NaBH_4$, P_2O_5, and Et_2Zn were used, but no product was obtained (entries 3–5). The best condition was at 110±2 °C, which gave (*S*)-**6** in 55% yield and 75% ee (entry 8). From this reaction, (*S*)-**7** was also isolated in 30% yield and >87% ee. We explored the addition of Lewis acid complexes such as $CeCl_3$, $Zn(OTf)_2$, $TbCl_3$, $InCl_3$, ZnI_2, LiCl, and $VO(acac)_2$, but no improvement was observed.

Table 1. Reaction of (*S*)-BINOL with morpholinomethanol under various conditions (under 30 psi nitrogen)

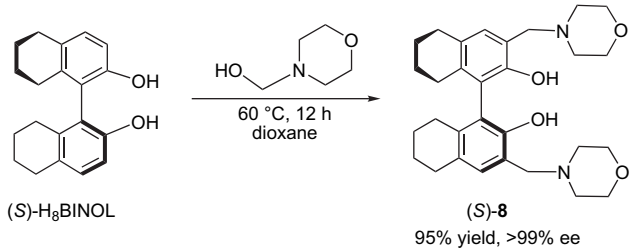
Entry	Temperature (°C)	Additive	Time (h)	Yield of (*S*)-**6** (%)	ee of (*S*)-**6** (%)
1	160	None	24	94	0
2	95–100	None	60	~5	>99
3	90	$NaBH_4$ (1 equiv)	24	~0	—
4	90	P_2O_5 (1 equiv)	24	~0	—
5	90	Et_2Zn (4–6 equiv)	24	~0	—
6	130	None	48	90	<30
7	120	None	72	63	<50
8	110	None	72	55	75

Compound (*S*)-**6** obtained in entry 8 of Table 1 was purified by recrystallization to give the optically pure product. It was first dissolved in a hot CH_2Cl_2/CH_3OH (3:1) mixture, which upon cooling gave white needle-like racemic crystals. After this process was repeated a couple of more times, the compound in the mother liquor was found to be the optically pure (*S*)-**6**. It was isolated as an off-white solid in 37% yield based on (*S*)-BINOL and the optical purity of this compound was over 99% ee. The specific optical rotation of (*S*)-**6** was $[\alpha]_D$ −152.1 (*c* 1.0, CH_2Cl_2). The side product (*S*)-**7** could be converted to (*S*)-**6** by further treatment with morpholinomethanol under the reaction conditions. We also obtained the optically pure (*R*)-**6** and (*R*)-**7** by starting from (*R*)-BINOL.

2.1.2. Reaction of H_8BINOL. Like BINOL, the partially hydrogenated derivative H_8BINOL is also very useful in asymmetric catalysis.[11,12] In a few reactions, the Lewis acid complexes based on H_8BINOL showed enhanced chiral induction over BINOL. This was attributed to the increased size of the partially hydrogenated rings in H_8BINOL. Although it should be very interesting to study the application of the bifunctional H_8BINOLs in asymmetric catalysis, very few functional H_8BINOL compounds have been prepared and studied.[12b–d]

We conducted the reaction of (*S*)-H_8BINOL with morpholinomethanol (Scheme 2). We expected that (*S*)-H_8BINOL should be more reactive in the Mannich-type reaction than (*S*)-BINOL because of its electron-donating alkyl groups on the phenol rings. Thus, the high-temperature condition employed in the reaction of BINOL that caused the partial racemization might not be necessary for H_8BINOL. In addition, it was previously reported that 2,2′-biphenol reacted with the in situ generated morpholinomethanol at 60 °C to give the 3,3′-bismorpholinomethyl substituted 2,2′-biphenol product in 50% yield.[13] Therefore, we treated the optically pure (*S*)-H_8BINOL with morpholinomethanol in dioxane at 60 °C. To our delight, the desired (*S*)-3,3′-bimorpholinomethyl H_8BINOL, (*S*)-**8**, was obtained in 95% yield and

over 99% ee. The specific optical rotation of (*S*)-**8** was $[\alpha]_D$ −35.4 (*c* 1.04, THF).



Scheme 2. Reaction of (*S*)-H_8BINOL with morpholinomethanol.

2.2. X-ray structures of (*S*)-6 and (*S*)-8

The bifunctional BINOL ligand (*S*)-**6** was crystallized by slow evaporation from a CH_2Cl_2/methanol (1:1) solution, whereas the X-ray quality crystals of the bifunctional H_8BINOL ligand (*S*)-**8** were obtained from its ethanol solution. The molecular structures of these compounds are shown in Figures 2 and 3. The most characteristic feature of these structures is the torsion angle C(2)–C(1)–C(1′)–C(2′) between the two binaphthyl moieties, which measures 113.7(2)° in (*S*)-**6** and 100.0(1)° in (*S*)-**8**. The 13.7° difference between the biaryl angles can be attributed to the increased steric interactions of the partially hydrogenated aryl rings, forcing the biaryl unit of (*S*)-**8** to move closer to the orthogonal (90°) conformation.

The molecules are stabilized by strong intramolecular hydrogen bonds O–H···N involving the alcohol groups and the morpholine ring N atoms. The O···N donor acceptor separations which are 2.681 and 2.732 Å in (*S*)-**6** become slightly shorter (2.650 and 2.671 Å) in (*S*)-**8.** The O–H···N angles in these bonds range from 147.3° to 157.4°.

2.3. Asymmetric diphenylzinc additions catalyzed by the bifunctional ligands[9c]

The asymmetric diphenylzinc addition to aldehydes can generate the synthetically useful chiral α-substituted benzyl alcohols. In 1999, we found that compound **9** showed high

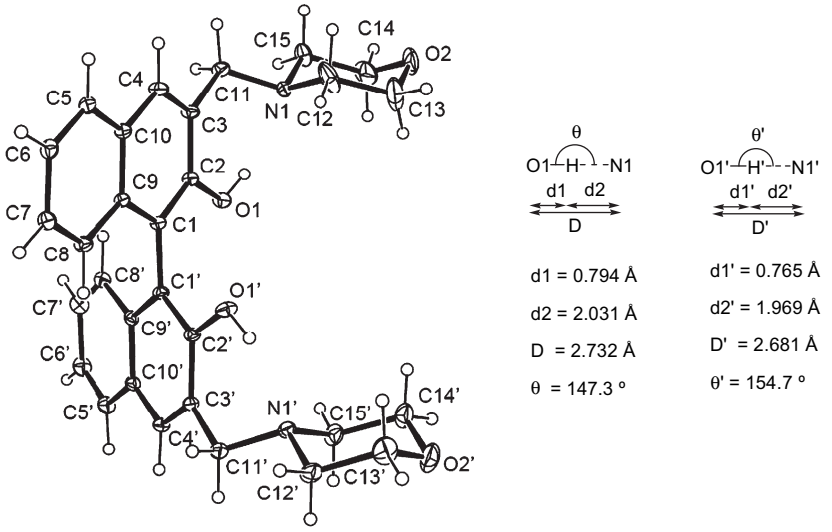


Figure 2. ORTEP drawing (30% probability ellipsoids) of (*S*)-**6**.

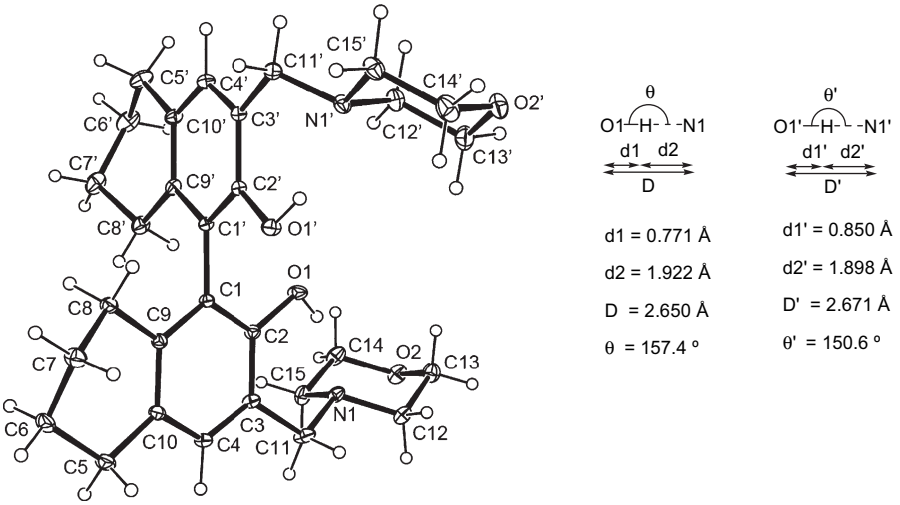
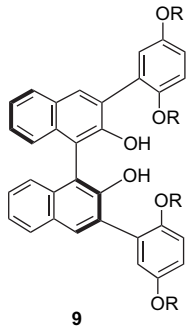
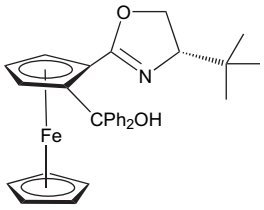


Figure 3. ORTEP drawing (30% probability ellipsoids) of (*S*)-**8**.

enantioselectivity for this reaction.[14] At a similar time, Bolm reported good results with the use of **10**.[15] Other chiral ligands were also developed for the asymmetric diphenylzinc addition.[14–20] A few of these compounds are able to catalyze the diphenylzinc addition to aromatic and α-branched aliphatic aldehydes with high enantioselectivity (>90% ee). However, the enantioselectivity for the reaction of linear aliphatic aldehydes is generally lower, and no catalyst has been reported to give over 90% ee for the reaction of diphenylzinc with a linear aliphatic aldehyde. In addition, the catalysts for the asymmetric diphenylzinc addition often require the use of a significant amount of the diethylzinc additive while cooling (or heating) the reaction mixtures.

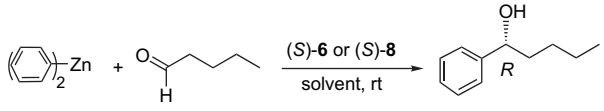


9



10

Since the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** are structurally analogous to **9**, we have examined their catalytic properties for the asymmetric diphenylzinc addition to aldehydes. We first studied the reaction of diphenylzinc with valeraldehydes in the presence of (*S*)-**6** and (*S*)-**8** (Scheme 3). Table 2 summarizes the results of this reaction under various conditions. In solvents such as methylene chloride, toluene, and diethyl ether, (*S*)-**8** showed very low enantioselectivity (35–39% ee, entries 1–3). However, a dramatic increase in enantioselectivity was observed when the reaction was carried out in THF (92% ee, entry 4). The absolute configuration of the alcohol product was determined to be *R* by comparing its optical rotation with that in literature.[21,22] The enantioselectivity using the BINOL derivative (*S*)-**6** is lower than that using the H_8BINOL derivative (*S*)-**8** (entry 5). Slow addition of the aldehyde did not significantly change the ee (entry 6). Using diethylzinc and/or methanol as the additive slightly reduced the enantioselectivity (entries 7–9). Both decreasing and increasing the amount of the chiral ligand gave lower ee (entries 10 and 11).



Scheme 3. Asymmetric diphenylzinc addition to valeraldehyde.

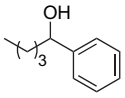
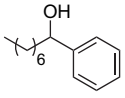
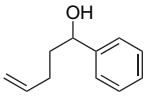
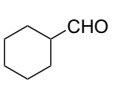
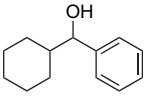
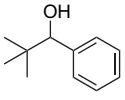
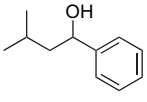
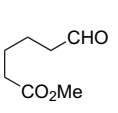
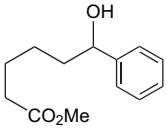
We then used (*S*)-**8** to catalyze the reaction of diphenylzinc with various aliphatic aldehydes by applying the conditions of entry 4 in Table 2. The results are summarized in Table 3. For the reactions of linear (entries 1–3), α-branched (entries 4 and 5) and β-branched (entry 6) aliphatic aldehydes, ee's were observed in the range of 92–98%. For the aldehyde containing an ester group (entry 7), 81% ee was observed. The yields for the reactions were in the range of 75–96%.

Table 2. Results for the diphenylzinc addition to valeraldehyde under various conditions catalyzed by (*S*)-**6** and (*S*)-**8**[a]

Entry	Ligand	Solvent	Ph_2Zn (equiv)	ee (%)[e,f]
1	(*S*)-**8** (10 mol %)	CH_2Cl_2	1.2	35
2	(*S*)-**8** (10 mol %)	Toluene	1.2	38
3	(*S*)-**8** (10 mol %)	Et_2O	1.2	39
4	(*S*)-**8** (10 mol %)	THF	1.2	92
5	(*S*)-**6** (10 mol %)	THF	1.2	87
6[b]	(*S*)-**8** (10 mol %)	THF	1.2	93
7[c]	(*S*)-**8** (10 mol %)	THF	1.0	91
8[d]	(*S*)-**8** (10 mol %)	THF	1.6	89
9[c,d]	(*S*)-**8** (10 mol %)	THF	1.6	91
10	(*S*)-**8** (5 mol %)	THF	1.2	84
11	(*S*)-**8** (20 mol %)	THF	1.4	87

[a] Unless indicated otherwise, the following procedure was used: Under nitrogen to a flask containing (*S*)-**8** (12.3 mg, 0.025 mmol) and diphenylzinc (66.0 mg, 0.3 mmol), a solvent (2 mL, dried) was added and the solution was stirred at room temperature for 1 h. Valeraldehyde (0.25 mmol) was then added and the resulting solution was stirred for 12 h. Aqueous work up and column chromatography on silica gel gave 1-phenyl-1-pentanol.
[b] Valeraldehyde was added dropwise over 2 h.
[c] (*S*)-**8** was pretreated with diethylzinc (20 mol %) for 1 h followed by the addition of diphenylzinc and aldehyde.
[d] MeOH (40 mol %) was added after (*S*)-**8** was treated with diphenylzinc or diethylzinc.
[e] Isolated yields of all these reactions were 82–89%.
[f] ee's were determined by HPLC-chiral OD column.

Table 3. Asymmetric diphenylzinc addition to aliphatic aldehydes catalyzed by (*S*)-**8**

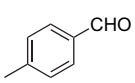
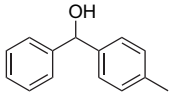
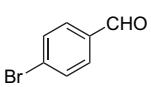
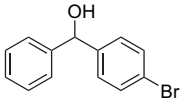
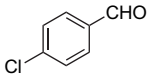
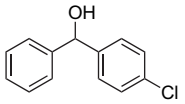
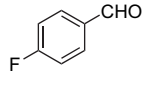
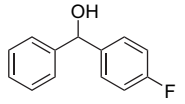
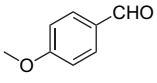
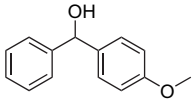
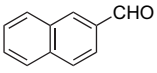
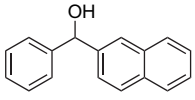
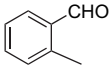
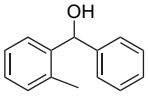
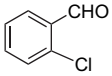
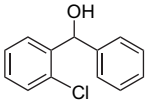
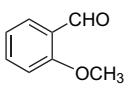
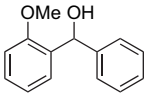
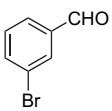
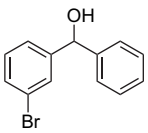
Entry	Aldehyde	Product	Time (h)	Yield (%)[a]	ee (%)[b,c]
1			12	87	92
2			12	78	93
3			12	75	92
4			8	96	98
5			6	93	98
6			16	82	92
7			12	80	81

[a] Isolated yield.
[b] Determined by HPLC-chiral column or GC-chiral column.
[c] All racemic compounds were prepared by mixing the aldehydes with diphenylzinc.

These results demonstrate that (*S*)-**8** is generally enantioselective for the reaction of diphenylzinc with both linear and branched aliphatic aldehydes. Optical rotation measurements showed that the absolute configurations of the alcohol products from the addition to the aliphatic aldehydes were *R* (entries 1 and 5).[21,22]

We also used (*S*)-**8** to catalyze the reaction of diphenylzinc with various aromatic aldehydes by applying the conditions of entry 4 in Table 2. The results are summarized in Table 4. High enantioselectivity was observed for the reaction of *para* substituted benzaldehydes (89–96% ee, entries 1–5).

Table 4. Diphenylzinc addition to various aromatic aldehydes catalyzed by (*S*)-**8**

Entry	Aldehyde	Product	Time (h)	Yield (%)[a]	ee (%)[b,c]
1			16	90	89
2			16	91	89
3			16	90	89
4			16	92	94
5			16	91	91
6			16	97	89
7			16	80	78
8			16	95	51
9			16	94	60
10			16	78	68

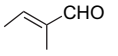
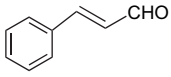
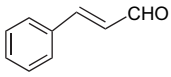
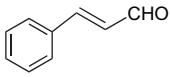
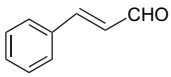
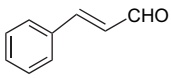
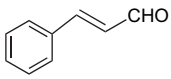
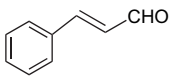
[a] Isolated yield.
[b] Determined by HPLC-chiral column or GC-chiral column.
[c] All racemic compounds were prepared by mixing the aldehydes with diphenylzinc.

The reaction of 2-naphthyl aldehyde gave 89% ee (entry 6). Moderate ee's were observed for the *ortho* and *meta* substituted benzaldehydes (51–78% ee, entries 7–10). The isolated yields for all the reactions were 75–97%. Optical rotation measurements showed that the addition to aromatic aldehydes gave (*S*)-alcohols (entries 3 and 4).[14a,23]

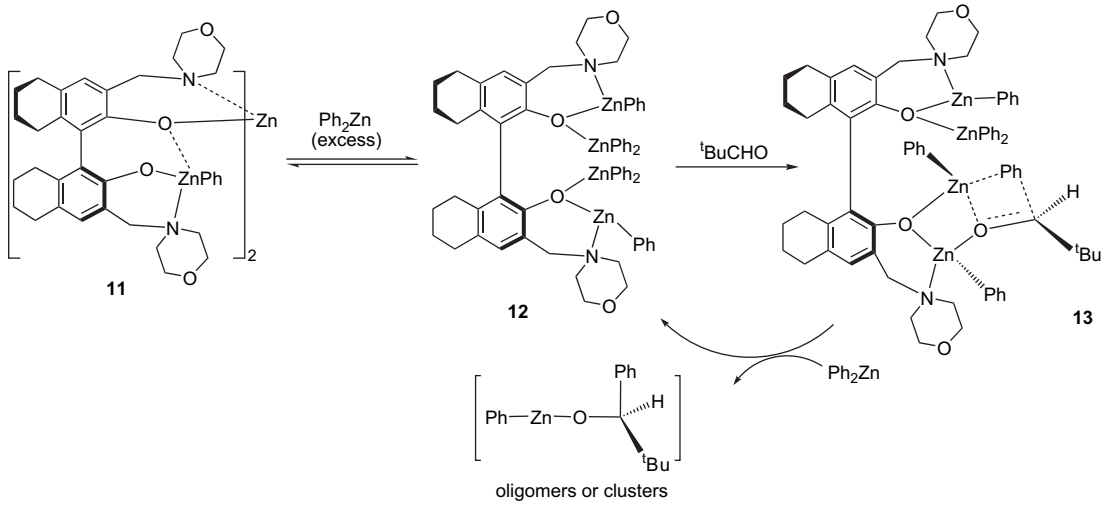
We further studied the reaction of α,β-unsaturated aldehydes with diphenylzinc in the presence of (*S*)-**8**. The results are summarized in Table 5. By using the conditions of entry 4 in Table 2, the reaction of 2-methyl-but-2-enal with diphenylzinc in the presence of (*S*)-**8** showed very high enantioselectivity and high yield (96% ee and 88% yield, entry 1). However, the reaction of cinnamaldehyde gave a significantly lower ee under the same conditions (77% ee, entry 2). Various reaction conditions were examined for the reaction of cinnamaldehyde, including lowering the reaction temperature (entry 3); increasing the amount of (*S*)-**8** and diphenylzinc (entry 4); using additives (entries 5 and 6); and changing the reaction concentration (entries 7 and 8), but no further improvement was observed. Apparently, an α-substituent is important for the high enantioselectivity in the reaction of the α,β-unsaturated aldehydes.

A linear relationship between the enantiomeric composition of the chiral ligand (*S*)-**8** and those of the diphenylzinc addition products was observed.[9c] This suggests that the catalysis for the diphenylzinc addition to either aliphatic or aromatic aldehydes might be catalyzed by a monomeric H_8BINOL catalyst. We also studied the mechanism of the diphenylzinc addition catalyzed by (*S*)-**8** by using NMR spectroscopy and

Table 5. Reaction of diphenylzinc with α,β-unsaturated aldehydes in the presence of (*S*)-**8**

Entry	Aldehyde	(*S*)-**8** (mol %)	Additive	*T*	THF (mL)	Ph_2Zn (equiv)	ee (%)
1		10	None	rt	2	1.2	96 (88)[a]
2		10	None	rt	2	1.2	77 (98)[a]
3		10	None	0 °C	2	1.2	70
4		20	None	rt	2	2.4	78
5		20	40 mol % MeOH	rt	2	2.4	73
6		10	20 mol % Et_2Zn	rt	2	1.2	78
7		10	None	rt	5	1.2	75
8		10	None	rt	1	1.0	78

[a] The isolated yield is given in the parentheses and the reaction time was 12 h.

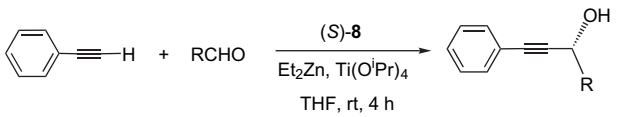


Scheme 4. A proposed mechanism for the catalytic diphenylzinc addition.

the detailed experiments were reported.[9c] The NMR study showed that 2 equiv of (*S*)-**8** reacted with 3 equiv of diphenylzinc to form a stable (2+3) complex with a proposed structure of **11** (Scheme 4). This complex then reacted with excess diphenylzinc to form a C_2-symmetric complex like **12**. Complex **12** might be the catalytically active species, which can activate an aldehyde and produce the phenyl addition product via the proposed transition state **13**.

2.4. Asymmetric alkyne addition to aldehydes catalyzed by (*S*)-8[9b]

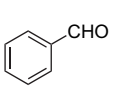
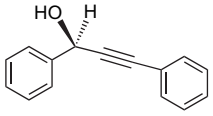
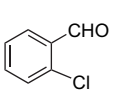
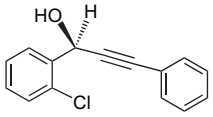
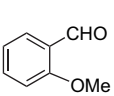
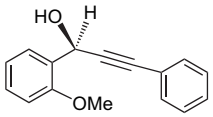
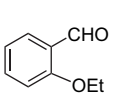
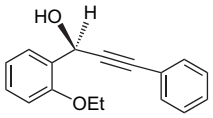
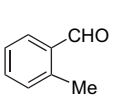
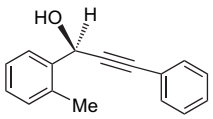
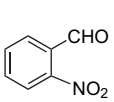
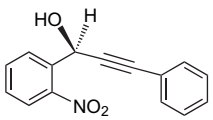
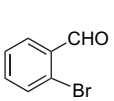
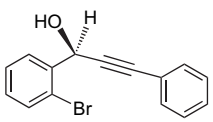
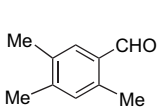
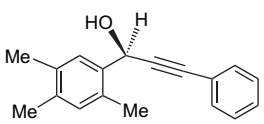
The bifunctional H_8BINOL ligand (*S*)-**8** was used to catalyze the asymmetric alkynylzinc addition to aldehydes to generate chiral propargylic alcohols that are of great utility in organic synthesis.[24–26] The results for the reactions of phenylacetylene with various aldehydes in the presence of (*S*)-**8** (Scheme 5) are summarized in Table 6. The reactions were completed in 4 h by mixing (*S*)-**8** (20 mol %), diethylzinc (4 equiv), $Ti(O^iPr)_4$ (100 mol %), 4 equiv of phenylacetylene (4 equiv), and benzaldehyde (1 equiv) at room temperature in THF. In the case of benzaldehyde, the product was (*R*)-1,3-diphenyl-prop-2-yn-1-ol obtained in 95% yield and 84% ee.



Scheme 5. Reaction of phenylacetylene with aldehydes catalyzed by (*S*)-**8**.

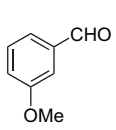
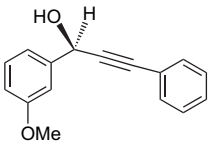
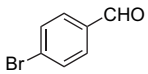
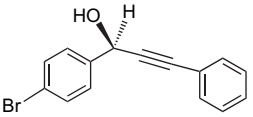
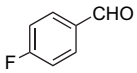
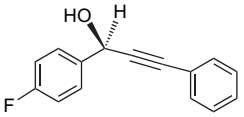
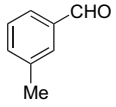
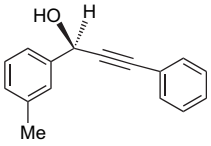
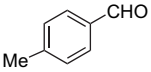
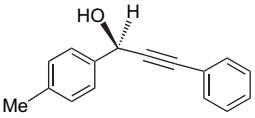
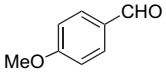
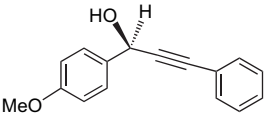
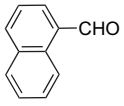
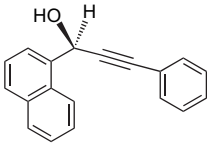
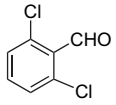
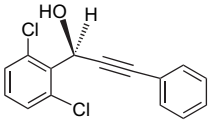
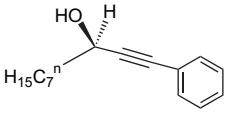
As shown in Table 6, (*S*)-**8** was highly enantioselective for the reaction of the alkyne with aromatic aldehydes. Earlier, Chan and co-workers found that H_8BINOL in combination with $Ti(O^iPr)_4$ and Me_2Zn catalyzed the reaction of phenylacetylene with certain aromatic aldehydes with high enantioselectivity at 0 °C.[27] Under these conditions, however, the reaction of an *ortho*-substituted benzaldehyde was not very good. Using H_8BINOL could give only 76% ee for the reaction of phenylacetylene with *o*-chlorobenzaldehyde. In contrast, the bifunctional H_8BINOL ligand (*S*)-**8** catalyzed the

Table 6. Asymmetric reactions of phenylacetylene with aromatic aldehydes in the presence of (*S*)-**8**, Et_2Zn, and $Ti(O^iPr)_4$[a]

Entry	Aldehyde	Product	Isolated yield (%)	ee (%)
1			93	83
2			88	97
3			76	93
4			83	92
5			88	89
6[b]			62	98
7			84	97
8			68	96

(*continued*)

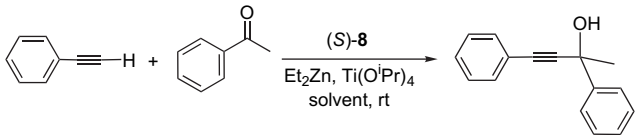
Table 6. (*continued*)

Entry	Aldehyde	Product	Isolated yield (%)	ee (%)
9			93	86
10			86	87
11			50	86
12			98	91
13			86	83
14			99	85
15			85	83
16[c]			62	86
17[d]	$CH_3(CH_2)_6CHO$		76	67

[a] Unless indicated otherwise, reactions were conducted by stirring (*S*)-**8**/Et_2Zn/PhCCH/$Ti(O^iPr)_4$/RCHO=0.1:4:4:1:1 at room temperature in THF for 4 h.
[b] 2 equiv of Et_2Zn and 2 equiv of PhCCH were used.
[c] The reaction time was 6 h.
[d] 20 mol % (*S*)-**8** was used.

same reaction with 97% ee (entry 2). This ligand was found to be good for the asymmetric reaction of a variety of *ortho*-substituted benzaldehydes with ee's in the range of 89–98% (entries 2–8). In addition, (*S*)-**8** was also generally good for other aromatic aldehydes (entries 9–16). The enantioselectivity for a linear aliphatic aldehyde was lower (67% ee, entry 17).

Although significant progress has been made on the asymmetric alkyne addition to aldehydes, not many good catalysts have been obtained for the asymmetric alkyne addition to ketones.[28] The lower reactivity of ketones requires more active catalysts than those for aldehydes. We also found that (*S*)-**8** was an active catalyst for the reaction of phenylacetylene with acetophenone at room temperature (Scheme 6). Table 7 summarizes the results under various reaction conditions. Generally, the reaction was conducted by mixing (*S*)-**8** (10 mol %), Et_2Zn (4 equiv), and phenylacetylene (4 equiv) at room temperature for 2 h in a solvent (1 mL) followed by the addition of $Ti(O^iPr)_4$ (100 mol %) and acetophenone. After 36 h, the reaction was quenched and the ee was determined by HPLC-chiral column. Less than 34% ee was observed for the reactions in toluene, methylene chloride, and diethyl ether (entries 1–3). A significant increase of the enantioselectivity was observed in THF (63% ee and 60% yield, entry 4). Reducing the amount of $Ti(O^iPr)_4$ or increasing the amount of THF decreased the enantioselectivity (entries 5 and 6). Changing the solvent from THF to 1,4-dioxane increased the ee to 69% (entry 7).



Scheme 6. Reaction of phenylacetylene with acetophenone catalyzed by (*S*)-**8**.

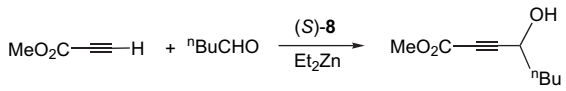
Table 7. Reaction of phenylacetylene with acetophenone in the presence of (*S*)-**8** under various conditions

Entry	(*S*)-**8** (mol %)	$Ti(O^iPr)_4$ (mol %)	Solvent	ee (%)
1	10	100	Toluene	0
2	10	100	CH_2Cl_2	34
3	10	100	Et_2O	19
4	10	100	THF	63 (60)[a]
5	10	40	THF	60
6	10	100	THF[b]	56
7	10	40	1,4-Dioxane	69

[a] Isolated yield in the parentheses.
[b] 3 mL THF was used.

We recently reported that the unfunctionalized BINOL in combination with Et_2Zn, $Ti(O^iPr)_4$, and HMPA can catalyze the highly enantioselective reaction of methyl propiolate with aldehydes to generate γ-hydroxy-α,β-acetylenic esters.[29] These compounds are used extensively in the synthesis of complex organic compounds.[30] We also studied the use of (*S*)-**8** to catalyze the reaction of methyl propiolate with valeraldehyde. It was found that (*S*)-**8** in combination with Et_2Zn was highly active at room temperature without the need for $Ti(O^iPr)_4$ and a Lewis base additive (Scheme 7). However, the enantioselectivity was low in various solvents such as Et_2O, CH_2Cl_2, and toluene. The highest enantioselectivity at room temperature was only 28% ee though the reaction was generally completed in 3–6 h (Table 8, entry 1). Other reaction conditions were examined and the results are shown in Table 8. In diethyl ether, decreasing the reaction temperature to −20 °C led to a significantly increased enantioselectivity (70% ee, entry 4). At −20 °C, all the reactions were completed in high yields in 16 h (entries 2–4). Further decreasing the temperature to −40 °C made the reaction sluggish and reduced both the yield and ee

(entry 5). Replacing diethylzinc with dimethylzinc decreased the enantioselectivity (entry 6). Increasing the amount of (*S*)-**8** and diethylzinc could not improve the reaction (entry 7). The ee of the product was determined by analyzing the ^{1}H NMR spectrum of the (*R*)-O–Ac mandelate derivative (Scheme 8).



Scheme 7. Asymmetric reaction of methyl propiolate with valeraldehyde.

Table 8. Results for the reaction of methyl propiolate with valeraldehyde in the presence of (*S*)-**8**

Entry	(*S*)-**8** (mol %)	Solvent	R_2Zn	*T* (°C)	ee (%)
1	10	Toluene	1.2 equiv Et_2Zn	25	28
2	10	Toluene	1.2 equiv Et_2Zn	−20	43
3	10	CH_2Cl_2	1.2 equiv Et_2Zn	−20	28
4	10	Et_2O	1.2 equiv Et_2Zn	−20	70
5	10	Et_2O	1.2 equiv Et_2Zn	−40	62
6	10	Et_2O	1.2 equiv Me_2Zn	−40	50
7	20	Et_2O	2.4 equiv Et_2Zn	−20	69

2.5. Asymmetric alkylzinc addition to aldehydes catalyzed by (*S*)-8

The use of (*S*)-**8** to catalyze the classical dimethylzinc and diethylzinc addition to aldehydes was tested.[25a,b] To our surprise, (*S*)-**8** could not give the desired product for the reaction of diethylzinc or dimethylzinc with valeraldehyde in THF at room temperature in spite of its high enantioselectivity for the diphenylzinc addition. For the reaction of diethylzinc with benzaldehyde in THF at room temperature, (*S*)-**8** produced 1-phenyl-propyl-1-ol in 78% yield and 73% ee.

2.6. Asymmetric TMSCN addition to aldehydes catalyzed by the bifunctional ligands

The asymmetric syntheses of cyanohydrins have attracted considerable research activity because these compounds are versatile starting materials for many functional organic molecules such as α-hydroxyacids, α-hydroxyketones, α-amino acids, and β-amino alcohols.[31] Previously, the aluminum complexes of the bifunctional ligands **1**[4] and **2**[5] have been used to catalyze the reaction of aldehydes with TMSCN to generate the chiral cyanohydrins with good enantioselectivity. These bifunctional ligands require either a six-step synthesis from the optically active BINOL[32] or an optical resolution in a multi-step synthesis from a naphthalene derivative.[5] This makes the use of the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** very attractive because of their one-step synthesis.

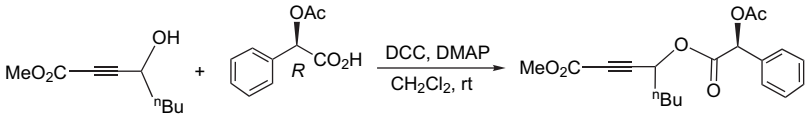
We studied the use of the ligands (*S*)-**6**, (*S*)-**7**, and (*S*)-**8** in combination with Me_2AlCl to catalyze the reaction of TMSCN with benzaldehyde (Scheme 9). The reaction conditions employed were similar to those using **1** and **2**. The catalyst was prepared by stirring Me_2AlCl (10 mol %) with ligand (10 mol %) in a solvent (1 mL) at room temperature for 1 h over 4 Å MS. Then Ph_3PO was added and the mixture was cooled down to −20 °C. Benzaldehyde and TMSCN were both added in one portion. After 48 h, the reaction was quenched with HCl (2 N), the product was converted to *O*-acetyl cyanohydrin. The ee of the acetate was analyzed by GC-chiral column. The results are summarized in Table 9.

As shown in Table 9, toluene was found to be the best solvent. The bifunctional BINOL ligand (*S*)-**6** was highly enantioselective for this reaction in toluene (96% ee, entry 2). The monosubstituted ligand (*S*)-**7** gave very low enantioselectivity (entries 5–7). The H_8BINOL ligand (*S*)-**8** showed significantly lower enantioselectivity than (*S*)-**6** (53% ee, entry 8).

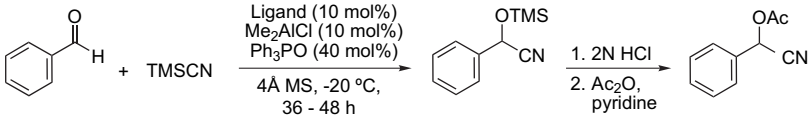
We also tested the use of $Ti(O^iPr)_4$ in place of Me_2AlCl in combination with the chiral ligands but only obtained moderate ee's. We found that switching the $Ph_3P{=}O$ additive to HMPA led to a shorter reaction time and a slightly higher yield. Thus the optimized conditions involved the use of (*S*)-**6** in combination with Me_2AlCl, HMPA, 4 Å MS in toluene at −20 °C. It gave 92% yield and 94% ee in 24 h for the TMSCN addition to benzaldehyde. The optimized conditions were applied for the reactions of TMSCN with various aromatic aldehydes and the results are summarized in Table 10. In general, good enantioselectivity was observed.

Table 9. Results for the TMSCN addition to benzaldehyde in the presence of the bifunctional ligands

Entry	Ligand	Solvent	ee (%)
1	(*S*)-**6**	THF	72
2	(*S*)-**6**	Toluene	96
3	(*S*)-**6**	Et_2O	73
4	(*S*)-**7**	THF	7
5	(*S*)-**7**	Toluene	20
6	(*S*)-**7**	Et_2O	11
7	(*S*)-**7**	CH_2Cl_2	7
8	(*S*)-**8**	Toluene	53

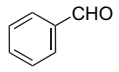
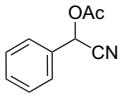
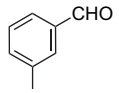
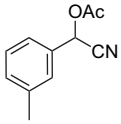
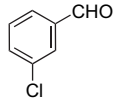
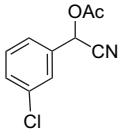
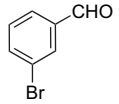
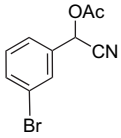
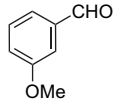
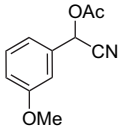
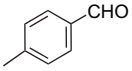
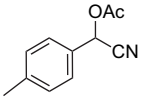
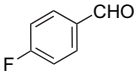
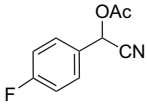
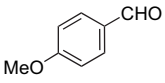
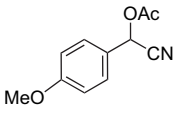
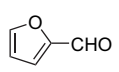
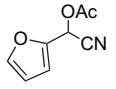
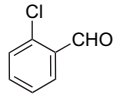
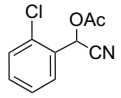


Scheme 8. Preparation of the O-Ac Mandelate derivative for NMR analysis.



Scheme 9. Catalytic reaction of benzaldehyde with TMSCN.

Table 10. Results of TMSCN addition to aromatic aldehydes

Entry	Aldehyde	Product	Yield (%)	ee (%)
1			92	94
2			90	93
3			77	94
4			88	82
5			82	80
6			86	75
7			85	90
8			80	80
9			70	74
10			94	80

Although ligand **2** was reported to be highly enantioselective for the reaction of aromatic aldehydes with TMSCN, it gave much lower ee's for the reaction of aliphatic aldehydes.[5] For example, even at −40 °C, (*S*)-**2** catalyzed the addition of TMSCN to heptaldehyde with only 66% ee. In general, very few catalysts could give consistently good results for the asymmetric reaction of aliphatic aldehydes with TMSCN in spite of a good number of highly enantioselective catalysts for the reaction of aromatic aldehydes.[31] Therefore, we explored the application of (*S*)-**6** for the asymmetric reaction of aliphatic aldehydes with TMSCN.

In Table 11, the results for the reaction of octyl aldehyde with TMSCN in the presence of (*S*)-**6** and Me_2AlCl under various conditions are summarized. In toluene solution, (*S*)-**6** showed up to 91% ee for this reaction (entry 1). Changing the solvent to THF reduced the ee (entry 2). In diethyl ether, however, a significant enhancement in ee was observed (97% ee, entry 3). Without the additive HMPA, a somewhat lower ee was observed (entry 4). Absence of molecular sieves led to a large reduction in enantioselectivity (entry 5). The room temperature reaction gave a lower but still significant ee (entry 6). Increasing the amount of molecular sieves at room temperature greatly decreased the enantioselectivity even with the increased amount of the chiral catalyst (entry 7). Changing the solvent to hexanes at room temperature diminished the enantioselectivity (entry 8).

Table 11. Asymmetric addition of TMSCN to octyl aldehyde in the presence of (*S*)-**6** and Me_2AlCl[a]

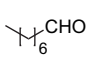
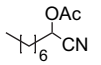
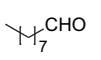
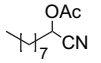
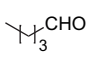
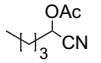
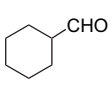
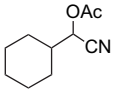
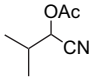
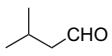
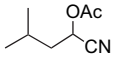
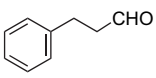
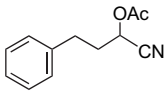
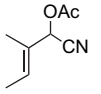
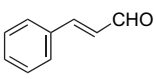
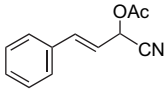
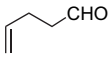
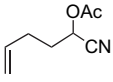
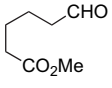
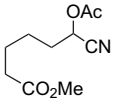
Entry	Solvent	4 Å MS (mg)	Time (h)	ee (%)
1	Toluene	5	24	91
2	THF	5	24	87
3	Et_2O	5	24	97
4[b]	Toluene	5	24	82
5	Toluene	None	24	46
6[c]	Et_2O	5	3	76
7[c,d]	Et_2O	15	4	31
8[c]	Hexane	5	24	6

[a] The following procedure was used unless otherwise indicated: (*S*)-**6** (0.025 mmol, 10 mol %), 4 Å molecular sieves, and Me_2AlCl (10 mol %, 1 M in hexanes) in a solvent (1 mL) were stirred under nitrogen at room temperature for 3 h. It was then combined with the additive HMPA (40 mol %) and cooled down to −20 °C. TMSCN (3.0 equiv) and an aldehyde were added.
[b] No additive.
[c] Reaction at rt.
[d] 20 mol % (*S*)-**6** and 20 mol % Me_2AlCl.

We applied the optimized conditions of entry 3 in Table 11 to the reaction of a variety of aliphatic aldehydes with TMSCN. As the results summarized in Table 12 show, in the presence of (*S*)-**6** (10 mol %) and Me_2AlCl (10 mol %), high enantioselectivities were achieved for the reactions of TMSCN with diverse aliphatic aldehydes including linear (entries 1–3), branched (entries 4–7), α,β-unsaturated (entries 8 and 9), and functionalized substrates (entries 10 and 11). The absolute configurations of the products from hydrocinnamaldehyde and cinnamaldehyde were determined to be *R* by comparing their optical rotations with those in the literature.

A large positive nonlinear effect was observed for the reaction of octyl aldehyde with TMSCN in the presence of (*S*)-**6** and Me_2AlCl.[9a] A chiral ligand of only 40% ee could generate the product of the same high ee as that by the ligand of high optical purity. The remarkable nonlinear effect indicates that the catalytic process may involve intermolecularly aggregated Al complexes. When (*S*)-**6** was treated with Me_2AlCl in toluene-d_8, the ^1H NMR spectrum showed a complete disappearance of all the signals of the ligand. A singlet at δ 0.16 appeared in the spectrum, which was attributed to methane generated from the protonation of Me_2AlCl by the chiral ligand. A white precipitate was produced in the toluene-d_8 solution, indicating the aggregation of the aluminum complexes. Octyl aldehyde and TMSCN were added to the NMR tube at room temperature. A triplet at δ 4.10

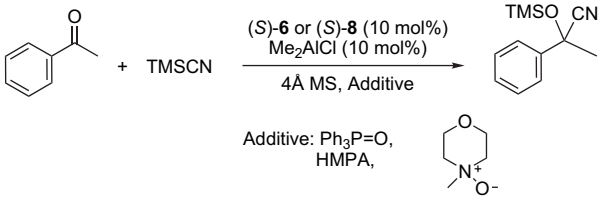
Table 12. Asymmetric addition of TMSCN to aliphatic aldehydes in the presence of (*S*)-**6** and Me_2AlCl

Entry	Aldehyde[a]	Product	Yield (%)	ee (%)
1			91	97
2			92	98
3			87	96
4			90	99
5			65	97
6			72	96
7			86	95
8			70	98
9			74	94
10			67	96
11			90	92

[a] Freshly distilled.

(J=6.4 Hz) appeared, which was attributed to –C*H*(CN)O-$Si(CH_3)_3$. Complicated aromatic signals were also observed, which were assigned to the aluminum complexes of the ligand. After the complete conversion of the aldehyde to the product, a C_2-symmetric complex might be generated because of the greatly simplified aromatic signals. However, the structure of this complex could not be determined yet.

We also used (*S*)-**6** and (*S*)-**8** to catalyze the cyanosilylation of acetophenone (Scheme 10).[33] The same amounts of ligands, Me_2AlCl, and 4 Å molecular sieves as used in the cyanosilylation of benzaldehyde were applied to this reaction. Various additives were examined. Using $Ph_3P{=}O$ (40 mol %) or HMPA (40 mol %) as the additive gave very low yield of the product with no enantioselectivity at −20 °C, 0 °C or room temperature. We also tested the use of *N*-methylmorpholine *N*-oxide (10, 20 or 40 mol %) as the additive at 0 °C or room temperature. Despite the high yield, only the racemic product was obtained.



Scheme 10. Reaction of acetophenone with TMSCN.

3. Summary

In summary, we have developed the efficient one-step synthesis of the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** from the reaction of BINOL and H_8BINOL with morpholinomethanol, respectively. The X-ray analyses of these compounds have revealed their structural similarity and difference. The bifunctional H_8BINOL (*S*)-**8** is found to be highly enantioselective for the reaction of diphenylzinc with many aliphatic and aromatic aldehydes and especially is the most enantioselective catalyst for linear aliphatic aldehydes. Unlike other catalysts developed for the diphenylzinc addition which often require the addition of a significant amount of *diethylzinc* with cooling (or heating) the reaction mixtures in order to achieve high enantioselectivity, using (*S*)-**8** needs no additive and gives excellent results at room temperature. (*S*)-**8** in combination with diethylzinc and $Ti(O^iPr)_4$ can catalyze the highly enantioselective phenylactylene addition to aromatic aldehydes. It can also promote the phenylacetylene addition to acetophenone at room temperature though the enantioselectivity is not very high yet. Without using $Ti(O^iPr)_4$ and a Lewis base additive, (*S*)-**8** in combination with diethylzinc can catalyze the reaction of methyl propiolate with an aldehyde to form the highly functional γ-hydroxy-α,β-acetylenic esters except that the enantioselectivity is low at this stage. The bifunctional BINOL ligand (*S*)-**6** in combination with Me_2AlCl is found to be a highly enantioselective catalyst for the addition of TMSCN to both aromatic and aliphatic aldehydes.

4. Experimental

4.1. Preparation and characterization of (*S*)-3,3′-morpholinomethyl-1,1′-bi-2-naphthol, (*S*)-6

To a 250 mL round bottom flask containing paraformaldehyde (30.0 g, 1.0 mol), morpholine (88 mL, 1.0 mol) was added dropwise at 0 °C over 1 h with rigorous stirring. (Caution: this was a highly exothermic reaction.) The reaction mixture was allowed to warm up to room temperature. After 4 h, the mixture was slowly heated to 60 °C and maintained at the temperature for 10 h. This led to the formation of morpholinomethanol as a clear syrup-like liquid. Morpholinomethanol (60 mL) was combined with (*S*)-BINOL (3.0 g, 0.0106 mol) and degassed by bubbling with N_2. The mixture was placed in a Parr Non-Stirred Pressure Vessel (Series 4750 1.50 Inch Inside diameter, 125 mL) under 25–30 psi N_2 and heated at 110±2 °C for 72 h. Diethyl ether was then added after the reaction, and part of the product (*S*)-**6** precipitated out as a white solid. The white solid was washed twice with diethyl ether. The diethyl ether solutions were

combined with ethyl acetate (100 mL) and washed three times with 3% $NaHCO_3$. The organic phase was then concentrated under vacuum and the residue was purified by column chromatography on silica gel (size: 36 mm ID and 30 cm L) eluted with CH_2Cl_2/ethyl acetate (8:1) to give (*S*)-**6** and (*S*)-**7**. The combined yield of (*S*)-**6** was 55% (2.8 g). The optical purity of (*S*)-**6** was determined by HPLC analysis (vide infra) to be 75% ee. Yield of (*S*)-**7** was 30% (1.2 g). The optical purity of this (*S*)-**7** was determined by optical rotation measurement to be >87% ee [$[\alpha]_D$ −30.8 (*c* 1.0, CH_2Cl_2)]. For the preparation of the optically pure (*S*)-**7**, see below. The product (*S*)-**6** of 75% ee was dissolved in hot CH_2Cl_2/MeOH (3:1). The solution was cooled to room temperature and needle-shaped crystals appeared, which were found to be predominantly the racemic compound [$[\alpha]_D$ −1.9 to −4.5 (*c* 1.0, CH_2Cl_2)]. After separation of the racemic crystals, the solution was concentrated under vacuum and redissolved in hot CH_2Cl_2/MeOH (3:1). Cooling again allowed the separation of the racemic crystals. After this process was conducted for 3–4 times, removal of the solvent from the mother liquor gave the optically pure (*S*)-**6** (>99% ee, determined by HPLC vide infra). Sometimes, a simple column chromatography on silica gel (size: 36 mm ID and 30 cm L; eluent: 6:1 CH_2Cl_2/ethyl acetate) may be needed to remove impurities in the mother liquor after the crystallization. Mp 309–310 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.04 (s, 2H), 7.80 (m, 2H), 7.67 (s, 2H), 7.28 (m, 2H), 7.21 (m, 2H), 7.16 (m, 2H), 4.13 (m, 2H), 3.90 (m, 2H), 3.70 (m, 8H), 2.66 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 134.0, 128.5, 127.9, 126.3, 125.0, 123.4, 123.3, 116.8, 66.8, 62.6, 53.1. $[\alpha]_D$ −152.1 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78. Found: C, 74.60; H, 6.82; N, 6.05. High-resolution mass analysis: calcd for $C_{30}H_{32}N_2O_4$: 484.2362. Found: 484.2350.

The enantiomeric purity of (*S*)-**6** was determined by HPLC analysis of its acetate derivative: To a CH_2Cl_2 (5 mL) solution of (*S*)-**6** (13 mg) were added Ac_2O (250 μL) and pyridine (250 μL). After the solution was stirred at room temperature for 6 h, the volatiles were removed under vacuum. The resulting acetate of (*S*)-**6** as a white solid was purified by column chromatography on aluminum oxide (size: 12 mm ID and 10 cm L) eluted with petroleum ether/ethyl acetate (4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.88 (m, 2H), 7.44 (m, 2H), 7.24 (m, 2H), 7.14 (m, 2H), 3.52–3.76 (m, 12H), 2.50 (m, 8H), 1.80 (s, 6H). HPLC (CHIRALCEL AD) was used to measure the ee% of the acetate. Solvent: hexane/isopropanol (98:2). Flow rate: 1.0 mL/min. Retention times: t_R=31.0 min and t_S=35.5 min.

4.2. Preparation and characterization of (*S*)-3-morpholinomethyl-1,1′-bi-2-naphthol, (*S*)-7

A mixture of (*S*)-BINOL (3.0 g, 0.0106 mol) and morpholinomethanol (50 mL) in a Parr Non-Stirred Pressure Vessel (Series 4750 1.50 Inch Inside diameter, 125 mL) was degassed with nitrogen and then sealed under 30 psi nitrogen. After being heated at 95–100 °C for 48 h, the reaction mixture was diluted with ethyl acetate (150 mL) at room temperature, and washed with 3% sodium bicarbonate (2×60 mL) and water (100 mL). After rotoevaporation of the organic solution, the residue was purified by column chromatography on silica gel (size: 36 mm ID and 30 cm L) eluted with CH_2Cl_2/ethyl acetate (12:1) to give (*S*)-**7** in 52% yield (1.9 g) and (*S*)-**6** in 10% yield (0.46 g, >99% ee by HPLC). (*S*)-**7** as a white solid from this reaction was considered to be optically pure since the optical purity of (*S*)-**6** obtained from this reaction was found to be >99% ee by HPLC. In addition, the optical purity of (*S*)-**7** (>97% ee) was supported by the ^{1}H NMR studies of (*S*)-**7**, (*R*)-**7**, and racemic-**7** in the presence of 10 mol % chiral shift reagent Eu(hfc)$_3$ {Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]} (vide infra). Mp 215.5–216.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.93 (m, 4H), 7.10–7.39 (m, 7H), 4.015 (s, 2H), 3.71 (m, 4H), 2.66 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 151.6, 134.1, 133.8, 130.2, 129.7, 129.5, 128.7, 128.6, 128.0, 127.3, 126.7, 125.0, 124.8, 124.1, 123.7, 123.5, 117.8, 115.2, 113.1, 66.7, 62.5, 53.1. $[\alpha]_D$ −35.1 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 78.16; H, 5.99; N, 3.80. High-resolution mass analysis: calcd for $C_{25}H_{23}NO_3$: 385.1677. Found: 385.1662.

Determination of the optical purity of (*S*)-**7** and (*R*)-**7**. ^{1}H NMR spectrums of (*S*)-**7**, (*R*)-**7**, and racemic-**7** in the presence of 10 mol % chiral shift reagent Eu(hfc)$_3$ {Europium tris[3-(heptafluoropropylhydroxyl methylene)-(+)-camphorate]} were studied. Before the addition of the chiral shifting reagent, there was no signal at δ 7.39–7.73. After the samples were treated with Eu(hfc)$_3$ (10 mol %), new peaks appeared at δ 7.63 and/or 7.53 as summarized in Table 13. These data support the high optical purity of (*S*)-**7** and (*R*)-**7**.

Table 13. Resolution of the ^{1}H NMR signals of the enantiomers of **7** in the presence of the chiral shift reagent

Sample	^{1}H NMR signals	
	δ=7.63	δ=7.53
(*S*)- or (*R*)- or Rac-**7**	0H	0H
Rac-**7**+10 mol % Eu(hfc)$_3$	1H	1H
(*S*)-**7**+10 mol % Eu(hfc)$_3$	0H	1H
(*R*)-**7**+10 mol % Eu(hfc)$_3$	1H	0H

4.3. Preparation and characterization of (*S*)-3,3′-bismorpholinomethyl-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol, (*S*)-8

To a 250 mL round bottom flask containing 1,4-dioxane (30 mL) solution of (*S*)-H_8BINOL (5.0 g, 0.017 mol) was added morpholinomethanol (50 mL) at room temperature. After the mixture was heated at 60 °C for 12 h with stirring, it was cooled down to room temperature and combined with ethyl acetate (150 mL) in a separation funnel. The organic layer was then washed with saturated $NaHCO_3$ (3× 100 mL) and water (2×100 mL). Removal of ethyl acetate gave (*S*)-**8** as a white solid (8.0 g, 95% yield). Recrystallization of this compound from ethanol gave white needle crystals. ^{1}H NMR (500 MHz, toluene-d_8) δ 9.99 (s, 2H), 6.62 (s, 2H), 3.20–3.36 (m, 12H), 2.75 (m, 6H), 2.42 (m, 2H), 2.07 (m, 8H), 1.63–1.72 (m, 8H). ^{13}C NMR (125 MHz, toluene-d_8) δ 153.14, 136.44, 128.54, 127.19, 125.031, 118.26, 66.72, 62.19, 53.04, 29.91, 27.61, 24.04, 23.91. $[\alpha]_D^{25}$ −35.4 (*c* 1.04, THF). Anal. Calcd for $C_{30}H_{40}N_2O_4$: C,

73.14; H, 8.18; N, 5.69. Found: C, 73.22; H, 8.20; N, 5.66. High-resolution mass analysis: calcd for $C_{30}H_{40}N_2O_4$: 492.2988. Found. 492.2969.

4.4. A typical procedure for the asymmetric diphenylzinc addition to aldehydes

Under nitrogen to a 10 mL round bottom flask (flame dried under vacuum) were added diphenylzinc (66 mg, 0.3 mmol, 1.2 equiv), (*S*)-**6** or (*S*)-**8** (0.025 mmol, 0.1 equiv), and a solvent (2.0 mL, anhydrous) sequentially. After the resulting solution was stirred at room temperature for 1 h, an aldehyde (0.25 mmol) was added and the reaction was monitored by TLC. At the completion of the reaction, ammonium chloride (saturated, aq) was added to quench the reaction. The mixture was extracted with methylene chloride three times. After removal of the solvents, the residue was purified by column chromatography on silica gel (size: 12 mm ID and 15 cm L) eluted with hexanes/ethyl acetate (12:1) to give the product as either colorless oil or white solid in 75–97% yield.

4.5. General procedure for the phenylacetylene addition to aromatic aldehydes catalyzed by (*S*)-8

Under nitrogen to a 10 mL round bottom flask (flame dried under vacuum) were added phenylacetylene (1.0 mmol, 113 μL), THF (3 mL), Et_2Zn (1.0 mmol, 110 μL), $Ti(O^iPr)_4$ (74 μL, 0.25 mmol), (*S*)-**8** (12.3 mg, 0.025 mmol), and an aldehyde (0.25 mmol). After the resulting reaction mixture was stirred at room temperature for 4 h, a saturated ammonium chloride solution was added to quench the reaction. The mixture was extracted with methylene chloride (3×5 mL) and the organic solution was concentrated under vacuum. The residue was purified by passing through a short silica gel column (size: 12 mm ID and 10 cm L) eluted with methylene chloride/hexane (1:1), which afforded the pure propargylic alcohol product.

4.6. A typical procedure for the asymmetric methyl propiolate addition to aldehyde in the presence of (*S*)-8

(*S*)-**8** (12.3 mg, 0.025 mmol, 0.1 equiv) and 3 mL solvent were added into a 10 mL round bottom flask (flame dried under vacuum). Then diethylzinc (33 μL, 0.3 mmol, 1.2 equiv) and phenylacetylene (26 μL, 0.3 mmol, 1.2 equiv) were added sequentially. After the resulting solution was stirred at room temperature for 1 h, it was cooled down to −20 °C. Valeraldehyde (27 μL, 0.25 mmol) was added and the reaction was monitored by TLC at −20 °C. At the completion of the reaction in 6–12 h, ammonium chloride (saturated, aq) was added to quench the reaction. The mixture was extracted with methylene chloride three times. After removal of the solvents, the residue was purified by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (12:1) to give the product as colorless oil.

4.7. A typical procedure for preparation of the derivative of 4-hydroxy-oct-2-ynoic acid methyl ester

To a solution of 4-hydroxy-oct-2-ynoic acid methyl ester (0.09 mmol) at room temperature was added 1,3-dicyclohexylcabodiimde (37 mg, 0.18 mmol), 4-(*N*,*N*-dimethylamino)pyridine (22 mg, 0.18 mmol), and (*R*)-acetoxyphenylacetic acid (30.0 mg, 0.18 mmol). The reaction was monitored by TLC and was judged to be completed after 15 min. The reaction mixture was concentrated and purified by flash column chromatography on silica gel (size: 36 mm ID and 30 cm L) eluted with 20% ether in hexane to give a clear oil. The NMR integrations of chemical shift at δ 5.96, 5.91, 3.78, and 3.75 were used to determine the enantiomeric excess.

4.8. A typical procedure for the catalytic cyanosilylation of aldehydes in the presence of (*S*)-6

Under nitrogen, a mixture of (*S*)-**6** (12.1 mg, 0.025 mmol), 4 Å molecular sieves (5 mg, activated at 180 °C 30 min under 0.09 mmHg vacuum), and diethyl ether (1 mL, dried) was stirred for 10 min and Me_2AlCl (25 μL, 0.025 mmol, 1 M hexane solution) was added. After stirred for 3 h, a white suspension formed to which HMPA (16 μL, 0.1 mmol) was added. The mixture was cooled down to −20 °C, and TMSCN (105 μL, 0.75 mmol) was added in one portion. In 5 min, an aldehyde (0.25 mmol, freshly distilled) was also added in one portion. After the reaction mixture was stirred at −20 °C for 24 h, water (1 mL) was added to quench the reaction at −20 °C. At room temperature, diethyl ether (2 mL) was added to dilute the reaction, and the diethyl ether solution was washed twice with water. (Removal of the solvent followed by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (20:1) would give the pure cyanosilyl ether product.) In order to prepare the acetate derivative for ee determination, the diethyl ether solution of the crude silyl ether was treated with 2 N HCl (5 mL) and stirred for 2 h to remove the trimethylsilyl group. Then, CH_2Cl_2 (3×4 mL) was used for extraction. The organic layers were combined and then treated with acetic anhydride (0.2 mL) and pyridine (50 μL). After stirred for 1 h, the reaction mixture was concentrated by rotoevaporation and the residue was purified by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (15:1) to give the cyano acetate product. The enantiomeric purity of *O*-acetyl cyanohydrin was determined by GC analysis. Conditions: HP 6890 series GC; Supelco Beta-Dex 120 Fused silica capillary column (30 m length×0.25 mm ID×0.25 μm film thickness); constant flow rate at 1.0 mL/min; inlet temperature 250 °C; FID detector temperature 280 °C.

4.9. Catalytic cyanosilylation of acetophenone in the presence of (*S*)-6 and (*S*)-8

Under nitrogen, a mixture of (*S*)-**6** or (*S*)-**8** (0.025 mmol), 4 Å molecular sieves (5 mg, activated at 180 °C for 30 min under 0.09 mmHg vacuum), and a solvent (1 mL, dried) was stirred for 10 min and Me_2AlCl (25 μL, 0.025 mmol, 1 M hexane solution) was added. After stirred for 3 h, a white suspension formed to which an additive was added. The mixture was cooled down to −20 °C (or kept at room temperature), and TMSCN (105 μL, 0.75 mmol) was added in one portion. In 5 min, acetophenone (30 μL, 0.25 mmol, freshly distilled) was also added in one portion. After the reaction mixture was stirred at −20 °C for 24–48 h, water (1 mL) was added to quench the reaction. At room temperature, diethyl ether (2 mL) was added to dilute the reaction, and the diethyl ether

solution was washed twice with water. Removal of the solvent followed by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (20:1) would give the pure cyanosilyl ether product. The enantiomeric purity was determined by GC analysis. Conditions: HP 6890 series GC; Supelco Beta-Dex 120 Fused silica capillary column (30 m length×0.25 mm ID×0.25 μm film thickness); constant flow rate at 1.0 mL/min; inlet temperature 250 °C; FID detector temperature 280 °C.

Acknowledgements

Support of this work from the National Institute of Health (R01GM58454/R01EB002037) is gratefully acknowledged.

Supplementary data

Analytical data for the catalytic addition products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.049.

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Tetrahedron 62 (2006) 9349–9358

A concise synthesis of (−)-cytoxazone and (−)-4-*epi*-cytoxazone using chlorosulfonyl isocyanate

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Received 3 July 2006; revised 25 July 2006; accepted 26 July 2006
Available online 14 August 2006

Abstract—A concise synthesis of (–)-cytoxazone and its stereoisomer (–)-4-*epi*-cytoxazone, novel cytokine modulators, has been accomplished each in six steps from readily available *p*-anisaldehyde with good diastereoselectivity. Key steps in the synthesis include the regioselective and diastereoselective amination of *anti*- and *syn*-1,2-dimethyl ethers with chlorosulfonyl isocyanate and the subsequent regioselective cyclization of the diol to construct the oxazolidin-2-one core. The diastereoselectivity of amination reaction using CSI was explained by the Cieplak electronic model via S_N1 mechanism and neighboring group effect, leading to the retention of the configuration.

1. Introduction

Cytoxazone (**1**) containing a 4,5-disubstituted oxazolidin-2-one ring is a novel cytokine modulator that was isolated from *Streptomyces* sp., and was found to interfere with the productions of IL4, IL10, and IgG via the selective inhibition of the signaling pathway in Th2 cells. The absolute configuration of **1** was determined to be (4*R*,5*R*)-5-hydroxymethyl-4-*p*-methoxyphenyl-1,3-oxazolidin-2-one based on NMR, CD, and X-ray data,[1] and was unambiguously confirmed by the first total asymmetric synthesis reported by Nakata et al. (Fig. 1).[2a]

Due to its potent bioactivity, several methods of synthesizing (–)-cytoxazone and (–)-4-*epi*-cytoxazone have been reported. These include Sharpless asymmetric dihydroxylation and the introduction of amine,[2] Sharpless asymmetric aminohydroxylation,[3] asymmetric epoxidation and the regioselective introduction of azide,[4] the use of Petasis reaction,[5] asymmetric aldol reaction,[6] imino-1,2-Wittig rearrangement,[7] the addition of Grignard reagents to protected imines,[8] and the conjugated addition of chiral lithium amide.[9] Moreover, very recently, we reported a stereoselective synthesis of **1** via the regioselective and diastereoselective introduction of an *N*-protected amine group using chlorosulfonyl isocyanate (CSI) and subsequent regioselective cyclization to give the oxazolidin-2-one unit.[10] In this paper, we describe a concise synthesis of (–)-cytoxazone (**1**) and its stereoisomer (–)-4-*epi*-cytoxazone (**2**), based on the regioselective and diastereoselective reaction using CSI.[11]

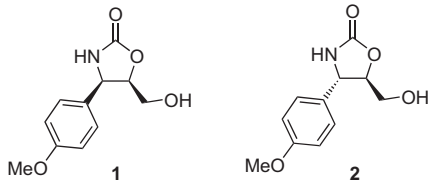

Figure 1. Structure of (−)-cytoxazone **1** and (−)-4-*epi*-cytoxazone **2**.

2. Results and discussion

Retrosynthetic analyses of **1** and **2** are shown in Scheme 1. Key steps for the synthesis of **1** and **2** are the regioselective and diastereoselective introduction of an *N*-protected amine group into *anti*-1,2-dimethyl ether **4** and *syn*-1,2-dimethyl ether **5** to give the protected *anti*-1,2-amino alcohol **3a** and *syn*-1,2-amino alcohol **3b**, respectively, using CSI and regioselective intramolecular cyclization. Compounds **4** and **5** can be easily prepared from commercially available *p*-anisaldehyde by using the chiral borane reagents.[12,13]

We first investigated the regioselectivity and diastereoselectivity of the reaction between CSI and *anti*- and *syn*-1,2-dimethyl ethers **4** and **5** prior to addressing the total synthesis of **1** and **2** (Scheme 2).

In initial studies, we examined the diastereoselectivity of the reaction of *anti*-1,2-dimethyl ether **4** with CSI. Treatment of **4** with CSI afforded *anti*-1,2-amino alcohol **3a** as the major product. The ratio of *anti*-1,2-amino alcohol **3a**

Keywords: Chlorosulfonyl isocyanate; Cytoxazone; 4-*epi*-Cytoxazone; Amination.
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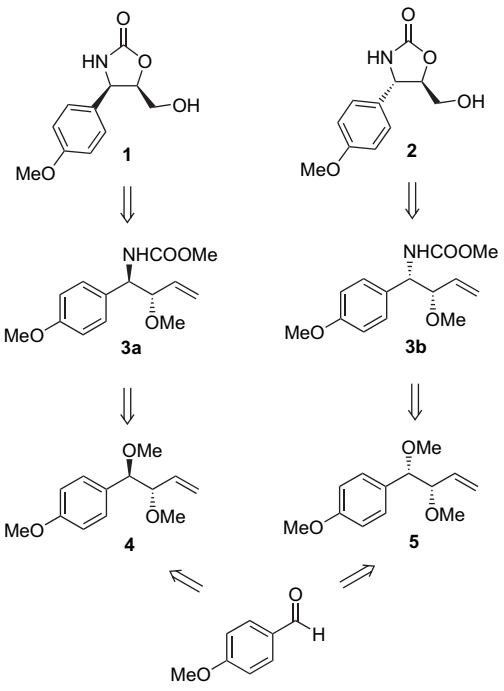
doi:10.1016/j.tet.2006.07.073



Scheme 1. Retrosynthetic analyses of **1** and **2**.

to *syn*-1,2-amino alcohol **3b** depended on solvent and temperature, as shown in Table 1.

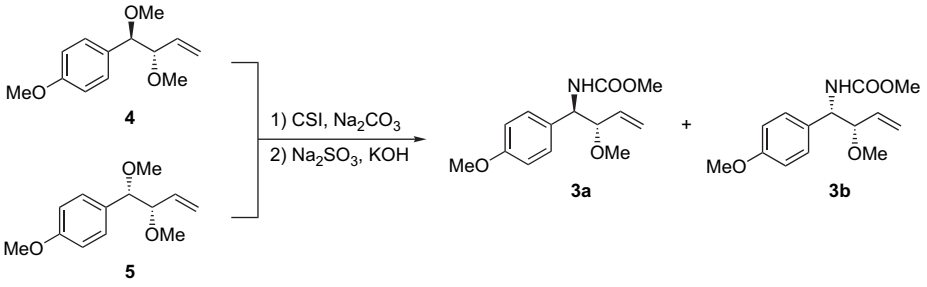
The reaction in methylene chloride at 0 °C gave a 5.7:1 inseparable mixture of diastereoisomers in 94% yield, and at −78 °C furnished a 7.0:1 ratio (entries 1 and 2). In particular, in toluene at −78 °C (entry 6), the highest diastereoselectivity of 27:1 was obtained in 95% yield. Table 1 shows that *anti*-stereoisomer of the 1,2-amino alcohol tends to be formed as the solvent polarity is reduced.

We also examined the reaction of *syn*-1,2-dimethyl ether **5** with CSI in various solvents and at different temperatures. The results are summarized in Table 2. In the case of **5**, *syn*-1,2-amino alcohol **3b** was obtained as the major product.

Although the ratio of stereoisomers was reduced versus *anti*-1,2-dimethyl ether case, reaction in hexane afforded a high diastereoselectivity of 1:9.3 in 91% yield.

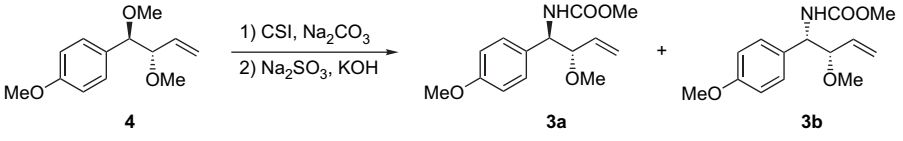
By reacting *anti*- and *syn*-1,2-dimethyl ethers with CSI, it was found that the stereochemistry of the major product was the same as that of the starting material, even though the reaction between CSI and *p*-methoxybenzylic methyl ether progresses via a carbocation intermediate and a S_N1 mechanism.

The results of these reactions can be explained as follows: First, regioselective substitution at the *p*-methoxybenzylic position is expected. This is because regioselectivity was controlled by the stability of the carbocation intermediate, i.e., the *p*-methoxybenzylic carbocation is more stable than the allyl carbocation.[14] Second, the formation of *anti*-1,2-amino alcohol **3a** from *anti*-1,2-dimethyl ether **4** can be explained by the Cieplak electronic model[11c,15] via a S_N1 mechanism. In this model, the vinyl group takes up an *anti* position to nucleophile attack (Fig. 2).



Scheme 2. CSI reactions of *anti*- and *syn*-1,2-dimethyl ethers **4** and **5** with CSI.

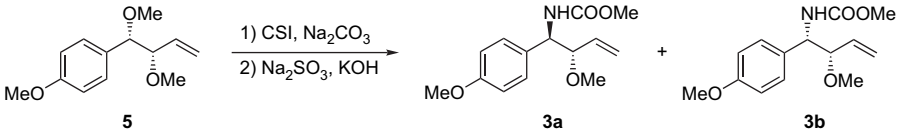
Table 1. Reactions of *anti*-1,2-dimethyl ether **4** with CSI in various solvents and at different temperatures



	Solvent	Temperature (°C)	Yield (%)[a]	Ratio (**3a**:**3b**)[b]
1	CH_2Cl_2	0	94	5.7:1
2		−78	92	7.0:1
3	$CHCl_3$	0	89	7.6:1
4	Et_2O	0	96	12:1
5	Toluene	0	94	16:1
6		−78	95	27:1
7	CCl_4	0	91	18:1
8	Hexane	0	67	13:1
9		−78	91	15:1

[a] Isolated yield of pure material.
[b] Isomer ratio determined by ^1H NMR.

Table 2. Reactions of *syn*-1,2-dimethyl ether **5** with CSI in various solvents and at different temperatures



5 **3a** **3b**

	Solvent	Temperature (°C)	Yield (%)[a]	Ratio (**3a**:**3b**)[b]
1	CH_2Cl_2	0	91	1.1:1
2		−78	92	1:1.1
3	$CHCl_3$	0	89	1:1.2
4	Et_2O	0	74	1:1.3
5	Toluene	0	84	1:1.4
6		−78	94	1:2.6
7	CCl_4	0	59	1:1.5
8	Hexane	0	81	1:4.8
9		−78	91	1:9.3

[a] Isolated yield of pure material.
[b] Isomer ratio determined by ^{1}H NMR.

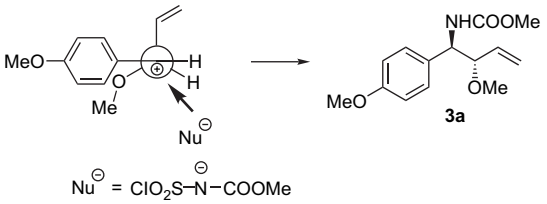


Figure 2. Cieplak electronic model of nucleophilic attack on the *p*-methoxybenzylic carbocation.

However, this mechanism cannot explain the formation of *syn*-stereoisomer as a major product in the case of *syn*-1,2-dimethyl ether.

Therefore, another mechanism for diastereoselectivity should be suggested. One plausible mechanism is offered by the neighboring group effect, as shown in Figure 3. This neighboring group (OMe) can use its electron pair to interact with the backside of the carbon atom undergoing substitution, and then nucleophile attack can only take place from the front side—thus leading to retention of configuration.[16]

Initial attack by the oxygen of *p*-methoxybenzylic methyl ether on CSI yields a *p*-methoxybenzylic carbocation. This attack is following an internal attack by the vicinal OMe to yield the oxiranium with an inversion of configuration at the *p*-methoxybenzylic carbon. This *p*-methoxybenzylic carbon atom, in turn, undergoes an ordinary S_N2 attack by $ClSO_2$–N^-–CO_2Me, with a second inversion of configuration. In this case, the configuration of the product is the same as that of the starting material. In case of *syn*-1,2-dimethyl ether **5**, the formation of *syn*-stereoisomer **3b** was slightly reduced due to the increasing steric repulsion

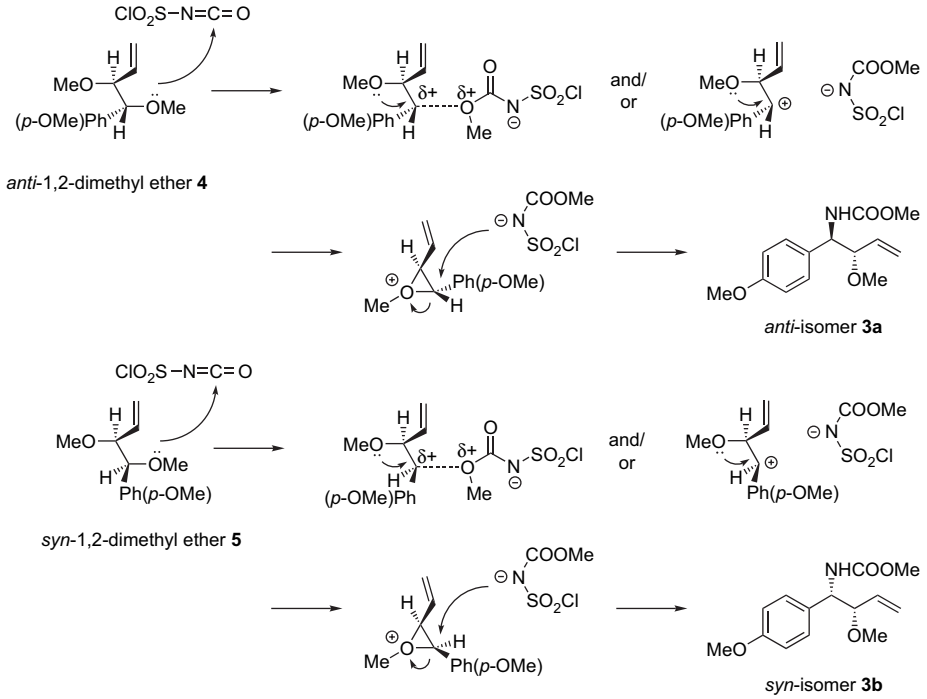
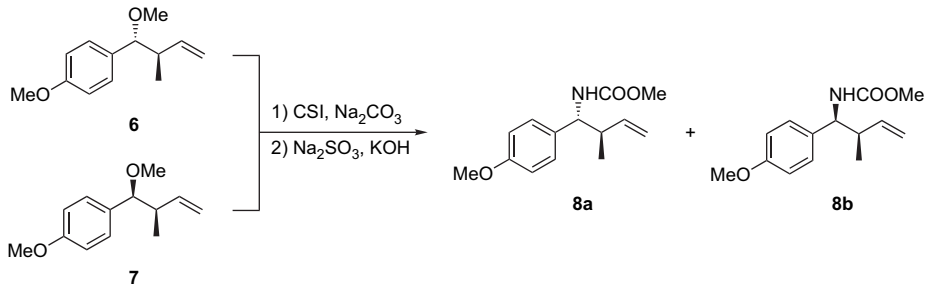


Figure 3. Neighboring group effect of nucleophilic attack on the *p*-methoxybenzylic carbocation.



Scheme 3. CSI reactions of β-methyl homoallyl ethers **6** and **7** with CSI.

between the *p*-methoxyphenyl ring and the vinyl group oriented in the cis form.

As the polarity of the solvent decreased, the attack of the vicinal OMe (the neighboring group effect) become more rapid than nucleophile attack and the diastereoselectivity of 1,2-amino alcohol increased, and therefore, this reaction is more efficient in nonpolar solvents.

A methyl moiety instead of a methoxy group was introduced at the allylic position in order to confirm the neighboring group effect (Scheme 3).

The treatment of *threo*-ether **6** with CSI in methylene chloride furnished an 1:1.8 mixture of *threo*-stereoisomer **8a** and *erythro*-carbamate **8b** in 91% yield (entry 1). Other results are summarized in Table 3.

The reaction between CSI and compound **6** in toluene and hexane afforded a ratio similar to that obtained in methylene chloride (entries 2 and 3). In addition, in the case of the *erythro*-ether **7**, the ratio of diastereoisomers was similar to that obtained for the reaction between CSI and compound **6**.

The results shown in Table 3 reveal that the reaction between the β-methyl homoallyl ether and CSI is not affected by solvent and progresses through a free carbocation intermediate. Therefore, it is clear that the diastereoselectivity of the reaction between CSI and 1,2-dimethyl ethers **4** and **5** can be explained by the neighboring group effect and a partial S_N1 mechanism.

On the basis of the above results, the total synthesis of (–)-cytoxazone (**1**) was achieved from *p*-anisaldehyde as a starting material (Scheme 4).

p-Anisaldehyde was reacted with *B*-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocamphenylborane[12] (**9**), derived from (–)-*B*-methoxydiisopinocamphenyl borane and allyl(diisopropylamino)dimethylsilane, *n*-butyllithium, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in ether at 0 °C, to provide, upon workup with hydrogen peroxide under basic conditions, an optically pure (1*R*,2*S*)-*anti*-diol **10** with high enantioselectivity (95% ee via the Mosher ester) and diastereoselectivity (>99% ds) in 52% yield after recrystallization (toluene). Dimethylation of compound **10** with sodium hydride and iodomethane in tetrahydrofuran furnished the *anti*-1,2-dimethyl ether **4** in 96% yield. The key reaction is the regioselective and diastereoselective introduction of an *N*-protected amine group to compound **4** using CSI. The treatment of compound **4** with CSI in the presence of sodium carbonate in anhydrous toluene at −78 °C, followed by reduction of an *N*-chlorosulfonyl group with an aqueous solution of 25% sodium sulfite furnished the desired *anti*-1,2-amino alcohol **3a** with a high diastereoselectivity of 27:1 in 95% yield. The conversion of compound **3a** into the terminal primary alcohol **11** was achieved in 94% yield by ozonolysis of the double bond followed by sodium borohydride reduction.[17] The regioselective deprotection of the methyl ether of compound **11** with boron tribromide[18] in methylene chloride at 0 °C gave the desired diol **12** in 80% yield without affecting the *p*-methoxy group of the phenyl ring. Finally, the regioselective intramolecular cyclization of compound **12** using sodium hydride[7] in tetrahydrofuran at 0 °C, led to formation of (–)-cytoxazone (**1**) in 95% yield. Spectroscopic data and specific rotation data of **1** were in full agreement with values reported in the literature.[2a]

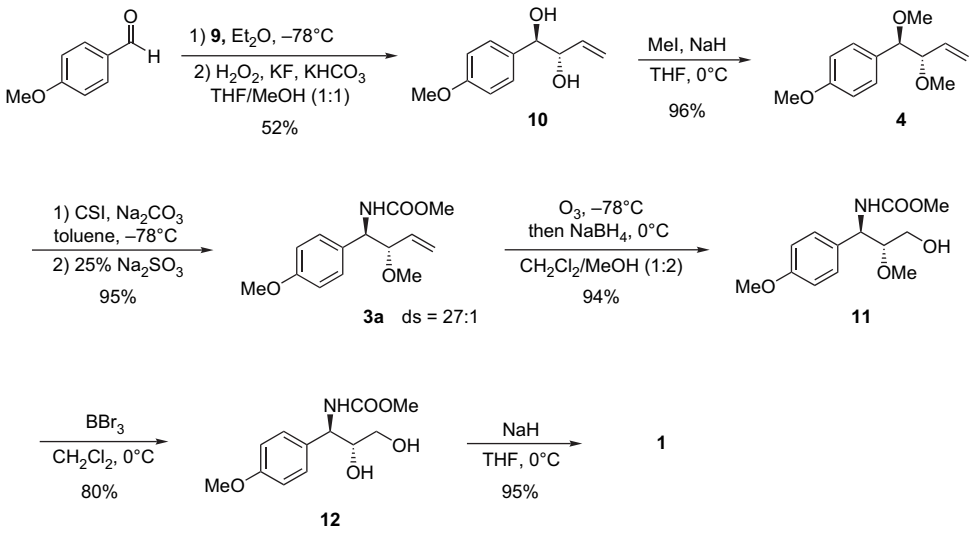
The total synthesis of (–)-4-*epi*-cytoxazone (**2**) was accomplished from *p*-anisaldehyde by using a sequence similar to that described for the synthesis of (–)-cytoxazone (Scheme 5).

Treatment of *p*-anisaldehyde with allylmethyl ether, (+)-*B*-methoxydiisopinocamphenyl borane,[13] and *sec*-BuLi in THF at −78 °C gave alcohol **13** with moderate enantioselectivity (80% ee via the Mosher ester) and high diastereoselectivity (>99% ds) in 63% yield. Alcohol **13** was then methylated with iodomethane in the presence of sodium hydride to afford *syn*-1,2-dimethyl ether **5** in 78% yield, and treatment of compound **5** with CSI in the presence of sodium carbonate in anhydrous hexane at −78 °C, followed by reduction of an *N*-chlorosulfonyl group with an aqueous solution of 25% sodium sulfite furnished the desired *syn*-1,2-amino alcohol **3b** in high diastereoselectivity of 1:9.3 in 91% yield. Ozonolysis of the double bond of **3b** followed by direct reduction of the resulting ozonide then gave the

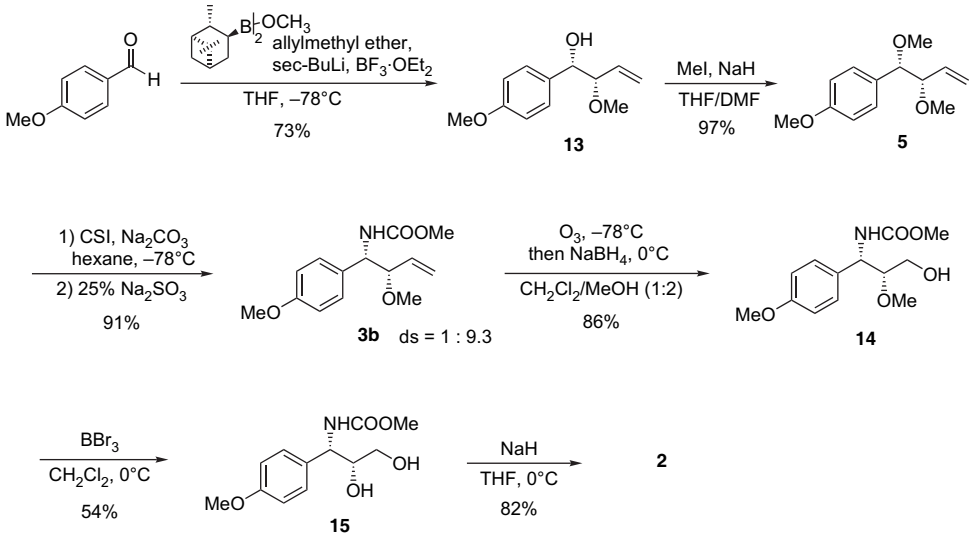
Table 3. Reactions of the β-methyl homoallyl ethers **6** and **7** with CSI in various solvents

	Ether	Solvent	Yield (%)[a]	Ratio (**8a**:**8b**)[b]
1	**6**	CH_2Cl_2	91	1:1.8
2		Toluene	83	1:1.7
3		Hexane	81	1:1.6
4	**7**	CH_2Cl_2	83	1:1.2
5		Toluene	88	1:1.7
6		Hexane	75	1:1.8

[a] Isolated yield of pure material.
[b] Isomer ratio determined from the ^{1}H NMR.



Scheme 4. Total synthesis of (−)-cytoxazone (**1**).



Scheme 5. Total synthesis of (−)-4-*epi*-cytoxazone (**2**).

primary alcohol **14** in 86% yield. The regioselective deprotection of the methyl ether of compound **14** with boron tribromide gave the desired diol **15** in 54% yield. Finally, the regioselective intramolecular cyclization of compound **15** afforded the (–)-4-*epi*-cytoxazone (**2**) as a crystalline form, mp 110–112 °C (EtOAc) [lit.[7b] 121–123 °C], which also had spectral properties (^{1}H and ^{13}C NMR) that were in full agreement with values reported in the literature.[7b]

3. Conclusion

In conclusion, we accomplished the total synthesis of (–)-cytoxazone (**1**) and its stereoisomer (–)-4-*epi*-cytoxazone (**2**), in six linear steps, starting from readily available *p*-anisaldehyde via the regioselective and diastereoselective introduction of an *N*-protected amine group using the reaction of *anti*- and *syn*-1,2-dimethyl ethers with CSI, and subsequently used regioselective cyclization to construct the oxazolidin-2-one ring. In addition, the optimum reaction conditions for the diastereoselective reaction of *anti*- and *syn*-1,2-dimethyl ethers with CSI were identified. Moreover, the retention of configuration is explained by the neighboring group effect and a partial S_N1 mechanism, and the described synthetic protocol using CSI can be applied to the formation of various natural products containing more complex amines.

4. Experimental

4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus or Electrothermal IA9300 melting point apparatus and

were not corrected. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a Varian Unity Inova 500 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer or Bruker Vector 22 Infrared spectrophotometer and are reported as cm^{-1}. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505 or JMS-600 spectrometer using the chemical ionization (CI) method.

4.1.1. (1*R*,2*S*)-1-*p*-Methoxyphenylbut-3-ene-1,2-diol (10). To a stirred solution of allyl(diisopropylamino)dimethylsilane (5.10 mL, 20.86 mmol) in anhydrous Et_2O (25 mL) were added TMEDA (3.15 mL, 20.86 mmol) and *n*-BuLi (13.04 mL, 20.86 mmol, 1.6 M in hexane) at 0 °C under N_2. The solution was kept at 0 °C for 4 h and cooled to −78 °C. The reaction mixture was treated with (–)-*B*-methoxydiisopinocamphenyl borane (7.85 g, 24.83 mmol) in anhydrous Et_2O (5 mL) and stirred at −78 °C for 2 h. To this solution were added boron trifluoride etherate (3.43 mL, 27.03 mmol) and a solution of *p*-anisaldehyde (2.00 g, 14.69 mmol) in anhydrous Et_2O (5 mL). The reaction mixture was kept at −78 °C for 3 h. To this mixture were added THF (20 mL), MeOH (20 mL), KF (2.43 g, 41.87 mmol), $KHCO_3$ (4.19 g, 41.87 mmol), and 30% H_2O_2 (45 mL). The reaction mixture was stirred at room temperature for 20 h and cooled to 0 °C, and the excess H_2O_2 was quenched by the addition of $Na_2S_2O_3$. The mixture was diluted with EtOAc (100 mL) and filtered through Celite pad. The Celite pad was washed with EtOAc and the filtrate was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) and recrystallization (toluene) to give 1.48 g (52%) of diol **10** as a colorless crystal; R_f 0.25 (hexane/EtOAc 1:1); mp 87–89 °C; $[\alpha]_D^{29}$ −73.2 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3408, 2954, 2837, 1612, 1514, 1463, 1303, 1248, 1176, 1116, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93–1.99 (br, 1H), 2.30–2.37 (br, 1H), 3.81 (s, 3H), 4.25–4.33 (br, 1H), 4.66–4.70 (br, 1H), 5.24 (dd, 1H, *J*=10.5, 1.5 Hz), 5.31 (dd, 1H, *J*=17.0, 1.5 Hz), 5.83 (ddd, 1H, *J*=17.0, 10.5, 6.5 Hz), 6.89 (dd, 2H, *J*=7.0, 2.0 Hz), 7.29 (dd, 2H, *J*=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.52, 76.44, 77.53, 114.03, 118.07, 128.19, 132.12, 136.36, 159.59; Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.22; H, 7.29.

4.1.2. (1*R*,2*S*)-1,2-Dimethoxy-1-*p*-methoxyphenylbut-3-ene (4). To a stirred solution of diol **10** (1.20 g, 6.18 mmol) in anhydrous THF (25 mL) were added NaH (0.54 g, 13.59 mmol, 60% in mineral oil) and MeI (1.15 mL, 18.53 mmol) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 3 h, H_2O (30 mL) was added and the solution was extracted with EtOAc (50 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 10:1) to afford 1.32 g (96%) of *anti*-1,2-dimethyl ether **4** as a colorless oil; R_f 0.40 (hexane/EtOAc 6:1); $[\alpha]_D^{29}$ −44.6 (*c* 0.1, $CDCl_3$); IR (neat) 2934, 2822, 1612, 1512, 1464, 1302, 1248, 1174, 1093, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.24 (s, 3H), 3.65 (dd, 1H, *J*=8.0, 5.0 Hz), 3.81 (s, 3H), 4.80 (d, 1H, *J*=5.0 Hz), 5.15 (dd, 1H, *J*=17.5, 1.5 Hz), 5.27 (dd, 1H, *J*=10.0, 1.5 Hz), 5.74 (ddd, 1H, *J*=17.5, 10.0, 8.0 Hz), 6.88 (dd, 2H, *J*=6.5, 2.0 Hz), 7.23 (dd, 2H, *J*=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.19, 56.80, 56.95, 85.51, 86.33, 113.41, 119.17, 128.99, 130.58, 134.69, 159.14; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.04.

4.1.3. (1*R*,2*R*)-2-Methoxy-1-*p*-methoxyphenylbut-3-en-1-ol (13). To a stirred solution of allylmethyl ether (2.0 g, 27.50 mmol) in anhydrous THF (15 mL) was added *sec*-BuLi (19.7 mL, 27.54 mmol, 1.4 M in cyclohexane) at −78 °C under N_2. The reaction mixture was treated with (+)-*B*-methoxydiisopinocamphenylborane (6.97 g, 22.04 mmol) in anhydrous THF (19 mL) and stirred at −78 °C for 1 h. To this solution were added boron trifluoride etherate (3.71 mL, 29.31 mmol) and a solution of *p*-anisaldehyde (3.0 g, 22.04 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred at −78 °C for 3 h and then slowly warmed to room temperature. The reaction mixture was concentrated in vacuo. The residue was washed with pentane and the pentane layer decanted. The combined pentane layers were cooled at 0 °C and treated with ethanolamine (2.7 mL). After the reaction mixture was stirred at 0 °C for 2 h, the white turbid solution was filtered through Celite pad and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford 3.35 g (73%) of **13** as a colorless oil; R_f 0.26 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$ +15.8 (*c* 0.5, $CDCl_3$); IR (neat) 3468, 2936, 2834, 1614, 1512, 1464, 1303, 1249, 1175, 1097, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (d, 1H, *J*=1.5 Hz), 3.38 (s, 3H), 3.60 (dd, 1H, *J*=8.0, 7.5 Hz), 3.80 (s, 3H), 4.44 (dd, 1H, *J*=8.0, 3.5 Hz), 5.07 (dd, 1H, *J*=17.5, 1.5 Hz), 5.17 (dd, 1H, *J*=17.5, 1.5 Hz), 5.51 (ddd, 1H, *J*=17.5, 10.5, 7.5 Hz), 6.85 (dd, 2H, *J*=7.0, 2.5 Hz), 7.25 (dd, 2H, *J*=7.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.21, 56.76, 76.32, 87.60, 113.52, 119.63, 128.55, 131.77, 134.03, 159.28; HRMS (CI) calcd for $C_{12}H_{16}O_3$ [M+H$^+$] 209.1178, found 209.1172.

4.1.4. (1*R*,2*R*)-1,2-Dimethoxy-1-*p*-methoxyphenylbut-3-ene (5). To a stirred solution of **13** (3.67 g, 17.62 mmol) in anhydrous THF (36 mL) and DMF (36 mL) were added NaH (0.85 g, 21.15 mmol, 60% in mineral oil) and MeI (1.65 mL, 26.44 mmol) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 1 h and quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (50 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 6:1) to afford 3.81 g (97%) of *syn*-1,2-dimethyl ether **5** as a colorless oil; R_f 0.28 (hexane/EtOAc 6:1); $[\alpha]_D^{29}$ +66.8 (*c* 0.1, $CDCl_3$); IR (neat) 2934, 2822, 1612, 1586, 1512, 1464, 1303, 1247, 1174, 1094, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.33 (s, 3H), 3.74 (dd, 1H, *J*=7.5, 6.5 Hz), 3.81 (s, 3H), 4.10 (d, 1H, *J*=6.5 Hz), 5.08 (dd, 1H, *J*=17.5, 1.5 Hz),

5.12 (dd, 1H, J=10.0, 1.5 Hz), 5.49 (ddd, 1H, J=17.5, 10.0, 7.5 Hz), 6.87 (dd, 2H, J=6.5, 2.0 Hz), 7.20 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.19, 56.88, 56.98, 85.76, 86.12, 113.51, 118.72, 129.08, 130.49, 134.84, 159.27; HRMS (CI) calcd for $C_{13}H_{18}O_3$ [M+H$^+$] 223.1334, found 223.1326.

4.1.5. (1*R*,2*R*)-1-Methoxy-1-*p*-methoxyphenyl-2-methylbut-3-ene (6). To a suspension of potassium *tert*-butoxide (0.58 g, 5.14 mmol) in anhydrous THF (5 mL) were added excess of *trans*-2-butene[19] and *n*-BuLi (3.21 mL, 5.14 mmol, 1.6 M in hexane) at −78 °C under N_2. The reaction mixture was stirred at −45 °C for 10 min and recooled to −78 °C. To this mixture was added (+)-*B*-methoxydiisopinocamphenyl borane (1.95 g, 6.17 mmol) in anhydrous Et_2O (3 mL) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. To this mixture were added boron trifluoride etherate (0.87 mL, 6.89 mmol) and a solution of *p*-anisaldehyde (0.70 g, 5.14 mmol) in anhydrous Et_2O (3 mL). The reaction mixture was stirred at −78 °C for 3 h, and then treated with 3 N NaOH (3.76 mL) and 30% H_2O_2 (1.54 mL), and the mixture was refluxed for 1 h. The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 6:1) to give 0.64 g (65%) of (1*R*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol as a colorless oil; R_f 0.40 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$ +43.2 (*c* 0.2, $CDCl_3$); IR (neat) 3432, 2962, 2836, 1612, 1513, 1461, 1303, 1248, 1175, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, 3H, J=6.5 Hz), 2.06–2.11 (br d, 1H, J=2.5 Hz), 2.47 (ddq, 1H, J=8.0, 8.0, 6.5 Hz), 3.82 (s, 3H), 4.33 (dd, 1H, J=8.0, 2.5 Hz), 5.19 (dd, 1H, J=11.0, 1.5 Hz), 5.23 (dd, 1H, J=17.0, 1.5 Hz), 5.84 (ddd, 1H, J=17.0, 11.0, 8.0 Hz), 6.91 (dd, 2H, J=7.0, 2.0 Hz), 7.26 (dd, 2H, J=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.82, 46.63, 55.49, 77.75, 113.91, 116.89, 128.22, 134.86, 141.19, 159.39; HRMS (CI) calcd for $C_{12}H_{16}O_2$ [M+H$^+$] 193.1228, found 193.1226. To a stirred solution of (1*R*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol (0.50 g, 2.60 mmol) in THF (10 mL) were added NaH (0.11 g, 2.86 mmol, 60% in mineral oil) and MeI (0.24 mL, 3.90 mmol) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 3 h and quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (20 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The reaction mixture was purified by column chromatography (hexane/EtOAc 30:1) to give 0.51 g (95%) of the homoallyl ether **6** as a colorless oil; R_f 0.40 (hexane/EtOAc 15:1); $[\alpha]_D^{29}$ +82.8 (*c* 0.2, $CDCl_3$); IR (neat) 2976, 2932, 2835, 1612, 1512, 1463, 1302, 1249, 1173, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, 3H, J=7.0 Hz), 2.52 (ddq, 1H, J=8.0, 7.0, 7.0 Hz), 3.19 (s, 3H), 3.84 (s, 3H), 3.88 (d, 1H, J=8.0 Hz), 5.04 (dd, 1H, J=10.5, 1.5 Hz), 5.06 (dd, 1H, J=16.5, 1.5 Hz), 5.91 (ddd, 1H, J=16.5, 10.5, 7.0 Hz), 6.90 (dd, 2H, J=6.5, 2.0 Hz), 7.19 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.63, 44.58, 55.45, 56.96, 87.99, 113.73, 114.39, 128.85, 132.73, 141.71, 159.29; HRMS (CI) calcd for $C_{13}H_{18}O_2$ [M+H$^+$] 207.1385, found 207.1387.

4.1.6. (1*S*,2*R*)-1-Methoxy-1-*p*-methoxyphenyl-2-methylbut-3-ene (7). The similar procedure for **6** was followed using *p*-anisaldehyde (0.70 g, 5.14 mmol), excess of *cis*-2-butene,[19] *n*-BuLi (3.21 mL, 5.14 mmol, 1.6 M in hexane), KO^{t}Bu (0.58 g, 5.14 mmol), (−)-*B*-methoxydiisopinocamphenyl borane (1.95 g, 6.17 mmol), and boron trifluoride etherate (0.87 mL, 6.89 mmol), and then treated with 3 N NaOH (3.76 mL) and 30% H_2O_2 (1.54 mL), and the mixture was refluxed for 2 h. The reaction mixture was purified by column chromatography (hexane/EtOAc 6:1) to give 0.66 g (67%) of (1*S*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol as a colorless oil; R_f 0.40 (hexane/EtOAc 3:1); IR (neat) 3419, 2963, 2836, 1612, 1513, 1460, 1303, 1248, 1175, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, 3H, J=6.5 Hz), 1.83–1.90 (br, 1H), 2.56 (ddq, 1H, J=7.0, 6.5, 5.5 Hz), 3.81 (s, 3H), 4.54 (d, 1H, J=5.5 Hz), 5.03 (dd, 1H, J=16.0, 1.5 Hz), 5.05 (dd, 1H, J=10.5, 1.5 Hz), 5.72 (ddd, 1H, J=16.0, 10.5, 7.0 Hz), 6.87 (dd, 2H, J=6.5, 2.0 Hz), 7.22 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.64, 44.95, 55.53, 77.81, 113.72, 115.75, 127.97, 135.01, 140.59, 159.13; HRMS (CI) calcd for $C_{12}H_{16}O_2$ [M+H$^+$] 193.1228, found 193.1225. To a stirred solution of (1*S*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol (0.50 g, 2.60 mmol) in THF (10 mL) were added NaH (0.11 g, 2.86 mmol, 60% in mineral oil) and MeI (0.24 mL, 3.90 mmol) at 0 °C under N_2. The reaction mixture was purified by column chromatography (hexane/EtOAc 30:1) to give 0.52 g (97%) of **7** as a colorless oil; R_f 0.40 (hexane/EtOAc 15:1); IR (neat) 2976, 2932, 2835, 1612, 1512, 1463, 1302, 1249, 1173, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, 3H, J=6.5 Hz), 2.51 (ddq, 1H, J=7.0, 7.0, 6.5 Hz), 3.21 (s, 3H), 3.83 (s, 3H), 3.90 (d, 1H, J=7.0 Hz), 4.90 (dd, 1H, J=16.0, 1.5 Hz), 4.92 (dd, 1H, J=10.5, 1.5 Hz), 5.65 (ddd, 1H, J=16.0, 10.5, 7.0 Hz), 6.88 (dd, 2H, J=6.5, 2.0 Hz), 7.15 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.87, 44.49, 55.43, 56.99, 87.68, 113.61, 114.61, 128.88, 134.79, 140.83, 159.18; HRMS (CI) calcd for $C_{13}H_{18}O_2$ [M+H$^+$] 207.1385, found 207.1381.

4.2. General procedure for the reaction of *p*-methoxybenzylic ethers with CSI

A stirred solution of Na_2CO_3 (6.75 mmol) in anhydrous solvent (12 mL) was adjusted to −78 °C, then CSI (4.50 mmol) and *p*-methoxybenzylic ether (3.00 mmol) were added under N_2. The reaction mixture was stirred at −78 °C, and quenched with H_2O (10 mL) when the reaction was completed (TLC monitoring), then extracted with EtOAc (10 mL×2). The organic layer was added to an aqueous solution of Na_2SO_3 (25%) and KOH (10%), and the reaction mixture was stirred at room temperature for overnight. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc).

4.2.1. (1*R*,2*S*)-Methyl *N*-(2-methoxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (3a). The above general procedure was followed using *anti*-1,2-dimethyl ether **4** (0.70 g, 3.15 mmol), Na_2CO_3 (1.10 g, 10.39 mmol), and CSI (0.60 mL, 6.93 mmol) in anhydrous toluene (13 mL) at −78 °C. The reaction mixture was purified by column chromatography (hexane/EtOAc 3:1) to give 0.79 g (95%, *anti*:*syn*=27:1) of *anti*-1,2-amino alcohol **3a** as a white solid; R_f 0.28 (hexane/EtOAc 3:1); mp 93–95 °C; $[\alpha]_D^{29}$

−66.0 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3330, 2938, 2836, 1710, 1612, 1514, 1464, 1296, 1246, 1181, 1101, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.66 (s, 3H), 3.81 (s, 3H), 3.86–3.93 (br, 1H), 4.72–4.80 (br, 1H), 5.26 (dd, 1H, *J*=11.0, 2.0 Hz), 5.29 (dd, 1H, *J*=17.5, 2.0 Hz), 5.35–5.42 (m, 1H), 5.50–5.60 (br, 1H), 6.86 (dd, 2H, *J*=8.0, 2.0 Hz), 7.23 (dd, 2H, *J*=8.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.37, 55.45, 57.08, 57.72, 85.08, 113.77, 119.71, 129.30, 131.17, 135.06, 156.52, 159.10; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.50; H, 7.25; N, 5.33.

4.2.2. (1*R*,2*R*)-Methyl *N*-(2-methoxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (3b). The above general procedure was followed using *syn*-1,2-dimethyl ether **5** (2.96 g, 13.32 mmol), Na_2CO_3 (6.35 g, 59.93 mmol), and CSI (3.48 mL, 39.95 mmol) in anhydrous hexane (67 mL) at −78 °C. The reaction mixture was purified by column chromatography (hexane/EtOAc 3:1) to afford 3.21 g (91%, *syn*:*anti*=9.3:1) of *syn*-1,2-amino alcohol **3b** as a white solid; R_f 0.28 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$ +55.4 (*c* 0.1, $CDCl_3$); IR (neat) 3340, 2938, 2852, 1725, 1612, 1514, 1463, 1295, 1246, 1179, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.24 (s, 3H), 3.65 (s, 3H), 3.75–3.82 (br, 1H), 3.81 (s, 3H), 4.65–4.72 (br, 1H), 5.28 (dd, 1H, *J*=17.0, 1.0 Hz), 5.30 (dd, 1H, *J*=10.5, 1.0 Hz), 5.50–5.58 (br, 1H), 5.78 (ddd, 1H, *J*=17.0, 10.5, 7.5 Hz), 6.87 (dd, 2H, *J*=7.5, 2.0 Hz), 7.26 (dd, 2H, *J*=7.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.46, 55.50, 57.11, 58.07, 85.24, 113.93, 119.36, 128.39, 133.05, 135.53, 156.96, 159.08; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.51; H, 7.25; N, 5.23.

4.2.3. (1*R*,2*R*)-Methyl *N*-(1-*p*-methoxyphenyl-2-methylbut-3-enyl)carbamate (8a) and (1*S*,2*R*)-methyl *N*-(1-*p*-methoxyphenyl-2-methylbut-3-enyl)carbamate (8b). The above general procedure was followed using **6** (50 mg, 0.24 mmol), Na_2CO_3 (58 mg, 0.55 mmol), and CSI (32 μL, 0.36 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The reaction mixture was purified by column chromatography (hexane/EtOAc 3:1) to give inseparable mixture (55 mg, 91%) of *anti*-homoallyl ether **8a** and *syn*-homoallyl ether **8b** (ratio=1:1.8) as a white solid; **8a**: R_f 0.31 (hexane/EtOAc 3:1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, 3H, *J*=7.0 Hz), 6.86 (dd, 2H, *J*=8.5, 2.5 Hz), 2.60 (ddq, 1H, *J*=8.0, 7.0, 7.0 Hz), 3.66 (s, 3H), 3.82 (s, 3H), 4.58–4.65 (br, 1H), 4.95–5.05 (br, 1H), 5.06 (dd, 1H, *J*=10.5, 1.5 Hz), 5.09 (dd, 1H, *J*=16.0, 1.5 Hz), 5.60 (ddd, 1H, *J*=16.0, 10.5, 8.0 Hz), 6.86 (dd, 2H, *J*=8.5, 2.5 Hz), 7.12 (dd, 2H, *J*=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.41, 43.42, 52.38, 55.50, 58.72, 113.85, 116.35, 128.53, 132.68, 139.96, 156.54, 159.01. Compound **8b**: IR (CH_2Cl_2) 3329, 2958, 2857, 1699, 1612, 1514, 1459, 1247, 1179, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, 3H, *J*=6.5 Hz), 2.53 (ddq, 1H, *J*=8.0, 7.0, 6.5 Hz), 3.64 (s, 3H), 3.81 (s, 3H), 4.42–4.53 (br, 1H), 4.95–5.05 (br, 1H), 5.08 (dd, 1H, *J*=10.5, 1.5 Hz), 5.11 (dd, 1H, *J*=16.5, 1.5 Hz), 5.74 (ddd, 1H, *J*=16.5, 10.5, 8.0 Hz), 6.87 (dd, 2H, *J*=8.5, 2.5 Hz), 7.17 (dd, 2H, *J*=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.79, 43.97, 52.36, 55.51, 59.01, 114.24, 116.47, 128.02, 133.76, 139.98, 156.64, 158.98; HRMS (CI) calcd for $C_{14}H_{19}NO_3$ [M+H$^+$] 250.1443, found 250.1451.

4.2.4. (2*R*,3*R*)-2-Methoxy-3-methoxycarbonylamino-3-*p*-methoxyphenylpropan-1-ol (11). Ozone was bubbled through a solution of *anti*-1,2-amino alcohol **3a** (0.70 g, 2.64 mmol) in anhydrous CH_2Cl_2 (10 mL) and MeOH (20 mL) at −78 °C until blue color persisted, the excess was then purged out with N_2 until decolorization, and $NaBH_4$ (1.00 g, 26.38 mmol) was added at −78 °C. The reaction mixture was slowly warmed to 0 °C, stirred at 0 °C for 1 h and concentrated in vacuo. The residue was dissolved in H_2O (30 mL) and EtOAc (50 mL), the organic layer was separated and washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:2) to give 0.67 g (94%) of alcohol **11** as a colorless syrup; R_f 0.21 (hexane/EtOAc 1:2); $[\alpha]_D^{29}$ −48.6 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3390, 2951, 2836, 1704, 1612, 1514, 1463, 1295, 1247, 1180, 1115, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.20–2.28 (br, 1H), 3.43 (ddd, 1H, *J*=7.5, 5.5, 3.5 Hz), 3.46 (s, 3H), 3.50–3.56 (br d, 1H, *J*=2.0 Hz), 3.68 (s, 3H), 3.64–3.75 (br, 1H), 3.82 (s, 3H), 4.97–5.03 (br, 1H), 5.82 (br d, 1H, *J*=8.5 Hz), 6.89 (dd, 2H, *J*=7.0, 2.0 Hz), 7.25 (dd, 2H, *J*=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.59, 55.24, 55.55, 58.21, 61.19, 82.84, 114.28, 128.42, 131.52, 157.15, 159.24; HRMS (CI) calcd for $C_{13}H_{19}NO_5$ [M+H$^+$] 270.1341, found 270.1341.

4.2.5. (2*R*,3*R*)-3-Methoxycarbonylamino-3-*p*-methoxyphenylpropane-1,2-diol (12). To a stirred solution of alcohol **11** (0.50 g, 1.86 mmol) in anhydrous CH_2Cl_2 (20 mL) was added BBr_3 (2.04 mL, 2.04 mmol, 1.0 M in CH_2Cl_2) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 30 min, quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.38 g (80%) of diol **12** as a white solid; R_f 0.31 ($CHCl_3$/MeOH 6:1); mp 81–84 °C; $[\alpha]_D^{29}$ −60.0 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3347, 2953, 2836, 1699, 1612, 1514, 1462, 1296, 1248, 1179, 1101, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.42–2.48 (br, 1H), 2.62–2.72 (br, 1H), 3.67 (s, 3H), 3.60–3.75 (br, 2H), 3.80 (s, 3H), 3.84–3.93 (br d, 1H, *J*=13.5 Hz), 4.72 (dd, 1H, *J*=8.0, 7.0 Hz), 5.40–5.46 (br, 1H), 6.90 (dd, 2H, *J*=9.5, 2.0 Hz), 7.25 (dd, 2H, *J*=9.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.73, 55.54, 57.04, 63.53, 74.04, 114.48, 128.75, 130.94, 157.48, 159.53; Anal. Calcd for $C_{12}H_{17}NO_4$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.34; H, 6.73; N, 5.39.

4.2.6. (4*R*,5*R*)-5-Hydroxymethyl-4-*p*-methoxyphenyl-1,3-oxazolidin-2-one [(−)-cytoxazone] (1). To a stirred solution of diol **12** (0.30 g, 1.18 mmol) in anhydrous THF (12 mL) was added NaH (52 mg, 1.29 mmol, 60% in mineral oil) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 2 h and quenched with H_2O (10 mL), then extracted with EtOAc (10 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.25 g (95%) of (−)-cytoxazone (**1**) as a white solid; R_f 0.37 ($CHCl_3$/MeOH 6:1); mp 118–120 °C; $[\alpha]_D^{24}$ −70.9 (*c* 0.1, MeOH); ^1H NMR (500 MHz, DMSO-d_6) δ 2.94–2.99 (m, 2H), 3.75

(s, 3H), 4.70 (ddd, 1H, J=8.5, 7.5, 4.5 Hz), 4.81 (t, 1H, J=5.0 Hz), 4.90 (d, 1H, J=8.5 Hz), 6.93 (dd, 2H, J=8.5, 3.0 Hz), 7.15 (dd, 2H, J=8.5, 3.0 Hz), 8.03–8.06 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.81, 56.92, 61.76, 80.77, 114.39, 128.74, 129.99, 159.47, 159.72; HRMS (CI) calcd for $C_{11}H_{14}NO_4$ [M+H$^+$] 224.0923, found 224.0925.

4.2.7. (2*S*,3*R*)-2-Methoxy-3-methoxycarbonylamino-3-*p*-methoxyphenylpropan-1-ol (14). Ozone was bubbled through a solution of *syn*-1,2-amino alcohol **3b** (2.15 g, 8.10 mmol) in anhydrous CH_2Cl_2 (20 mL) and MeOH (40 mL) at −78 °C until blue color persisted, the excess was then purged out with N_2 until decolorization, and $NaBH_4$ (0.77 g, 20.25 mmol) was added at −78 °C. The reaction mixture was slowly warmed to 0 °C, stirred at 0 °C for 2 h and concentrated in vacuo. The residue was dissolved in H_2O (40 mL) and EtOAc (70 mL), the organic layer was separated and washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:2) to give 1.88 g (86%) of alcohol **14** as a colorless syrup; R_f 0.30 (hexane/EtOAc 1:2); $[\alpha]_D^{29}$ +64.1 (c 0.1, $CDCl_3$); IR (neat) 3336, 2922, 2856, 2357, 1702, 1608, 1510, 1456, 1373, 1241, 1180, 1107, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05–2.07 (br, 1H), 3.29 (s, 3H), 3.50 (ddd, 1H, J=11.5, 7.0, 2.5 Hz), 3.60 (dd, 1H, J=11.5, 7.0 Hz), 3.60–3.71 (m, 4H), 3.81 (s, 3H), 4.88–4.91 (br, 1H), 5.50 (br d, 1H, J=8.0 Hz), 6.89 (dd, 2H, J=7.5, 2.0 Hz), 7.27 (dd, 2H, J=7.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.65, 54.39, 55.49, 59.47, 61.39, 84.34, 114.21, 128.03, 132.52, 157.55, 159.17; HRMS (CI) calcd for $C_{13}H_{20}NO_5$ [M+H$^+$] 270.1341, found 270.1342.

4.2.8. (2*S*,3*R*)-3-Methoxycarbonylamino-3-*p*-methoxyphenylpropane-1,2-diol (15). To a stirred solution of alcohol **14** (1.65 g, 6.13 mmol) in anhydrous CH_2Cl_2 (61 mL) was added BBr_3 (7.4 mL, 7.36 mmol, 1.0 M in CH_2Cl_2) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 4 h, quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.74 g (54%) of diol **15** as a white solid; R_f 0.28 ($CHCl_3$/MeOH 10:1); mp 110–113 °C; $[\alpha]_D^{29}$ +16.3 (c 1.0, $CDCl_3$); IR (neat) 3352, 2956, 1690, 1615, 1543, 1517, 1464, 1345, 1300, 1251, 1180, 1095, 1032, 1008 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64–1.81 (br, 2H), 3.56 (dd, 1H, J=11.0, 6.0 Hz), 3.62 (dd, 1H, J=11.0, 4.5 Hz), 3.70 (s, 3H), 3.81 (s, 3H), 3.94–3.98 (br, 1H), 4.78–4.81 (br, 1H), 5.41–5.43 (br, 1H), 6.91 (d, 2H, J=7.5 Hz), 7.26 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.74, 55.54, 56.31, 64.02, 75.21, 114.50, 128.13, 131.86, 157.81, 159.45; HRMS (CI) calcd for $C_{12}H_{18}NO_5$ [M+H$^+$] 256.1185, found 256.1186.

4.2.9. (4*R*,5*S*)-5-Hydroxymethyl-4-*p*-methoxyphenyl-1,3-oxazolidin-2-one [(−)-4-*epi*-cytoxazone] (2). To a stirred solution of diol **15** (0.60 g, 2.66 mmol) in anhydrous THF (13 mL) was added NaH (0.13 g, 3.19 mmol, 60% in mineral oil) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 4 h and quenched with H_2O (12 mL), then extracted with EtOAc (18 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.43 g (82%) of (–)-4-*epi*-cytoxazone (**2**) as a white solid; R_f 0.27 (CH_2Cl_2/MeOH 15:1); mp 110–112 °C (EtOAc); $[\alpha]_D^{28}$ −22.8 (c 0.5, MeOH); IR (neat) 3256, 2962, 1746, 1725, 1614, 1515, 1417, 1305, 1252, 1175, 1102, 1023 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 3.73 (ddd, 1H, J=12.0, 6.0, 4.0 Hz), 3.82 (s, 3H), 3.84 (ddd, 1H, J=12.0, 6.0, 4.0 Hz), 4.27 (dt, 1H, J=6.0, 4.0 Hz), 4.79 (d, 1H, J=6.5 Hz), 6.93 (br s, 1H), 6.98 (d, 1H, J=8.5 Hz), 7.35 (d, 1H, J=8.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 54.95, 57.04, 61.84, 84.92, 114.41, 127.75, 133.29, 158.26, 160.01; HRMS (CI) calcd for $C_{11}H_{14}NO_4$ [M+H$^+$] 224.0923, found 224.0923.

Acknowledgements

This work was supported by the Korea Research Foundation Grant (KRF-2003-015-E00232), and partially by the Brain Korea 21 Program.

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Tetrahedron 62 (2006) 9359–9364

PEG (300)–$PdCl_2$ promoted efficient and convenient Suzuki–Miyaura coupling of aryl chlorides with arylboronic acids

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Received 12 April 2006; revised 22 July 2006; accepted 25 July 2006

Abstract—PEG (300) was found as an effective medium for the $PdCl_2$-catalyzed Suzuki–Miyaura cross-coupling of aryl chlorides with various phenylboronic acids. This cross-coupling pathway conveniently and efficiently gave good to excellent yields of corresponding biaryl nucleus under mild conditions.

1. Introduction

The palladium-catalyzed Suzuki–Miyaura cross-coupling has become one of the most versatile and powerful reactions for the construction of carbon–carbon bonds, in particular for the formation of biaryls.[1,2] The traditional protocols for the Suzuki–Miyaura reaction prescribe a palladium species with phosphine ligands as the catalyst. However, many phosphines, which are necessary to stabilize the catalytically active Pd species, are toxic and/or expensive. Meanwhile, some phosphines are sensitive to air and moisture with conversion to, for example, phosphine oxide species. Consequently, the development of phosphine-free catalytic systems to overcome these difficulties is considered to be one of the most challenging fields in organic chemistry. Improved conditions have been developed for the Suzuki–Miyaura reaction, including the use of palladium nanoparticles,[3] water-soluble phosphines as ligands,[4] microwave technology,[5] nucleophilic carbene ligands,[6] ionic liquids,[7] and so on.[8] While aryl iodides and bromides are the more reactive substrates in the reaction, it is aryl chlorides which have an attraction to synthetic chemists due to the availability of a broad range of inexpensive materials in this class. As a result, significant research effort has been focused on the preparation and use of catalysts capable of activating aryl chloride substrates.[9] Complexes bearing bulky phosphines,[10] *N*-heterocyclic carbenes[11,12] or palladacyclic complexes[13] have recently been introduced as particularly active catalysts. Now, it is a new challenge to utilize phosphine-free catalytic systems to couple aryl chlorides with arylboronic acids.

PEGs have clear advantages as solvents for use in chemistry because they are inexpensive, readily available, easily degradable, and possess low toxicity.[14] Recently, the phosphine-free Suzuki reaction involving PEG (400) as the solvent was reported by Li and co-workers.[15] In the presence of $Pd(OAc)_2$ and DABCO, coupling of aryl iodides or aryl bromides with arylboronic acids was carried out to afford good to excellent yields on the condition of heating for 110 °C. At the same time, Zhang and co-workers developed an easier method of Suzuki reaction by using water combining with PEG (2000) as solvent and $Pd(OAc)_2$ as the catalyst.[16] The reaction can be conducted to give biaryl nucleus under heating conditions (50 °C) without the use of microwave or ligand in high yield. However, in the case of aryl chlorides, the above mentioned $Pd(OAc)_2$–DABCO–PEG (400) and $Pd(OAc)_2$–H_2O–PEG (2000) systems proved not to be effective. Here, we report that $PdCl_2$, in combination with PEG (300) as the solvent, is quite an efficient system for the coupling of aryl chlorides with arylboronic acids at room temperature.

2. Results and discussion

We initiated our study of the Suzuki–Miyaura cross-coupling reaction by optimizing the conditions in terms of Pd species, solvents, and bases. The Suzuki–Miyaura cross-coupling reaction was first evaluated with some Pd species in order to study their catalytic activity. We chose as a model reaction the coupling between *p*-nitrochlorobenzene and phenylboronic acid in PEG (300) at room temperature (Table 1). Both reactions catalyzed by $PdCl_2$ and $Pd(OAc)_2$ provided good yields in 1.5 h (Table 1, entries 1

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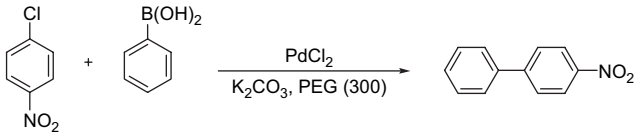
doi:10.1016/j.tet.2006.07.067

Table 1. Effect of Pd species on cross-coupling of *p*-nitrochlorobenzene with phenylboronic acid[a]



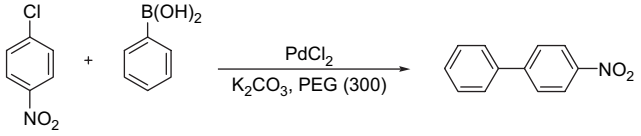
Entry	Pd species	Time (h)[b]	Yield (%)[c]
1	$PdCl_2$	1.5	92
2	$PdCl_2(PPh_3)_4$	6	85
3	$Pd(OAc)_2$	1.5	93
4	$Pd(PPh_3)_4$	12	Trace

[a] Reaction conditions: 1.0 mmol *p*-nitrochlorobenzene, 1.1 mmol phenylboronic acid, 2.5 mmol K_2CO_3, 5 mmol % Pd species, 4 mL PEG (300), at room temperature.
[b] The reaction was monitored by TLC.
[c] Isolated yield.

and 3). $PdCl_2(PPh_3)_4$ also presented good yield but needed longer time (Table 1, entry 2). However, $Pd(PPh_3)_4$ was not an effective catalyst for the Suzuki–Miyaura cross-coupling reaction in PEG (300). In view of the cheaper price of $PdCl_2$ than $Pd(OAc)_2$, we selected $PdCl_2$ as the catalyst for our research.

Our next investigation into an effective Suzuki reaction began with *p*-nitrochlorobenzene, phenylboronic acid, and an array of solvents combined with PEG (300). The results are summarized in Table 2. The choice of solvent has a significant impact on the efficiency of the cross-coupling: the reaction of *p*-nitrochlorobenzene with 1.1 equiv of phenylboronic acid in PEG/DMSO, PEG/H_2O at room temperature for 12 h scarcely afforded the corresponding biaryl. When PEG/CH_3OH, PEG/C_2H_5OH, PEG/*n*-C_3H_7OH, PEG/*i*-C_3H_7OH, PEG/toluene, PEG/CH_3CN or PEG/dioxane were used as solvents, the yields of *p*-nitro-biphenyl were also very low. In the case of employing DMF, the reaction was carried out smoothly to give a marked enhancement in yield in 12 h (entry 4, 75%). Evidently, the best solvent for the reaction was pure PEG (300), which produced 92% of *p*-nitro-biphenyl in only 1.5 h (entry 1).

Table 2. Effect of solvent on $PdCl_2$-catalyzed cross-coupling of *p*-nitrochlorobenzene with phenylboronic acid[a]

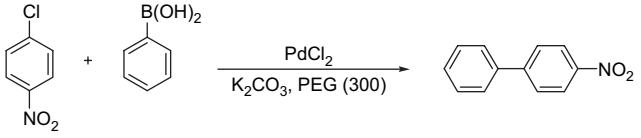


Entry	Solvent	Time (h)[b]	Yield (%)[c]
1	PEG	1.5	92
2	PEG/DMSO	12	Trace
3	PEG/toluene	12	25
4	PEG/DMF	12	75
5	PEG/CH_3CN	12	8
6	PEG/dioxane	12	36
7	PEG/H_2O	12	Trace
8	PEG/CH_3OH	12	6
9	PEG/C_2H_5OH	12	8
10	PEG/*n*-C_3H_7OH	12	15
11	PEG/*i*-C_3H_7OH	12	17

[a] Reaction conditions: 1.0 mmol *p*-nitrochlorobenzene, 1.1 mmol phenylboronic acid, 2.5 mmol K_2CO_3, 5 mmol % $PdCl_2$, 4 mL PEG (300), and 4 mL other solvents, at room temperature.
[b] The reaction was monitored by TLC.
[c] Isolated yield.

In our following experiments, when we used K_2CO_3 as base, the optimum yield was obtained by using 3.0 equiv with respect to the aryl halide (Table 3, entries 1–3). Use of less or more than the amount resulted in a lower yield. Employing 1.5 equiv of phenylboronic acid gave *p*-nitro-biphenyl in a better yield of 98% compared to the above 1.1 equiv amount (Table 3, entry 4). Using 1.5 equiv of phenylboronic acid, we screened a range of other bases. $KF\cdot 2H_2O$, KOAc, KOH, Na_2CO_3, NaOAc, NaOH, and *n*-Bu_4NOH were found to be effective in the reaction. $NaHCO_3$, Cs_2CO_3, and $K_3PO_4\cdot 3H_2O$ led to acceptable moderate yields of product, while $BaCO_3$ resulted in *p*-nitro-biphenyl in a lower yield. Ag_2CO_3 and Et_3N proved to be particularly inefficient bases, while MgF_2, AlF_3, DMAP were completely inactive. Finally, K_2CO_3, an effective base for the cyclopalladated-imine catalyst for the Suzuki–Miyaura reaction,[17] proved to be the most effective, leading to 98% isolated yield in 1.5 h.

Table 3. Effect of base on PEG (300)–$PdCl_2$-catalyzed cross-coupling of *p*-nitrochlorobenzene with phenylboronic acid[a]

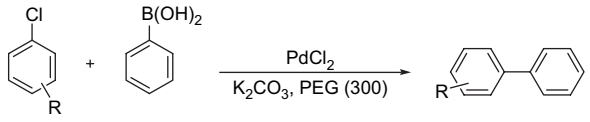


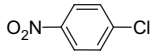
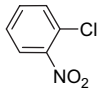
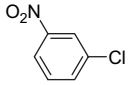
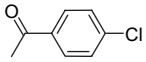
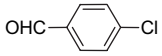
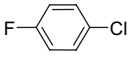
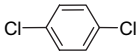
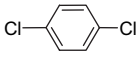
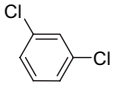
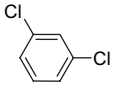
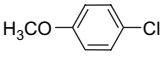
Entry	Base	Time (h)[b]	Yield (%)[c]
1[d,e]	K_2CO_3	2	87
2[d]	K_2CO_3	1.5	92
3[d,f]	K_2CO_3	1.5	90
4	K_2CO_3	1.5	98
5	$K_3PO_4\cdot 3H_2O$	12	72
6	$KF\cdot 2H_2O$	4	98
7	KOAc	8	92
8	KOH	1.5	90
9	Na_2CO_3	8	95
10	$NaHCO_3$	12	60
11	NaOAc	12	90
12	NaOH	8	98
13	Cs_2CO_3	12	50
14	Ag_2CO_3	12	Trace
15	$BaCO_3$	12	30
16	AlF_3	12	—
17	MgF_2	12	—
18[g]	*n*-Bu_4NOH	3	94
19	Et_3N	12	Trace
20	DMAP	12	—

[a] Reaction conditions: 1.0 mmol *p*-nitrochlorobenzene, 1.5 mmol phenylboronic acid, 3.0 mmol base, 5 mmol % $PdCl_2$, 4 mL PEG (400), at room temperature.
[b] The reaction was monitored by TLC.
[c] Isolated yield.
[d] Phenylboronic acid: 1.1 mmol.
[e] Base: 2.5 mmol.
[f] Base: 3.5 mmol.
[g] 25% in methanol.

As illustrated in Table 4, the PEG (300)–$PdCl_2$ system was applicable to a wide range of aryl chloride substrates to give the products with good to excellent yields. A wide array of functional groups such as aldehyde, nitro, ketone, and

Table 4. PEG (300)–$PdCl_2$-catalyzed cross-coupling of aryl chlorides with phenylboronic acid[a]



Entry	Aryl chloride	Time (h)[b]	Yield (%)[c]
1		1.5	98
2		8	93
3		8	52
4		4	96
5		4	96
6		5	84
7[d]		3	86
8[e,f]		12	50
9[d,g]		8	45
10[e,g]		12	82
11[d]		12	Trace
12		6	98
13		8	80

[a] Reaction conditions: 1.0 mmol aryl halide, 1.5 mmol phenylboronic acid, 3 mmol K_2CO_3, 5 mmol % $PdCl_2$, 4 mL PEG (300), at room temperature.
[b] The reaction was monitored by TLC.
[c] Isolated yield.
[d] Phenylboronic acid: 1.1 mmol.
[e] Phenylboronic acid: 3.0 mmol.
[f] Product: 50% *p*-terphenyl and 52% 4-chloro-biphenyl.
[g] Product: *m*-terphenyl.

methoxy were tolerated in the reaction and not affected by the system. For example, with *p*-chlorobenzaldehyde, a high yield of coupling product (96%) was obtained (entry 5). We found that electron-withdrawing chlorides such as *p*-nitrochlorobenzene (entry 1) and 1-(4-chloro-phenyl)-ethanone (entry 4) were more efficiently utilized as substrates, compared to chlorides with electron-donating groups such as *p*-methoxychlorobenzene (entry 13). Surprisingly, the reaction of *m*-nitrochlorobenzene with phenylboronic acid only gave a moderate yield of 52% after 8 h and 45% material was recovered. Furthermore, it was noteworthy that the treatment of *p*-dichlorobenzene with 1 equiv of phenylboronic acid produced 4-chloro-biphenyl in 86% yield after 3 h at room temperature. Utilization of 3 equiv of phenylboronic acid afforded 50% *p*-terphenyl and 52% 4-chloro-biphenyl (entries 7 and 8). However, both 1 and 3 equiv of phenylboronic acid generated *m*-terphenyl as the only main product (entries 9 and 10). It was quite surprising that treatment of *o*-dichlorobenzene with phenylboronic acid scarcely afforded any main product (entry 11).

The effect of varying the phenylboronic acids in the Suzuki–Miyaura cross-coupling reactions was also investigated using various aryl chlorides (Table 5). From Table 5, it is evident that the reaction of phenylboronic acid with electron-donating groups such as methoxy occurred faster than when electron-withdrawing groups such as fluoro were employed. For example, treatment of chlorobenzene with *p*-methoxyphenylboronic acid afforded the corresponding coupled product in shorter time and higher yield than coupling of chlorobenzene with *p*-fluorophenylboronic acid (entries 5 and 10). Compared to *p*-nitrochlorobenzene and *m*-nitrochlorobenzene, 2,4-dinitrochlorobenzene afforded the corresponding product in lesser time and with higher yield, which suggested that the electron-withdrawing effect of a nitro group had more influence on the chloride than the effect of static hindrance. Remarkably, phenylboronic acid containing electron-withdrawing groups or electron-donating groups could be coupled in good to excellent yields at room temperature. However, when *p*-methoxychlorobenzene was utilized, the reaction with *p*-fluorophenylboronic acid and 3,4,5-trifluorophenylboronic acid only gave moderate yields (65 and 60%, entries 12 and 16). Moreover, we were pleased to observe that 1-naphthylboronic acid could be coupled with *p*-nitrophenylboronic acid to afford 1-(4-nitro-phenyl)-naphthalene with 90% yield (entry 19), while when 1-(4-chloro-phenyl)-ethanone was employed, only 50% yield of the corresponding product was isolated (entry 20).

3. Conclusion

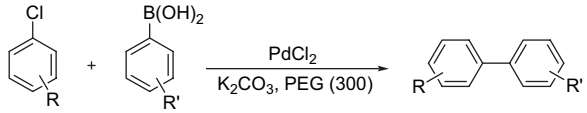
In conclusion, we have disclosed an efficient and convenient system for the Suzuki coupling of aryl chlorides with various phenylboronic acids using $PdCl_2$ as catalyst and PEG (300) as solvent at room temperature. The system proved to be quite efficient for a wide array of electron-withdrawing and electron-donating groups in both aryl chlorides and phenylboronic acids. Currently, further studies are underway in our laboratory, addressing extension of the system to other palladium-catalyzed transformations.

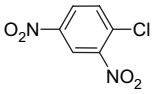
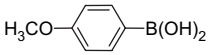
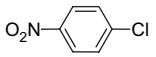
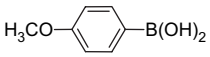
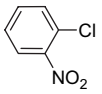
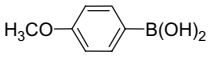
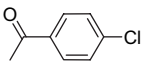
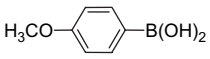
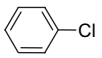
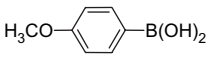
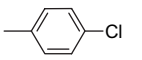
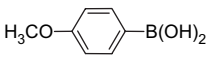
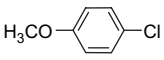
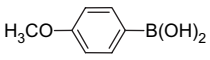
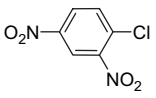
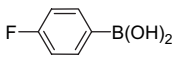
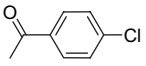
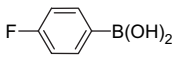
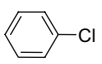
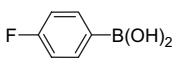
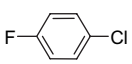
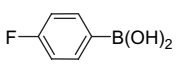
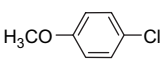
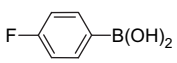
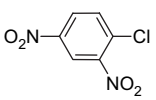
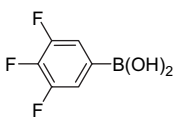
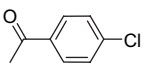
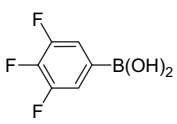
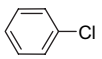
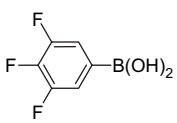
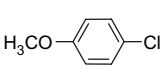
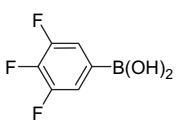
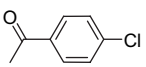
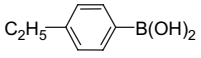
4. Experimental

4.1. Typical experimental procedure for the PEG (300)–$PdCl_2$-catalyzed Suzuki–Miyaura cross-coupling reaction

A mixture of aryl chlorides (1.0 mmol), arylboronic acid (1.5 mmol), $PdCl_2$ (0.05 mmol), K_2CO_3 (3 mmol), and PEG (300) (4 mL) were added to a 100 mL round-flask, and stirred at room temperature for the desired time until complete consumption of starting material as judged by

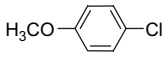
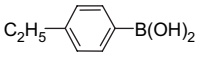
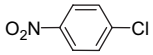
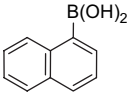
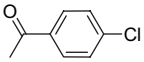
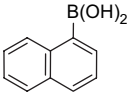
Table 5. PEG (300)–$PdCl_2$-catalyzed cross-coupling of aryl halides with various phenylboronic acids[a]



Entry	Aryl chloride	Phenylboronic acid	Time (h)[b]	Yield (%)[c]
1			0.5	98
2			1	95
3			5	90
4			4	92
5			5	87
6			3.5	93
7			5	98
8			2	96
9			6	90
10			10	83
11			5	95
12			10	65
13			3	87
14			6	85
15			10	82
16			12	60
17			5	86

(*continued*)

Table 5. (*continued*)

Entry	Aryl chloride	Phenylboronic acid	Time (h)[b]	Yield (%)[c]
18			6	80
19			5	90
20			8	50

[a] Reaction conditions: 1.0 mmol aryl halide, 1.5 mmol phenylboronic acid, 3 mmol K_2CO_3, 5 mmol % $PdCl_2$, 4 mL PEG (300), at room temperature.
[b] The reaction was monitored by TLC.
[c] Isolated yield.

TLC. Thus, after the mixture was extracted with dry ethyl ether (5×10 mL) and evaporated, the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled products.

4.2. Analytical data for new compounds

4.2.1. 2,4-Binitro-4′-fluoro-biphenyl (Table 5, entry 8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72 (d, J=2.4 Hz, 1H), 8.48 (dd, J=2.4 Hz, J=8.4 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.36–7.30 (m, 2H), 7.21–7.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.8, 149.1, 147.0, 141.2, 133.2, 131.2, 130.0, 126.5, 119.8, 116.3. HRMS: calcd for $C_{12}H_7FN_2O_4$ 262.0390; found 262.0381.

4.2.2. 2,4-Binitro-3′,4′,5′-trifluoro-biphenyl (Table 5, entry 13). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.80 (d, J=2.4 Hz, 1H), 8.52 (dd, J=2.4 Hz, J=8.4 Hz, 1H), 7.65 (d, J=8.4 Hz, 1H), 6.99 (dd, J=6.3 Hz, J=7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.4, 153.2, 147.7, 139.1, 133.1, 130.9, 128.8, 126.9, 120.1, 112.6. HRMS: calcd for $C_{12}H_5F_3N_2O_4$ 298.0201; found 298.0205.

4.2.3. 1-(3′,4′,5′-Trifluoro-biphenyl-4-yl)-ethanone (Table 5, entry 14). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J=8.5 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 7.24 (dd, J=6.3 Hz, J=8.5 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.4, 153.2, 150.0, 142.5, 138.2, 136.8, 129.2, 127.1, 111.4, 26.7. HRMS: calcd for $C_{14}H_9F_3O$ 250.0606; found 250.0598.

4.2.4. 3,4,5-Trifluoro-biphenyl (Table 5, entry 15). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51–7.39 (m, 5H), 7.19 (dd, J=6.6 Hz, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.3, 153.1, 149.8, 138.2, 129.1, 129.4, 126.8, 111.0. HRMS: calcd for $C_{12}H_7F_3$ 208.0500; found 208.0499.

4.2.5. 4-Methoxy-3′,4′,5′-trifluoro-biphenyl (Table 5, entry 16). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (d, J=8.7 Hz, 2H), 7.13 (dd, J=6.6 Hz, J=9.0 Hz, 2H), 6.97 (d, J=8.7 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.4, 159.9, 127.9, 114.5, 110.6, 110.5, 110.4, 110.3, 55.4. HRMS: calcd for $C_{13}H_9F_3O$ 238.0606; found 238.0607.

4.2.6. 1-(4′-Ethyl-biphenyl-4-yl)-ethanone (Table 5, entry 17). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J=8.4 Hz, 2H), 7.68 (d, J=8.4 Hz, 2H), 7.57 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 2.71 (q, J=7.5 Hz, 2H), 2.64 (s, 3H), 1.29 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.7, 145.8, 144.6, 137.2, 135.7, 128.9, 128.5, 127.2, 127.0, 28.6, 26.6, 15.5. HRMS: calcd for $C_{16}H_{16}O$ 224.1201; found 224.1200.

4.2.7. 4-Methoxy-4′-ethyl-biphenyl (Table 5, entry 18). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (d, J=8.7 Hz, 2H), 7.47 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.1 Hz, 2H), 6.96 (d, J=8.7 Hz, 2H), 3.84 (s, 3H), 2.68 (q, J=7.5 Hz, 2H), 1.27 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.9, 142.7, 138.2, 133.8, 128.2, 128.0, 126.7, 114.2, 55.3, 28.5, 15.9. HRMS: calcd for $C_{15}H_{16}O$ 212.1201; found 212.1199.

Acknowledgements

We are grateful for the financial support provided by the National Natural Science Foundation of China (No. 20472032).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.067.

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The novel reaction of ketones with *o*-oxazoline-substituted anilines

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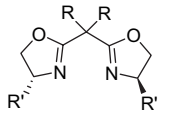
Received 13 June 2006; revised 20 July 2006; accepted 21 July 2006
Available online 9 August 2006

Abstract—A variety of ketones react with *o*-oxazoline-substituted anilines in the presence of catalytic amount of *p*-toluenesulfonic acid in dry *n*-butanol to form 4-amino-substituted quinolines or 4-quinolones in fair to good yields.

1. Introduction

Oxazolines, especially chiral bis(oxazoline) (BOX, **1**), have been successfully used in many catalytic asymmetric reactions as versatile ligands in the past decade.[1] In addition, the oxazoline unit and adjacent hydroxy group may function together to control the catalytic process.[2] On the other hand, Hong and his co-workers have reported the use of Schiff-bases as ligands in the palladium-catalyzed Suzuki cross-coupling reactions.[3] Thus, in the presence of an *N*,*O*-bidentate ligand such as 2-[1-(2,4,6-trimethyl-phenylimino)-ethyl]-phenol **2**, Suzuki cross-coupling reactions could be carried out efficiently at room temperature with a wide variety of arylbromides even with electronically deactivated arenes. As a continuation of our ongoing project on the development of novel chiral ligands on polymer-supported palladium catalyst,[4] we attempted to put the chiral oxazolines on the *N*,*O*-bidentate ligand in order to prepare some chiral Schiff-bases as the ligands for palladium-catalyzed coupling reactions. However, to our surprise, we found that the oxazoline ring underwent ring opening very easily during the preparation of Schiff-bases. As to our knowledge, there is no report so far for this kind of ring opening of oxazoline to form quinoline or quinolone derivatives from *o*-oxazoline-substituted anilines in the presence of acid catalyst. In view of the importance of 4-amino-substituted quinolines in medicinal chemistry[5] such as tacrine, which was used as a drug to cure Alzheimer's disease, and the strong desire for a general synthetic route for their preparations,[6] herein, we report a new entry to 4-amino-substituted quinolines or 4-quinolones by reaction of various ketones with *o*-oxazoline-substituted anilines (Tables 1 and 2).



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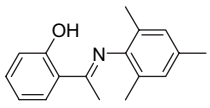

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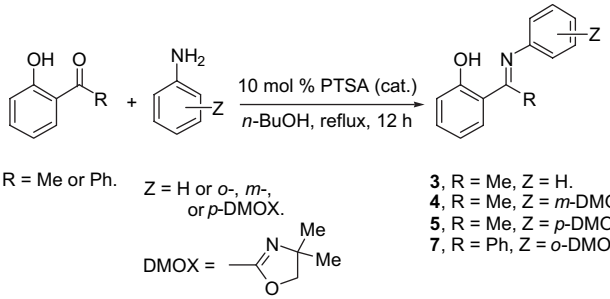
2. Results and discussion

In the synthesis of imine 2-[1-(phenylimino)-ethyl]phenol **3**, by treatment of *o*-hydroxyacetophenone with aniline in distilled *n*-butanol in the presence of 10 mol % of dry PTSA at reflux, the desired product was obtained (Eq. 1). It was found that the use of very dry *n*-butanol[7] is crucial for obtaining good yield (88%). Similar reactions of *m*- or *p*-(oxazolin-2-yl)aniline with *o*-hydroxyacetophenone formed **4** or **5**, respectively, and the reaction of 2-(4,4-dimethyl-1,3-oxazolin-2-yl)phenylamine **6**[8] with 2-hydroxyphenyl phenyl ketone gave 2-{(1*E*)-2-aza-2-[2-(4,4-dimethyl(1,3-oxazolin-2-yl))phenyl]-1-phenylvinyl}phenol **7** (Fig. 1) in 82% yield. To our surprise, under the same conditions, the reaction of **6** with *o*-hydroxyacetophenone gave, unexpectedly, quinoline derivative **8a** as the major product in 79% yield (entry 1, Table 1). The structure of **8a** was established based on the ^{1}H, ^{13}C, and 2D NOESY NMR assignments and was approved by single-crystal X-ray diffraction analysis (Fig. 2).



(1)

Keywords: 4-Amino-substituted quinoline; 4-Quinolone; 4-Hydroxy-quinoline; Oxazoline.
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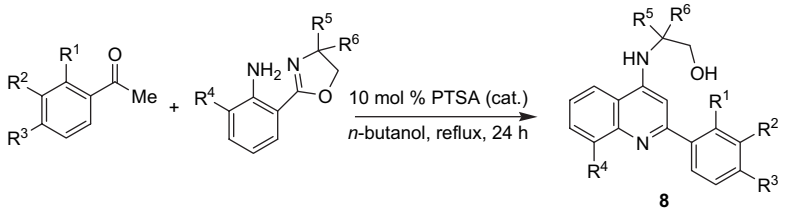
doi:10.1016/j.tet.2006.07.057

Table 1. Reaction with acetylbenzenes and *o*-oxazoline-substituted aniline for the preparation of *N*-alkyl-substituted 4-aminoquinolines **8**

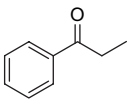
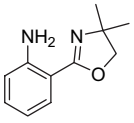
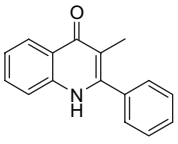
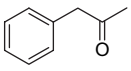
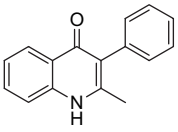
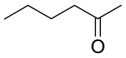
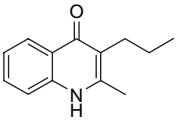
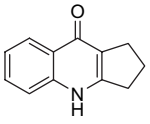
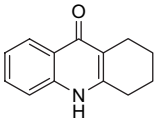


Entry	R^1	R^2	R^3	R^4	R^5	R^6	**8**, Yield (%)[a,b]
1	OH	H	H	H	CH_3	CH_3	**8a** (79)
2	Br	H	H	H	CH_3	CH_3	**8b** (89)
3	CH_3	H	H	H	CH_3	CH_3	**8c** (86)
4	OCH_3	H	H	H	CH_3	CH_3	**8d** (60)
5	H	CH_3	H	H	CH_3	CH_3	**8e** (82)
6	H	H	Br	H	CH_3	CH_3	**8f** (84)
7	H	H	F	H	CH_3	CH_3	**8g** (82)
8	H	H	H	H	CH_3	CH_3	**8h** (88)
9	H	–CH=CH–CH=CH–		H	CH_3	CH_3	**8i** (86)
10	H	H	H	Cl	CH_3	CH_3	**8j** (83)
11	OH	H	H	H	H	Ph	**8k** (75)

[a] All reactions were performed using acetylbenzene (5 mmol), *o*-oxazoline-substituted aniline (5 mmol), and PTSA (10 mol %) in *n*-butanol (5 mL) at reflux temperature for 24 h.
[b] Isolated yields after column chromatography.

Other acetophenones with or without a substituent on the benzene ring may undergo the similar reaction transformations with **6** to form the corresponding quinoline derivatives

Table 2. The formation of 4-quinolone derivative **9**–**13** from the reaction of ketones with *o*-oxazoline-substituted aniline **6**

Entry	Ketones	Anilines	Products, yield (%)[a,b]
1		 **6**	 **9** (90)
2		**6**	 **10** (88)
3		**6**	 **11** (70)
4		**6**	 **12** (76)
5		**6**	 **13** (80)

[a] One equivalent of amine **6** was used unless otherwise stated.
[b] Isolated yields after column chromatography.

8b–**8h** in 60–89% yields (entries 2–8, Table 1). Thus, changing the substituent at R^1, R^2, or R^3 in acetophenones shown in Table 1 seemed to have no effect on the formation of the quinolines. β-Acetonaphthone formed 2-(2-naphthyl)-quinoline derivative **8i** in 86% yield (entry 9, Table 1). The reaction of 6-(4,4-dimethyl(1,3-oxazolin-2-yl))-2-chlorophenylamine with acetophenone could form 8-chloro-2-phenyl-quinoline derivative **8j** in 83% yield (entry 10, Table 1). The use of chiral 2-[(4*R*)-4,5-dihydro-4-phenyl-2-oxazolyl]benzenamine in the reaction with *o*-hydroxyacetophenone gave the chiral product **8k** in 75% yield (entry 11, Table 1). Unfortunately, we did not isolate any other plausible intermediates for the formation of these quinolines. It is

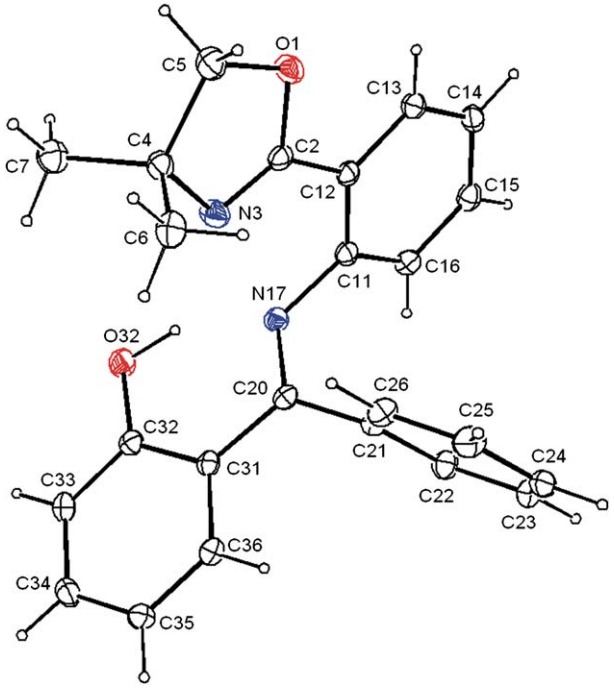


Figure 1. ORTEP diagram of **7**.

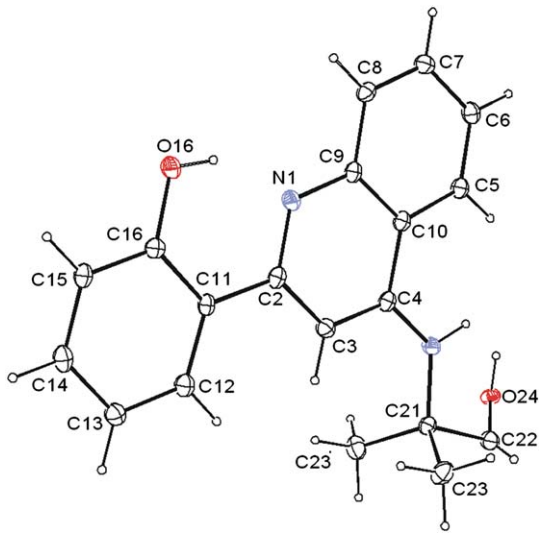
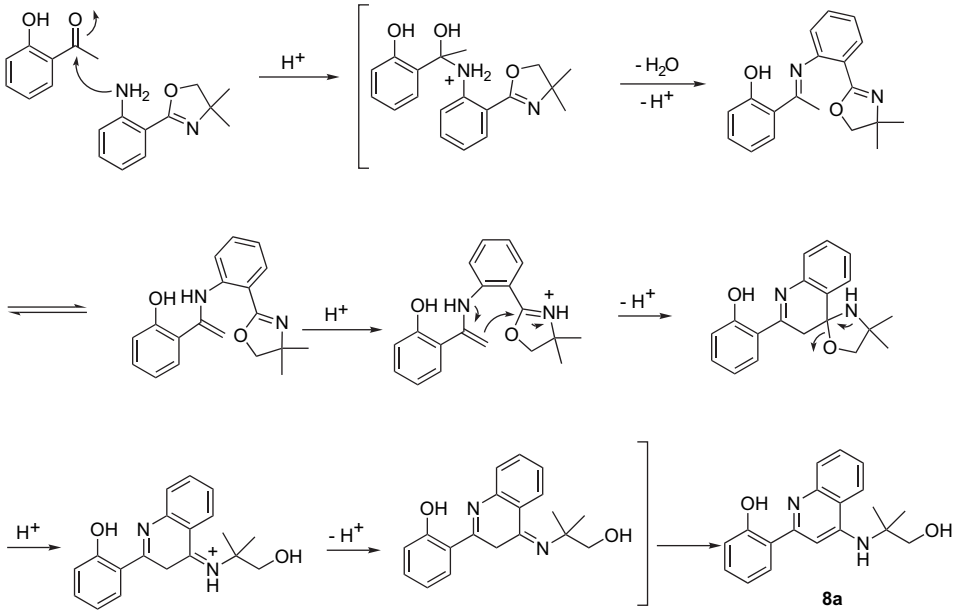


Figure 2. ORTEP diagram of **8a**.

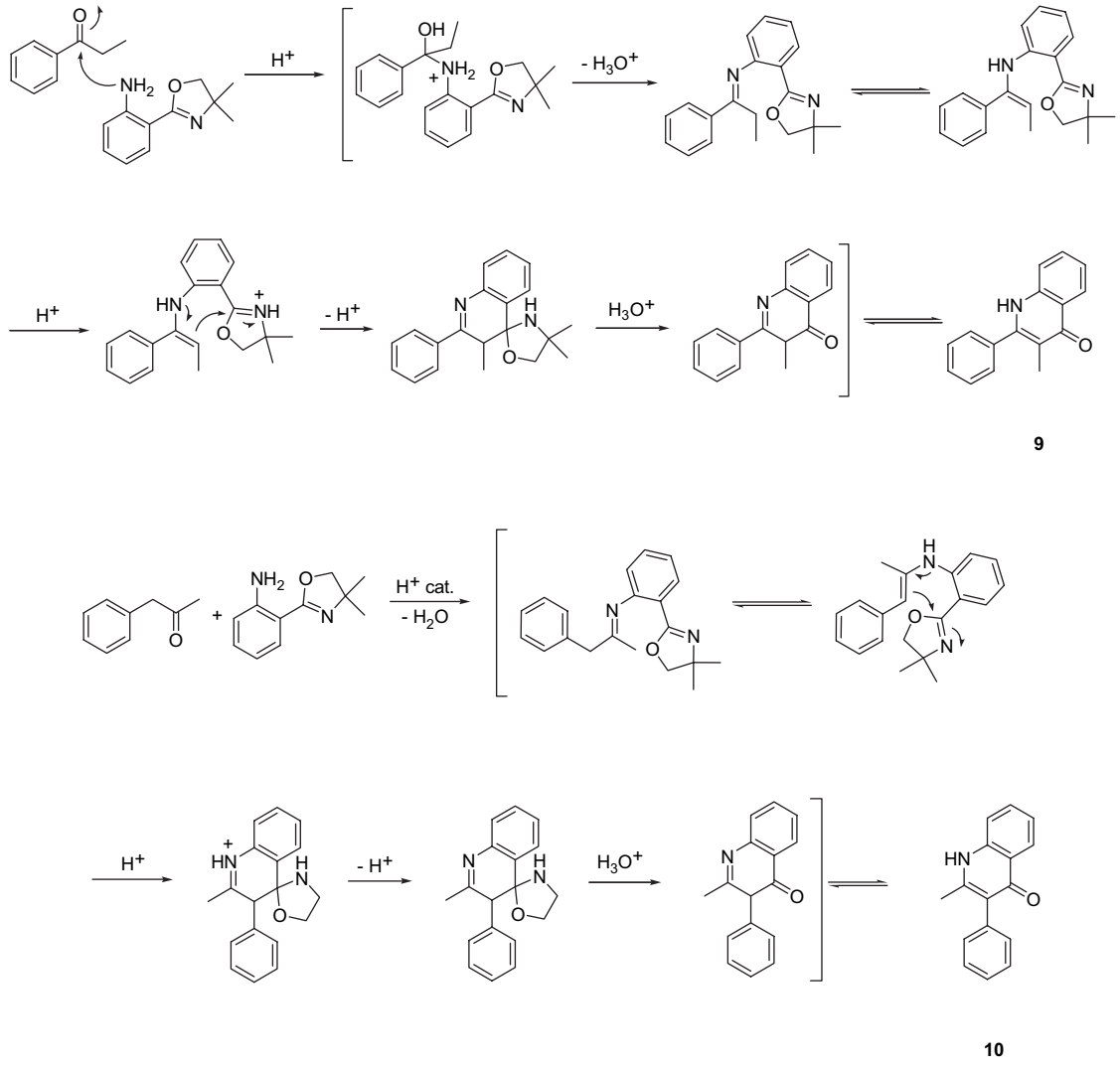
known that the dealkylation of a tertiary alkyl group from alkylaniline derivatives is well documented in the literature.[9] Thus, this procedure was an alternative method for the preparation of 4-amino-substituted quinolines, which may be obtained by the dealkylation of the amino group containing a tertiary alkyl group in **8**.[9,10]

In order to test the generality of the formation of 4-amino-substituted quinolines from acetophenones and **6**, we attempted to use propiophenone instead of acetophenone. However, to our surprise, we found that 3-methyl-2-phenyl-hydroquinolin-4-one **9** was isolated as the major product in 90% yield (entry 1, Table 2). The structure of **9** was confirmed by its IR (ν 1628 cm^{-1} for the conjugated carbonyl group), ^{1}H, and ^{13}C NMR as well as by its 2D NOESY NMR, MS, and high-resolution MS spectral analysis.[11] The reaction of 1-phenyl-2-propanone with **6** gave hydroquinolin-4-one derivative **10** in 88% yield (entry 2, Table 2). The reaction of 2-hexanone with **6** gave hydroquinolin-4-one derivative **11** in 70% yield (entry 3, Table 2). The reaction of cyclic ketones, such as cyclopentanone and cyclohexanone, gave the corresponding hydroquinolin-4-one derivative **12** and **13** in 76 and 80% yields, respectively. Attempts to run the reaction with acetone under the similar reaction conditions failed, only starting material **6** was isolated. The transformation of 4-quinolones to 4-amino-substituted quinolines was also documented in the literature.[9] Again, this procedure was an alternative method for the preparation of 4-amino-substituted quinolines.[9,10]

The plausible reaction mechanism for the formation of **8a** was shown in Scheme 1. Thus, the carbonyl group of acetophenone can react with the amino group of 2-oxazoline-substituted aniline to form the imine intermediate in the presence of acid catalyst. Then, the imine intermediate will be tautomerized into enamine intermediate.[12] The following intramolecular ring formation will be promoted by the protonation of the nitrogen atom in oxazoline ring, and followed by acid-catalyzed ring opening and tautomerization to give 4-amino-substituted quinolines **8**. In the case of these cyclic or acyclic ketone substrates shown in Table 2, the formation of the carbonyl group at 4-position of quinolones may be rationalized as shown in Scheme 2. Thus, the intermediate 1,3-oxazolidine with a neighboring methyl of phenyl group will be hydrolyzed more easily due to steric reason to form the carbonyl group.[13] Alternatively, the formation of stable tetra-substituted carbon–carbon double bond may also further accelerate the hydrolysis of 1,3-oxazolidine ring to form the carbonyl group. While in the case of ketone substrates shown in Table 1, the intermediate with 1,3-oxazolidine at benzylic position will be hydrolyzed slowly when hydrogens were substituted at the homobenzylic position adjacent to the 1,3-oxazolidine ring. Thus, the acid-catalyzed ring opening will overwhelm the hydrolysis and the following tautomerization could form the 4-amino-substituted quinolines **8a**.



Scheme 1. Plausible reaction mechanism for the formation of **8a** from acetophenones and *o*-oxazoline-substituted aniline.



Scheme 2. Plausible reaction mechanisms for the formation of **9** and **10**.

3. Conclusion

In summary, we have demonstrated a novel reaction of various ketones with *o*-oxazoline-substituted anilines in the presence of catalytic amount of PTSA in dry *n*-butanol to provide a new route for the preparation of 4-amino-substituted quinolines or 4-quinolones. Typically, acetophenones formed 4-amino-substituted quinolines, while either cyclic or acyclic ketones with more than three carbons in a chain involving the keto group formed 4-quinolones.

4. Experimental

4.1. General experimental methods

All reactions were carried out in oven-dried glassware under argon or nitrogen atmosphere. *n*-Butanol was dried over $MgSO_4$ and followed by refluxing and distilling from magnesium activated by iodine. Other solvents were purified and dried by appropriate methods wherever needed. TLC was done on aluminum sheets with precoated silica gel 60 F_{254} (40×80 mm). Purification by column chromatography was carried out with neutral silica gel 60 (70–230 mesh ASTM). The purity of each compound was judged to be >95% by ^1H or ^{13}C NMR spectral analyses. Melting points were taken on a capillary tube apparatus and are uncorrected. IR spectra were recorded as either Nujol mulls or in the solution form as denoted. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 or their mixture solution on either a 400 or a 500 MHz instrument using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. HRMS spectra were collected on an orthogonal acceleration-time-of-flight mass spectrometer with a resolution of 6000 (5% valley definition) and fitted with a magnet bypass flight tube. MS spectra were determined on a quadrupole spectrometer or on a GC–MS spectrometer.

4.2. Representative procedure for the synthesis of quinoline 8a or other quinolines and quinolones from ketones and *o*-oxazoline-substituted anilines

A solution of **6** (1.9 g, 10 mmol), *o*-hydroxyacetophenone (1.2 mL, 10 mmol), and PTSA (60 mg, 10 mol %) in dry *n*-butanol (10 mL) was stirred at reflux temperature for 24 h. The reaction mixture was then cooled to room temperature, *n*-butanol was removed under low pressure, and to the residue was added water (20 mL) and the solution

was extracted with ethyl acetate (20 mL×3). The combined organic layers were dried over $MgSO_4$. Filtration and concentration followed by column chromatography (silica gel, hexane/EtOAc=1:1) gave 2.44 g of **8a** in 79% yield as a yellow solid,[14] mp 172–174 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.61 (s, 6H), 3.82 (s, 2H), 6.91 (t, J=7.7 Hz, 1H), 7.05 (d, J=7.7 Hz, 1H), 7.25 (s, 1H), 7.32 (t, J=7.7 Hz, 1H), 7.44 (t, J=7.6 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 7.74 (d, J=7.7 Hz, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.89 (d, J=7.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 23.65, 54.93, 69.95, 95.70, 118.06, 118.27, 118.71, 119.01, 119.32, 124.88, 126.28, 127.67, 129.85, 131.48, 144.65, 149.12, 157.68, 161.80 ppm. IR (KBr) ν 3395 (br), 1587, 1535 cm^{-1}. MS m/z 309 (M^++H), 308, 277, 237. HRMS calcd for $C_{19}H_{21}N_2O_2$: 309.1603; found: 309.1600. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.53; H, 6.10; N, 8.88.

4.2.1. Preparation of 2-((1*E*)-2-aza-1-methyl-2-phenylvinyl)phenol (3). A solution of aniline (0.9 mL, 10 mmol), *o*-hydroxyacetophenone (1.2 mL, 10 mmol), and *p*-toluenesulfonic acid (0.17 g, 10 mol %) in dry *n*-butanol (10 mL) was stirred at reflux temperature for 24 h. The reaction mixture was then cooled to room temperature, the *n*-butanol was removed, and the residue was purified by recrystallization (hexane) to afford 1.86 g (88% yield) of the title compound as yellow solid. Mp 80–81 °C (lit.[15] 81–82 °C).

4.2.2. Preparation of 2-(4,4-dimethyl-1,3-oxazolin-2-yl)-phenylamine (6). Zinc chloride (0.34 g, 2.5 mmol) was put in a 50 mL two-necked flask and melted under high vacuum. After cooling down to room temperature under argon, a solution of 2-aminobenzonitrile (5.90 g, 50 mmol) and 2-amino-2-methylpropanol (6.70 g, 75 mmol) in 150 mL of chlorobenzene was added. The mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in 150 mL of dichloromethane. The solution was washed three times with 100 mL of water and the aqueous phase was extracted with 150 mL of dichloromethane. The combined organic layers were dried over magnesium sulfate, and the solvent was removed in vacuo. The resulting solid was purified by recrystallization (ethyl acetate/hexane) to afford 6.95 g (73% yield) of the title compound. Mp 106–108 °C (lit.[16] 103–106 °C).

4.2.3. Preparation of 2-[(4*R*)-4,5-dihydro-4-phenyl-2-oxazolyl]benzenamine. The procedure for preparing the title compound is similar to that for the preparation of **6** by using zinc chloride (0.34 g, 2.5 mmol), 2-aminobenzonitrile (5.90 g, 50 mmol), and (*R*)-(−)-phenylglycinol (10.3 g, 75 mmol) in 200 mL of chlorobenzene. The compound was purified by chromatography (silica gel, ethyl acetate/hexane=1:4) to afford 6.90 g (58% yield) of the title compound. Mp 77–79 °C (lit.[17] 71 °C).

4.2.4. Preparation of 2-chloro-6-cyanoaniline. CuCN (3.45 g, 38.5 mmol) was added in small portions with vigorous stirring to a warm (~80 °C) solution of 2,6-dichloroaniline (2.5 g, 15.4 mmol) in *N*-methyl-pyrrolidinone (20 mL). The mixture was then heated to 150–170 °C. After 0.5 h, the reaction mixture was cooled to about 80 °C. Another CuCN (3.45 g, 38.5 mmol) was added in small portions and the reaction mixture was again heated to 150–170 °C for an additional 2 h. It was then cooled to 60 °C and poured into a 50:50 (v/v) mixture of ammonia and ice water (60 mL), stirred well for 1 h, and filtered. The residue was washed with CH_2Cl_2 (20 mL) and all the filtrates were combined, and extracted with CH_2Cl_2 (60 mL×3). The CH_2Cl_2 extracts were combined and washed well with water (50 mL×3), and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane=2:3) to afford 0.73 g (31% yield) of the title compound. Mp 94–96 °C (lit.[18] 94–96 °C).

4.2.5. Preparation of 6-(4,4-dimethyl(1,3-oxazoline-2-yl))-2-chlorophenylamine. The procedure for preparing the title compound is similar to that for the preparation of **6** by using zinc chloride (22 mg, 0.16 mmol), 2-chloro-6-cyanoaniline (0.50 g, 3.26 mmol), and 2-amino-2-methylpropanol (0.46 mL, 4.90 mmol) in 10 mL of chlorobenzene. The compound was purified by chromatography (silica gel, ethyl acetate/hexane=1:4) to afford 0.45 g (62% yield) of the title compound. ^{1}H NMR ($CDCl_3$, TMS) δ 1.37 (s, 6H), 4.00 (s, 2H), 6.58 (t, J=7.9 Hz, 1H), 7.31 (d, J=7.9 Hz, 1H), 7.62 (d, J=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 28.60, 67.83, 77.59, 110.23, 115.53, 119.29, 128.08, 131.63, 144.74, 161.66 ppm. IR (KBr) ν 3466, 3266, 1632, 742 cm^{-1}. MS m/z 225 (M^++H), 224, 209, 153. HRMS calcd for $C_{11}H_{14}N_2OCl$: 225.0795; found: 225.0798.

4.2.6. 2-{[2-(2-Bromophenyl)(4-quinolyl)]amino}-2-methylpropan-1-ol (8b). Yield: 89%. Mp 184–186 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 1.47 (s, 6H), 3.61 (s, 2H), 6.88 (s, 1H), 7.26 (t, J=7.7 Hz, 1H), 7.39–7.44 (m, 2H), 7.59–7.68 (m, 3H), 7.89 (d, J=8.4 Hz, 1H), 7.99 (d, J=8.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 22.94, 54.40, 70.15, 102.37, 118.69, 119.66, 121.45, 124.23, 127.21, 128.66, 129.21, 129.72, 131.18, 132.75, 142.59, 147.76, 148.16, 158.40 ppm. IR (KBr) ν 3395, 1587 cm^{-1}. MS m/z 371 (M^++H), 373, 339. HRMS calcd for $C_{19}H_{20}N_2OBr$: 371.0759; found: 371.0753.

4.2.7. 2-Methyl-2{[2-(2-methylphenyl)(4-quinolyl)]-amino}propan-1-ol (8c). Yield: 85%. Mp 169–171 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.42 (s, 6H), 2.37 (s, 3H), 3.60 (s, 2H), 6.70 (s, 1H), 7.23–7.30 (m, 3H), 7.34–7.44 (m, 2H), 7.60 (t, J=7.5 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 8.05 (d, J=8.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 20.21, 23.31, 54.91, 69.97, 102.10, 118.36, 119.82, 124.81, 125.83, 128.42, 128.80, 129.35, 129.57, 130.62, 135.80, 140.95, 147.13, 148.84, 159.47 ppm. IR (KBr) ν 3387, 1587, 1528 cm^{-1}. MS m/z 307 (M^++H), 176. HRMS calcd for $C_{20}H_{23}N_2O$: 307.1810; found: 307.1807.

4.2.8. 2-{[2-(2-Methoxyphenyl)(4-quinolyl)]amino}-2-methylpropan-1-ol (8d). Yield: 60%. Mp 187–189 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.47 (s, 6H), 3.70 (s, 2H), 3.83 (s, 3H), 6.99 (d, J=8.2 Hz, 1H), 7.09 (t, J=7.3 Hz, 1H), 7.15 (s, 1H), 7.34–7.38 (m, 2H), 7.56 (t, J=7.3 Hz, 1H), 7.78–7.82 (m, 2H), 8.05 (d, J=8.2 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 23.49, 54.93, 55.77, 69.71, 103.46, 111.52, 118.56, 119.65, 121.17, 124.58, 129.02, 129.12, 129.71, 130.17, 131.21, 147.57, 147.97, 156, 157.03 ppm. IR (KBr) ν 3395, 1587, 1528 cm^{-1}. MS m/z 323 (M^++H),

251. HRMS calcd for $C_{20}H_{23}N_2O_2$: 323.1760; found: 323.1755.

4.2.9. 2-Methyl-2-{[2-(3-methylphenyl)(4-quinolyl)]-amino}propan-1-ol (8e). Yield: 82%. Mp 132–134 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.47 (s, 6H), 2.44 (s, 3H), 3.70 (s, 2H), 6.90 (s, 1H), 7.23 (d, J=7.6 Hz, 1H), 7.30 (t, J=7.6 Hz, 1H), 7.35 (t, J=7.6 Hz, 1H), 7.55–7.61 (m, 2H), 7.67 (d, J=7.9 Hz, 1H), 8.06 (d, J=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 21.56, 23.90, 55.02, 69.14, 99.19, 118.70, 119.44, 124.52, 124.70, 128.26, 128.48, 129.23, 129.39, 129.82, 138.25, 140.28, 148.04, 148.82, 157.71 ppm. IR (KBr) ν 3395, 1587, 1528 cm^{-1}. MS m/z 307 (M^++H), 275, 235. HRMS calcd for $C_{20}H_{23}N_2O$: 307.1810; found: 307.1808.

4.2.10. 2-{[2-(4-Bromophenyl)(4-quinolyl)]amino}-2-methylpropan-1-ol (8f). Yield: 84%. Mp 171–174 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.50 (s, 6H), 3.75 (s, 2H), 6.90 (s, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.58–7.64 (m, 4H), 7.81–7.83 (m, 2H), 8.03 (d, J=8.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 24.11, 55.06, 68.52, 98.37, 118.69, 119.29, 123.36, 124.70, 129.04, 129.28, 129.68, 131.65, 139.30, 148.39, 148.66, 156.29 ppm. IR (KBr) ν 3395, 1587, 1532 cm^{-1}. MS m/z 373, 371 (M^++H), 339, 299. HRMS calcd for $C_{19}H_{20}N_2OBr$: 371.0759; found: 371.0753.

4.2.11. 2-{[2-(4-Fluorophenyl)(4-quinolyl)]amino}-2-methylpropan-1-ol (8g). Yield: 82%. Mp 176–178 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.49 (s, 6H), 3.73 (s, 2H), 6.85 (s, 1H), 7.14 (t, J=8.6 Hz, 2H), 7.34 (t, J=7.6 Hz, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.88–7.91 (m, 2H), 8.02 (d, J=8.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 24.03, 55.16, 68.63, 98.45, 115.37, 115.59, 118.48, 119.45, 124.64, 129.15, 129.31, 129.39, 136.11, 147.83, 148.91, 156.19, 162.31, 164.79 ppm. IR (KBr) ν 3395, 1587, 1532, 1510, 1226, 828 cm^{-1}. MS m/z 311 (M^++H), 279, 239. HRMS calcd for $C_{19}H_{20}N_2OF$: 311.1560; found: 311.1564.

4.2.12. 2-Methyl-2-[(2-phenyl(4-quinolyl))amino]propan-1-ol (8h). Yield: 88%. Mp 168–170 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.52 (s, 6H), 3.75 (s, 2H), 7.01 (s, 1H), 7.37 (t, J=7.6 Hz, 1H), 7.41–7.51 (m, 3H), 7.60–7.65 (m, 2H), 7.97–7.99 (m, 2H), 8.05 (d, J=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 24.03, 54.96, 68.64, 98.97, 118.72, 119.29, 124.49, 127.56, 128.55, 128.89, 129.09, 129.71, 140.56, 148.45, 148.54, 157.68 ppm. IR (KBr) ν 3395, 1587 cm^{-1}. MS m/z 293 (M^++H), 261, 221. HRMS calcd for $C_{19}H_{21}N_2O$: 293.1655; found: 293.1654.

4.2.13. 2-Methyl-2-[(2-naphthyl(4-quinolyl))amino]propan-1-ol (8i). Yield: 86%. Mp 162–164 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 1.57 (s, 6H), 3.82 (s, 2H), 7.18 (s, 1H), 7.39 (t, J=7.1 Hz, 1H), 7.50–7.52 (m, 2H), 7.63–7.69 (m, 2H), 7.89–7.90 (m, 1H), 7.96–7.98 (m, 2H), 8.11 (d, J=7.1 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), 8.45 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 24.16, 55.09, 68.44, 99.03, 118.74, 119.31, 124.56, 125.28, 126.12, 126.46, 126.80, 127.62, 128.21, 128.85, 129.14, 129.59, 133.32, 133.66, 137.71, 148.57, 157.33 ppm. IR (KBr) ν 3395, 1583, 1528 cm^{-1}. MS m/z 343 (M^++H), 271. HRMS calcd for $C_{23}H_{23}N_2O$: 343.1810; found: 343.1804.

4.2.14. 2-[(8-Chloro-2-phenyl(4-quinolyl))amino]-2-methylpropan-1-ol (8j). Yield: 83%. ^{1}H NMR ($CDCl_3$, TMS) δ 1.53 (s, 6H), 3.76 (s, 2H), 7.16 (s, 1H), 7.29 (t, J=8.0 Hz, 1H), 7.44–7.54 (m, 3H), 7.73–7.78 (m, 2H), 8.13 (d, J=7.6 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 23.41, 55.68, 70.05, 99.39, 119.74, 120.06, 124.44, 127.48, 128.95, 129.86, 130.06, 132.57, 139.09, 143.23, 150.28, 156.54 ppm. IR (KBr) ν 3387, 1583, 1528, 694 cm^{-1}. MS m/z 326 (M^+), 295, 245. HRMS calcd for $C_{19}H_{19}N_2OCl$: 326.1186; found: 326.1190.

4.2.15. (2*R*)-2-{[2-(2-Hydroxyphenyl)(4-quinolyl)]-amino}-2-phenylethan-1-ol (8k). Yield: 75%. ^{1}H NMR ($CDCl_3$, TMS) δ 3.88 (dd, J=7.4, 11.4 Hz, 1H), 4.11 (dd, J=3.8, 11.4 Hz, 1H), 4.52 (t, J=3.8 Hz, 1H), 6.47 (s, 1H), 6.81 (t, J=7.9 Hz, 1H), 7.01 (d, J=7.9 Hz, 1H), 7.26–7.36 (m, 7H), 7.52 (t, J=8.0 Hz, 2H), 7.70 (d, J=8.0 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 59.42, 66.91, 95.39, 117.34, 117.91, 118.70, 118.94, 119.43, 124.97, 126.33, 126.46, 126.92, 128.20, 129.16, 130.04, 131.72, 138.29, 143.48, 149.89, 157.45, 162.30 ppm. IR (KBr) ν 3365, 1594 cm^{-1}. MS m/z 357 (M^++H), 356, 237. HRMS calcd for $C_{23}H_{21}N_2O_2$: 357.1603; found: 357.1610.

4.2.16. 2-{(1*E*)-2-Aza-2-[3-(4,4-dimethyl(1,3-oxazolin-2-yl))phenyl]-1-methylvinyl}phenol (4). Yield: 86%. Yellow oil. ^{1}H NMR ($CDCl_3$, TMS) δ 1.39 (s, 6H), 2.34 (s, 3H), 4.13 (s, 2H), 6.89 (t, J=7.6 Hz, 1H), 7.00–7.02 (m, 2H), 7.37 (t, J=7.9 Hz, 1H), 7.43 (t, J=7.9 Hz, 1H), 7.52 (s, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.77 (d, J=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 17.27, 28.38, 67.65, 79.25, 118.19, 118.26, 119.62, 120.97, 124.03, 124.60, 128.95, 129.02, 129.12, 133.18, 147.23, 161.74, 161.87, 171.70 ppm. IR (KBr) ν 1644, 1610 cm^{-1}. MS m/z 308 (M^+), 307, 293. HRMS calcd for $C_{19}H_{20}N_2O_2$: 308.1525; found: 308.1523.

4.2.17. 2-{(1*E*)-2-Aza-2-[4-(4,4-dimethyl(1,3-oxazolin-2-yl))phenyl]-1-methylvinyl}phenol (5). Yield: 74%. Yellow oil. ^{1}H NMR ($CDCl_3$, TMS) δ 1.36 (s, 6H), 2.28 (s, 3H), 4.09 (s, 2H), 6.84–6.91 (m, 3H), 6.98 (d, J=7.8 Hz, 1H), 7.34 (t, J=7.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.93–7.95 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 17.20, 28.37, 67.53, 76.68, 79.11, 118.23, 119.54, 121.08, 124.59, 128.92, 129.21, 133.25, 149.71, 161.72, 161.73, 171.33 ppm. IR (KBr) ν 1645, 1608, 1574 cm^{-1}. MS m/z 308 (M^+), 307, 293, 221. HRMS calcd for $C_{19}H_{20}N_2O_2$: 308.1525; found: 308.1523.

4.2.18. 2-{(1*E*)-2-Aza-2-[2-(4,4-dimethyl(1,3-oxazolin-2-yl))phenyl]-1-phenylvinyl}phenol (7). Yield: 82%. Yellow solid.[19] Mp 107–109 °C (recrystallization from ethanol). ^{1}H NMR ($CDCl_3$, TMS) δ 1.36 (s, 6H), 4.08 (s, 2H), 6.55 (d, J=7.5 Hz, 1H), 6.74 (t, J=7.5 Hz, 1H), 7.01 (t, J=7.5 Hz, 1H), 7.04–7.09 (m, 2H), 7.12 (t, J=7.7 Hz, 1H), 7.19–7.22 (m, 2H), 7.26–7.28 (m, 3H), 7.36 (t, J=7.7 Hz, 1H), 7.77 (d, J=7.7 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, TMS) δ 28.21, 67.19, 79.45, 117.86, 117.92, 120.13, 122.43, 124.09, 127.98, 128.32, 128.39, 128.82, 129.13, 130.01, 131.04, 132.29, 133.12, 134.45, 147.15, 162.10, 172.51 ppm. IR (KBr) ν 1645, 1607, 1569 cm^{-1}. MS m/z 371 (M^++H), 299, 191, 190, 119. HRMS calcd for $C_{24}H_{23}N_2O_2$: 371.1760; found: 371.1758.

4.2.19. 3-Methyl-2-phenylhydroquinolin-4-one (9).[20] Yield: 90%. Mp 287–290 °C. ^{1}H NMR ($CDCl_3$, TMS) δ 2.03 (s, 3H), 7.29 (t, J=7.6 Hz, 1H), 7.50 (s, 5H), 7.55 (t, J=7.6 Hz, 1H), 7.62 (d, J=7.6 Hz, 1H), 8.33 (d, J=7.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 11.94, 115.26, 117.75, 122.51, 123.15, 125.18, 128.10, 128.65, 128.87, 130.81, 135.32, 139.30, 147.65, 177.73 ppm. IR (KBr) ν 3255, 1628 cm^{-1}. MS m/z 236 (M^++H). HRMS calcd for $C_{16}H_{14}NO$: 236.1075; found: 236.1078.

4.2.20. 2-Methyl-3-phenylhydroquinolin-4-one (10). Yield: 88%. Mp 304–306 °C (lit.[21] 302–304 °C). ^{1}H NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 2.74 (s, 3H), 7.30–7.32 (m, 2H), 7.51–7.59 (m, 3H), 7.68 (t, J=7.7 Hz, 1H), 7.90 (t, J=7.7 Hz, 1H), 8.45 (d, J=7.7 Hz, 1H), 8.79 (d, J=7.7 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 19.48, 119.27, 119.92, 120.63, 123.36, 127.24, 128.99, 129.24, 130.32, 131.13, 133.39, 138.95, 156.01, 164.81 ppm. IR (KBr) ν 3261, 1628 cm^{-1}. MS m/z 236 (M^++H), 235 (M^+). HRMS calcd for $C_{16}H_{14}NO$: 236.1075; found: 236.1074.

4.2.21. 2-Methyl-3-propylhydroquinolin-4-one (11). Yield: 70%. Mp>360 °C (decomp.). ^{1}H NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 0.99 (t, J=7.5 Hz, 3H), 1.55 (sextet, J=7.5 Hz, 2H), 2.59 (s, 3H), 2.67 (t, J=7.5 Hz, 2H), 7.33 (t, J=7.9 Hz, 1H), 7.58 (t, J=7.9 Hz, 1H), 7.75 (d, J=7.9 Hz, 1H), 8.37 (d, J=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 13.76, 17.72, 21.67, 26.91, 117.71, 119.62, 122.39, 123.18, 124.69, 130.80, 138.72 (2C's), 148.04 ppm. IR (KBr) ν 3262, 1635 cm^{-1}. MS m/z 201 (M^+), 186, 172. HRMS calcd for $C_{13}H_{15}NO$: 201.1154; found: 201.1155.

4.2.22. 1,2,3,4-Tetrahydrocyclopenta[2,1-*b*]quinolin-9-one (12).[22] Yield: 76%. Mp 312–314 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 2.27 (q, J=7.6 Hz, 2H), 3.18 (t, J=7.6 Hz, 2H), 3.47 (t, J=7.6 Hz, 2H), 7.58 (t, J=7.6 Hz, 1H), 7.78 (t, J=7.6 Hz, 1H), 8.37–8.40 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$+DMSO-d_6 (10:1, v/v), TMS) δ 21.86, 27.56, 32.08, 118.18, 120.02, 123.34, 123.82, 124.71, 130.77, 139.86, 156.53, 172.94 ppm. IR (KBr) ν 3225, 1628 cm^{-1}. MS m/z 185 (M^+), 184, 156. HRMS calcd for $C_{12}H_{11}NO$: 185.0841; found: 185.0841.

4.2.23. 5,6,7,8,10-Pentahydroacridin-9-one (13). Yield: 80%. Mp 354–356 °C (lit.[23] 357–358 °C). ^{1}H NMR (DMSO-d_6) δ 1.68–1.78 (m, 4H), 2.43 (t, J=6.1 Hz, 2H), 2.69 (t, J=6.1 Hz, 2H), 7.22 (t, J=7.9 Hz, 1H), 7.45 (d, J=7.9 Hz, 1H), 7.56 (t, J=7.9 Hz, 1H), 8.04 (d, J=7.9 Hz, 1H) ppm. ^{13}C NMR (DMSO-d_6) δ 21.56, 21.75, 21.95, 27.21, 115.66, 117.44, 122.16, 123.24, 124.92, 131.11, 139.30, 147.05, 176.12 ppm. IR (KBr) ν 3402, 1635 cm^{-1}. MS m/z 200 (M^++H), 176. HRMS calcd for $C_{13}H_{14}NO$: 200.1075; found: 200.1073.

Acknowledgements

We thank the National Science Council of the Republic of China for financial support.

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Tetrahedron 62 (2006) 9373–9382

Synthesis of some cyclic indolic peptoids as potential antibacterials

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Received 6 June 2006; revised 30 June 2006; accepted 20 July 2006

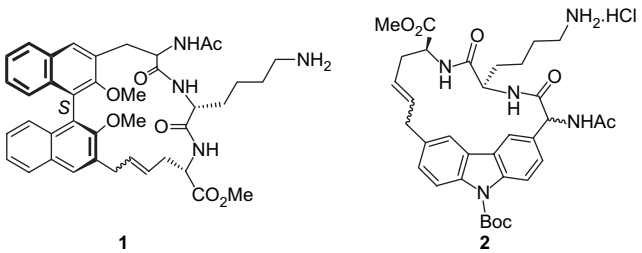
Abstract—The synthesis of cyclic peptoids containing an indole hydrophobic scaffold has been realised through the ring-closing metathesis of diallylated precursors. The precursors and their cyclic counterparts possessed poor antibacterial activity in contrast to previously reported cyclic peptoids containing hydrophobic scaffolds.

1. Introduction

The development and clinical application of antibiotics in the late 1930s enabled the control of the majority of bacterial infections. However, by the late 1950s up to 85% of clinical staphylococci isolates were found to be penicillin resistant.[1] Bacteria now have the ability to pass genetic information onto different strains leading to the widespread resistance of bacteria to many of the currently used antibiotics. The recent report of resistance to vancomycin is of the greatest concern as it represents the last line of defence against infections of multi-drug resistant staphylococci and enterococci.[2] Resistance to vancomycin was first documented in 1988,[3] from hospitals in both Europe,[4] and the USA.[5] This emergence of vancomycin resistant enterococci (VRE) is significant and points to the prospect of widespread vancomycin resistance to multi-drug resistant pathogenic bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA). 'Super-resistant' bacterial strains such as these have been demonstrated in a controlled environment, highlighting the ease in which resistance may spread to pathogenic bacteria,[3] and there are now cases of fully resistant isolates of *S. aureus* being reported.[6]

The advent of untreatable multi-drug resistant bacteria has created an unmet medical need to create new antibacterial agents. The development of new therapeutic agents is even more critical considering only one new class of antibacterial agents, the oxazolidinone linezolid,[7] has been launched in the last 35 years, and already resistance to this therapeutic has started to emerge.[8–10]

With the increasing spread of antibacterial resistance, including resistance by pathogenic bacteria to vancomycin, there is a compelling imperative for new antibacterials.[10] We have undertaken a programme for investigating the design and synthesis of cyclic peptoids linked by a hydrophobic scaffold as potential antibacterial agents, and thus far, have shown that the binaphthyl[11] and carbazole scaffolds[12,13] within these cyclic peptoids produce antibacterial agents, for example **1** and **2**, of reasonable potency (Fig. 1). Therefore, as a part of this programme targeting the design and synthesis of new peptoid derivatives as antibacterial agents and attempting to address the resistance mechanism against vancomycin, we investigated the synthesis of some acyclic and cyclic indole-based derivatives. These derivatives were designed to explore the effect on activity of a smaller rigid scaffold in which the indolic nitrogen was to serve as one of the anchor points. The results are reported in this paper.



1 MIC 7 g/mL **2** MIC 15 g/mL

Figure 1. Cyclic peptoids containing a hydrophobic scaffold that show antibacterial activity.[11–13] MIC = minimum inhibitory concentration and activities are against a wild type *S. aureus* strain.

Keywords: Cyclic peptoid; Antibacterial; Ring-closing metathesis; Indole.
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doi:10.1016/j.tet.2006.07.059

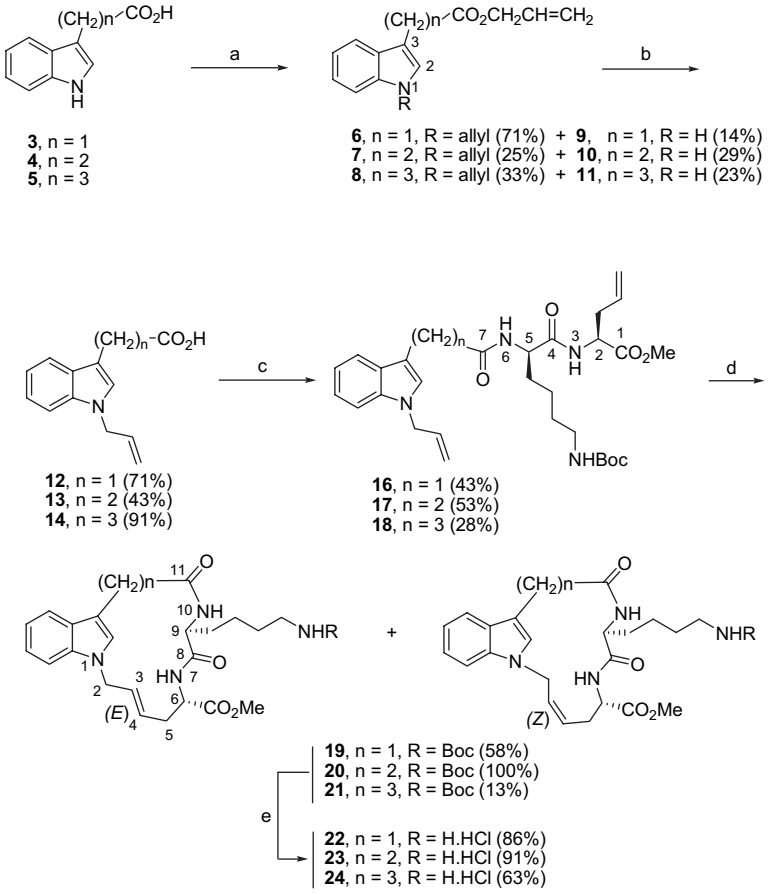
2. Results and discussion

2.1. Synthesis of indole-based peptoids

The synthesis of cyclic peptoids incorporating an indolic scaffold is outlined in Scheme 1. The strategy involved the addition of a dipeptide to an indole unit that contained a linking group at C3 as well as utilising the N1 position as a linking group via the addition of an allyl substituent. Cyclisation was to be achieved using reliable ring-closing metathesis (RCM) reactions.[11–14] While the choice of dipeptide to use is potentially extensive, a limitation is that one of the amino acids must also contain an additional allyl group such that the ring-closing metathesis reaction is possible. Cyclic peptoids of different sizes were synthesised by extending the number of methylene linkers between the indole C3 position and the first carboxylic acid unit.

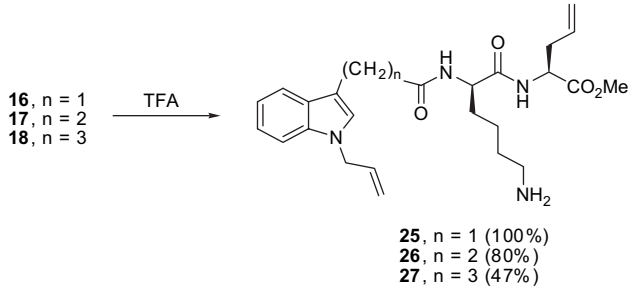
Therefore, treatment of commercially available indole acids **3**–**5** with base, followed by an excess of allyl bromide gave a mixture of both the allyl esters **9**–**11** and the diallylated products **6**–**8** (Scheme 1). Subsequent saponification with LiOH yielded the desired carboxylic acids **12**–**14**. This two-step process was the most efficient method of *N*-allylation in the presence of the carboxylic acid, although with the lengthening of the C3 chain, the yield of the monoallyl ester byproducts, **10** and **11**, became more prominent. The coupling of the dipeptide, L-allylGlyOMe-D-Lys **15**, to **12**–**14** was achieved through well established EDCI coupling. The key RCM of dienes **16**–**18** proceeded efficiently in the case of the products **19**–**20** producing a discernible mixture of both *E* and *Z* isomers, which could not be separated by silica gel chromatography. In contrast, the yield of **21** was lower, presumably due to the difficulties in forming the larger ring. However, further optimisation of this reaction may improve this outcome. The structures of the cyclised products were elucidated on the basis of high-resolution mass spectrometric and NMR spectroscopic evidence. In the ^{1}H NMR spectrum of **19**, for example, the signal ascribed to H3 appeared as a doublet of triplets at δ 5.52 (J=15, 6 Hz) with an associated multiplet at δ 5.90 assigned as either the corresponding *Z* isomer or rotamers. The larger coupling constants of 15–16 Hz for H3 in **19** and **20** were consistent with the *E*-geometry of the major isomers of these compounds. Unfortunately, $J_{3,4}$ for **21** could not be determined due to peak overlap. The *E*/*Z* ratio of **19**, **20** and **21** was thus estimated as 4:1, 7:3 and 3:2, respectively, from ^{1}H NMR analysis. Final unmasking of the lysine side chain and crystallisation from diethyl ether. HCl solution gave the cyclic peptoids as their hydrochloride salts **22**–**24**.

The corresponding hydrochloride salts of the deprotected acyclic precursors (**25**–**27**) were also synthesised using typical acidic conditions starting from **16**–**18** (Scheme 2). Further, the corresponding guanidine derivatives of the cyclic peptoids **31**–**33** were also produced via **28**–**30**, again



Scheme 1. (a) NaH (2.2 equiv), allyl bromide (2.5 equiv), DMF, rt, 12 h; (b) LiOH (0.15 M), THF, water, 0 °C; (c) L-allylGlyOMe-D-Lys **15**, EDCI, DMAP, MeCN, CH_2Cl_2, rt, 18 h; (d) Grubbs I catalyst (10 mol %), CH_2Cl_2, reflux 18 h; and (e) TFA, CH_2Cl_2, rt, 2 h.

using standard reaction conditions starting from **22**–**24**, and using *N*,*N*′-diBoc-*N*-triflylguanidine in the key guanidation step (Scheme 3).



Scheme 2. Deprotection of acyclic indole peptides.

The chemical yields for all transformations were not optimised, leading to some inconsistencies in outcome for individual steps. However, the ease of formation of all derivatives ensured facile access to the desired cyclic derivatives for testing.

2.2. Antibacterial results

The synthesised cyclic dipeptoids **22**–**24** and **31**–**33** were tested against the Gram-positive bacterium *S. aureus* ATCC6538 and showed MIC values greater than $\geq$125 μg/mL, indicating that these indole-based scaffolds are not good hydrophobic units for incorporation into the design programme for antibacterial development. In view of the success of some of our previous cyclic peptoid structures that showed antibacterial activities of MIC 7 μg/mL and 15 μg/mL for **1** and **2**, respectively (Fig. 1), the biological results for the new indole-based molecules were disappointing. The binaphthyl scaffold would contain a degree of flexibility by comparison, and might be able to orientate more easily into an active conformation. However, the carbazole scaffold in **2** is quite rigid, a conformational characteristic which is anticipated to be closer to that shown by the indole-based molecules. Although the mode of action of this class of compounds has not yet been established, we anticipate that the lack of activity for the new derivatives must arise from the wrong three-dimensional array of the relevant substituents. The smaller macrocyclic ring sizes in **22**–**24** compared with those in **1** or **2** may also be relevant in this context. Given that the same dipeptide is used in all three cases, we therefore presume that the presence of a particular hydrophobic moiety becomes an additional important element in establishing antibacterial activity, and that the indole scaffold itself is simply not appropriate. We are currently investigating other hydrophobic scaffolds in order to improve antibacterial activity.

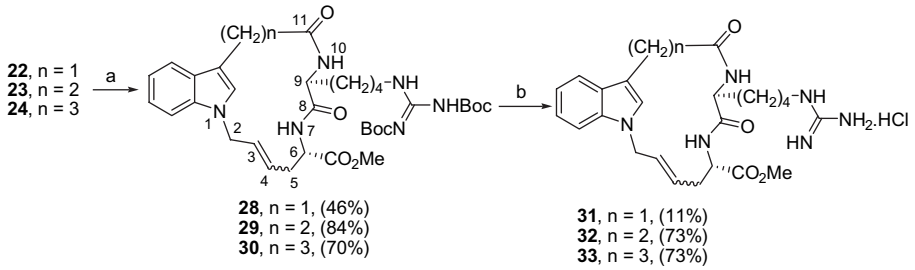
3. Experimental

3.1. General

All NMR spectra were determined in $CDCl_3$ solution at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) unless otherwise indicated. On occasions, the ^{13}C and ^{1}H NMR spectra indicated the presence of a minor component, which could be either rotamers or geometric isomers through the doubling of peaks. These have been reported and are assigned with an asterix (*). Petroleum spirit has a bp range of 40–60 °C. TLC was performed on Merck Al-backed plates. Other general experimental procedures have been reported previously.[13]

3.2. Allylation of indolyl-3-carboxylates—general procedure A. Allyl 1-allyl-1*H*-indole-3-acetate (6) and allyl 1*H*-indole-3-acetate (9)

To a suspension of sodium hydride (1.0 g, 25.1 mmol, 60% in paraffin), that had been washed twice with petroleum spirit under a N_2 atmosphere, in dry DMF (8 mL) was added a solution of 1*H*-indole acetic acid **3** (2.00 g, 11.4 mmol) in DMF (5 mL) under N_2 at rt. The mixture was stirred for 30 min before allyl bromide (2.5 mL, 28.6 mmol) was added dropwise. The reaction mixture was stirred for 18 h, concentrated and the residue partitioned between water (20 mL) and diethyl ether (2×20 mL). The combined extracts were washed (water), dried (Na_2SO_4) and concentrated. The crude product was subjected to flash silica gel column chromatography (20% CH_2Cl_2 in petroleum spirit) to produce **6** (2.08 g, 71%) as an oil. TLC (petroleum spirit/DCM 5:1) R_f=0.89; ^{1}H NMR δ=7.68 (d, J=8 Hz, 1H, ArH4), 7.34 (d, J=8 Hz, 1H, ArH7), 7.26 (apparent t, J=7 Hz, 1H, ArH6), 7.18 (apparent t, J=7 Hz, 1H, ArH5), 7.14 (s, 1H, ArH2), 5.99 (m, 2H, 2×C*H*=CH$_2$), 5.37–5.10 (m, 4H, 2×CH=C*H*$_2$), 4.70 (d, J=5 Hz, 2H, C*H*$_2$CH=CH$_2$), 4.66 (d, J=5 Hz, 2H, CH$_2$CH=CH$_2$), 3.86 (s, 2H, CH$_2$CO); ^{13}C NMR δ=171.1 (CO), 136.0 (ArC), 133.2 and 131.9 (*C*H=CH$_2$), 127.6 (ArC), 126.6, 121.5 and 119.1 (ArCH), 118.9 (CH=*C*H$_2$), 117.9 (ArCH), 117.1 (*C*H=CH$_2$), 109.4 (ArCH), 106.9 (ArC), 65.2 (OCH$_2$), 48.6 (NCH$_2$), 31.1 (CH$_2$); MS (CI) m/z 256 (100% MH$^+$). HRMS (CI) calcd for $C_{16}H_{18}NO_2$: 256.1338; found: 256.1338.



Scheme 3. Reagents: (a) *N*,*N*′-diBoc-*N*-triflylguanidine, Et_3N, CH_2Cl_2 and (b) TFA, CH_2Cl_2.

Further elution with 50% CH_2Cl_2 in petroleum spirit gave **9** (0.35 g, 14%). TLC (petroleum spirit/CH_2Cl_2 1:1) R_f=0.54; ^{1}H NMR δ=8.2 (1H, br s, NH), 7.68 (d, J=7 Hz, 1H, ArH4), 7.31–7.17 (m, 3H, ArH7,6,5), 7.01 (d, J=3 Hz, 1H, ArH2), 5.98 (ddt, J=17, 10, 5 Hz, 1H, C*H*=CH$_2$), 5.35 (dd, J=16, 1 Hz, 2H, CH=C*H*$_2$), 5.27* (dd, J=10, 1 Hz, 2H, CH=CH$_2$), 4.68 (dd, J=5, 1 Hz, 2H, NCH$_2$CH=CH$_2$), 3.86 (s, 2H, CH$_2$CO); ^{13}C NMR δ=171.2 (CO), 135.9 (ArC), 132.0 (*C*H=CH$_2$), 127.0 (ArC), 123.3, 121.9 and 119.4 (ArCH), 118.6 (CH=*C*H$_2$), 118.2 (ArCH), 111.2 (ArCH), 107.7 (ArC), 65.4 (OCH$_2$), 31.2 (CH$_2$); MS (CI) m/z 216 (100% MH$^+$). HRMS (CI) calcd for $C_{13}H_{14}NO_2$: 216.1024; found: 216.1021.

3.2.1. Allyl 1-allyl-1*H*-indole-3-propanoate (7) and allyl 1*H*-indole-3-propanoate (10). These were prepared by *general procedure A* using 1*H*-indole-3-propanoic acid **4** (2.36 g, 12.5 mmol), NaH (660 mg, 16.5 mmol) allyl bromide (2.7 mL, 31.2 mmol) and DMF (9 mL). The crude residue was subjected to flash silica gel column chromatography (20% $CHCl_2$ in petroleum spirit) to give **7** (0.84 g, 25%) as an oil. TLC (petroleum spirit/DCM 5:1) R_f=0.92; ^{1}H NMR δ=7.67 (d, J=8 Hz, 1H, ArH4), 7.34 (d, J=8 Hz, 1H, ArH7), 7.27 (t, J=8 Hz, 1H, ArH6), 7.18 (t, J=8 Hz, 1H, ArH5), 6.96 (s, 1H, ArH2), 6.07–5.90 (m, 2H, 2×C*H*=CH$_2$), 5.38–5.08 (m, 4H, CH=C*H*$_2$), 4.69 (d, J=5 Hz, 2H, C*H*$_2$CH=CH$_2$), 4.65 (d, J=5 Hz, 2H, C*H*$_2$CH=CH$_2$), 3.19 (t, J=8 Hz, 2H, C*H*$_2$CH$_2$CO), 2.81 (t, J=8 Hz, 2H, CH$_2$CO); ^{13}C NMR δ=172.8 (CO), 136.2 (ArC), 133.5 and 132.1 (C*H*=CH$_2$), 127.6 (ArC), 125.1 and 121.5 (ArCH), 118.8 (ArCH), 118.7 (CH=*C*H$_2$), 118.0 (ArCH) 116.9 (CH=*C*H$_2$), 113.6 (ArC), 109.5 (ArCH), 64.9 (OCH$_2$), 48.4 (NCH$_2$), 34.9 and 20.5 (CH$_2$); MS (ES) m/z 270 (100% MH$^+$), 212 (25%), 170 (88%). HRMS (ES) calcd for $C_{17}H_{19}NO_2$: 269.1416; found: 269.1412.

Further elution with 50% petroleum spirit in DCM gave **10** (0.84 g, 29%): TLC (petroleum spirit/DCM 1:2) R_f=0.75; ^{1}H NMR δ=8.16 (br s, 1H, NH), 7.70 (dd, J=8, 2 Hz, 1H, ArH4), 7.36 (dd, J=8, 2 Hz, 1H, ArH7), 7.28 (dd, J=8 Hz, 1H, ArH6), 7.22 (dt, J=8, 2 Hz, 1H, ArH5), 6.98 (d, J=3 Hz, 1H, ArH2), 5.98 (ddt, J=17, 10, 6 Hz, 1H, C*H*=CH$_2$), 5.37 (ddd, J=17, 2, 1 Hz, 2H, CH=C*H*$_2$), 5.30* (ddd, J=10, 2, 1 Hz, 2H, CH=C*H*$_2$), 4.68 (2×t, J=6 Hz, 2H, C*H*$_2$CH=CH$_2$), 3.22 (t, J=8 Hz, 2H, CH$_2$CO), 2.85 (t, J=8 Hz, 2H, C*H*$_2$CH$_2$CO); ^{13}C NMR δ=173.1 (CO), 136.1 (ArC), 132.0 (*C*H=CH$_2$), 126.9 (ArC), 121.7, 121.4 and 119.0 (ArCH), 118.4 (CH=*C*H$_2$), 118.0 (ArCH), 114.3 (ArC), 111.1 (ArCH), 65.0 (OCH$_2$), 34.7 and 20.4 (CH$_2$); MS (ES) m/z 230 (100% MH$^+$), 172 (55%), 130 (75%). HRMS (ES) calcd for $C_{14}H_{15}NO_2$: 229.1103; found: 229.1100.

3.2.2. Allyl 1-allyl-1*H*-indole-3-butanoate (8) and allyl 1*H*-indole-3-butanoate (11). These were prepared by *general procedure A* using 1*H*-indole-3-butanoic acid **5** (1.00 g, 4.9 mmol), NaH (217 mg, 5.4 mg), allyl bromide (1.1 mL, 12.7 mmol) and DMF (6 mL). The crude product was subjected to flash silica gel column chromatography (50% DCM in petroleum spirit) to give **8** (0.46 g, 33%) as an oil. TLC (petroleum spirit/DCM 2:1) R_f=0.91; ^{1}H NMR δ=7.58 (dt, J=8, 1 Hz, 1H, ArH4), 7.24 (dd, J=8, 1 Hz, 1H, ArH7), 7.17 (dt, J=8, 1 Hz, 1H, ArH6), 7.08 (dt, J=8, 1 Hz, 1H, ArH5), 6.84 (s, 1H, ArH2), 5.90 (m, 2H, 2×C*H*=CH$_2$), 5.28 (ddd, J=17, 2, 1 Hz, 2H, CH=C*H*$_2$), 5.19* (ddd, J=11, 2, 1 Hz, 2H, CH=C*H*$_2$), 5.13* (ddd, J=10, 2, 1 Hz, 2H, CH=C*H*$_2$), 5.03 (ddd, J=18, 2, 1 Hz, 2H, CH=C*H*$_2$), 4.57 (dd, J=5, 1 Hz, 4H, C*H*$_2$CH=CH$_2$), 2.78 (t, J=7 Hz, 2H, C*H*$_2$CH$_2$CH$_2$CO), 2.38 (t, J=7 Hz, 2H, CH$_2$CO), 2.03 (pent, J=7 Hz, 2H, C*H*$_2$CH$_2$CO); ^{13}C NMR δ=173.2 (CO), 136.3 (ArC), 133.5 and 132.2 (*C*H=CH$_2$), 127.9 (ArC), 125.1, 121.4 and 118.9 (ArCH), 118.6 (CH=*C*H$_2$), 118.0 (ArCH), 116.9 (CH=*C*H$_2$), 114.3 (ArC), 109.4 (ArCH), 64.8 (OCH$_2$), 48.4 (NCH$_2$), 33.7, 25.3 and 24.3 (CH$_2$); MS (CI) m/z 284 (100% MH$^+$). HRMS (CI) calcd for $C_{18}H_{22}NO_2$: 284.1650; found: 284.1639.

Further elution with 50% petroleum spirit in DCM gave **11** (0.27 g, 23%). TLC (petroleum spirit/DCM 1:2) R_f=0.66; ^{1}H NMR δ=8.0 (br s, 1H, NH), 7.59 (d, J=8 Hz, 1H, ArH4), 7.34 (d, J=8 Hz, 1H, ArH7), 7.17 (t, J=8 Hz, 1H, ArH6), 7.09 (t, J=8 Hz, 1H, ArH5), 6.97 (d, J=2 Hz, 1H, ArH2), 5.89 (ddt, J=10, 5, 1 Hz, 1H, C*H*=CH$_2$), 5.29 (dd, J=16, 1 Hz, 2H, CH=C*H*$_2$), 5.21* (dd, J=10, 1 Hz, 2H, CH=C*H*$_2$), 4.55 (d, J=6 Hz, 2H, C*H*$_2$CH=CH$_2$), 2.80 (t, J=7 Hz, 2H, C*H*$_2$CH$_2$CH$_2$CO), 2.40 (t, J=7 Hz, 2H, CH$_2$CO), 2.05 (t, J=7 Hz, 2H, C*H*$_2$CH$_2$CO); ^{13}C NMR δ=173.2 (CO), 136.2 (ArC), 132.1 (*C*H=CH$_2$), 127.3 (ArC), 121.8, 121.3 and 119.1 (ArCH), 118.8 (CH=*C*H$_2$), 118.1 (ArCH), 115.5 (ArC), 111.0 (ArCH), 65.0 (OCH$_2$), 33.9, 29.8, 25.4 and 24.5 (CH$_2$); MS (CI) m/z 244 (100% MH$^+$), 186 (45% M$^+$−OCH$_2$CH=CH$_2$). HRMS (CI) calcd for $C_{15}H_{18}NO_2$: 244.1338; found: 244.1332.

3.3. Hydrolysis of allyl esters—general procedure B. 1-Allyl-1*H*-indole-3-acetic acid (12)

To a solution of **6** (1.84 g, 7.2 mmol) in THF/water (5:2, 35 mL) was added lithium hydroxide (0.3 g, 12.5 mmol) and the reaction mixture was placed in an ice bath and stirred at 0 °C for 3 h. It was then concentrated and the residue was partitioned between diethyl ether and water (2×30 mL). The combined aqueous layers were acidified with HCl (10%) to pH<2. The aqueous layer was then saturated with sodium chloride and extracted with DCM (20 mL), dried (Na_2SO_4) and evaporated to give **12** (1.1 g, 71%) as an oil. ^{1}H NMR δ=7.60 (d, J=8 Hz, 1H, ArH4), 7.30 (d, J=8 Hz, 1H, ArH7), 7.22 (dt, J=8, 1 Hz, 1H, ArH6), 7.13 (dt, J=8, 1 Hz, 1H, ArH5), 7.08 (s, 1H, ArH2), 5.98 (ddt, J=17, 11, 5 Hz, 1H, C*H*=CH$_2$), 5.20* (dd, J=9, 1 Hz, 2H, CH=C*H*$_2$), 5.11 (dd, J=16, 1 Hz, 2H, CH=C*H*$_2$), 4.68 (dd, J=5, 1 Hz, 2H, NC*H*$_2$CH=CH$_2$), 3.80 (s, 2H, CH$_2$CO); ^{13}C NMR δ=177.5 (CO), 136.1 (ArC), 133.2 (*C*H=CH$_2$), 127.6 (ArC), 126.8, 121.8 and 119.3 (ArCH), 118.9 (CH=*C*H$_2$), 117.4 and 109.6 (ArCH), 106.4 (ArC), 48.8 (NCH$_2$), 31.0 (CH$_2$); MS (CI) m/z 216 (100% MH$^+$). HRMS (CI) calcd for $C_{13}H_{14}NO_2$: 216.1024; found: 216.1039.

3.3.1. 1-Allyl-1*H*-indole-3-propanoic acid (13). This was prepared by *general procedure B* from **7** (0.650 g, 2.4 mmol), LiOH (0.220 g, 9.2 mmol) and 35 mL of solvent to give **13** (0.24 g, 43%) as an oil. ^{1}H NMR δ=7.59 (d, J=8 Hz, 1H, ArH4), 7.34 (d, J=8 Hz, 1H, ArH7), 7.16–7.01 (m, 3H, ArH2,5,6), 6.07–5.94 (m, 1H, C*H*=CH$_2$),

5.12* (dd, J=10, 1 Hz, 2H, CH=CH_2), 5.04 (dd, J=17, 1 Hz, 2H, CH=CH_2), 4.77 (d, J=3 Hz, 2H, NCH_2CH=CH_2), 3.04 (t, J=10 Hz, 2H, C$H_2$$CH_2$CO), 2.68 (t, J=8 Hz, 2H, CH_2CO); ^{13}C NMR δ=179.3 (CO), 136.4 (ArC), 133.5 (*C*H=CH_2), 127.7 (ArC), 125.2, 121.7 and 118.9 (ArCH), 118.8 (CH=*C*H_2), 117.1 (ArCH), 113.5 (ArC), 109.6 (ArCH), 48.6 (NCH_2), 31.5 and 20.3 (CH_2); MS (CI) *m*/*z* 230 (100% MH^+); (ES) 170 (M^+-CH_2COOH). HRMS (CI) calcd for $C_{14}H_{16}NO_2$: 230.1181; found: 230.1181.

3.3.2. 1-Allyl-1*H*-indole-3-butanoic acid (14). This was prepared by *general procedure B* from **8** (0.460 g, 1.6 mmol), LiOH (0.220 g, 9.2 mmol) and solvent (35 mL) to give **14** (0.36 g, 91%) as an oil. ^{1}H NMR δ=7.61 (d, J=8 Hz, 1H, ArH4), 7.30 (d, J=8 Hz, 1H, ArH7), 7.21 (t, J=8 Hz, 1H, ArH6), 7.12 (t, J=8 Hz, 1H, ArH5), 6.91 (s, 1H, ArH2), 5.99 (ddt, J=17, 11, 5 Hz, 1H, C*H*=CH_2), 5.20* (dd, J=10, 2 Hz, 2H, CH=CH_2), 5.10 (dd, J=17, 2 Hz, 2H, CH=CH_2), 4.69 (d, J=5 Hz, 2H, NCH_2CH=CH_2), 2.84 (t, J=7 Hz, 2H, C$H_2$$CH_2$$CH_2$CO), 2.45 (t, J=7 Hz, 2H, CH_2CO), 2.07 (t, J=7 Hz, 2H, C$H_2$$CH_2$CO); ^{13}C NMR δ=179.7 (CO), 136.4 (ArC), 133.6 (*C*H=CH_2), 127.9 (ArC), 125.3, 121.5 and 119.0 (ArCH), 118.8 (CH=*C*H_2), 117.0 (ArCH), 114.3 (ArC), 109.5 (ArCH), 48.6 (NCH_2), 33.5, 15.1 and 24.3 (CH_2); MS (ES) *m*/*z* 244 (100% MH^+), 226 (55% MH^+-H_2O). HRMS (CI) calcd for $C_{15}H_{18}NO_2$: 244.1337; found: 244.1336.

3.4. Preparation of methyl (2*S*,5*R*)-2-allyl-5-amino-3-aza-9-(*tert*-butoxycarbonyl)amino-4-oxononanoate—L-allylGlyOMe-D-Lys (15)

To a mixture of *N*-Fmoc-D-Lys(Boc)OH (1.22 g, 2.61 mmol), methyl (*S*)-2-amino-4-pentenoate hydrochloride (430 mg, 2.61 mmol) and 4-dimethylaminopyridine (DMAP) (1 crystal) was added dry DCM (10 mL) followed by *N*,*N*-diisopropylethylamine (0.45 mL, 2.61 mmol) under a nitrogen atmosphere. The mixture was stirred at rt for 5 min before EDCI (500 mg, 2.61 mmol) was added, and the reaction mixture was then stirred for 23.5 h. After this period, the reaction mixture was diluted with DCM, washed with brine and then water, and the DCM layer was dried and evaporated. The crude product was purified by column chromatography (PS with gradient elution to DCM/MeOH 10:1) to afford the protected coupled dipeptide (1.25 g, 2.16 mmol, 83%) as a pale yellow solid, mp 118–119 °C. R_f=0.52 in 10% MeOH in DCM; ^{1}H NMR δ=7.73 (d, J=7.5 Hz, 2H, ArH4 and ArH5), 7.56 (d, J=7.2 Hz, 2H, ArH1 and ArH8), 7.36 (dd, J=7.3, 7.2 Hz, 2H, ArH3 and ArH6), 7.27 (dd, J=7.3, 7.2 Hz, 2H, ArH2 and ArH7), 6.82 (d, J=6.6 Hz, 1H, NH-3), 5.76–5.52 (m, 2H, CH_2C*H*=CH_2 and N*H*Boc), 5.05 (d, J=16.5 Hz, 1H, CH_2CH=C*H*H), 5.04 (d, J=10.5 Hz, 1H, CH_2CH=CH*H*), 4.64 (m, 2H, NCH-2 and N*H*Fmoc), 4.35 (d, J 6.9 Hz, 2H, OCH_2), 4.18 (t, J=6.9 Hz, 2H, Fmoc CH and NCH-5 (obscured)), 3.67 (s, 3H, OCH_3), 3.07 (m, 2H, NC$H_2$$(CH_2)_3$), 2.50 (m, 2H, C$H_2$CH=$CH_2$), 1.82 (m, N$(CH_2)_3CH_2$), 1.63 (m, N$(CH_2)_3CH_2$), 1.53–1.25 (m, 4H, NCH_2(CH_2)$_2$$CH_2$), 1.40 (s, 9H, C$(CH_3)_3$); ^{13}C NMR δ 171.8 (*C*OOCH_3), 171.4 (CO-4), 156.2 (Fmoc CO), 156.1 (Boc CO), 143.7 and 143.6 (ArC8a and ArC9a), 141.2 (ArC4a and ArC4b), 132.0 (CH_2*C*H=CH_2), 127.7 (ArCH3 and ArCH6), 127.0 (ArCH2 and ArCH7), 125.0 (ArCH1 and ArCH8), 119.9 (ArCH4 and ArCH5), 119.3 (CH_2CH=*C*H_2), 79.1 (*C*$(CH_3)_3$), 67.1 (OCH_2), 54.6 (NCH-5), 52.4 (OCH_3), 51.5 (NCH2), 47.0 (Fmoc CH), 39.8 (N*C*$H_2$$(CH_2)_3$), 36.3 (*C*$H_2$CH=$CH_2$), 32.1 (N$(CH_2)_3$*C*$H_2$), 29.6 ($NCH_2$*C*$H_2$$(CH_2)_2$), 28.3 (C(*C*$H_3)_3$), 22.3 (N$(CH_2)_2$*C*$H_2$$CH_2$); MS (ES) *m*/*z* 580 (100% MH^+), 524 (88%), 480 (66%). HRMS (ES) calcd for $C_{32}H_{42}N_3O_7$: 580.3023; found: 580.3002.

To a solution of the protected dipeptide (500 mg, 0.86 mmol) in anhydrous CH_3CN (10 mL) was added a solution of piperidine (0.04 mL, 0.43 mmol) in anhydrous CH_3CN under a nitrogen atmosphere, and the reaction mixture was stirred at rt for 3.25 h. The reaction solvent was evaporated and the crude product was purified by column chromatography (PS with gradient elution to DCM/MeOH 10:1) to afford **15** (308 mg, 0.86 mmol, 100%) as a yellow oil. R_f=0.24 in 10% MeOH in DCM; ^{1}H NMR δ 7.66 (d, J=8.1 Hz, 1H, NH-3), 5.60 (ddt, J=17.1, 10.5, 6.9 Hz, 1H, CH_2C*H*=CH_2), 5.03 (dd, J=16.5, 1.2 Hz, 1H, CH_2CH=C*H*H), 5.02, (dd, J=10.8, 0.9 Hz, 1H, CH_2CH=CH*H*), 4.79 (br s, 1H, N*H*Boc), 4.52 (dt, J=8.1, 6.0 Hz, 1H, NCH-2), 3.64* (s, OCH_3), 3.64 (s, OCH_3), 3.27 (m, 1H, NCH-5), 3.01 (m, 2H, NC$H_2$$(CH_2)_3$), 2.45 (m, 2H, C$H_2$CH=$CH_2$), 1.80–1.64 (m, NH_2 and N$(CH_2)_3$CH_2), 1.56–1.25 (m, NCH_2(CH_2)$_3$), 1.33 (s, 9H, C$(CH_3)_3$); ^{13}C NMR δ 174.9 (*C*OOCH_3), 172.0 (CO-4), 156.0 (Boc CO), 132.2 (CH_2*C*H=CH_2), 118.8 (CH_2CH=*C*H_2), 78.8 (*C*$(CH_3)_3$), 54.7 (NCH-5), 52.1 (OCH_3), 51.1 (NCH-2), 39.9 (N*C*$H_2$$(CH_2)_3$), 36.1 (*C*$H_2$CH=$CH_2$), 34.3 (N$(CH_2)_3$*C*$H_2$), 29.6 ($NCH_2$*C*$H_2$$(CH_2)_2$), 28.2 (C(*C*$H_3)_3$), 22.4 (N$(CH_2)_2$*C*$H_2$$CH_2$); MS (ES) *m*/*z* 358 (89% MH^+), 302 (100%), 258 (93%). HRMS (ES) calcd for $C_{17}H_{32}N_3O_5$: 358.2342; found: 358.2329.

3.5. Coupling of indole carboxylates with dipeptides—general procedure C. Methyl (2*S*,5*R*)-2-allyl-8-(*N*-allyl-1*H*-indol-3-yl)-3,6-diaza-5-(*tert*-butoxycarbonylamino)-butyl-4,7-dioxooctanoate (16)

To a solution of **12** (0.048 g, 0.2 mmol) in DCM (3 mL) was added **15** (0.080 g, 0.22 mmol) in acetonitrile (3 mL) and a catalytic amount of DMAP. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.043 g, 0.2 mmol) was then added and the mixture was stirred for 18 h under a N_2 atmosphere at rt. The solvents were evaporated and the mixture was partitioned between DCM and water. The DCM layer was separated and washed several times with water, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on a flash silica gel column (2% methanol in DCM) to produce **16** (0.090 g, 43%) as a solid. TLC (DCM/MeOH 50:1) R_f=0.22; ^{1}H NMR δ=7.52 (d, J=8 Hz, 1H, ArH4), 7.29 (d, J=8 Hz, 1H, ArH7), 7.20 (t, J=8 Hz, 1H, ArH6), 7.10 (t, J=8 Hz, 1H, ArH5), 7.06 (s, 1H, ArH2), 6.78 (d, J=8 Hz, 1H, NH-3), 6.21 (d, J=8 Hz, 1H, NH-6), 5.97 (ddt, J=17, 11, 5 Hz, 1H, NCH_2C*H*=CH_2), 5.61 (m, 1H, $CHCH_2$C*H*=CH_2), 5.18 (d, J=10 Hz, 1H, CH=C*H*H), 5.09–5.04 (m, 3H, CH=CH_2+CH=CH*H*), 4.69 (d, J=6 Hz, 2H, NCH_2CH=CH_2), 4.53 (m, 1H, H2), 4.43 (m, 1H H5), 3.72 (s, 2H, H8), 3.68 (s, 3H, OCH_3), 2.93 (d, J=5 Hz, 2H, NC$H_2$$(CH_2)_3$), 2.53–2.35 (m, 2H, $CHCH_2$CH=CH_2), 1.77–1.66 (m, 1H, N$(CH_2)_3$CH_2), 1.41 (s, 9H, C$(CH_3)_3$), 1.45–1.27 (m, 4H, N$(CH_2)_3$CH_2+NCH_2CH_2(CH_2)$_2$), 1.15–1.08 (m, 2H, N$(CH_2)_2$C$H_2$$CH_2$); ^{13}C NMR δ=171.7 (7-CO), 171.5 (*C*OOCH_3), 170.9

(5-CO), 155.8 (N*C*O$_2$^{t}Bu), 136.4 (ArC7), 133.1 (NCH$_2$*C*H=CH$_2$), 132.0 (CH$_2$*C*H=CH$_2$), 127.4 (ArC3a), 127.2 (ArC2), 122.1 (ArC6), 119.6 (ArC4), 119.1 (CH$_2$CH=*C*H$_2$), 118.7 (ArCH5), 117.4 (NCH$_2$CH=*C*H$_2$), 109.8 (ArCH7), 107.4 (ArC3), 79.1 (OCMe$_3$), 52.7 (C2), 52.4 (OCH$_3$), 51.6 (C5), 48.8 (N*C*H$_2$CH=CH$_2$), 40.1 (N*C*H$_2$(CH$_2$)$_3$), 36.3 (C8), 33.3 (CH*C*H$_2$CH=CH$_2$), 31.5 (N(CH$_2$)$_3$*C*H$_2$), 29.5 (NCH$_2$*C*H$_2$(CH$_2$)$_2$), 28.5 (C(*C*H$_3$)$_3$), 22.5 (N(CH$_2$)$_2$*C*H$_2$CH$_2$); MS (ES) *m*/*z* 555 (95% MH$^+$), 499 (89%), 455 (100%). HRMS (ES) calcd for $C_{30}H_{43}N_4O_6$: 555.3184; found: 555.3163.

3.5.1. Methyl (2*S*,5*R*)-2-allyl-9-(*N*-allyl-1*H*-indol-3-yl)-3,6-diaza-5-(*tert*-butoxycarbonylamino)butyl-4,7-dioxononanoate (17). This was prepared by *general procedure C* using **13** (0.220 g, 0.96 mmol), **15** (0.210 g), DCM (3 mL), AcCN (6 mL) and EDCI (0.114 g), to give **17** (0.290 g, 53%). TLC (DCM/MeOH 50:1) R_f=0.45; ^{1}H NMR (CDCl$_3$, 500 MHz) δ=7.57 (d, *J*=8 Hz, 1H, H4), 7.25 (d, *J*=8 Hz, 1H, H7), 7.17 (dd, *J*=8, 4 Hz, 1H, H6), 7.07 (dd, *J*=8, 4 Hz, 1H, H5), 7.01 (d, *J*=4 Hz, 1H, NH-3), 6.88 (s, 1H, H2), 6.49 (d, *J*=4 Hz, 1H, NH-6), 5.97–5.88 (m, 1H, NCH$_2$C*H*=CH$_2$), 5.65 (ddt, *J*=17, 10, 4 Hz, 1H, CH$_2$C*H*=CH$_2$), 5.15–5.03 (m, 4H, 2×CH=C*H*$_2$), 4.67–4.61 (m, 2H, NC*H*$_2$CH=CH$_2$ and N*H*Boc), 4.62 (m, 1H, H2), 4.47 (dd, *J*=14, 7 Hz, 1H, H5), 3.69 (s, 3H, OCH$_3$), 3.15–3.00 (m, 2H, H9), 3.05–2.93 (m, 2H, NC*H*$_2$(CH$_2$)$_3$), 2.72 (m, 1H, H8), 2.60 (m, 1H, H8), 2.60–2.52 (m, 1H, CHC*H*$_2$CH=CH$_2$), 1.74–1.66 (m, 1H, N(CH$_2$)$_3$C*H*$_2$), 1.54–1.44 (m, 2H, N(CH$_2$)$_3$C*H*$_2$), 1.41 (s, 9H, C(CH$_3$)$_3$), 1.42–1.34 (m, 2H, NCH$_2$(C*H*$_2$)$_2$), 1.22–1.14 (m, 2H, N(CH$_2$)$_2$C*H*$_2$CH$_2$); ^{13}C NMR δ=176.8* (7-CO), 172.9 (7-CO), 171.5 (*C*OOCH$_3$), 171.5 (4-CO), 155.9 (N*C*O$_2$^{t}Bu), 136.3 (C7), 133.4 (C*H*=CH$_2$), 132.0 (C*H*=CH$_2$), 127.7 (ArC3a), 125.2 (ArC2), 125.0* (ArC2), 121.5 (ArC6), 119.1 (CH$_2$CH=*C*H$_2$), 118.9 (ArC4 and ArC5), 118.8* (ArC4), 118.7* (ArC5), 117.0 (NCH$_2$CH=*C*H$_2$), 113.7* (ArC3), 113.6 (ArC3), 109.4 (ArC7), 79.0 (O*C*Me$_3$), 52.7 (C5), 52.4 (OCH$_3$), 51.7 (C2), 48.6 (NCH$_2$CH=CH$_2$), 40.0 (N*C*H$_2$(CH$_2$)$_3$), 37.2 (H8), 36.3 (CHCH$_2$–CH=CH$_2$), 34.8* (H8), 31.9 (N(CH$_2$)$_3$*C*H$_2$), 29.5 (NCH$_2$*C*H$_2$(CH$_2$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 22.4 (N(CH$_2$)$_2$*C*H$_2$CH$_2$), 21.3 (C9), 20.5* (C9); MS (ES) *m*/*z* 569 (100% MH$^+$), 513 (49% MH$^+$−C(Me$_3$)), 469 (64% MH$^+$−Boc). HRMS (ES) calcd for $C_{31}H_{45}N_4O_6$: 569.3339; found: 569.3308.

3.5.2. Methyl (2*S*,5*R*)-2-allyl-10-(*N*-allyl-1*H*-indol-3-yl)-3,6-diaza-5-(*tert*-butoxycarbonylamino)butyl-4,7-dioxodecanoate (18). This was prepared by *general procedure C* using **14** (0.200 g, 0.79 mmol), **15** (0.230 g), DCM (3 mL), AcCN (6 mL) and EDCI (0.124 g) to give **18** (130 mg, 28%) as a solid. TLC (DCM/MeOH 50:1) R_f=0.45; ^{1}H NMR δ=7.56 (d, *J*=8 Hz, 1H, ArH4), 7.27 (d, *J*=8 Hz, 1H, ArH7), 7.17 (dt, *J*=8, 1 Hz, 1H, ArH6), 7.07 (t, *J*=8 Hz, 1H, ArH5), 6.99 (d, *J*=8 Hz, 1H, 3-NH), 6.88 (s, 1H, ArH2), 6.34 (d, *J*=8 Hz, 1H, 6-NH), 5.96 (ddt, *J*=18, 11, 6 Hz, 1H, NCH$_2$C*H*=CH$_2$), 5.66 (ddt, *J*=17, 9, 7 Hz, 1H, CHCH$_2$C*H*=CH$_2$), 5.18–5.03 (m, 4H, 2×CH=C*H*$_2$), 4.71–4.65 (m, 3H, NC*H*$_2$CH=CH$_2$ and N*H*Boc), 4.60 (dd, *J*=6, 2 Hz, 1H, H2), 4.50 (dt, *J*=6, 8 Hz, 1H, H5), 3.68 (s, 3H, OC*H*$_3$), 3.06 (d, *J*=6 Hz, 2H, NC*H*$_2$(CH$_2$)$_3$), 2.77 (t, *J*=7 Hz, 2H, H10), 2.52 (ddd, *J*=15, 9, 5 Hz, 2H, CHC*H*$_2$CH=CH$_2$), 2.28 (t, *J*=7 Hz, 2H, CH$_2$8), 2.03 (pent, *J*=7 Hz, 2H, H9), 1.81 (m, 1H, N(CH$_2$)$_3$C*H*H), 1.63 (m, 1H, N(CH$_2$)$_3$CH*H*), 1.41 (s, 9H, C(CH$_3$)$_3$), 1.48–1.29 (m, 4 H, NCH$_2$C*H*$_2$(CH$_2$)$_2$ and N(CH$_2$)$_2$C*H*$_2$CH$_2$); ^{13}C NMR δ=173.2 (7-CO), 171.7 (*C*OOCH$_3$), 171.4 (4-CO), 156.1 (N*C*O$_2$^{t}Bu), 136.4 (ArC7a), 133.6 (NCH$_2$*C*H=CH$_2$), 132.1 (CH$_2$*C*H=CH$_2$), 127.9 (ArC3a), 125.2 (ArC2), 121.4 (ArC6), 119.2 (ArC4), 119.0 (CH$_2$CH=*C*H$_2$), 118.7 (ArC5), 117.0 (NCH$_2$CH=*C*H$_2$), 114.4 (ArC3), 109.4 (ArC7), 79.0 (O*C*(CH$_3$)$_3$), 52.6 (C2), 52.3 (OCH$_3$), 51.6 (C5), 48.5 (N*C*H$_2$CH=CH$_2$), 39.9 (N*C*H$_2$(CH$_2$)$_3$), 36.2 (CH*C*H$_2$CH=CH$_2$), 35.9 (H8), 31.9 (N(CH$_2$)$_3$*C*H$_2$), 29.6 (NCH$_2$*C*H$_2$(CH$_2$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 26.0 (H10), 24.4 (H9), 22.4 (N(CH$_2$)$_2$*C*H$_2$CH$_2$); MS (ES) *m*/*z* 583 (100% MH$^+$), 527 (44%), 483 (46%). HRMS (ES) calcd for $C_{32}H_{47}N_4O_6$: 583.3496; found: 583.3506.

3.6. Amino acid deprotection—general procedure D. Methyl (2*S*,5*R*)-2-allyl-8-(*N*-allyl-1*H*-indol-3-yl)-3,6-diaza-5-(4-aminobutyl)-4,7-dioxooctanoate hydrochloride (25)

To a solution of **16** (0.07 g, 0.1 mmol) in DCM (2 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred under a N$_2$ atmosphere at rt for 2 h. The solvents were evaporated and the residue was dissolved in methanol. Hydrochloric acid (1 M, 0.2 mL, 0.2 mmol) in diethyl ether was added and the solution was evaporated. Recrystallization from a minimum amount of petroleum spirit and DCM/diethyl ether produced **25** as a brown solid in quantitative yield, mp 103–106 °C; TLC (MeOH) R_f=0.74; ^{1}H NMR (CD$_3$OD) δ=7.56 (d, *J*=8 Hz, 1H, ArH4), 7.28 (d, *J*=8 Hz, 1H, ArH7), 7.15 (s, 1H, ArH2), 7.10 (t, *J*=8 Hz, 1H, ArH6), 7.00 (t, *J*=8 Hz, 1H, ArH5), 6.00–5.92 (m, 1H, NCH$_2$C*H*=CH$_2$), 5.67–5.54 (m, 1H, CH$_2$C*H*=CH$_2$), 5.09 (d, *J*=10 Hz, 1H, CH=C*H*H), 5.11–4.86 (m, 4H, 2×CH=C*H*$_2$), 4.71 (d, *J*=6 Hz, 2H, NC*H*$_2$CH=CH$_2$), 4.37 (m, 2H, H2 and H5), 3.68 (s, 2H, H8), 3.62 (s, 3H, OCH$_3$), 2.70 (br s, 2H, NC*H*$_2$(CH$_2$)$_3$), 2.49–2.41 (m, 1H, CHC*H*HCH=CH$_2$), 2.38–2.24 (m, 1H, CHCH*H*CH=CH$_2$), 1.84–1.68 (br s, 2H, N(CH$_2$)$_3$C*H*$_2$), 1.68–1.46 (m, 2H, NCH$_2$C*H*$_2$(CH$_2$)$_2$), 1.34–1.22 (m, 2H, N(CH$_2$)$_2$C*H*$_2$CH$_2$); ^{13}C NMR δ=174.1 (7-CO), 173.2 (*C*OOCH$_3$), 172.8 (4-CO), 137.8 (ArC7a), 135.1 (NCH$_2$*C*H=CH$_2$), 134.0 (CH$_2$*C*H=CH$_2$), 128.9 (ArC3a), 128.4 (ArH2), 122.6 (ArH6), 120.0 (ArH4), 119.8 (ArH5), 118.8 (CH$_2$CH=*C*H$_2$), 116.9 (NCH$_2$CH=*C*H$_2$), 110.8 (ArH7), 109.1 (ArC3), 54.1 (C2), 53.3 (OCH$_3$), 52.7 (C5), 49.4 (N*C*H$_2$CH=CH$_2$), 40.4 (N*C*H$_2$(CH$_2$)$_3$), 36.7 (CH*C*H$_2$CH=CH$_2$), 33.8 (CH$_2$8), 32.6 (N(CH$_2$)$_3$*C*H$_2$), 28.0 (NCH$_2$*C*H$_2$(CH$_2$)$_2$), 23.5 (N(CH$_2$)$_2$*C*H$_2$CH$_2$); MS (ES) *m*/*z* 455 (100% MH$^+$), 326 (79%). HRMS (ES) calcd for $C_{25}H_{35}N_4O_4$: 455.2658; found: 455.2663.

3.6.1. Methyl (2*S*,5*R*)-2-allyl-9-(*N*-allyl-1*H*-indol-3-yl)-3,6-diaza-5-(4-aminobutyl)-4,7-dioxononanoate hydrochloride (26). This was prepared by *general procedure D* using **17** (70 mg, 0.12 mmol) giving **26** as a solid (0.050 g, 80%), mp 145–148 °C; TLC (MeOH) R_f=0.67; ^{1}H NMR δ 7.94 (br s, 1H, 3-NH), 7.54 (d, *J*=7 Hz, 1H, ArH4), 7.24–7.04 (m, 4H, ArH2,5,6,7), 6.86 (br s, 1H, 6-NH), 5.87 (m, 1H, NCH$_2$C*H*=CH$_2$), 5.64 (m, 1H, CH$_2$C*H*=CH$_2$), 5.12–4.97 (m, 4H, 2×CH=C*H*$_2$), 4.62–4.44 (m, 4H, NC*H*$_2$CH=CH$_2$ and H2 and H5), 3.64 (s, 3H, OCH$_3$), 3.09–2.81 (m, 4H, H9 and NC*H*$_2$(CH$_2$)$_3$), 2.75–2.37 (m,

4H, H8+CHCH_2CH=CH_2), 1.81–1.52 (m, 2H, N(CH_2)$_3$CH_2), 1.40–1.25 (m, 4H, NCH_2CH_2(CH_2)$_2$ and N(CH_2)$_2$CH_2CH_2); ^{13}C NMR δ=175.1 (7-CO), 172.3 (*C*OOCH$_3$), 171.9 (4-CO), 136.3 (ArC7a), 133.5 (NCH$_2$C*H*=CH$_2$), 132.3 (CH$_2$C*H*=CH$_2$), 127.7 (ArC3a), 125.6 (ArC2), 121.6 (ArC6), 119.2 (ArC4), 119.0 (CH$_2$CH=*C*H$_2$), 118.9 (ArC5), 117.1 (NCH$_2$CH=*C*H$_2$), 113.1 (ArC3), 109.6 (ArC7), 52.9 (C2), 52.5 (OCH$_3$), 52.2 (C5), 48.6 (N*C*H$_2$CH=CH$_2$), 39.2 (N*C*H$_2$(CH$_2$)$_3$), 36.7 (CH*C*H$_2$CH=CH$_2$), 35.8 (H8), 31.8 (N(CH$_2$)$_3$*C*H$_2$), 27.3 (NCH$_2$*C*H$_2$(CH$_2$)$_2$), 22.0 (N(CH$_2$)$_2$*C*H$_2$CH$_2$), 21.3 (H9); MS (ES) *m/z* 469 (100% MH$^+$). HRMS (ES) calcd for $C_{26}H_{37}N_4O_4$: 469.2815; found: 469.2805.

3.6.2. Methyl (2*S*,5*R*)-2-allyl-10-(*N*-allyl-1*H*-indol-3-yl)-3,6-diaza-5-(4-aminobutyl)-4,7-dioxodecanoate hydrochloride (27). This was prepared by *general procedure D* using **18** (0.070 g, 0.12 mmol) giving **27** as a solid (0.030 g, 47%), mp 121–123 °C; TLC (MeOH) R_f=0.75; ^{1}H NMR (CD$_3$OD) δ=7.43 (d, *J*=8 Hz, 1H, ArH4), 7.17 (d, *J*=8 Hz, 1H, ArH7), 7.00 (t, *J*=7 Hz, 1H, ArH6), 6.92–6.88 (m, 2H, ArH2,5), 5.88 (ddt, *J*=17, 10, 5 Hz, 1H, NCH$_2$C*H*=CH$_2$), 5.61 (m, 1H, CH$_2$C*H*=CH$_2$), 5.03–4.85 (m, 4H, 2×CH=C*H*$_2$), 4.61 (dd, *J*=5 Hz, 2H, NC*H*$_2$CH=CH$_2$), 4.37–4.26 (m, 2H, H2 and H5), 3.56 (s, 3H, OCH$_3$), 3.20–3.19 (m, 2H, NC*H*$_2$(CH$_2$)$_3$), 2.78* (t, *J*=7 Hz, H10), 2.67 (t, *J*=7 Hz, 2H, H10), 2.51–2.29 (m, 2H, CHC*H*$_2$CH=CH$_2$), 2.22 (t, *J*=7 Hz, 2H, H8), 1.89 (pent, *J*=7 Hz, 2H, N(CH$_2$)$_3$C*H*$_2$), 1.77–1.62 (m, 1H, N(CH$_2$)$_3$CH*H*), 1.60–1.48 (m, 2H, NCH$_2$C*H*$_2$(CH$_2$)$_2$), 1.39–1.22 (m, 2H, N(CH$_2$)$_2$C*H*$_2$CH$_2$); ^{13}C NMR δ=175.2 (7-CO), 172.9 (*C*OOCH$_3$), 172.0 (4-CO), 136.9 (ArC7a), 134.4 (NCH$_2$*C*H=CH$_2$), 133.1 (CH$_2$*C*H=CH$_2$), 128.2 (ArC3a), 125.5 (ArC2), 121.2 (ArC6), 118.6 (ArC4), 118.4 (CH$_2$CH=*C*H$_2$), 117.8 (ArC5), 115.6 (NCH$_2$CH=*C*H$_2$), 114.4 (ArC3), 109.4 (ArC7), 53.0 (C2), 52.2 (OCH$_3$), 51.6 (C5), 48.9 (N*C*H$_2$CH=CH$_2$), 39.3 (N*C*H$_2$(CH$_2$)$_3$), 35.6 (C8), 35.4 (CH*C*H$_2$CH=CH$_2$), 31.3 (N(CH$_2$)$_3$*C*H$_2$), 26.9 (C10), 24.4 (C9), 22.6 (NCH$_2$*C*H$_2$(CH$_2$)$_2$); MS (ES) *m/z* 483 (100% MH$^+$). HRMS (ES) calcd for $C_{27}H_{39}N_4O_4$: 483.2971; found: 483.2991.

3.7. Ring-closing metathesis reaction—general procedure E. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1,13-metheno-8,11-dioxo-9-(4′-*tert*-butoxycarbonylaminobutyl)-2*H*-1,7,10-benzotriazacyclopentadecine-6-carboxylate (19)

To a solution of **16** (0.110 g, 0.20 mmol) in DCM (50 mL) was added benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium catalyst (0.016 g, 0.02 mmol, 10 mol %). The reaction mixture was heated at reflux under a N$_2$ atmosphere for 24 h. After the solvent was evaporated, the crude product was chromatographed on a flash silica gel column (1% MeOH in DCM) to produce **19** (0.060 g, 58%) as a brown amorphous solid. TLC (DCM/MeOH 10:1) R_f=0.85; ^{1}H NMR δ=7.57 (d, *J*=8 Hz, 1H, ArH14), 7.53* (d, *J*=8 Hz, ArH14), 7.35* (d, *J*=7 Hz, ArH17), 7.29 (d, *J*=8 Hz, 1H, ArH17), 7.21 (t, *J*=8 Hz, 1H, ArH16), 7.11 (t, *J*=8 Hz, 1H, ArH15), 7.03 (s, 1H, ArH18), 6.86 (d, *J*=8 Hz, 1H, 10-NH), 6.32 (d, *J*=7 Hz, 1H, 7-NH), 6.09* (d, *J*=8 Hz, 7-NH), 5.90* (m, H3), 5.52 (dt, *J*=15, 6 Hz, 1H, H3), 4.93 (m, 1H, H4), 4.79–4.71 (m, 2H, C*H*H2 and NHBoc), 4.63* (d, *J*=5 Hz, CH*H*2), 4.61–4.55 (m, 1H, CH*H*2), 4.54–4.43 (m, 2H, unresolved resonance from the (*Z*)-isomer and H9), 4.33 (ddd, *J*=12, 7 Hz, 1H, H6), 3.70 (d, *J*=14 Hz, 1H, C*H*H12), 3.65 (s, 3H, OCH$_3$), 3.64* (s, OCH$_3$), 3.53 (d, *J*=14 Hz, 1H, CH*H*12), 3.11–2.99 (m, 2H, NC*H*$_2$(CH$_2$)$_3$), 2.45–2.22 (m, 2H, CH$_2$5), 1.84–1.56 (m, 4H, N(CH$_2$)$_3$C*H*$_2$ and NCH$_2$C*H*$_2$(CH$_2$)$_2$), 1.38 (s, 9H, C(CH$_3$)$_3$), 1.34* (s, C(CH$_3$)$_3$), 1.45–1.26 (m, 2H, N(CH$_2$)$_2$C*H*$_2$CH$_2$); ^{13}C NMR δ=174.1 (11-CO), 172.3 (8-CO), 172.1 (*C*OOCH$_3$), 156.2 (N*C*O$_2$^{t}Bu), 137.2 (ArC17a), 130.5 (C3), 127.8 (ArC13a), 127.6 (C4), 126.5 (ArC17), 122.2 (ArC16), 119.7 (ArC15), 118.8 (ArC14), 113.1 (ArC13), 109.3 (ArC18), 79.1 (O*C*Me$_3$), 53.7 (C6), 52.5 (OCH$_3$), 52.3 (C9), 46.8 (C2), 39.8 (N*C*H$_2$(CH$_2$)$_3$), 33.6 (C12), 32.9 (C5), 31.3 (N(CH$_2$)$_3$*C*H$_2$), 29.7 (NCH$_2$*C*H$_2$(CH$_2$)$_2$), 28.5 (C(*C*H$_3$)$_3$), 22.6 (N(CH$_2$)$_2$*C*H$_2$CH$_2$); MS (ES) *m/z* 527 (45% MH$^+$), 471 (56%), 453 (74%), 427 (100%). HRMS (ES) calcd for $C_{23}H_{31}N_4O_4$: 527.2870; found: 527.2870.

3.7.1. Methyl (6*S*,9*R*,3*E*/*Z*)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-1,14-metheno-8,11-dioxo-9-(4′-*tert*-butoxycarbonylaminobutyl)-1,7,10-benzotriazacyclohexadecine-6-carboxylate (20). This was prepared by *general procedure E* using **17** (0.040 g, 0.07 mmol), Ru catalyst (586 mg), and DCM (17.5 mL) giving **20** as a brown solid (0.038 g, 100%). TLC (DCM/MeOH 50:1) R_f=0.68; ^{1}H NMR δ=7.55 (d, *J*=8 Hz, 1H, ArH15), 7.56* (d, *J*=8 Hz, ArH15), 7.32* (d, *J*=8 Hz, ArH18), 7.23 (d, *J*=8 Hz, 1H, ArH18), 7.17 (dt, *J*=8, 1 Hz, 1H, ArH17), 7.08 (dt, *J*=8, 1 Hz, 1H, ArH16), 6.91 (s, 1H, ArH19), 6.88* (s, ArH19), 6.53 (d, *J*=7 Hz, 1H, 10-NH), 6.20 (d, *J*=7 Hz, 1H, 7-NH), 6.12* (d, 8 Hz, 7-NH), 5.96* (m, H3), 5.67 (dt, *J*=16, 5 Hz, 1H, H3), 5.56* (m, H4), 4.94 (dt, *J*=16, 7 Hz, 1H, H4), 4.62 (dd, *J*=16, 5 Hz, 2H, C*H*H2), 4.56–4.51 (m, 2H, CH*H*2 and N*H*Boc), 4.50–4.42* (m, H9), 4.40–4.26 (m, 2H, H9 and H6), 3.68* (s, OCH$_3$), 3.62 (s, 3H, OCH$_3$), 3.37–3.21 (m, 1H, H13), 3.11–2.90 (m, 4H, NHCH_2 and H13+CH_2CH13 (*Z*)), 2.75–2.56 (m, 3H, H12 and C*H*H5), 2.55–2.38 (m, 1H, CH*H*5), 1.91–1.50 (m, 2H, N(CH$_2$)$_3$CH_2), 1.46–1.22 (m, 4H, NCH$_2$CH_2(CH$_2$)$_2$) and N(CH$_2$)$_2$CH_2CH$_2$), 1.39 (s, 9H, C(CH$_3$)$_3$), 1.32* (s, C(CH$_3$)$_3$), 1.23* (s, C(CH$_3$)$_3$); ^{13}C NMR δ=173.6* (11-CO), 173.1 (11-CO), 171.6 (8-CO), 171.4 (*C*OOCH$_3$), 156.3 (N*C*O$_2$^{t}Bu), 136.3 (ArC18a), 130.0 (C3), 127.5 (ArC14a), 126.2 (C4), 125.7 (ArC19), 121.6 (ArC17), 118.9 (ArC16), 118.6 (ArCH15), 114.1 (ArC14), 109.0 (ArC18), 79.2 (OCMe$_3$), 54.2 (C6), 52.6 (OCH$_3$), 52.4 (C9), 46.3 (C2), 39.6 (N*C*H$_2$(CH$_2$)$_3$), 36.4 (C12), 33.0 (C5), 30.8* (N(CH$_2$)$_3$*C*H$_2$), 29.8 (N(CH$_2$)$_3$*C*H$_2$), 28.5 (C(*C*H$_3$)$_3$), 22.4 (N(CH$_2$)$_2$*C*H$_2$CH$_2$), 19.6 (C13); MS (ES) *m/z* 541 (100% MH$^+$), 485 (56%). HRMS (ES) calcd for $C_{29}H_{41}N_4O_6$: 541.3026; found: 541.3014.

3.7.2. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1,15-metheno-8,11-dioxo-9-(4′-*tert*-butoxycarbonylaminobutyl)-2*H*-1,7,10-benzotriazacycloheptadecine-6-carboxylate (21). This was prepared by *general procedure E* using **18** (0.80 g, 0.014 mmol), Ru cat (11.4 mg) and DCM (24 mL) giving **21** as a brown solid (0.013 g, 13%). TLC (DCM/MeOH 50:1) R_f=0.59; ^{1}H NMR δ=7.54* (d, *J*=8 Hz, 1H, ArH16), 7.55 (d, *J*=8 Hz, 1H, ArH16), 7.33–7.03 (m, 3H, ArH17,18,19), 6.88 (s, 1H, ArH20), 6.84 (d, *J*=8 Hz, 1H, 10-NH), 6.74* (s, ArH20),

6.44 (d, J=6 Hz, 1H, 7-NH), 5.96–5.89* (m, H3), 5.88–5.71 (m, 1H, H3), 5.59–5.36 (m, 1H, H4), 4.73–4.38 (m, 4H, H2, H9 and H6), 3.73* (s, OCH_3), 3.68* (s, OCH_3), 3.67* (s, OCH_3), 3.66 (3H, s, OCH_3), 3.06–2.89 (m, 2H, ArH14), 2.88–2.79* (m, H14), 2.78–2.70 (m, 2H, H2), 2.66–2.48 (m, 2H, H12), 2.32–2.14 (m, 2H, H5), 2.03–1.94 (m, 2H, H13), 1.82–1.58 (m, 2H, $N(CH_2)_3CH_2$), 1.44–1.23 (m, 4H, $NCH_2CH_2(CH_2)_2$ and $N(CH_2)_2CH_2CH_2$), 1.41–1.38 (m, 9H, $C(CH_3)_3$); ^{13}C NMR δ=174.4 (11-CO), 173.3 (8-CO), 171.9 ($COOCH_3$), 156.0 ($NCO_2{}^tBu$), 136.3 (ArC19a), 130.1 (C3), 128.9 (ArC15a), 127.9* (ArCH15a), 125.0 (ArC20), 121.6 (ArC18), 119.1 (ArC17), 118.8 (ArC16), 113.8 (C15), 108.9 (CH19), 79.1 ($OCMe_3$), 53.4 (C6), 52.5 (OCH_3), 52.0 (C9), 46.8 (C2), 40.7 ($NCH_2(CH_2)_3$), 33.8 (C12), 32.7 (C5), 31.3 ($N(CH_2)_3CH_2$), 29.7 ($NCH_2CH_2(CH_2)_2$), 28.5 ($C(CH_3)_3$), 23.2 (C14), 22.7 ($N(CH_2)_2CH_2CH_2$), 21.8 (C13); MS (ES) m/z 555 (100% MH^+), 297 (53%). HRMS (ES) calcd for $C_{30}H_{43}N_4O_6$: 555.3183; found: 555.3187.

3.8. Amino acid deprotection—general procedure F. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1,13-metheno-8,11-dioxo-9-(4-aminobutyl)-2*H*-1,7,10-benzotriazacyclopentadecine-6-carboxylate hydrochloride (22)

To a solution of **19** (0.08 g, 0.011 mmol) in DCM (2 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred under a N_2 atmosphere at rt for 2 h. After the removal of solvent, DCM was added and the solution was re-evaporated. The residue was dissolved in methanol (5 mL), and then a solution of HCl (1 M, 0.3 mL, 0.3 mmol, 2 molar equiv) in diethyl ether was added. The solvents were then evaporated. The product was precipitated from diethyl ether and a minimum amount of petroleum spirit followed by DCM to give **22** (0.06 g, 86%) as a brown solid, mp 168–170 °C; TLC (MeOH) R_f=0.81; ^{1}H NMR (CD_3OD, 500 MHz) δ=7.39 (d, J=8 Hz, 1H, ArH14), 7.27* (d, J=8 Hz, ArH17), 7.21 (d, J=8 Hz, 1H, ArH17), 6.98 (t, J=8 Hz, 1H, ArH16), 6.93 (s, 1H, ArH18), 6.88 (t, J=8 Hz, 1H, ArH15), 5.78* (dd, J=10, 5 Hz, H3), 5.52 (dt, J=15, 5 Hz, 1H, H3), 5.40* (dd, J=10, 5 Hz, H4), 4.88–4.83 (dt, J=15, 8 Hz, 1H, H4), 4.59 (dd, J=9, 3 Hz, 1H, C*H*H2), 4.36 (dd, J=9, 6 Hz, 1H, CH*H*2), 4.20 (t, J=7 Hz, 1H, H9), 4.10 (dd, J=9, 5 Hz, 1H, H6), 3.67 (d, J=9 Hz, 1H, C*H*H12), 3.51 (s, 3H, OCH_3), 3.31 (d, J=9 Hz, 1H, CH*H*12), 2.74 (dd, 2H, $NCH_2(CH_2)_3$), 2.51–2.42* (m, C*H*H5), 2.41–2.34 (m, 1H, C*H*H5), 2.12 (ddd, J=14, 6 Hz, 1H, CH*H*5), 1.69–1.49 (m, 2H, $N(CH_2)_3CH_2$), 1.58–1.48 (m, 2H, $NCH_2CH_2(CH_2)_2$), 1.36–1.23 (m, 2H, $N(CH_2)_2CH_2CH_2$); ^{13}C NMR (CD_3OD) δ=174.9 (11-CO), 174.8 (8-CO), 173.2 ($COOCH_3$), 138.7 (ArC17a), 131.6 (C3), 129.2 (ArC13a), 129.2 (C4), 127.8 (ArC18), 122.5 (ArC16), 120.3 (ArC15), 119.6 (ArC14), 111.1 (ArC13), 110.3 (ArC17), 55.9 (C6), 54.4 (OCH_3), 52.8 (C9), 47.5 (C2), 40.5 ($NCH_2(CH_2)_3$), 33.9 (C12), 33.5* (C12), 32.2 ($N(CH_2)_3CH_2$), 27.9 ($NCH_2CH_2(CH_2)_2$), 23.7 ($N(CH_2)_2CH_2CH_2$); MS (ES) m/z 427 (100% MH^+). HRMS (ES) calcd for $C_{23}H_{31}N_4O_4$: 427.2345; found: 427.2343.

3.8.1. Methyl (6*S*,9*R*,3*E*/*Z*)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-1,14-metheno-8,11-dioxo-9-(4-aminobutyl)-1,7,10-benzotriazacyclohexadecine-6-carboxylate hydrochloride (23). This was prepared by *general procedure F* using **20** (0.15 g, 0.28 mmol), TFA (3 mL) and DCM (3 mL) giving **23** (0.120 g, 91%), mp 176–179 °C; TLC (MeOH) R_f=0.76; ^{1}H NMR (CD_3OD, 500 MHz) δ=8.20* (d, J=8 Hz, 10-NH), 8.00 (d, J=7 Hz, 1H, 10-NH), 7.78 (d, J=7 Hz, 1H, 7-NH), 7.59* (d, J=7 Hz, 7-NH), 7.53 (d, J=7 Hz, 1H, ArH15), 7.51 (d, J=8 Hz, 1H, ArH15), 7.38* (d, J=8 Hz, ArH18), 7.26 (d, J=8 Hz, 1H, ArH18), 7.15* (t, J=7 Hz, ArH17), 7.10 (t, J=7 Hz, 1H, ArH17), 7.03* (t, J=7 Hz, ArH16), 7.01 (t, J=7 Hz, 1H, H16), 6.94* (s, ArH19), 6.93 (s, 1H, ArH19), 5.86–5.75* (m, H3), 5.79–5.72 (dt, J=16, 4 Hz, 1H, H3), 5.59–5.51* (dt, J=10, 5 Hz, H4), 4.95–4.85 (m, 1H, H4), 4.78–4.70 (dd, J=16, 3 Hz, 1H, C*H*H2), 4.73–4.66* (m, C*H*H2), 4.61–4.54* (m, CH*H*2), 4.52 (dd, J=16, 5 Hz, 1H, CH*H*2), 4.52–4.46* (m, H6), 4.45–4.39* (m, H9), 4.30–4.24 (m, 1H, H9), 4.21–4.14 (m, 1H, H6), 3.71* (s, OCH_3), 3.65 (s, 3H, OCH_3), 3.27–3.14 (m, 2H, H13), 2.99–2.89* (m, H13), 2.98–2.87* (m, C*H*H5), 2.97–2.86 (m, 2H, $NCH_2(CH_2)_3$), 2.72–2.61* (m, CH*H*5), 2.71–2.60 (m, 2H, H12), 2.57–2.49 (m, 1H, C*H*H5), 2.37–2.28 (m, 1H, CH*H*5), 1.88–1.78* (m, $N(CH_2)_3CH$*H*), 1.74–1.65* (m, $N(CH_2)_3CH$*H*), 1.80–1.60 (m, 2H, $N(CH_2)_3CH_2$), 1.73–1.62 (m, 2H, $NCH_2CH_2(CH_2)_2$), 1.55–1.36 (m, 2H, $N(CH_2)_2CH_2CH_2$); ^{13}C NMR δ=174.3 (11-CO), 174.2* (11-CO), 174.0 (8-CO), 173.8* (8-CO), 172.1 ($COOCH_3$), 171.8* ($COOCH_3$), 136.7 (ArC18a), 129.6 (C3), 127.9 (ArC14a), 127.3* (C4), 126.4 (C4), 125.7 (ArC19), 121.5 (ArC17), 121.4 (ArC17), 118.6 (ArC16), 118.3 (ArC15), 113.8 (ArC14), 109.2 (ArC18), 109.0* (ArC18), 54.6 (C6), 53.6* (C6), 53.4 (C9), 52.5* (C9), 52.1* (OCH_3), 51.9 (OCH_3), 46.3 (C2), 41.2* (C2), 39.4 ($NCH_2(CH_2)_3$), 35.7 (C12), 32.3 (C5), 32.0* ($N(CH_2)_3CH_2$), 31.5 ($N(CH_2)_3CH_2$), 28.5* (C5), 26.9 ($NCH_2CH_2(CH_2)_2$), 22.6 ($N(CH_2)_2CH_2CH_2$), 20.4 (C13); MS (ES) m/z 441 (100% MH^+). HRMS (ES^+) calcd for $C_{24}H_{33}N_4O_4$: 541.3026; found: 541.3014.

3.8.2. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1,15-metheno-8,11-dioxo-9-(4-aminobutyl)-2*H*-1,7,10-benzotriazacycloheptadecine-6-carboxylate hydrochloride (24). This was prepared by *general procedure F* using **21** (0.90 g, 0.16 mmol), TFA (2 mL) and DCM (2 mL) giving **24** (0.050 g, 63%), mp 156–159 °C; TLC (MeOH) R_f=0.69; ^{1}H NMR (CD_3OD, 500 MHz) δ=7.43 (d, J=8 Hz, 1H, ArH16), 7.30* (d, J=8 Hz, ArH19), 7.25 (d, J=8 Hz, 1H, ArH19), 7.07* (t, J=8 Hz, ArH18), 7.03 (t, J=8 Hz, 1H, ArH18), 6.91 (t, J=8 Hz, 1H, ArH17), 6.76 (s, 1H, ArH20), 6.70* (s, ArH20), 5.82–5.75 (m, 1H, H3), 5.61–5.53* (m, H3), 5.52–5.44 (dt, J=5, 8 Hz, 1H, H4), 4.35–4.24* (m, H4), 4.65–4.59 (dd, J=5, 3 Hz, 1H, C*H*H2), 4.49* (d, C*H*H2), 4.44–4.41* (d, CH*H*2), 4.38 (apparent t, J=7 Hz, 1H, CH*H*2), 4.35–4.26 (m, 1H, CH9), 4.20 (dd, J=9, 2 Hz, 1H, H6), 3.66* (s, OCH_3), 3.62 (s, 3H, OCH_3), 2.84–2.77 (m, 4H, H14 and $NCH_2(CH_2)_3$), 2.38–2.29 (m, 2H, H12), 2.21 (dt, J=16, 5 Hz, 1H, CH*H*5), 2.13–2.05 (m, 1H, CH*H*5), 1.97–1.80 (m, 2H, H13), 1.75–1.50 (m, 2H, $N(CH_2)_3CH_2$), 1.57 (m, 2H, $NCH_2CH_2(CH_2)_2$), 1.41–1.26 (m, 2H, $N(CH_2)_2CH_2CH_2$), ^{13}C NMR δ=175.0 (12-CO), 174.9 (8-CO), 173.3 ($COOCH_3$), 172.9* ($COOCH_3$), 138.0 (ArC19a), 131.4 (C3), 129.4 (ArC15a), 128.9 (C4), 126.6 (ArC20), 122.3 (ArC18), 119.8 (ArC17), 119.6 (ArC16), 119.5 (ArC16), 114.2 (ArC15), 110.0 (ArCH17), 54.6

(CHN), 54.4 (OCH_3), 53.0 (CHN), 47.4 ($CH_2$2), 40.4 ($NCH_2(CH_2)_3$), 34.3 (C12), 33.3 (C5), 32.6 ($N(CH_2)_3CH_2$), 27.8 ($NCH_2CH_2(CH_2)_2$), 23.7 (C14), 23.5 ($N(CH_2)_2CH_2CH_2$), 23.1 ($CH_2$13); MS (ES) *m/z* 455 (100% MH^+). HRMS (ES) calcd for $C_{25}H_{35}N_4O_4$: 455.2658; found: 455.2647.

3.9. Guanidation reactions—general procedure G. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1,13-metheno-8,11-dioxo-9-[4-(*N*,*N*′-di*tert*-butoxycarbonylguanidino)aminobutyl]-2*H*-1,7,10-benzotriazacyclopentadecine-6-carboxylate (28)

To a solution of *N*,*N*′-diBoc-*N*-triflylguanidine (0.024 g, 0.06 mmol) in DCM was added **22** (0.03 g, 0.06 mmol) and triethylamine (9.0 μL, 0.06 mmol). Triethylamine (0.1 mL) in DCM (0.9 mL) was pre-prepared and a portion (0.1 mL) of this solution was taken for the reaction. The reaction mixture was stirred under a N_2 atmosphere at rt for 3 h. The solvent was evaporated and the reaction mixture was diluted with DCM and washed with sodium bisulfate (2 M), saturated sodium bicarbonate and brine, dried and evaporated giving **28** (20 mg, 46%). ^{1}H NMR (CD_3OD, 500 MHz) δ=7.66 (d, *J*=8 Hz, 1H, ArH14), 7.31 (d, *J*=8 Hz, 1H, ArH17), 7.23 (t, *J*=8 Hz, 1H, ArH16), 7.15–7.23 (t, *J*=8 Hz, 1H, ArH15), 7.08 (s, 1H, ArH18), 6.36 (d, *J*=5 Hz, 1H, 10-NH), 6.04 (d, *J*=5 Hz, 1H, 7-NH), 5.61 (dt, *J*=16, 5 Hz, 1H, H3), 4.91 (dt, *J*=16, 7 Hz, 1H, H4), 4.60 (d, *J*=6 Hz, 2H, H2), 4.52 (dt, *J*=12, 6 Hz, 1H, H9), 4.43 (dd, *J*=13, 6 Hz, 1H, H6), 3.69* (s, OCH_3), 3.67 (s, 3H, OCH_3), 3.64–3.62 (m, 2H, H12), 3.37 (dt, *J*=8, 5 Hz, 2H, $NHCH_2$), 2.39 (dd, *J*=4 Hz, 2H, H5), 1.90–1.40 (m, 4H, 2×CH_2), 1.51 (s, 9H, $C(CH_3)_3$), 1.47* (s, $C(CH_3)_3$); ^{13}C NMR δ=171.9 (11-CO), 171.7 (8-CO), 163.4 ($COOCH_3$), 162.1* ($COOCH_3$), 156.0* ($NCO_2{}^t$Bu), 151.2 ($NCO_2{}^t$Bu), 137.4 (ArC17a), 130.7 (C2), 127.8 (ArC13a), 127.1 (C4), 126.5 (ArCH18), 122.5 (ArCH16), 121.3 (ArCH15), 117.0 (ArC13), 112.8 (ArC14), 109.5 (ArC17), 86.0 (*C*NHBoc), 83.1* ($NCMe_3$), 79.1 ($OCMe_3$), 53.7 (C6), 52.8 (OCH_3), 52.6 (C9), 46.9 (C2), 40.6 ($NCH_2(CH_2)_3$), 33.7 (C12), 32.9 (CH5), 31.4 ($N(CH_2)_3CH_2$), 29.7 ($NCH_2CH_2(CH_2)_2$), 28.4, 28.1 and 27.9 ($C(CH_3)_3$), 22.9 ($N(CH_2)_2CH_2CH_2$); MS (ES) *m/z* 669 (27% MH^+). HRMS (ES) calcd for $C_{34}H_{49}N_6O_8$: 669.3612; found: 669.3624.

3.9.1. Methyl (6*S*,9*R*,3*E*/*Z*)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-1,14-metheno-8,11-dioxo-9-[4-(*N*,*N*′-di*tert*-butoxycarbonylguanidino)aminobutyl]-1,7,10-benzotriazacyclohexadecine-6-carboxylate (29).

This was prepared by *general procedure G* using **23** (0.050 g, 0.11 mmol), *N*,*N*′-diBoc-*N*-triflylguanidine (0.040 g) and triethylamine (15 μL) giving **29** (0.060 g, 84%). TLC (DCM/MeOH 50:1) R_f=0.20; ^{1}H NMR δ=8.28 (br s, 1H, NHBoc), 7.55 (d, *J*=8 Hz, 1H, ArH15), 7.31* (d, *J*=8 Hz, ArH15), 7.23 (d, *J*=8 Hz, 1H, ArH18), 7.17 (dt, *J*=8, 1 Hz, 1H, ArH17), 7.08 (dt, *J*=8, 1 Hz, 1H, ArH16), 6.91 (s, 1H, ArH19), 6.88* (s, ArH19), 6.68 (d, *J*=8 Hz, 1H, 10-NH), 6.18* (d, *J*=8 Hz, 7-NH), 6.02 (d, *J*=8 Hz, 1H, 7-NH), 5.95* (m, H3), 5.65 (dt, *J*=15, 5 Hz, 1H, H3), 4.97 (dt, *J*=15, 8 Hz, 1H, H4), 4.68–4.44 (m, 3H, H2 and H9), 4.41–4.33 (m, 1H, H6), 3.67* (s, OCH_3), 3.63 (s, 3H, OCH_3), 3.36–3.24 (m, 2H, H13), 3.03–2.92 (m, 1H, CH*H*5), 2.75–2.72* (m, CH*H*5), 2.71–2.67 (m, 1H, CH*H*5), 2.59–2.54 (m, 2H, $N(CH_2)_3CH_2$), 2.46 (dd, *J*=13, 6 Hz, 2H, $NCH_2CH_2(CH_2)_2$), 1.95–1.83 (m, 2H, $N(CH_2)_2CH_2CH_2$), 1.47 (s, 18H, $C(CH_3)_3$), 1.45* (s, $C(CH_3)_3$); ^{13}C NMR δ=172.9 (11-CO), 171.4 (8-CO), 171.3 ($COOCH_3$), 163.4 (ArC), 156.0 and 153.1 ($NCO_2{}^t$Bu), 136.3 (ArC18a), 130.1 (C3), 127.5 (ArC14a), 126.3 (C4), 125.5 (ArCH19), 121.6 (ArCH17), 118.9 (ArCH16), 118.5 (ArCH15), 114.1 (ArC14), 109.0 (ArCH18), 83.1 (CNHBoc), 79.3 ($OCMe_3$), 54.1 (C6), 52.5 (OCH_3), 52.4 (C9), 46.3 (C2), 40.5 ($NCH_2(CH_2)_3$), 36,4 (C12), 33.0 (C5), 31.0 ($N(CH_2)_3CH_2$), 29.8 ($NCH_2CH_2(CH_2)_2$), 28.4 and 28.1 ($C(CH_3)_3$), 23.1 ($N(CH_2)_2CH_2CH_2$), 19.7 (ArC13); MS (ES) *m/z* 683 (23% MH^+). HRMS (ES) calcd for $C_{35}H_{51}N_6O_8$: 683.3768; found: 683.3792.

3.9.2. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1,15-metheno-8,11-dioxo-9-[4-(*N*,*N*′-di*tert*-butoxycarbonylguanidino)aminobutyl]-2*H*-1,7,10-benzotriazacycloheptadecine-6-carboxylate (30).

This was prepared by *general procedure G* using **24** (0.030 g, 0.06 mmol), *N*,*N*′-diBoc-*N*-triflylguanidine (0.023 g) and triethylamine (8.5 μL) to give **30** (30 mg, 70%). TLC (DCM/MeOH 50:1) R_f=0.20; ^{1}H NMR ($CDCl_3$, 500 MHz) δ=8.26 (s, 1H, NHBoc), 7.56 (d, *J*=8 Hz, 1H, ArH16), 7.32* (d, *J*=8 Hz, ArH19), 7.24–7.16 (m, 2H, ArH18,19), 7.08 (t, *J*=7 Hz, 1H, ArH17), 6.87 (s, 1H, ArH20), 6.74* (s, ArH20), 6.43 (d, *J*=7 Hz, 1H, 10-NH), 6.38* (d, *J*=7 Hz, 7-NH), 5.94* (m, H3), 5.80–5.71 (m, 1H, H3), 5.65 (d, *J*=9 Hz, 1H, 7-NH), 5.54* (m, H4), 5.43 (dt, *J*=15, 9 Hz, 1H, H4), 4.68–4.57 (m, 2H, C*H*H2 and H9), 4.50–4.43 (m, 2H, CH*H*2 and H6), 3.73* (s, OCH_3), 3.68 (s, 3H, OCH_3), 3.39–3.31 (m, 2H, H14), 3.03–2.97 (m, 2H, $NCH_2(CH_2)_3$), 2.89–2.81 (m, 2H, H12), 2.75* (m, H12), 2.60–2.49 (m, 2H, H5), 2.30–2.24 (m, 2H, H13), 2.18–1.97 (m, 2H, $N(CH_2)_3CH_2$), 2.00–1.99 (m, 2H, $NCH_2CH_2(CH_2)_2$), 1.97–1.80 (m, 2H, $N(CH_2)_2CH_2CH_2$), 1.60 (s, 9H, $C(CH_3)_3$), 1.46 and 1.45* (9H, $C(CH_3)_3$); ^{13}C NMR δ=173.2 (11-CO), 171.7 (8-CO), 171.6 ($COOCH_3$), 163.3 (ArC), 156.0 ($NCO_2{}^t$Bu), 153.1* ($NCO_2{}^t$Bu), 136.3 (ArC19a), 130.1 (C3), 128.2 (ArC15a), 127.8 (C4), 126.4* (C4), 124.9 (ArC20), 121.6 (ArC18), 119.1 (ArC17), 118.9 (ArC16), 113.8 (ArC15), 108.9 (ArC19), 83.1 (*C*NHBoc), 79.3 ($OCMe_3$), 53.7 (C6), 52.5 (OCH_3), 51.9 (C9), 46.8 (C2), 40.4 ($NCH_2(CH_2)_3$), 33.7 (C12), 32.7 (C5), 31.5 ($N(CH_2)_3CH_2$), 29.8 ($NCH_2CH_2(CH_2)_2$), 28.3 and 28.1 ($C(CH_3)_3$), 23.2 (C14), 23.0 ($N(CH_2)_2CH_2CH_2$), 21.9 (C13); MS (ES) *m/z* 697 (100% MH^+). HRMS (ES) calcd for $C_{36}H_{53}N_6O_8$: 697.3925; found: 697.3943.

3.10. Guanidation deprotection—general procedure H. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1,13-metheno-8,11-dioxo-9-(4-guanidylbutyl)-2*H*-1,7,10-benzotriazacyclopentadecine-6-carboxylate hydrochloride (31)

To a solution of **28** (0.010 g, 0.11 mmol) in DCM (2 mL) was added trifluoroacetic acid (4 mL). The reaction mixture was stirred under a N_2 atmosphere at rt for 2 h. The solution was evaporated and the crude product dissolved in methanol (5 mL). Hydrochloric acid (0.3 mL, 0.3 mmol, 2 molar equiv, 1 M) in diethyl ether was added and the solvent was then evaporated. Recrystallization from a minimum amount

of petroleum spirit and DCM/diethyl ether gave **31** (0.006 g, 11%) as a brown solid, mp 151–154 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ=7.59 (d, J=8 Hz, 1H, ArH14), 7.47* (d, J=8 Hz, ArH17), 7.41 (d, J=8 Hz, 1H, ArH17), 7.18 (m, 1H, ArH16), 7.10 (m, 2H, ArH15,18), 5.99* (m, H3), 5.70 (dt, J=15, 6 Hz, 1H, H3), 5.62–5.58* (m, H4), 5.06 (dt, J=15, 9 Hz, 1H, H4), 4.89 (m, 1H, C*H*H2), 4.59 (dd, J=16, 7 Hz, 1H, CH*H*2), 4.42 (dd, J=9, 7 Hz, 1H, H9), 4.33 (dd, J=10, 4 Hz, 1H, H6), 3.81 (d, J=15 Hz, 1H, C*H*H12), 3.70 (s, 3H, OCH_3), 3.64* (s, OCH_3), 3.53 (d, J=9 Hz, 1H, CH*H*12), 3.19–3.16 (m, 2H, $NCH_2(CH_2)_3$), 2.57 (dt, J=8, 3 Hz, 1H, C*H*H5), 2.35–2.26 (m, 1H, CH*H*5), 1.86–1.80 (m, 2H, $N(CH_2)_3CH_2$), 1.69–1.60 (m, 2H, $NCH_2CH_2(CH_2)_2$), 1.49–1.42 (m, 2H, $N(CH_2)_2CH_2CH_2$); MS (ES) *m*/*z* 469 (100% MH^+). HRMS (ES) calcd for $C_{24}H_{33}N_6O_4$: 469.2563; found: 469.2576.

3.10.1. Methyl (6*S*,9*R*,3*E*/*Z*)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-1,14-metheno-8,11-dioxo-9-(4-guanidylbutyl)-1,7,10-benzotriazacyclohexadecine-6-carboxylate hydrochloride (32). This was prepared by *general procedure H* using **29** (0.020 g, 0.03 mmol), TFA (4 mL) and DCM (2 mL) to give **32** (0.010 g, 73%), mp 176–179 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ=7.47 (d, J=8 Hz, 1H, ArH15), 7.32* (d, J=8 Hz, ArH18), 7.21 (d, J=8 Hz, 1H, ArH18), 7.11–6.92 (m, 2H, ArH16,17), 6.86 (s, 1H, ArH19), 5.71 (dt, J=15, 5 Hz, 1H, H3), 4.87–4.62 (m, 1H, H4), 4.57–4.46 (m, 1H, CHH2), 4.44–4.33 (m, 1H, CH*H*2), 4.20 (t, J=8 Hz, 1H, H9), 4.12 (dd, J=11, 4 Hz, 1H, H6), 3.65* (s, OCH_3), 3.59 (s, 3H, OCH_3), 3.25–3.13 (m, 2H, H13), 3.11–3.06 (m, 2H, $NCH_2(CH_2)_3$), 2.96–2.82 (m, 2H, H12), 2.61–2.43 (m, 1H, C*H*H5), 2.35–2.20 (m, 1H, CH*H*5), 1.74–1.63 (m, 2H, $N(CH_2)_3CH_2$), 1.58–1.47 (m, 4H, $NCH_2CH_2(CH_2)_2$ and $N(CH_2)_2CH_2CH_2$); MS (ES) *m*/*z* 484 (100% MH^+). HRMS (ES) calcd for $C_{25}H_{36}N_6O_4$: 484.2798; found: 484.2805.

3.10.2. Methyl (6*S*,9*R*,3*E*/*Z*)-1,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1,15-metheno-8,11-dioxo-9-(4-guanidylbutyl)-2*H*-1,7,10-benzotriazacycloheptadecine-6-carboxylate hydrochloride (33). This was prepared by *general procedure H* using **30** (0.020 g, 0.03 mmol), TFA (4 mL) and DCM (2 mL) to give **33** (0.010 g, 73%), as a light brown solid, mp>228 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ=7.62* (d, J=8 Hz, ArH16), 7.45 (d, J=8 Hz, 1H, ArH16), 7.32* (d, J=8 Hz, ArH19), 7.27 (1H, d, J=8 Hz, ArH19), 7.07–7.01 (m, 1H, ArH18), 6,92 (t, J=8 Hz, 1H, ArH17), 6.79 (s, 1H, ArH20), 6.72* (s, ArH20), 5.83–5.76 (m, 1H, H3), 5.68–5.56* (m, H3), 5.62–5.48 (m, 1H, H4), 5.34–5.30* (m, H4), 4.84–4.63 (m, 2H, H2), 4.41–4.31 (m, 1H, H9), 4.25–4.21 (m, 1H, H6), 3.68* (s, OCH_3), 3.64 (s, 3H, OCH_3), 3.07 (apparent t, J=6 Hz, 2H, $NCH_2(CH_2)_3$), 2.82–2.81 (m, 1H, C*H*H14), 2.65–2.62 (m, 2H, H12), 2.34–2.32 (m, 2H, H5), 2.22 (dt, J=10, 3 Hz, 1H, CH*H*14), 2.12–2.08 (m, 2H, H13), 1.98–1.88 (m, 2H, $N(CH_2)_3CH_2$), 1.72–1.66 (m, 2H, $NCH_2CH_2(CH_2)_2$), 1.56–1.51 (m, 2H, $N(CH_2)_2CH_2CH_2$); MS (ES) *m*/*z* 497 (100% MH^+). HRMS (ES) calcd for $C_{26}H_{37}N_6O_4$: 497.2876; found: 497.2878.

3.11. Antibacterial testing

Antibacterial testing against *S. aureus* ATCC6538P was performed at Amrad Corporation Ltd, Melbourne, Australia.

Assay procedure: A standardised inoculate for assays was prepared in 1/10 dilution of seed culture. To a 96 well microtitre plate was added 50 μL of liquid medium [Mueller–Hinton broth medium (MHB) and Mueller–Hinton agar medium (MHA)]. The peptoid compounds were dissolved in a 50% MeOH/H_2O solution for the final concentration of 1 mg/mL. Test solution (50 μL) was added into the top row of the plate. A dilution series was continued until it reached the last row of the plate and the excess was discarded. The plates (two peptoid samples were tested per plate) were incubated at 37 °C and shaken at 100 rpm for 18 h.

Acknowledgements

We would like to thank Amrad Corporation Ltd and the Institute for Biomolecular Science, University of Wollongong, for financial support and Daniel Coghlan and Helen Witchard for initial work associated with dipeptide synthesis.

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The effect of polar substituents on the heterocyclic benzoxazoles

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Received 22 May 2006; revised 3 July 2006; accepted 20 July 2006
Available online 10 August 2006

Abstract—The synthesis, characterization, and mesomorphic properties of a new type of heterocyclic compounds **1**, **2** derived from benzoxazole are reported. In order to understand the relationship between the structure and the mesomorphic behavior, compounds containing a variety of polar substituents (i.e., X=H, F, Cl, Br, CH_3, CF_3, OCH_3, NO_2, CN, OH, NMe_2, $COOCH_3$) on the terminal end were prepared. The phase behavior of these mesogenic compounds was characterized and studied by differential scanning calorimetry (DSC) and polarization optical microscopy. The formation of mesophases was strongly dependent on the electronic and/or the steric factors of the substituents. In general, a mesophase was better induced by introduction of a polar substituent. Compounds (X=H) formed a crystalline phase, however, other compounds, except for X=OH, exhibited nematic or smectic A phases. Interestingly all compounds with electron-donating substituents (X=CH_3, OCH_3, NMe_2) exhibited nematic phases, however, other compounds with electron-withdrawing substituents (X=F, Cl, Br, CF_3, NO_2, CN, $COOCH_3$) formed smectic A phases. Compounds (X=NO_2, CN, $COOCH_3$) have higher clearing temperatures than those of other homologues, and the higher T_{cl} was attributed to an enhanced conjugative interaction. However, no linear correlation between the clearing temperature or the temperature range of mesophases with Hammett σ_p constants was found. The fluorescent properties of the compounds were examined. All λ_{max} peaks of the absorption and photoluminescence spectra of compounds occurred at ca. 348–381 and 389–478 nm, respectively. Whereas, the quantum yields of some compounds were relatively low.

1. Introduction

A delicate balance of molecular interactions in a specific state[1] is crucially essential to the formation of a predesigned structure. This is particularly important in liquid crystalline materials, and liquid crystals form a state of matter intermediate between the solid and the liquid. This type of molecular interaction[1c,d] induced to form mesophases can be weak dipole–dipole interaction, dispersion, H-bonding, coordinative force, and others. Forces which are too strong or too weak can lead to the formation of a solid or liquid state.

Numerous heterocyclic compounds[2] derived from compounds such as 1,3,4-oxadiazole,[3] 1,2,4-triazole,[4] and benzoxazole[5] exhibiting interesting mesophases have recently been explored due to their varieties in structures and/or known chemistry. Better mesomorphic behavior[6] formed by these heterocyclic structures was attributed to their unsaturation and/or more polarizable nature. On the other hand, a lower symmetry[3] and/or non-planar structure caused by nitrogen, oxygen, sulfur, or other atoms incorporated on such heterocyclic rings also explained the preferred or better mesomorphic properties. Materials with lower melting temperatures, potential candidates for further applications, are often generated by such compounds. It is well known that the stability[7] of the mesophase may be augmented by an increase of the polarity or polarization along the mesogenic core of the molecule. A substantial change of the micro- as well as macro-polarizability in a specific structure or molecule can be easily achieved by the introduction of polar substituent along the preferred molecular direction. The effect of polar substituents in a variety of mesogenic systems[8] has been studied and investigated during the past years. Some predictions were successfully made in terms of mesomorphic behavior. The transition temperature of M→I has been correlated with the polarizability anisotropy of bonds to the substituent in 4-(4-substituted phenylazo)-phenyl-4-alkoxybenzoates.[8d] Previous studies[7,8c] also showed that compounds substituted with polar groups, such as –NO_2, –CN, might lead to a higher clearing temperature, which has been attributed to the conjugative interaction increase between the substituent and the ester moiety. On the other hand, the effect of polar substituents on the mesogenic 1,3,4-oxadiazoles-based materials was also studied. The mesophase and optical properties of these oxadiazole materials[3a] were also found to be strongly influenced by the presence of a terminal polar group.

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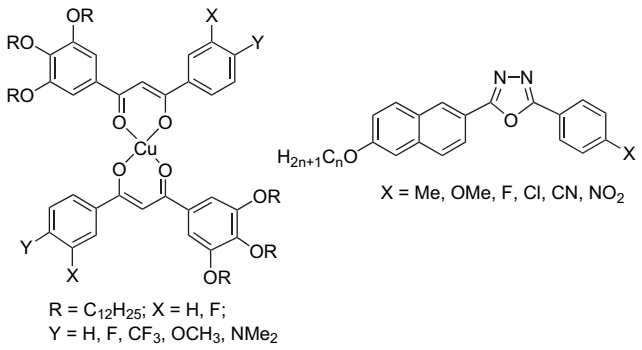
doi:10.1016/j.tet.2006.07.058

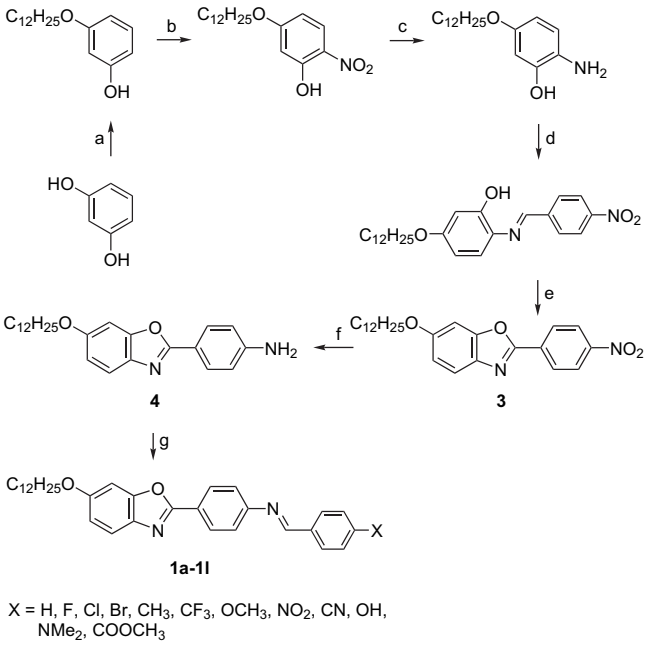


Benzoxazoles, as an important type of heterocyclic compound, have been studied in a variety of research areas, including non-linear optics (NLO),[9] organic light-emitting diodes (OLED),[10] and polymeric materials.[11] However, benzoxazole derivatives exhibiting mesophases[5a,12] have been less often reported. Nematic or/and smectic C mesophases formed by these rod-like compounds were observed. Benzothiazole-derived compounds were also found to have photophysical and fluorescent applications.[13] In a previous paper, the substituent effect on the columnar formation in β-diketonate metallomesogens[14] was investigated. A rectangular columnar phase (Col_r) was observed for substituents with bulkier groups (i.e., X=Me, Et), however, a hexagonal columnar phase (Col_h) was observed for substituents with electron-withdrawing groups (i.e., X=Cl, Br, I). Interestingly, a satisfactory linear relationship with a correlation coefficient of 0.974 between the clearing temperatures and Hammett σ_p constants was obtained for the copper complexes.

As part of our studies of heterocyclic mesogens, in this paper, we describe the synthesis, characterization, and the mesomorphic properties of a series of calamitic benzoxazole derivatives with various substituents on the terminal phenyl ring. Their fluorescent properties were also examined. Nematic or smectic phases were observed depending on the electronic nature of the substituents. However, the observed optical properties were not sensitive to the substituents except for the compound with an NMe_2 group.

2. Results and discussion

The synthetic procedures[5a] for the benzoxazole derivatives **1a**–**1l** are summarized in Scheme 1. The majority of benzoxazole-based derivatives were prepared by the condensation of 2-aminophenols with benzaldehydes or benzoic acid and subsequent intramolecular cyclization. The compounds of 5-dodecyloxy-2-nitrophenol, 2-amino-5-dodecyloxyphenol, 5-dodecyloxy-2-[(4-nitrobenzylidene)amino]phenol, 6-dodecyloxy-2-(4-nitrophenyl)benzoxazole **3**, and 4-(6-dodecyloxybenzoxazol-2-yl)phenylamine **4** were prepared by reported procedures.[5a] The final compounds, benzylidene-4-(6-dodecyloxybenzoxazol-2-yl)phenylamine were prepared by the condensation reaction of 4-(6-dodecyloxybenzoxazol-2-yl)phenylamine and appropriate aldehydes in refluxing absolute ethanol with a yield ranging from 67–82%. ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis were used to characterize the intermediates and the final products.



Scheme 1. Reactions and reagents: (a) RBr (1.1 equiv), $KHCO_3$ (1.3 equiv), KI, refluxed in dry CH_3COCH_3, 48 h, 60 °C; (b) HNO_3 (1.2 equiv), $NaNO_2$ (0.2 equiv), stirred at 0 °C in CH_2Cl_2, 12 h, 25 °C; (c) N_2H_4 (1.2 equiv), Pd/C (0.1 equiv), refluxed in absolute C_2H_5OH, 6 h, 85 °C; (d) 4-Nitrobenzaldehyde (1.0 equiv), CH_3COOH (drops), refluxed in absolute C_2H_5OH, 12 h, 90 °C; (e) $Pb(OAc)_4$ (1.3 equiv), refluxed in CH_2Cl_2, 6 h, 85 °C; (f) N_2H_4 (1.2 equiv), Pd/C (0.1 equiv), refluxed in absolute ethanol, 6 h, 80%; (g) substituted benzaldehyde (1.0 equiv), CH_3COOH (drops), refluxed in absolute C_2H_5OH, 12 h, 68–90 °C.

2.1. Mesomorphic properties

The mesomorphic behavior of compounds **1a**–**1l** was characterized and studied by differential scanning calorimetry (DSC) and polarizing optical microscopy. The phase transitions and thermodynamic data were summarized in Table 1. In order to study the substituent effect on the formation of the mesophases, a variety of compounds with a variety of polar groups (i.e., X=H, F, Cl, Br, CH_3, CF_3, OCH_3, NO_2, CN, OH, NMe_2, $COOCH_3$) substituted on the opposite end of the benzoxazole ring were studied. Among these polar groups, some are known as strong π-acceptors (i.e., X=CN, NO_2) or π-donors (X=Cl, Br, OH), and others are known as intermediate (X=Cl, $COOCH_3$), besides being classified as electron-donating or electron-withdrawing groups. The results indicated that the formation of mesophases in this type of electron-deficient heterocyclic system was strongly dependent on the electronic and/or the steric factors of the substituents. Compound **1a** (X=H) was in fact non-mesogenic. A transition of crystal-to-isotropic at 99.8 °C was observed, and the lack of liquid crystallinity of compound **1a** can probably be attributed to the insufficient dipole over the entire molecule. When a polar functional group was substituted on the phenyl ring located on the opposite side to the benzoxale core, the mesomorphic properties were improved. All compounds except for **1j** (X=OH) were truly mesogenic, in which introducing a polar group was used to enhance or/and induce the formation of the mesophases. The results also indicated that compounds (**1e**, **1g**, **1k**) with an electron-donating substituent (–CH_3, OCH_3, NMe_2) exhibited nematic (N) phases, however, other

Table 1. Phase transitions and enthalpies of compounds **1a**–**1l**

1a						Cr	99.8 (60.1) / 79.8 (60.8)	I
1b			Cr	101.7 (59.2) / 74.9 (56.7)		SmA	155.6 (4.25) / 154.7 (4.12)	I
1c	Cr_1	82.4 (2.03)	Cr_2	92.1 (45.3) / 74.3 (10.3)		SmA	174.0 (4.24) / 173.2 (3.28)	I
1d	Cr_1	63.3 (14.6) / 50.0 (25.5)	Cr_2	97.9 (59.9) / 80.2 (13.1)		SmA	194.3 (6.42) / 192.8 (6.36)	I
1e			Cr	103.9 (55.4) / 86.7 (56.5)		N	137.4 (0.38) / 137.0 (0.40)	I
1f			Cr	90.8 (47.6) / 75.3 (50.4)		SmA	180.9 (6.22) / 179.5 (6.11)	I
1g	Cr_1	92.0 (4.61)	Cr_2	108.3 (51.6) / 76.3 (51.5)		N	169.5 (0.49) / 169.2 (0.47)	I
1h	Cr_1	95.6 (2.28) / 88.1 (1.96)	Cr_2	129.3 (7.85) / 127.0 (8.03)		SmA	224.8 (2.64) / 224.2 (2.66)	I
1i	Cr_1	102.9 (8.93) / 86.3 (6.08)	Cr_2	120.7 (40.1) / 102.7 (30.7)		SmA	219.1 (3.27) / 217.3 (3.21)	I
1j						Cr	130.7 (16.7) / 117.2 (16.4)	I
1k	Cr_1	123.3 (34.6) / 111.8 (33.8)	SmX	156.7 (0.29) / 156.2 (0.23)		N	161.0 (0.60) / 160.5 (0.53)	I
1l	Cr_1	103.1 (35.6)	Cr_2	133.0 (51.6) / 115.2 (12.7)		SmA	212.5 (5.68) / 210.8 (5.54)	I

Cr_1, Cr_2=crystalline phases, SmX=unidentified smectic phase, SmC=smectic C phase, SmA=Smectic A phase, N=nematic phase, I=isotropic phase.

compounds (**1b**, **1c**, **1d**, **1f**, **1h**, **1i**, **1l**) with an electron-withdrawing substituent (–F, –Cl, –Br, $–CF_3$, $–NO_2$, –CN, $–COOCH_3$) formed smectic A (SmA) phases. The N and SmA phases were observed and identified by optical texture, as shown in Figure 1.

Among them, compounds **1b**, **1c** , **1d** formed SmA phases, however, compound **1d** containing a larger and/or more polarized group (X=Br) enhanced the SmA phase more than compounds with a smaller and/or less polarized group (X=F, Cl). The clearing temperature of compound **1d** was higher than those of compounds **1b** and **1c**, i.e., 194.3 °C>174.0 °C>155.6 °C. This order in clearing temperatures and the temperature of mesophase was parallel to the increased polarizability in the order of Br>Cl>F. On the other hand, the temperature range of the mesophase was also wider for compound **1d** than those of compounds **1a** and **1b**, i.e., 96.4 °C>81.9 °C>53.9 °C on heating. Interestingly, among these electron-withdrawing substituents, compounds **1h**, **1i**, **1l** (X=NO_2, CN, $COOCH_3$) appeared to have clearing temperatures higher than those of other homologues, which ranged from 212.5 and 224.8 °C. These polar groups are also known as good π-acceptors, and have a more planar structure (i.e., sp or sp^2 hybrid orbital). The increase in T_{cl} might be attributed to two factors. Electronically, a conjugative interaction over the entire molecule was better achieved between the polar substituent and the other side of benzoxazole, and also a better packing arrangement due to a more overall molecular planar structure may be achieved in the solid and liquid crystal states. The temperature range of mesophases were relatively wide with these three compounds, at ca. 79.5 °C (**1l**)–98.4 °C (**1i**). Among these three substituents, the NO_2 group is particularly worthy to note. Compound **1h** (X=NO_2) has the highest clearing temperature in the whole series, and this is probably due to NO_2 group having the largest dipole. The range of mesophase temperature is relatively high; 98.4 °C (**1i**; CN)>96.4 °C (**1d**; Br)>95.5 °C (**1h**; NO_2). The effect of lateral and terminal $–NO_2$ as a substituent in achiral calamitic liquid crystals has been reviewed.[8e] The results indicated that substantial changes in clearing and/or melting temperatures were obviously observed depending on the molecular structures and the substituted position. A polar NO_2 group attached to the hydrocarbon moiety changes substantially the electron affinity of the molecules, and the strong mesomeric effect caused by the NO_2 group induces a positive charge on the nitrogen atom and increases the electronegativity of the group.[8e,15] The transition enthalpies of SmA→I in the whole series of the compounds, measured with 2.64 kJ/mol (**1h**)–6.42 kJ/mol (**1d**), varied slightly with the substituents. On the other hand, compounds **1e** and **1f**, which are relatively equal in molecular size, exhibited a different mesophase; N phase for **1e** and SmA phase for **1f**, respectively. On the other hand, a higher T_{cl} in compound **1f** (180.9 °C) over **1e** (137.4 °C) by ca. 43.4 °C, as well as a wider mesophase range by ΔT=56.6 °C

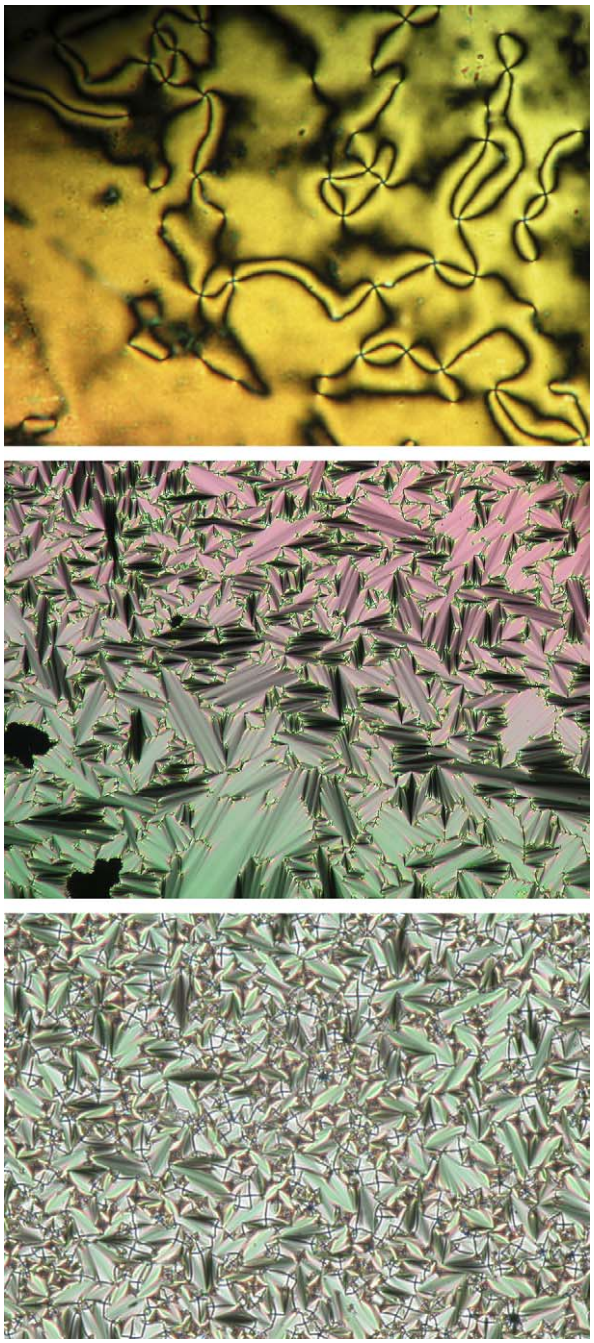


Figure 1. Optical textures observed by **1e** (X=CH_3) at 119.0 °C (top plate), **1f** (X=CF_3) at 165.0 °C (middle plate), and **1l** (X=$COOCH_3$) at 175.0 °C (bottom plate).

(i.e., 90.1 °C for **1f** vs 33.5 °C for **1e**) might be attributed to a better or larger dipole on **1f** (CF_3) over **1e** (CH_3). The electronic factor of the substituent, but not the steric factor, might have played a more important role in forming or inducing the phase. Heterocyclic benzoxazole is known as an electron-deficient moiety, and polarization or electron distribution by an electron-donating group, such as –CH_3, is better achieved by compound **1f** than by compound **1e**. Compound **1g** formed a N phase.

The transition enthalpies of N→I, measured with 0.38 kJ/mol (**1e**)–0.60 kJ/mol (**1k**), were insensitive to the substituents. Compound **1j** (X=OH) was non-mesogenic, and only

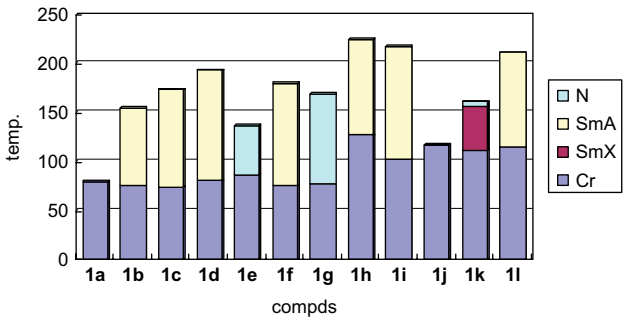


Figure 2. Bar graph showing the phase behavior of compounds **1a**–**1l**.

a transition of crystal-to-isotropic at 130.7 °C was observed. The lack of mesomorphic properties might result from the intermolecular H-bonds formed, which can lead to a stronger molecular interaction between the molecules. Figure 2 showed the bar graph of the transition temperatures of compounds **1a**–**1l**. The relationship between the melting temperatures, the clearing temperatures or the temperature ranges of the mesophases with the electronic properties of the substituents was plotted. However, no linear correlation between the clearing temperature or the temperature range of mesophases with Hammett σ_p constants for the substituents was found in this system (Fig. 3).

In order to understand the effect of terminal carbon chain length on the formation of mesophase, the compounds **2a** (X=OCH_3) and **2b** (X=CN) with a carbon chain length of n=8 and 16 were also prepared and studied. The phase transitions and thermodynamic data are summarized in Table 2. The mesomorphic properties exhibited by three compounds **2a** and **1g** with different carbon chain length (n=8, 12, 16) were compared. Compounds **2a** (n=8) and **1g** (n=12) exhibited nematic phases, however, the compound **2a** with a longer carbon chain length (n=16) formed a N phase and a SmA phase. This phase behavior is expected for rod-like molecules. The melting temperature increased slightly with the carbon chain length, i.e., T_{mp}: 106.1 °C (n=8)< 108.3 °C (n=12)<112.5 °C (n=16), however, the clearing temperatures decreased with the carbon chain length, i.e., T_{cl}: 186.0 °C (n=8)>169.5 °C (n=12)>158.1 °C (n=16). The temperature range of the mesophase increased with carbon chain length, ΔT=82.9 °C (n=8)>61.2 °C>45.6 °C (n=16) (Fig. 4). Elongation of the overall molecular length by increasing the carbon length on the other side of terminal chains led to the formation of more ordered SmA phases beside for N phase at higher temperature. This can probably

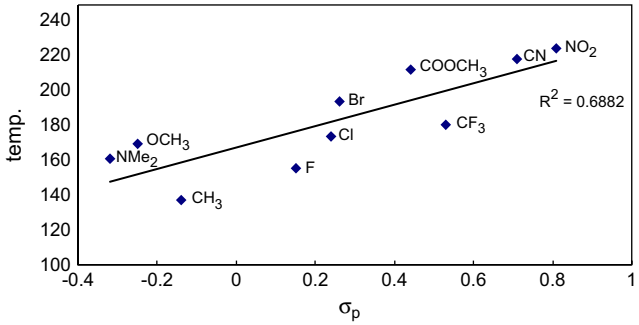


Figure 3. The plot of clearing temperature (°C) with Hammett σ_p constants of substituents in **1a**–**1l**.

Table 2. Phase transitions and enthalpies of compounds **1g**, **1i**, **2a**, and **2b**

2a;	$n=8$			Cr	106.1 (43.6) / 78.0 (42.2)	N	186.0 (0.47) / 185.3 (0.46)	I		
1g;	12	Cr_1	92.0 (4.61)	Cr_2	108.3 (51.6) / 76.3 (51.5)	N	169.5 (0.49) / 169.2 (0.47)	I		
2a;	16	Cr	112.5 (63.4) / 88.3 (67.6)	SmA	154.8 (0.43) / 153.7 (0.42)	N	158.1 (0.63) / 157.0 (0.63)	I		
2b;	8	Cr	126.3 (31.9) / 106.2 (27.3)	SmA	195.0[a] / 187.0[a]	N	233.0 (0.45) / 232.2 (0.41)	I		
1i;	12	Cr_1	102.9 (8.93) / 86.3 (6.08)	Cr_2	120.7 (40.1) / 102.7 (30.7)	SmA	219.1 (3.27) / 217.3 (3.21)	I		
2b;	16			Cr	120.9 (12.2) / 100.7 (78.8)	SmA	213.7 (6.16) / 211.9 (6.09)	I		

Cr_1, Cr_2=crystalline phases, SmA=Smectic A phase, N=nematic phase, I=isotropic phase.
[a] Determined by optical microscope.

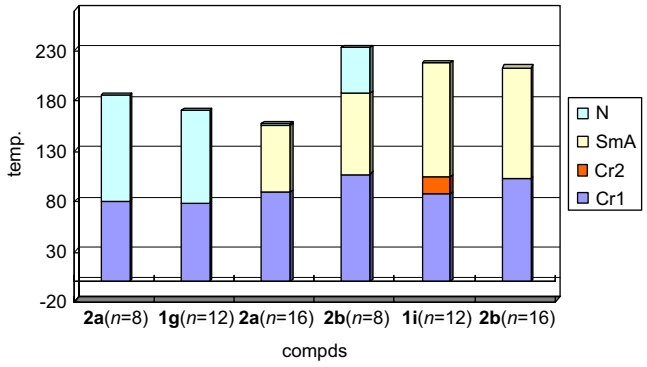
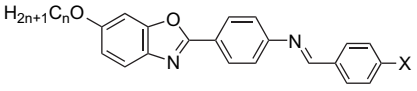


Figure 4. Bar graph showing the phase behavior of compounds **2a**, **2b**.

be attributed to an enhanced dispersive interaction between the terminal alkoxy chains. Similar mesomorphic behavior was also observed in compounds **2b** (n=8, 16) and **1i** (n=12), and compounds **2b** with longer carbon chain length (n=12, 16) favored the formation of the more ordered SmA over N phase.



n = 12
1a; X = H
1b; X = F
1c; X = Cl
1d; X = Br
1e; X = CH_3
1f; X = CF_3
1g; X = OCH_3
1h; X = NO_2
1i; X = CN
1j; X = OH
1k; X = NMe_2
1l; X = $COOCH_3$

n = 8, 16
2a; X = OCH_3
2b; X = CN

2.2. Optical properties

The UV–vis absorption and PL spectra of the compounds **1a**–**1l** in CH_2Cl_2 solution are presented in Figures 5 and 6. The data of λ_{max} peaks of UV–vis absorption and PL spectra in CH_2Cl_2 are listed in Table 3. The absorption and emission spectra of all compounds **1a**–**1l** were very similar in shape because of their structural similarity. The highest absorption peaks of all compounds were found to be insensitive to the substituents. Interestingly, they all occurred at ca. 348–365 nm except for two compounds **1h** and **1k**, for which

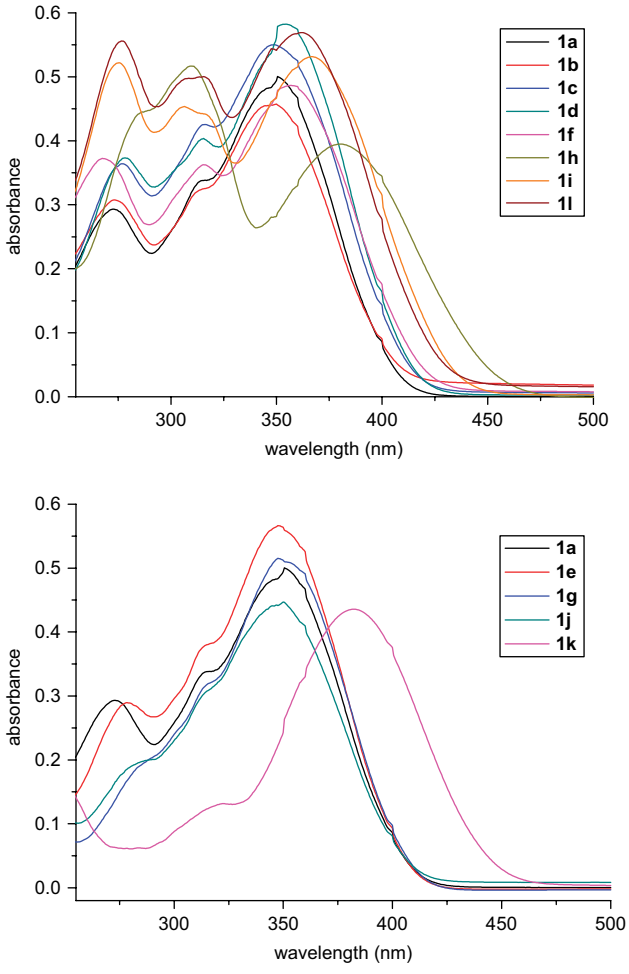


Figure 5. Normalized absorption spectra of compounds with electron-withdrawing (top) and electron-donating substituents (bottom) in CH_2Cl_2.

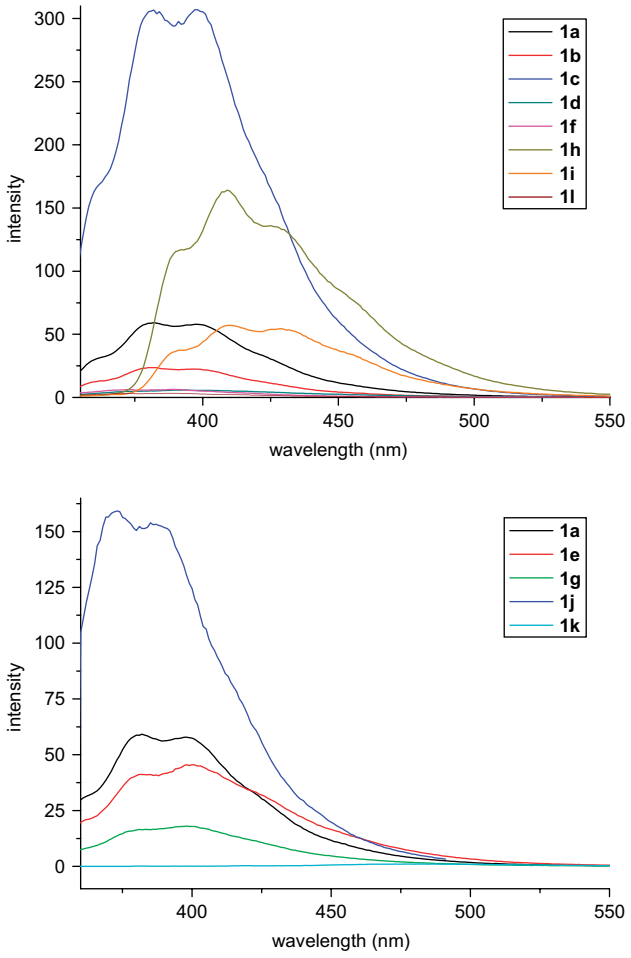


Figure 6. Normalized PL spectra of compounds with electron-withdrawing (top) and electron-donating substituents (bottom) in CH_2Cl_2.

the λ_{max} were all shifted to longer wavelength, by ca. 31 and 33 nm, respectively. The electronic properties of the substituents might not play an important role in the UV absorption spectra. The photoluminescence spectra measured in CH_2Cl_2 of compounds **1a–1l** are also shown in Figure 6. A similar trend was also observed in the photoluminescence spectra. The emission peaks occurred at 386–409 nm except for compounds **1k**, which the λ_{max} were slightly shifted to longer wavelength, by ca. 80 nm. The dependence of PL spectra is more sensitive to the electronic factor than that of UV-absorption. However, it is worth noting that the quantum yields of some compounds in CH_2Cl_2 estimated with anthracene as a standard (φ_f=0.27 in hexane) were relatively low. For example, the yields were all ranged between 0.05 and 0.07%.

Table 3. A summary of UV and PL peaks for compounds **1a–1l**

Compounds	σ_p	UV (nm)	PL (nm)
1a	0	273, 313 (sh), 348	382, 398
1b	0.15	273, 313 (sh), 348	382, 398
1c	0.24	277, 313 (sh), 348	387, 397
1d	0.26	277, 313, 352	392
1f	0.53	267, 313, 356	372, 389
1h	0.81	283 (sh), 309, 379	391 (sh), 409, 425 (sh)
1i	0.71	273, 309, 365	391 (sh), 409, 425
1l	0.44	273, 309, 362	372, 389
1e	−0.14	280, 313 (sh), 348	382, 398
1j	−0.22	280 (sh), 313 (sh), 348	372, 386
1g	−0.25	284 (sh), 313 (sh), 348	382, 398
1k	−0.32	319 (sh), 381	478

3. Conclusions

The effect of polar substituents on a series of heterocyclic benzoxazoles was systematically studied, and the formation of mesophases was observed depending on the electronic and/or the steric factors of the substituents. In general, the mesophase observed was improved by introducing a polar group. Most compounds (except **1j**) exhibited nematic or smectic A phases. Compounds with electron-donating substituents favored nematic phases, however, compounds with electron-withdrawing substituents formed smectic A phases. However, no linear correlation between the clearing temperature or the temperature range of mesophases with Hammett σ_p constants was found.

4. Experimental section

4.1. General

All chemicals and solvents were reagent grades from Lancaster or Aldrich. Solvents were dried by standard techniques. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300. FTIR spectra were performed on Nicolet Magna-IR 550 spectrometer. DSC thermographs were carried out on a Mettler DSC 821 and calibrated with a pure indium sample (mp=156.60 °C, 28.45 J/K), and all phase transitions are determined by a scan rate of 10.0°/min. Optical polarized microscopy was carried out on an Zeiss AxiaPlan equipped with a hot stage system of Mettler FP90/FP82HT. The UV–vis absorption and fluorescence spectra were obtained using HITACHI F-4500 or JASCO V-530 spectrometer, and all spectra were recorded at room temperature. Elemental analysis for carbon, hydrogen, and nitrogen were conducted on a Heraeus Vario EL-III elemental analyzer at National Taiwan University.

3-Alkoxyphenols, 5-alkoxy-2-nitrophenols, 2-amino-5-alkoxyphenols, 5-alkoxy-2-[(4-nitro-benzylidene)amino]-phenols, 6-alkoxy-2-(4-nitrophenyl)benzoxazoles, 4-(6-alkoxybenzoxazol-2-yl)phenylamines were prepared by similar procedures.[5a]

4.1.1. 3-Dodecyloxyphenol[5a] (*n*=12). White solid, yield 60%. ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H, $-CH_3$, J=6.9 Hz), 1.25–1.43 (m, 18H, $-CH_2$), 1.72–1.77 (m, 2H, $-OCH_2CH_2$), 3.90 (t, 2H, $-OCH_2$, J=6.6 Hz), 6.39–6.40 (m, 2H, Ar-H), 6.46–6.48 (m, 1H, Ar-H), 7.10 (t, 1H, Ar-H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 14.14, 22.71, 26.05, 29.23, 29.37, 29.42, 29.60, 29.63, 29.66, 29.68, 31.94, 68.10, 102.08, 107.10, 107.59, 130.10, 156.68, 160.51.

4.1.2. 5-Dodecyloxy-2-nitrophenol[5a] (*n*=12). Yellow solid, yield 25%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.9 Hz), 1.24–1.44 (m, 18H, $-CH_2$), 1.75–1.80 (m, 2H, $-CH_2$), 3.99 (t, 2H, $-OCH_2$, J=6.5 Hz), 6.47–6.49 (m, 2H, Ar-H), 8.00 (d, 1H, Ar-H, J=10.1 Hz), 11.02 (s, 1H,

Ar-OH). ^{13}C NMR ($CDCl_3$): δ 14.12, 22.69, 25.87, 28.83, 29.27, 29.35, 29.41, 29.52, 29.57, 29.63, 29.64, 29.71, 31.92, 69.15, 101.80, 109.83, 126.91, 127.54, 158.01, 166.74.

4.1.3. 2-Amino-5-dodecyloxyphenol[5a] (n=12). White solid, yield 85%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.24–1.41 (m, 18H, –CH_2), 1.68–1.73 (m, 2H, –CH_2), 3.84 (t, 2H, –OCH_2, J=6.6 Hz), 6.32 (dd, 1H, Ar-H, J=2.6 Hz, 8.6 Hz), 6.41 (d, 1H, Ar-H, J=2.7 Hz), 6.75 (d, 1H, Ar-H, J=8.6 Hz). ^{13}C NMR ($CDCl_3$): δ 13.94, 22.59, 26.02, 29.25, 29.34, 29.51, 29.53, 29.56, 29.58, 31.85, 68.67, 102.72, 106.75, 120.85, 125.58, 148.06, 154.94.

4.1.4. 5-Dodecyloxy-2-[(4-nitrobenzylidene)amino]phenol[5a] (n=12). Orange solid, yield 90%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.8 Hz), 1.25–1.44 (m, 18H, –CH_2), 1.74–1.79 (m, 2H, –CH_2), 3.94 (t, 2H, –OCH_2, J=6.5 Hz), 6.47 (dd, 1H, Ar-H, J=2.4 Hz, 8.9 Hz), 6.55 (d, 1H, Ar-H, J=2.5 Hz), 7.31 (d, 1H, Ar-H, J=8.9 Hz), 7.40 (s, 1H, Ar-OH), 7.99 (d, 2H, Ar-H, J=8.6 Hz), 8.29 (d, 2H, Ar-H, J=8.6 Hz), 8.66 (s, 1H, Ar–CH=N–Ar). ^{13}C NMR ($CDCl_3$): δ 14.12, 22.70, 26.02, 29.16, 29.36, 29.38, 29.58, 29.60, 29.65, 29.67, 31.93, 68.39, 100.57, 107.84, 116.45, 124.11, 127.46, 128.73, 141.71, 148.90, 149.83, 154.66, 161.56.

4.1.5. 6-Dodecyloxy-2-(4-nitrophenyl)benzoxazole[5a] (3; n=12). The mixture of 5-dodecyloxy-2-[(4-nitrobenzylidene)amino]phenol (3.2 g, 0.007 mol) dissolved in 125 mL of CH_2Cl_2 and $Pb(OAc)_4$ (4.32 g, 0.01 mol) was refluxed for 4 h. The solution was extracted with 100 mL of CH_2Cl_2/H_2O (1/2), and the organic layers were combined and dried over $MgSO_4$. The solution was concentrated and the brown solids were recrystallized from C_2H_5OH. The light yellow solids were isolated with a yield of 85%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.25–1.49 (m, 18H, –CH_2), 1.74–1.84 (m, 2H, –CH_2), 4.01 (t, 2H, –OCH_2, J=6.5 Hz), 6.99 (dd, 1H, Ar-H, J=2.28, 8.8 Hz), 7.09 (d, 1H, Ar-H, J=2.2 Hz), 7.65 (d, 1H, Ar-H, J=8.8 Hz), 8.34 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.12, 22.69, 26.05, 29.18, 29.35, 29.39, 29.58, 29.60, 29.64, 29.66, 31.92, 68.95, 95.92, 114.39, 120.67, 124.21, 127.82, 133.04, 135.61, 149.01, 152.07, 158.79, 159.70.

4.1.6. 4-(6-Dodecyloxybenzoxazol-2-yl)phenylamine[5a] (4; n=12). To a solution of 6-dodecyloxy-2-(4-nitrophenyl)-benzoxazole (2.54 g, 0.006 mol) dissolved in absolute C_2H_5OH (100 mL) was added powdered Pd/C (0.1 g, 0.001 mol) under nitrogen atmosphere. The solution was gently refluxed for 10 min and then N_2H_4 (0.36 g, 0.007 mol) was added. The mixture was refluxed for 6 h. The solution was filtered while hot. The filtrate was concentrated to give off-white solids. The products isolated as white solids were obtained after recrystallization from C_2H_5OH, yield 80%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.22–1.46 (m, 18H, –CH_2), 1.78–1.81 (m, 2H, –CH_2), 3.98 (t, 2H, –OCH_2, J=6.6 Hz), 6.73 (dd, 2H, Ar-H, J=1.57, 6.9 Hz), 6.88 (dd, 1H, Ar-H, J=2.31, 8.7 Hz), 7.04 (d, 1H, Ar-H, J=2.3 Hz), 7.53 (d, 1H, Ar-H, J=8.7 Hz), 7.97 (d, 2H, Ar-H, J=8.6 Hz). ^{13}C NMR ($CDCl_3$): δ 14.15, 22.71, 26.08, 29.28, 29.37, 29.43, 29.60, 29.62, 29.66, 29.68, 31.94, 68.88, 96.13, 112.74, 114.70, 117.27, 119.17, 128.93, 135.96, 149.26, 151.35, 157.19, 162.94.

4.1.7. Benzylidene-4-(6-dodecyloxybenzoxazol-2-yl)phenylamine (1a; n=12, X=H). A mixture of benzaldehyde (0.10 mL, 0.001 mol) and 4-(6-dodecyloxybenzoxazol-2-yl)phenylamine (0.4 g, 0.001 mol) was dissolved in 100 mL of absolute ethanol under nitrogen atmosphere. The solution was refluxed for 10 min, and 0.5 mL of acetic acid was slowly added. The solution was refluxed for 12 h. The brown solids were then collected. The products isolated as light yellow solids were obtained after recrystallization from C_2H_5OH, yield 78%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.8 Hz), 1.25–1.47 (m, 18H, –CH_2), 1.80–1.83 (m, 2H, –CH_2), 4.00 (t, 2H, –OCH_2, J=6.6 Hz), 6.94 (dd, 1H, Ar-H, J=2.3 Hz, 8.7 Hz), 7.09 (d, 1H, Ar-H, J=2.3 Hz), 7.31 (d, 2H, Ar-H, J=8.4 Hz), 7.47–7.50 (m, 3H, Ar-H), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.91–7.92 (m, 2H, Ar-H), 8.21 (d, 2H, Ar-H, J=8.5 Hz), 8.49 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.08, 29.26, 29.36, 29.42, 29.60, 29.62, 29.66, 29.68, 31.94, 68.90, 96.08, 113.33, 119.81, 121.44, 124.88, 128.29, 128.87, 129.04, 131.81, 135.86, 135.94, 151.67, 154.42, 157.78, 161.20, 162.04. IR (KBr): 2919, 2848, 1625, 1614, 1505, 1496, 1490, 1467, 1281, 1226, 1150, 1053, 1004, 968, 861, 840, 800 cm^{-1}. MS (FAB): calcd for $C_{32}H_{39}N_2O_2$: 482.3, found: 483.4 $[M+H]^+$. Anal. Calcd for $C_{32}H_{38}N_2O_2$: C, 79.61; H, 7.79; N, 5.42. Found: C, 79.63; H, 7.94; N, 5.80.

4.1.8. 4-(6-Dodecyloxybenzoxazol-2-yl)phenyl-(4-fluorobenzylidene)amine (1b; n=12, X=F). Light yellow solid, yield 81%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.25–1.48 (m, 18H, –CH_2), 1.79–1.82 (m, 2H, –CH_2), 3.99 (t, 2H, –OCH_2, J=6.7 Hz), 6.93 (dd, 1H, Ar-H, J=2.3 Hz, 8.70 Hz), 7.07 (d, 1H, Ar-H, J=2.2 Hz), 7.16 (t, 2H, Ar-H, J=8.6 Hz), 7.29 (d, 2H, Ar-H, J=8.5 Hz), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.91 (dd, 2H, Ar-H, J=5.6, 8.6 Hz), 8.20 (d, 2H, Ar-H, J=8.5 Hz), 8.44 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.07, 29.25, 29.36, 29.42, 29.59, 29.61, 29.65, 29.67, 31.93, 68.91, 96.09, 113.35, 115.99, 116.16, 119.81, 121.41, 124.96, 128.30, 131.02, 131.09, 132.31, 132.33, 135.85, 151.67, 154.15, 157.81, 159.58, 161.98, 163.95, 165.97. MS (FAB): calcd for $C_{32}H_{38}FN_2O_2$: 500.3, found: 501.4 $[M+H]^+$. Anal. Calcd for $C_{32}H_{37}FN_2O_2$: C, 76.77; H, 7.45; N, 5.60. Found: C, 76.48; H, 7.59; N, 5.45.

4.1.9. 4-Chlorobenzylidene-4-(6-dodecyloxybenzoxazol-2-yl)phenylamine (1c; n=12, X=Cl). Light yellow solid, yield 84%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.8 Hz), 1.25–1.48 (m, 18H, –CH_2), 1.79–1.82 (m, 2H, –CH_2), 4.00 (t, 2H, –OCH_2, J=6.6 Hz), 6.94 (dd, 1H, Ar-H, J=2.29, 8.7 Hz), 7.08 (d, 1H, Ar-H, J=2.2 Hz), 7.30 (t, 2H, Ar-H, J=8.5 Hz), 7.45 (d, 2H, Ar-H, J=8.4 Hz), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.85 (d, 2H, Ar-H, J=8.4 Hz), 8.21 (d, 2H, Ar-H, J=8.4 Hz), 8.45 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.07, 29.25, 29.36, 29.42, 29.59, 29.62, 29.65, 29.68, 31.93, 68.90, 96.08, 113.37, 114.69, 119.83, 121.43, 125.12, 128.30, 128.92, 129.19, 130.16, 134.43, 135.84, 137.86, 151.68, 153.96, 157.82, 159.60, 161.93. IR (KBr): 2918, 2852, 1612, 1503, 1489,

1472, 1361, 1321, 1230, 1223, 1148, 1052, 1011, 973, 852, 815 cm^{-1}. MS (FAB): calcd for $C_{32}H_{38}ClN_2O_2$: 516.3, found: 517.3 $[M+H]^+$. Anal. Calcd for $C_{32}H_{37}ClN_2O_2$: C, 74.33; H, 7.21; N, 5.42. Found: C, 74.35; H, 7.40; N, 5.31.

4.1.10. 4-Bromobenzylidene-4-(6-dodecyloxybenzoxazol-2-yl)phenylamine (1d; *n*=12, X=Br). Light yellow solid, yield 83%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.9 Hz), 1.25–1.48 (m, 18H, $-CH_2$), 1.79–1.84 (m, 2H, $-CH_2$), 4.00 (t, 2H, $-OCH_2$, J=6.6 Hz), 6.94 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 7.07 (d, 1H, Ar-H, J=2.3 Hz), 7.30 (d, 2H, Ar-H, J=8.5 Hz), 7.59–7.62 (m, 3H, Ar-H), 7.78 (d, 2H, Ar-H, J=8.4 Hz), 8.21 (d, 2H, Ar-H, J=8.5 Hz), 8.43 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.07, 29.25, 29.36, 29.41, 29.59, 29.61, 29.65, 29.67, 31.93, 68.91, 96.08, 119.83, 121.42, 125.15, 126.41, 128.31, 130.34, 132.16, 134.83, 135.84, 151.68, 153.94, 157.83, 159.73, 161.93. IR (KBr): 2915, 2848, 1625, 1612, 1583, 1566, 1487, 1470, 1397, 1320, 1299, 1219, 1147, 1114, 1068, 1054, 1009, 847, 820 cm^{-1}. MS (FAB): calcd for $C_{32}H_{38}BrN_2O_2$: 560.2, found: 561.2 $[M+H]^+$. Anal. Calcd for $C_{32}H_{37}BrN_2O_2$: C, 68.44; H, 6.64; N, 4.99. Found: C, 68.67; H, 6.63; N, 4.73.

4.1.11. 4-(6-Dodecyloxybenzoxazol-2-yl)phenyl-(4-methylbenzylidene)amine (1e; *n*=12, X=CH_3). Light yellow solid, yield 82%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.7 Hz), 1.25–1.48 (m, 18H, $-CH_2$), 1.79–1.82 (m, 2H, $-OCH_2CH_2$), 2.41 (s, 3H, Ar-CH_3), 3.99 (t, 2H, $-OCH_2$, J=6.5 Hz), 6.93 (dd, 1H, Ar-H, J=2.0, 8.65 Hz), 7.07 (d, 1H, Ar-H, J=1.9 Hz), 7.27–7.30 (m, 4H, Ar-H), 7.60 (d, 2H, Ar-H, J=8.7 Hz), 7.80 (d, 2H, Ar-H, J=7.9 Hz), 8.20 (d, 2H, Ar-H, J=8.4 Hz), 8.44 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.14, 21.70, 22.71, 26.08, 29.26, 29.37, 29.42, 29.60, 29.62, 29.66, 29.68, 31.94, 68.89, 96.07, 113.30, 119.78, 121.46, 124.67, 128.27, 129.05, 129.62, 133.40, 135.86, 142.42, 151.66, 154.62, 157.75, 161.14, 162.10. IR (KBr): 2919, 2848, 1628, 1507, 1489, 1466, 1347, 1282, 1227, 1152, 1137, 1052, 1008, 969, 861, 844, 810, 800 cm^{-1}. MS (FAB): calcd for $C_{32}H_{41}N_2O_2$: 496.3, found: 497.3 $[M+H]^+$. Anal. Calcd for $C_{32}H_{40}N_2O_2$: C, 79.80; H, 8.12; N, 5.64. Found: C, 79.84; H, 8.57; N, 5.30.

4.1.12. 4-(6-Dodecyloxybenzoxazol-2-yl)phenyl-(4-trifluoromethylbenzylidene)amine (1f; *n*=12, X=CF_3). Light yellow solid, yield 85%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.9 Hz), 1.25–1.48 (m, 18H, $-CH_2$), 1.79–1.82 (m, 2H, $-CH_2$), 3.99 (t, 2H, $-OCH_2$, J=6.5 Hz), 6.94 (dd, 1H, Ar-H, J=2.20, 8.7 Hz), 7.07 (d, 1H, Ar-H, J=2.1 Hz), 7.32 (d, 2H, Ar-H, J=8.4 Hz), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.73 (d, 2H, Ar-H, J=8.1 Hz), 8.02 (d, 2H, Ar-H, J=8.0 Hz), 8.22 (d, 2H, Ar-H, J=8.5 Hz), 8.52 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.07, 29.25, 29.37, 29.42, 29.60, 29.62, 29.66, 29.68, 31.94, 68.89, 96.05, 113.41, 119.87, 121.47, 122.75, 124.91, 125.48, 125.80, 125.83, 128.32, 129.17, 132.97, 133.23, 135.80, 138.95, 151.69, 153.57, 157.87, 159.37, 161.82. IR (KBr): 2918, 2849, 1623, 1610, 1575, 1487, 1470, 1361, 1332, 1299, 1225, 1178, 1169, 1148, 1131, 1106, 1069, 1014, 860, 842, 816 cm^{-1}. MS (FAB): calcd for $C_{33}H_{38}F_3N_2O_2$: 550.3, found: 551.3 $[M+H]^+$. Anal. Calcd for $C_{33}H_{37}F_3N_2O_2$: C, 71.78; H, 6.59; N, 4.82. Found: C, 71.98; H, 6.77; N, 5.09.

4.1.13. 4-(6-Dodecyloxybenzoxazol-2-yl)phenyl-(4-methoxybenzylidene)amine (1g; *n*=12, X=OCH_3). Light yellow solid, yield 82%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.9 Hz), 1.25–1.48 (m, 18H, $-CH_2$), 1.77–1.83 (m, 2H, $-CH_2$), 3.86 (s, 3H, Ar-OCH_3), 3.99 (t, 2H, $-OCH_2$, J=6.5 Hz), 6.93 (dd, 1H, Ar-H, J=2.4, 8.7 Hz), 6.98 (d, 2H, Ar-H, J=8.8 Hz), 7.07 (d, 1H, Ar-H, J=2.3 Hz), 7.28 (d, 2H, Ar-H, J=7.0 Hz), 7.59 (d, 1H, Ar-H, J=8.70 Hz), 7.85 (d, 2H, Ar-H, J=8.73 Hz), 8.19 (d, 2H, Ar-H, J=8.53 Hz), 8.40 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.08, 29.26, 29.36, 29.42, 29.60, 29.62, 29.66, 29.68, 31.93, 55.47, 68.90, 96.08, 113.28, 114.30, 119.75, 121.46, 124.48, 128.27, 128.99, 130.82, 135.88, 151.66, 154.74, 157.73, 160.43, 162.15, 162.61. IR (KBr): 2920, 2852, 1607, 1591, 1574, 1511, 1488, 1470, 1320, 1301, 1256, 1223, 1172, 1148, 1052, 1029, 1005, 860, 836, 815 cm^{-1}. MS (FAB): calcd for $C_{33}H_{41}N_2O_3$: 512.3, found: 513.4 $[M+H]^+$. Anal. Calcd for $C_{33}H_{40}N_2O_3$: C, 77.14; H, 7.59; N, 5.20. Found: C, 77.31; H, 7.86; N, 5.46.

4.1.14. [4-(6-Dodecyloxybenzoxazol-2-yl)phenyl]-(4-nitrobenzylidene)amine (1h; *n*=12, X=NO_2). Bright yellow solid, yield 85%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.9 Hz), 1.25–1.48 (m, 18H, $-CH_2$), 1.79–1.86 (m, 2H, $-CH_2$), 4.00 (t, 2H, $-OCH_2$–, J=6.6 Hz), 6.94 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 7.07 (d, 1H, Ar-H, J=2.3 Hz), 7.35 (d, 2H, Ar-H, J=8.5 Hz), 7.61 (d, 1H, Ar-H, J=8.7 Hz), 8.08 (d, 2H, Ar-H, J=8.8 Hz), 8.24 (d, 2H, Ar-H, J=8.5 Hz), 8.33 (d, 2H, Ar-H, J=8.7 Hz), 8.58 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.12, 22.70, 26.07, 29.24, 29.36, 29.41, 29.59, 29.61, 29.65, 29.67, 31.93, 68.92, 96.08, 113.49, 119.93, 121.54, 124.10, 125.95, 128.37, 129.63, 135.79, 141.22, 149.53, 151.72, 153.09, 157.95, 158.24, 161.68. IR (KBr): 2925, 2848, 1714, 1680, 1623, 1611, 1583, 1574, 1551, 1488, 1471, 1362, 1345, 1323, 1284, 1221, 1150, 1113, 1004, 971, 858, 846, 828 cm^{-1}. MS (FAB): calcd for $C_{32}H_{38}N_3O_4$: 527.3, found: 528.3 $[M+H]^+$. Anal. Calcd for $C_{32}H_{37}N_3O_4$: C, 72.84; H, 7.07; N, 7.96. Found: C, 73.01; H, 6.99; N, 7.81.

4.1.15. 4-{[4-(6-Dodecyloxybenzoxazol-2-yl)phenylimino]methyl}benzonitrile (1i; *n*=12, X=CN). Light yellow solid, yield 86%. ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, $-CH_3$, J=6.9 Hz), 1.25–1.48 (m, 18H, $-CH_2$), 1.80–1.83 (m, 2H, $-CH_2$), 4.00 (t, 2H, $-OCH_2$, J=6.6 Hz), 6.93 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 7.08 (d, 1H, Ar-H, J=2.3 Hz), 7.29 (d, 2H, Ar-H, J=9.6 Hz), 7.59–7.62 (m, 3H, Ar-H), 7.77 (d, 2H, Ar-H, J=8.4 Hz), 8.21 (d, 2H, Ar-H, J=8.5 Hz), 8.43 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.07, 29.24, 29.36, 29.41, 29.59, 29.61, 29.65, 29.67, 31.93, 68.92, 96.08, 113.47, 114.82, 118.35, 119.91, 121.50, 125.81, 128.36, 129.30, 132.62, 135.80, 139.63, 151.71, 153.21, 157.93, 158.73, 161.72. IR (KBr): 2921, 2849, 1714, 1681, 1626, 1613, 1495, 1488, 1467, 1361, 1281, 1223, 1152, 1135, 1050, 1010, 971, 861, 847, 799 cm^{-1}. MS (FAB): calcd for $C_{33}H_{38}N_3O_2$: 507.3, found: 508.3 $[M+H]^+$. Anal. Calcd for $C_{33}H_{37}N_3O_2$: C, 78.07; H, 7.35; N, 8.28. Found: C, 78.04; H, 7.23; N, 8.27.

4.1.16. [4-(6-Dodecyloxybenzoxazol-2-yl)phenyl]-(4-dimethylaminebenzylidene)amine (1k; n=12, X=NMe_2). Yellow solid, yield 85%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.25–1.48 (m, 18H, –CH_2), 1.79–1.82 (m, 2H, –CH_2), 3.05 (s, 6H, –NMe_2), 3.99 (t, 2H, –OCH_2, J=6.6 Hz), 6.72 (d, 2H, Ar-H, J=8.9 Hz), 6.92 (dd, 1H, Ar-H, J=2.3, 8.70 Hz), 7.07 (d, 1H, Ar-H, J=2.3 Hz), 7.28 (d, 2H, Ar-H, J=8.4 Hz), 7.59 (d, 1H, Ar-H, J=8.7 Hz), 7.77 (d, 2H, Ar-H, J=8.5 Hz), 8.18 (d, 2H, Ar-H, J=8.5 Hz), 8.34 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.14, 22.71, 26.08, 29.27, 29.37, 29.43, 29.60, 29.62, 29.66, 29.68, 31.94, 40.16, 68.89, 96.08, 111.56, 113.19, 119.68, 121.54, 123.86, 124.04, 128.24, 130.84, 135.94, 151.64, 152.79, 155.36, 157.64, 160.84, 162.36. IR (KBr): 2920, 2846, 1626, 1609, 1583, 1552, 1527, 1489, 1470, 1434, 1415, 1361, 1283, 1225, 1178, 1164, 1152, 1131, 1045, 1018, 1008, 941, 862, 839, 816 cm^{-1}. MS (FAB): calcd for $C_{34}H_{44}N_3O_2$: 525.3, found: 526.4 $[M+H]^+$. Anal. Calcd for $C_{34}H_{43}N_3O_2$: C, 77.68; H, 8.24; N, 7.99. Found: C, 77.63; H, 8.39; N, 8.31.

4.1.17. 4-{[4-(6-Dodecyloxybenzoxazol-2-yl)phenylimino]methyl}benzoic acid methyl ester (1l; n=12, X=$COOCH_3$). Light yellow solid, yield 78%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.25–1.46 (m, 18H, –CH_2), 1.79–1.82 (m, 2H, –CH_2), 3.93 (s, 3H, Ar–$COOCH_3$–), 3.99 (t, 2H, –OCH_2, J=6.6 Hz), 6.93 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 7.07 (d, 1H, Ar-H, J=2.3 Hz), 7.32 (d, 2H, Ar-H, J=8.5 Hz), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.97 (d, 2H, Ar-H, J=8.3 Hz), 8.13 (d, 2H, Ar-H, J=8.3 Hz), 8.21 (d, 2H, Ar-H, J=8.5 Hz), 8.53 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.14, 22.70, 26.07, 29.25, 29.37, 29.42, 29.60, 29.62, 29.66, 29.68, 31.93, 52.39, 68.89, 96.05, 113.40, 119.86, 121.49, 125.39, 128.85, 130.05, 132.68, 135.81, 139.66, 151.68, 153.76, 157.85, 159.92, 161.86, 166.51. IR (KBr): 2954, 2919, 2847, 1717, 1626, 1489, 1466, 1434, 1347, 1285, 1226, 1152, 1136, 1115, 1052, 1010, 968, 957, 854, 841, 800 cm^{-1}. MS (FAB): calcd for $C_{34}H_{41}N_2O_4$: 540.3, found: 541.3 $[M+H]^+$. Anal. Calcd for $C_{34}H_{40}N_2O_4$: C, 75.53; H, 7.46; N, 5.18. Found: C, 75.36; H, 7.35; N, 4.90.

4.1.18. (4-Methoxybenzylidene)-[4-(6-octyloxybenzoxazol-2-yl)phenyl]amine (2a; n=8, X=OCH_3). Light yellow solid, yield 77%. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, –CH_3, J=6.9 Hz), 1.28–1.47 (m, 10H, –CH_2), 1.79–1.82 (m, 2H, –CH_2), 3.86 (s, 3H, Ar-OCH_3), 3.99 (t, 2H, –OCH_2, J=6.5 Hz), 6.93 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 6.98 (d, 2H, Ar-H, J=8.7 Hz), 7.07 (d, 1H, Ar-H, J=2.3 Hz), 7.28 (d, 2H, Ar-H, J=6.7 Hz), 7.59 (d, 1H, Ar-H, J=8.7 Hz), 7.85 (d, 2H, Ar-H, J=8.7 Hz), 8.19 (d, 2H, Ar-H, J=8.5 Hz), 8.40 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.12, 22.67, 26.08, 29.26, 29.38, 31.83, 55.47, 68.90, 96.08, 113.28, 114.30, 119.75, 121.47, 124.48, 128.27, 128.98, 130.82, 135.88, 151.66, 154.74, 157.73, 160.44, 162.15, 162.62. Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 75.94; H, 7.20; N, 5.91.

4.1.19. [4-(6-Hexadecyloxybenzoxazol-2-yl)phenyl]-(4-methoxybenzylidene)amine (2a; n=16, X=OCH_3). Light yellow solid, yield 82%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.24–1.48 (m, 26H, –CH_2), 1.79–1.82 (m, 2H, –OCH_2), 3.87 (s, 3H, Ar-OCH_3), 3.99 (t, 2H, –OCH_2, J=6.6 Hz), 6.93 (dd, 1H, Ar-H, J=2.3, 8.71 Hz), 6.98 (d, 2H, Ar-H, J=8.7 Hz), 7.08 (d, 1H, Ar-H, J=2.3 Hz), 7.29 (d, 2H, Ar-H, J=8.5 Hz), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.86 (d, 2H, Ar-H, J=8.7 Hz), 8.19 (d, 2H, Ar-H, J=8.9 Hz), 8.41 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.08, 29.26, 29.37, 29.42, 29.60, 29.62, 29.68, 29.71, 31.94, 55.47, 68.89, 96.08, 113.28, 114.31, 119.76, 121.46, 124.51, 128.27, 128.92, 130.85, 135.89, 151.66, 157.73, 160.41, 162.14. Anal. Calcd for $C_{37}H_{48}N_2O_3$: C, 78.13; H, 8.51; N, 4.93. Found: C, 76.80; H, 8.99; N, 4.73.

4.1.20. 4-{[4-(6-Octyloxybenzoxazol-2-yl)phenylimino]methyl}benzonitrile (2b; n=8, X=CN). Light yellow solid, yield 80%. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, –CH_3, J=6.9 Hz), 1.28–1.49 (m, 10H, –CH_2), 1.78–1.83 (m, 2H, –OCH_2), 4.00 (t, 2H, –OCH_2, J=6.6 Hz), 6.94 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 7.08 (d, 1H, Ar-H, J=2.3 Hz), 7.33 (d, 2H, Ar-H, J=6.1 Hz), 7.61 (d, 1H, Ar-H, J=8.7 Hz), 7.77 (d, 2H, Ar-H, J=8.3 Hz), 8.02 (d, 2H, Ar-H, J=8.3 Hz), 8.23 (d, 2H, Ar-H, J=8.8 Hz), 8.53 (s, 1H, –CHN). ^{13}C NMR ($CDCl_3$): δ 14.11, 22.67, 26.08, 29.25, 29.37, 31.83, 68.92, 96.07, 113.47, 114.70, 114.83, 118.36, 119.91, 121.50, 125.81, 128.36, 129.30, 129.89, 132.63, 132.91, 135.80, 139.63, 151.72, 153.22, 157.93, 158.73, 161.72. Anal. Calcd for $C_{29}H_{29}N_3O_2$: C, 77.13; H, 6.47; N, 9.31. Found: C, 77.01; H, 6.45; N, 9.15.

4.1.21. 4-{[4-(6-Hexadecyloxybenzoxazol-2-yl)phenylimino]methyl}benzonitrile (2b; n=16, X=CN). Light yellow solid, yield 87%. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, –CH_3, J=6.9 Hz), 1.24–1.48 (m, 26H, –CH_2), 1.79–1.82 (m, 2H, –OCH_2), 3.99 (t, 2H, –OCH_2, J=6.5 Hz), 6.93 (dd, 1H, Ar-H, J=2.3, 8.7 Hz), 7.07 (d, 1H, Ar-H, J=2.2 Hz), 7.32 (d, 2H, Ar-H, J=8.5 Hz), 7.60 (d, 1H, Ar-H, J=8.7 Hz), 7.75 (d, 2H, Ar-H, J=8.2 Hz), 8.00 (d, 2H, Ar-H, J=8.3 Hz), 8.22 (d, 2H, Ar-H, J=8.5 Hz), 8.50 (s, 1H, Ar-CHN). ^{13}C NMR ($CDCl_3$): δ 14.13, 22.70, 26.07, 29.25, 29.37, 29.42, 29.59, 29.62, 29.67, 29.71, 31.94, 68.90, 96.06, 113.46, 114.79, 118.34, 119.90, 121.50, 125.79, 128.34, 129.29, 132.60, 135.78, 139.61, 151.70, 153.17, 157.92, 158.69, 161.70. Anal. Calcd for $C_{37}H_{45}N_3O_2$: C, 78.83; H, 8.05; N, 7.45. Found: C, 78.83; H, 8.16; N, 7.34.

Acknowledgements

We thank the National Science Council of Taiwan, ROC and the UST for funding (NSC-94-2113-M-008-011) in generous support of this work.

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Structure revision of HM-3, an aromatic sesquiterpene isolated from the phytopathogenic fungus *Helicobasidium mompa*. First total syntheses of HM-3 and HM-4

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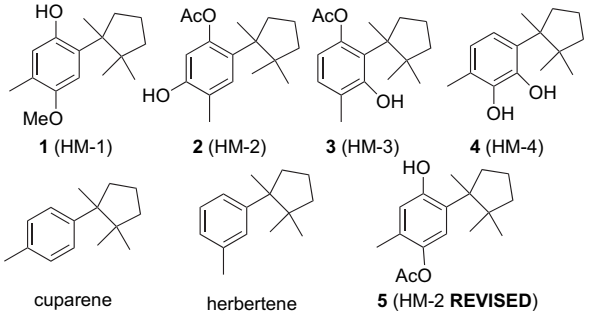
Received 24 April 2006; revised 2 July 2006; accepted 20 July 2006
Available online 10 August 2006

Abstract—The first total syntheses of HM-3 and HM-4, aromatic sesquiterpenes isolated from the phytopathogenic fungus *Helicobasidium mompa*, have been accomplished. The structure assigned to the sesquiterpene HM-3 was found to be incorrect by total synthesis. A Claisen rearrangement–RCM reaction based strategy was employed for the total synthesis of the aromatic sesquiterpene HM-4 (cuparene-1,2-diol), which on selective monoacetylation established the structure of HM-3, a cuparene derivative.

1. Introduction

The phytopathogenic fungus *Helicobasidium mompa* Tanaka is responsible for the violet root rot against mulberry and several other fruit trees. In the course of a study on the mechanism of violet root rot, Nohara and co-workers have investigated the fungus, and reported the isolation and structure elucidation of four aromatic sesquiterpenes from the methanolic extract of the mycelium grown with *H. mompa*, which was obtained from infected mulberry roots.[1] Based on preliminary observations, it was speculated that all the compounds possessed anti-oxidant as well as antibiotic activities similar to those of the higher oxygenated cuparene analogues, lagopodins and helicobasidins.[2] Of the four sesquiterpenes, two, HM-1 (**1**) and HM-4 (**4**), were found to belong to the cuparene class, whereas the structures of the remaining two, HM-2 (**2**) and HM-3 (**3**), were assigned as herbertanes on the basis of the 1D and 2D NMR spectroscopy. Incidentally, isolation of HM-4 (**4**) (same as cuparene-1,2-diol) has been reported earlier in 1982 from the liverwort *Raduia perrottetii* and subsequently from the liverwort *Herbertus aduncus*, and from the Japanese liverworts *Lejeunea aquatica* and *Lejeunea japonica*.[3] Since herbertanes are considered as chemical markers of the liverworts belonging to the genus *Herbertus*,[4] and *Helicobasidium* is known to contain helicobasidins,[2] which are higher oxygenated derivatives of cuparenes, we have undertaken the synthesis of HM-1 to 4 **1**–**4**. Recently, we carried out the total synthesis of putative structure **2** of HM-2, as well as cuparene-1,4-diol and its methyl and acetyl derivatives and revised the structure of HM-2 as cuparene-1,4-diol monoacetate **5**.[5] In continuation, herein, we describe our studies on the synthesis[6] of the compound having structure **3** and cuparene-1,2-diol **4**, and revision of the structure for HM-3 as a cuparenoid.



2. Results and discussion

For the synthesis of the putative structure **3** of HM-3, an orthoester Claisen rearrangement[7] and a ring-closing metathesis reaction (RCM)[8] based strategy were employed (Scheme 1) starting from 2,6-dimethoxy-3-methylacetophenone **6**. The acetophenone[9] **6** was prepared from 4-methylresorcinol dimethyl ether **7** in three steps (formylation, Grignard reaction, and oxidation). Since the Wittig or Horner–Wadsworth–Emmons reactions were unsuccessful, probably due to the steric crowding of the ketone group, a three-step protocol was used for the efficient conversion of the acetophenone **6** into the cinnamyl alcohol **8a**, the precursor for the Claisen rearrangement. Thus, Grignard reaction of the acetophenone **6** with vinylmagnesium bromide

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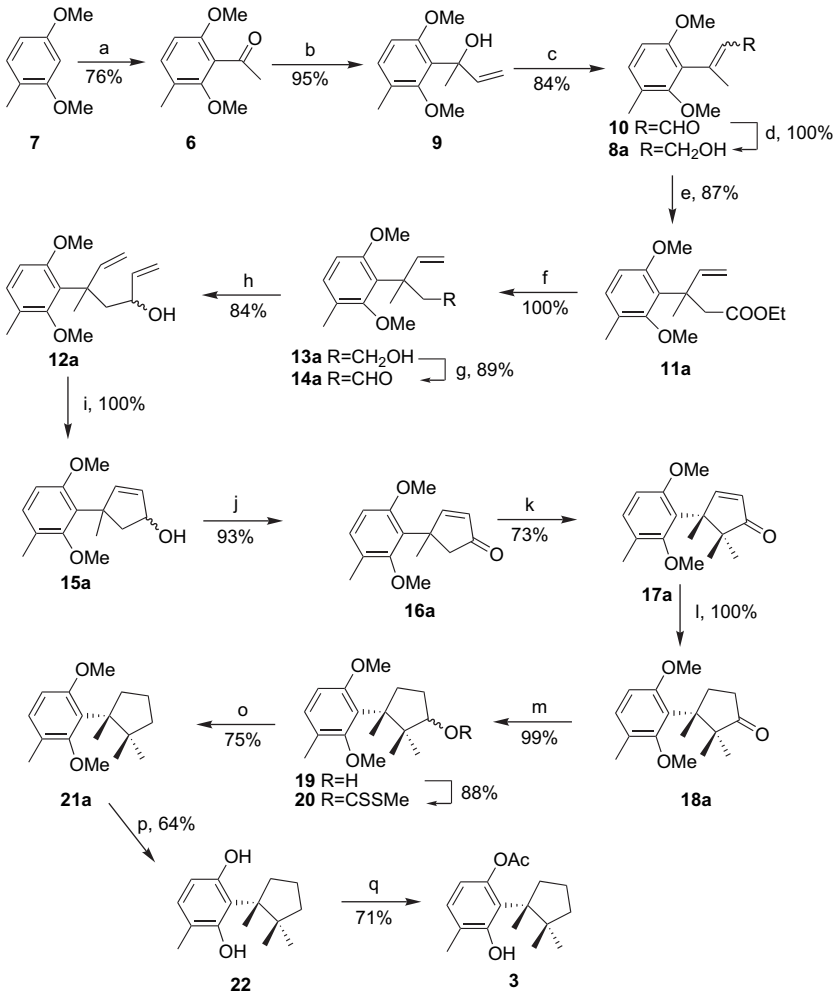
doi:10.1016/j.tet.2006.07.062



Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi, TMEDA, DMF, THF, 0 °C→rt, 4 h; (ii) MeMgI, Et_2O, 0 °C, 30 min; (iii) PCC, silica gel, CH_2Cl_2, 8 h; (b) CH_2=CHMgBr, THF, 0 °C→rt, 4 h; (c) PCC, silica gel, CH_2Cl_2, 8 h; (d) LAH, Et_2O, −50 °C, 45 min; (e) $CH_3C(OEt)_3$, $EtCO_2H$ (catalytic), 180 °C, 48 h; (f) LAH, Et_2O, 0 °C, 30 min; (g) PCC, silica gel CH_2Cl_2, 15 min; (h) CH_2=CHMgBr, THF, −20 °C, 10 min; (i) PhCH=$RuCl_2(PCy_3)_2$ (5 mol %), CH_2Cl_2, 3 h; (j) PCC, silica gel, CH_2Cl_2, 1 h; (k) NaH, CH_3I, THF, DMF, rt, 12 h; (l) H_2 (1 atm), 10% Pd–C, EtOH, 1 h; (m) $NaBH_4$, MeOH, 0 °C, 5 min; (n) NaH, THF, imidazole (catalytic), CS_2, CH_3I, reflux, 4.5 h; (o) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 3 h; (p) MeMgI, *p*-cymene, reflux, 8 h; (q) Ac_2O, py, DMAP, CH_2Cl_2, rt, 2 h.

furnished the tertiary allyl alcohol **9** in 95% yield. Oxidation of the alcohol **9** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride led to the 1,3-transposition[10] to generate the cinnamaldehyde **10**, which on reduction with lithium aluminum hydride (LAH) in ether generated the cinnamyl alcohol **8a** in 84% yield (two steps). Johnson's orthoester variant of the Claisen rearrangement was employed for the generation of the γ,δ-unsaturated ester containing the first quaternary carbon atom. Thermal activation of the cinnamyl alcohol **8a** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube furnished the pentenoate **11a** in 87% yield. A three-step protocol was employed for the conversion of the ester **11a** into the heptadienol **12a**, the precursor for the RCM reaction. Thus, reduction of the ester **11a** with LAH followed by oxidation of the resultant primary alcohol **13a** with PCC and silica gel in methylene chloride furnished the aldehyde **14a**. Grignard reaction of the aldehyde **14a** with vinylmagnesium bromide generated the heptadienol **12a**. RCM reaction of the dienol **12a** in methylene chloride with 5 mol % of Grubbs' first generation catalyst [PhCH=$RuCl_2(PCy_3)_2$] generated the cyclopentenol **15a** in quantitative yield, which on oxidation with PCC and silica gel in methylene chloride furnished the cyclopentenone **16a**. One-step dimethylation of the cyclopentenone **16a** with sodium hydride and methyl iodide in THF and DMF created the second quaternary carbon atom vicinal to the first one to furnish the cyclopentenone **17a** containing the complete carbon framework of herbertanes. Hydrogenation with 10% palladium over carbon as the catalyst quantitatively transformed the enone **17a** into cyclopentanone **18a**. Barton's radical deoxygenation protocol[11,12] was employed for the reductive deoxygenation of the ketone **18a**. Reduction of the ketone **18a** with sodium borohydride generated an epimeric mixture of the alcohol **19** in quantitative yield. Treatment of the alcohol **19** with sodium hydride and imidazole in THF followed by reaction of the resultant alkoxide with carbon disulfide and methyl iodide generated the dithiocarbonate **20**. Reaction of the dithiocarbonate **20** with tri-*n*-butyltin hydride and a catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene furnished herbertene-1,5-diol dimethyl ether **21a**. Boron tribromide or other acidic reagents mediated cleavage of the methyl ether in **21a**, however, failed to generate the herbertenediol **22**, and produced only the cleaved product,

4-methylresorcinol. Hence, demethylation was carried out using a Grignard reagent. Thus, refluxing a *p*-cymene solution of the dimethyl ether **21a** with methylmagnesium iodide furnished herbertene-1,5-diol **22**. Regioselective acetylation of the less hindered alcohol in the diol **22** with pyridine and acetic anhydride in methylene chloride for 2 h furnished the monoacetate **3** in 71% yield. The ^{1}H NMR spectrum of the monoacetate **3**, however, was found to be different[13] from that reported[1] for HM-3, which clearly established that the proposed structure needs to be revised.

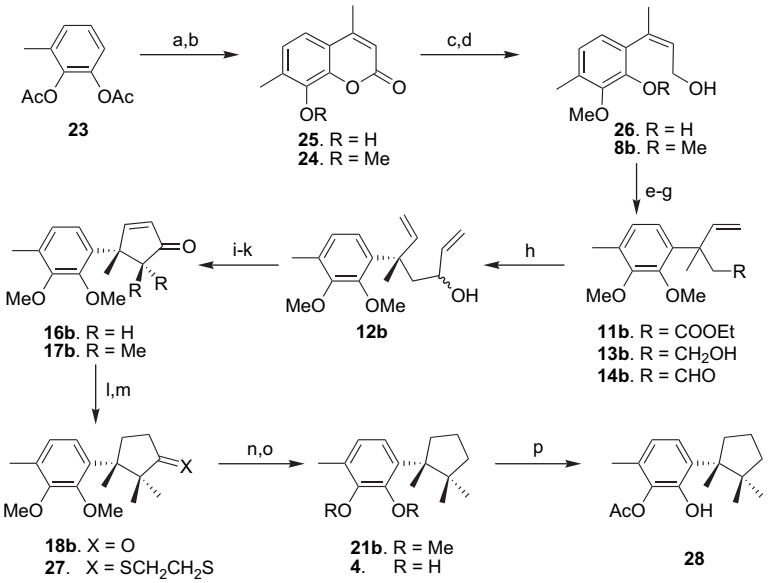
It was reasoned, like HM-1 (**1**), HM-2 (**5**),[5] and HM-4 (**4**), that HM-3 might also be a derivative of cuparene, and an acetate analog of HM-4 (cuparene-1,2-diol **4**) was considered as a possibility, since the NMR spectrum of the natural HM-3 clearly indicated that it contains two *ortho* coupled aromatic protons. To test the validity of this hypothesis and also to confirm the structure of HM-4,[6] the synthesis of cuparene-1,2-diol **4** was undertaken, Scheme 2.

The cinnamyl alcohol **8b** was identified as a suitable starting material, which was prepared starting from 3-methylcatechol diacetate **23** via the coumarin **24** as reported in the literature.[14] Thus, Pechmann reaction of the diacetate **23** with ethyl acetoacetate and 80% sulfuric acid generated the coumarin **25**, which on etherification with potassium carbonate and methyl iodide furnished the coumarin **24**. Reduction of the coumarin **24** with LAH in THF at −50 °C followed by regioselective etherification of the phenolic hydroxy group in the resultant diol **26** with potassium carbonate and methyl iodide in refluxing acetone furnished the cinnamyl alcohol **8b** in 81% yield. The orthoester Claisen rearrangement of the cinnamyl alcohol **8b** with triethyl orthoacetate and propionic acid generated the pentenoate **11b**, which was converted into the aldehyde **14b** via the alcohol **13b**. Grignard reaction of the aldehyde **14b** with vinylmagnesium bromide followed by RCM reaction of the resultant dienol **12b** with Grubbs' catalyst generated the cyclopentenol **15b**, which on PCC oxidation furnished the enone **16b**. One-pot dimethylation of the enone **16b** followed by catalytic hydrogenation of the resultant enone **17b** furnished 1,2-dimethoxy-α-cuparenone **18b**. Treatment of the ketone **18b** with 1,2-ethanedithiol in the presence of a catalytic amount of iodine[15] generated the thioketal **27**, which on desulfurization with Raney nickel furnished cuparene-1,2-diol dimethyl ether **21b** in 80% yield (two steps). Cleavage of the methyl ethers in **21b** with boron tribromide furnished cuparene-1,2-diol **4**, which exhibited ^{1}H NMR spectrum identical to that reported[1,3] for HM-4. Regioselective acetylation of the less hindered alcohol in the diol **4** with acetic anhydride and pyridine in methylene chloride furnished the monoacetate **28**. The ^{1}H NMR spectral data of the monoacetate **28** was found to be identical to that reported[1] for HM-3, which established the structure of the natural product HM-3 as a cuparene derivative **28**.[16]

In conclusion, we have accomplished an efficient total synthesis (in 16 steps from the acetophenone **6** with an average yield of 88% for each step) of the putative structure **3** of HM-3 and proved that the structure needs revision. We reasoned it to be a cuparene derivative. To substantiate further, the first total synthesis of cuparene-1,2-diol (HM-4) **4** was accomplished (in 13 steps from the coumarin **24** with an average yield of 90% for each step). Selective monoacetylation of cuparene-1,2-diol **4** established the structure of HM-3 as **28**. A combination of a Claisen rearrangement, a RCM reaction and an alkylation was strategically employed for the efficient construction of cyclopentanes containing two vicinal quaternary carbon atoms.

3. Experimental

Melting points were recorded using Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR



Scheme 2. Reagents and conditions: (a) CH_3COCH_2COOEt, 80% aq H_2SO_4, 80 °C, 45 min; (b) K_2CO_3, Me_2CO, MeI, reflux, 5 h; (c) LAH, THF, −50 °C, 30 min, 92%; (d) K_2CO_3, MeI, Me_2CO, reflux, 5 h, 88%; (e) $CH_3C(OEt)_3$, $EtCO_2H$, sealed tube, 180 °C, 36 h, 80%; (f) LAH, THF, 0 °C, 30 min, 95%; (g) PCC, silica gel CH_2Cl_2, rt, 15 min, 84%; (h) CH_2=CHMgBr, THF, −20 °C, 10 min, 77%; (i) PhCH=$RuCl_2(PCy_3)_2$ (5 mol %), CH_2Cl_2, 3 h, 100%; (j) PCC, silica gel, CH_2Cl_2, 1 h, 96%; (k) NaH, CH_3I, THF, DMF, rt, 12 h, 98%; (l) H_2 (1 atm), 10% Pd–C, EtOH, 1 h, 100%; (m) $(CH_2SH)_2$, I_2, 0 °C→rt, 12 h, 93%; (n) Raney Ni, EtOH, reflux, 3 h, 100%; (o) BBr_3, CH_2Cl_2, −40 °C, 4 h, 62%; (p) Ac_2O, py, CH_2Cl_2, rt, 3 h, 68%.

spectra were recorded on Jasco FTIR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JNM λ-300 spectrometer. Unless otherwise specified a 1:1 mixture of $CDCl_3$ and CCl_4 was used as solvent for preparing the NMR samples. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micromass spectrometer using electrospray ionization.

3.1. 2,6-Dimethoxy-3-methylbenzaldehyde

To a cold (0 °C) magnetically stirred solution of 4-methylresorcinol dimethyl ether **7** (1.11 g, 7.24 mmol) and *N*,*N*,*N*,*N*-tetramethylethylenediamine (1.14 mL, 7.6 mmol) in anhydrous THF (5 mL) was added drop wise a solution of *n*-BuLi (2.5 M in hexane, 3.48 mL, 8.69 mmol) over a period of 10 min and stirred at rt for 1 h. It was cooled to 0 °C and DMF (0.85 mL, 10.9 mmol) was added drop wise and stirred at rt for 4 h. It was slowly poured onto cold saturated aq NH_4Cl (20 mL) and extracted with ether (2×10 mL). The combined organic layer was washed with 3 N aq HCl (20 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished 2,6-dimethoxy-3-methylbenzaldehyde[9a] (1.21 g, 92%) as a solid. Mp: 87–88 °C; IR (Neat): ν_{max}/cm^{-1} 2767, 1690, 1597, 1581; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 10.41 (1H, s), 7.28 and 6.63 (2H, 2×d, *J* 9.0 Hz), 3.87 (3H, s), 3.80 (3H, s), 2.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 188.7 (CH), 160.4 (C), 160.3 (C), 136.8 (CH), 123.9 (C), 118.8 (C), 106.7 (CH), 61.9 (CH_3), 55.8 (CH_3), 15.0 (CH_3).

3.2. 2,6-Dimethoxy-3-methylacetophenone (6)

To a freshly prepared magnetically stirred cold (−20 °C) solution of MeMgI [prepared from Mg (297 mg, 12.22 mmol) and MeI (1.14 mL, 18.33 mmol) in dry ether (5 mL)] was added a solution of 2,6-dimethoxy-3-methylbenzaldehyde (1.1 g, 6.11 mmol) in dry ether (3 mL) over a period of 10 min and stirred at rt for 30 min. The reaction mixture was poured into ice cold aq NH_4Cl solution and extracted with ether (3×10 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished 1-(2,6-dimethoxy-3-methylphenyl)ethanol (1.15 g, 97%) as oil. IR (Neat): ν_{max}/cm^{-1} 3566, 1603; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 and 6.57 (2H, 2×d, *J* 8.4 Hz), 5.15 (1H, dq, *J* 11.4 and 6.6 Hz), 3.84 (3H, s), 3.74 (3H, s), 3.66 (1H, d, *J* 11.4 Hz), 2.21 (3H, s), 1.52 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.4 (C), 156.0 (C), 129.6 (CH), 126.1 (C), 123.5 (C), 106.8 (CH), 64.8 (CH), 60.9 (CH_3), 55.4 (CH_3), 24.4 (CH_3), 15.8 (CH_3); HRMS: *m*/*z* calcd for $C_{11}H_{16}O_3Na$ (M+Na): 219.0997, found: 219.0992.

To a magnetically stirred suspension of PCC (2.52 g, 11.7 mmol) and silica gel (2.5 g) in CH_2Cl_2 (8 mL) was added a solution of the alcohol (1.15 g, 5.87 mmol) obtained above in CH_2Cl_2 (4 mL) and vigorously stirred for 8 h at rt. The reaction mixture was then filtered through a small silica gel column with excess CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the acetophenone **6** (970 mg, 85%) as oil.[9b,c] IR (Neat): ν_{max}/cm^{-1} 1706, 1600; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.07 and 6.56 (2H, 2×d, *J* 8.4 Hz), 3.78 (3H, s), 3.70 (3H, s), 2.46 (3H, s), 2.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.0 (C), 155.2 (C), 154.7 (C), 131.7 (CH), 126.1 (C), 123.4 (C), 106.6 (CH), 62.0 (CH_3), 55.7 (CH_3), 32.3 (CH_3), 15.2 (CH_3); HRMS: *m*/*z* calcd for $C_{11}H_{14}O_3Na$ (M+Na): 217.0841, found: 217.0846.

3.3. 2-(2,6-Dimethoxy-3-methylphenyl)but-3-en-2-ol (9)

To a cold (−20 °C) magnetically stirred solution of the ketone **6** (520 mg, 2.68 mmol) in THF (3 mL) was added a solution of vinylmagnesium bromide [prepared from Mg (129 mg, 5.36 mmol) and vinyl bromide (0.57 mL, 8.04 mmol) in THF (8 mL)] and stirred at −20 °C for 30 min. The reaction was then quenched with cold saturated aq NH_4Cl solution and extracted with ether (2×10 mL). The organic layer was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the tertiary alcohol **9** (567 mg, 95%) as oil. IR (Neat): ν_{max}/cm^{-1} 3454, 1597; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.96 and 6.57 (2H, 2×d, *J* 8.4 Hz), 6.27 (1H, dd, *J* 17.1 and 10.2 Hz), 5.81 (1H, s), 5.16 (1H, dd, *J* 17.1 and 1.5 Hz), 4.91 (1H, dd, *J* 10.2 and 1.5 Hz), 3.78 (3H, s), 3.65 (3H, s), 2.19 (3H, s), 1.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.8 (C), 156.2 (C), 146.0 (CH), 129.8 (CH), 127.4 (C), 124.4 (C), 109.9 (CH_2), 108.2 (CH), 75.9 (C), 61.0 (CH_3), 55.8 (CH_3), 29.5 (CH_3), 16.1 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154, found: 245.1166.

3.4. *E*-3-(2,6-Dimethoxy-3-methylphenyl)but-2-enal (10)

To a magnetically stirred suspension of PCC (1.36 g, 6.3 mmol) and silica gel (1.35 g) in CH_2Cl_2 (5 mL) was added a solution of the alcohol **9** (560 mg, 2.52 mmol) in CH_2Cl_2 (4 mL) and vigorously stirred for 8 h at rt. The reaction mixture was then filtered through a small silica gel column with excess CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the aldehyde **10** (466 mg, 84%) as oil. IR (Neat): ν_{max}/cm^{-1} 2752, 1672, 1635, 1598; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 10.15 (1H, d, *J* 8.1 Hz), 7.01 and 6.54 (2H, 2×d, *J* 8.4 Hz), 5.93 (1H, d, *J* 8.1 Hz), 3.73 (3H, s), 3.63 (3H, s), 2.42 (3H, s), 2.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 190.2 (CH), 155.6 (C), 155.1 (C), 154.7 (C), 131.5 (CH), 130.8 (CH), 125.8 (C), 123.4 (C), 106.6 (CH), 60.9 (CH_3), 55.7 (CH_3), 18.9 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{16}O_3Na$ (M+Na): 243.0997, found: 243.1008.

3.5. *E*-3-(2,6-Dimethoxy-3-methylphenyl)but-2-en-1-ol (8a)

To a cold (−30 °C) magnetically stirred solution of the aldehyde **10** (900 mg, 4.1 mmol) in ether (5 mL) was added

LAH (156 mg, 4.1 mmol) in portions. The reaction mixture was stirred at the same temperature for 30 min and ethyl acetate (2 mL) was added to consume the excess LAH. It was then quenched with water (5 mL) and extracted with ether (3×5 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (2:5) as eluent furnished the alcohol **8a** (896 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3425, 1598; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.98 and 6.55 (2H, 2×d, *J* 8.4 Hz), 5.88 (1H, t, *J* 7.5 Hz), 3.74 (3H, s), 3.69 (2H, dd, *J* 6.6 and 2.7 Hz), 3.61 (3H, s), 2.30 (1H, br s), 2.20 (3H, s), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.0 (C), 155.5 (C), 134.0 (C), 129.9 (CH), 128.2 (CH), 123.5 (C), 123.3 (C), 106.9 (CH), 60.6 (CH_2), 60.2 (CH_3), 55.8 (CH_3), 24.2 (CH_3), 15.8 (CH_3); HRMS: *m/z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154, found: 245.1161.

3.6. Ethyl 3-(2,6-dimethoxy-3-methylphenyl)-3-methylpent-4-enoate (11a)

A solution of the allyl alcohol **8a** (130 mg, 0.59 mmol), triethyl orthoacetate (0.5 mL, 2.93 mmol), and a catalytic amount of propionic acid (5 μL) was placed in a sealed tube and heated to 180 °C for 36 h in an oil bath. The reaction mixture was cooled, diluted with ether (5 mL), washed with 3 N aq HCl (5 mL), saturated aq $NaHCO_3$ solution (5 mL), and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:40) as eluent furnished the pentenoate **11a** (148 mg, 87%) as oil. IR (Neat): ν_{max}/cm^{-1} 1734, 1633, 1595; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 (1H, d, *J* 8.4 Hz), 6.55 (1H, dd, *J* 17.7 and 11.1 Hz), 6.52 (1H, d, *J* 8.4 Hz), 4.88 (1H, d, *J* 17.7 Hz), 4.80 (1H, d, *J* 11.1 Hz), 3.93 (2H, q, *J* 6.9 Hz), 3.73 (3H, s), 3.49 (3H, s), 3.12 and 2.85 (2H, 2×d, *J* 15.0 Hz), 2.19 (3H, s), 1.58 (3H, s), 1.07 (3H, t, *J* 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.7 (C), 158.1 (C), 157.4 (C), 148.5 (CH), 129.3 (CH), 127.3 (C), 124.3 (C), 107.8 (CH), 105.7 (CH_2), 60.5 (CH_3), 59.4 (CH_2), 55.5 (CH_3), 46.5 (CH_2), 43.2 (C), 25.5 (CH_3), 14.2 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_4Na$ (M+Na): 315.1572, found: 315.1551.

3.7. 3-(2,6-Dimethoxy-3-methylphenyl)-3-methylpent-4-en-1-ol (13a)

LAH (39 mg, 1.03 mmol) was added to a magnetically stirred solution of the pentenoate **11a** (300 mg, 1.03 mmol) in dry ether (2 mL) at 0 °C and stirred for 1 h. EtOAc (1 mL) was carefully added to consume excess reagent and the reaction was quenched with ice cold water (10 mL). The solution was then filtered through a sintered funnel and the residue thoroughly washed with ether (3×5 mL). The ether layer was separated, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the primary alcohol **13a** (258 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3367, 1633, 1594; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 and 6.56 (2H, 2×d, *J* 8.4 Hz), 6.44 (1H, dd, *J* 17.4 and 10.5 Hz), 4.88 (1H, d, *J* 17.4 Hz), 4.79 (1H, d, *J* 10.5 Hz), 3.76 (3H, s), 3.50 (3H, s), 3.53–3.47 (2H, m), 3.50 (1H, br s), 2.40–2.10 (2H, m), 2.21 (3H, s), 1.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 158.2 (C), 157.7 (C), 149.3 (CH), 129.3 (CH), 127.5 (C), 124.4 (C), 107.9 (CH), 104.9 (CH_2), 60.6 (CH_2), 60.5 (CH_3), 55.4 (CH_3), 43.5 (C), 43.4 (CH_2), 25.9 (CH_3), 16.4 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1467, found: 273.1474.

3.8. 3-(2,6-Dimethoxy-3-methylphenyl)-3-methylpent-4-enal (14a)

To a magnetically stirred suspension of PCC (555 mg, 2.58 mmol) and silica gel (550 mg) in CH_2Cl_2 (2 mL) was added a solution of the alcohol **13a** (258 mg, 1.03 mmol) in CH_2Cl_2 (2 mL) and stirred at rt for 15 min. The reaction mixture was then filtered through a small silica gel column with excess CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the aldehyde **14a** (220 mg, 89%) as oil. IR (Neat): ν_{max}/cm^{-1} 2737, 1717, 1677, 1597; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.52 (1H, t, *J* 2.7 Hz), 6.99 and 6.56 (2H, 2×d, *J* 8.4 Hz), 6.39 (1H, dd, *J* 17.7 and 10.5 Hz), 4.88 (1H, d, *J* 17.7 Hz), 4.87 (1H, d, *J* 10.5 Hz), 3.73 (3H, s), 3.51 (3H, s), 3.01 and 2.80 (2H, 2×dd, *J* 16.8 and 2.7 Hz), 2.20 (3H, s), 1.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.3 (CH), 158.0 (C), 157.0 (C), 148.2 (CH), 130.0 (CH), 126.2 (C), 124.6 (C), 108.0 (CH), 106.9 (CH_2), 60.3 (CH_3), 55.3 (CH_3), 53.9 (CH_2), 42.4 (C), 26.3 (CH_3), 16.4 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310, found: 271.1309.

3.9. 5-(2,6-Dimethoxy-3-methylphenyl)-5-methylhepta-1,6-dien-3-ol (12a)

To a cold (−20 °C) magnetically stirred solution of the aldehyde **14a** (160 mg, 0.645 mmol) in THF was added a solution of vinylmagnesium bromide [prepared from Mg (31 mg, 1.29 mmol) and vinyl bromide (0.136 mL, 1.94 mmol) in THF (3 mL)] and stirred for 10 min. The reaction was then quenched with cold saturated aq NH_4Cl (5 mL) and extracted with ether (3×3 mL). The organic layer was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished a ≈1:1 diastereomeric mixture of the dienol **12a** (151 mg, 84%) as oil. IR (Neat): ν_{max}/cm^{-1} 3457, 1631, 1594, 917; ^1H NMR (300 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 6.98 (1H, d, *J* 8.4 Hz), 6.64–6.47 (2H, m), 5.81–5.71 (1H, m), 5.10–4.78 (4H, m), 4.04 (1H, br s), 3.75 (3H, s), 3.52 (3H, s), 2.30–2.03 (2H, m), 2.21 (3H, s), 1.90–1.70 (1H, br s), 1.60 and 1.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 158.4 (C), 157.6 and 157.5 (C), 150.0 (CH), 142.2 (CH), 129.5 (CH), 127.6 (C), 127.5 and 124.6 (C), 112.9 and 112.7 (CH_2), 108.2 and 107.8 (CH), 105.3 and 104.6 (CH_2), 71.2 and 70.9 (CH), 60.7 and 60.6 (CH_3), 55.5 and 55.3 (CH_3), 48.0 and 47.8 (CH_2), 44.3 and 44.0 (C), 26.6 and 26.5 (CH_3), 16.5 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1625.

3.10. 4-(2,6-Dimethoxy-3-methylphenyl)-4-methylcyclopent-2-enol (15a)

To a magnetically stirred solution of a 1:1 diastereomeric mixture of the diene **12a** (150 mg, 0.60 mmol) in anhydrous

CH_2Cl_2 (20 mL) was added a solution of Grubbs' catalyst (25 mg, 5 mol %) in CH_2Cl_2 (10 mL) and stirred at rt for 3 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished a 1:1 diastereomeric mixture of the enol **15a** (133 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3410, 1595; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.92 (1H, d, *J* 8.1 Hz), 6.68 (1H, d, *J* 5.1 Hz), 6.55 (1H, d, *J* 8.1 Hz), 5.65 (1H, m), 4.70–4.90 (1H, m), 3.80 (3H, s), 3.58 and 3.47 (3H, s), 2.74 and 2.54 (1 H, dd, *J* 14.1 and 7.2 Hz), 2.19 (3H, s), 2.02 (1H, dd, *J* 14.7 and 4.2 Hz), 1.40 and 1.53 (3H, s), 1.60 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 157.3 and 157.2 (C), 156.9 (C), 145.5 and 145.3 (CH), 130.6 and 130.5 (C), 128.9 and 128.7 (CH), 127.2 and 126.8 (CH), 124.0 and 123.9 (C), 107.6 (CH), 60.9 and 60.8 (CH_3), 55.4 (CH_3), 51.4 and 50.3 (C), 50.8 and 50.2 (CH_2), 30.8 and 29.3 (CH_3), 16.4 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1317, found: 271.1310.

3.11. 4-(2,6-Dimethoxy-3-methylphenyl)-4-methylcyclopent-2-enone (16a)

To a magnetically stirred suspension of PCC (288 mg, 1.34 mmol) and silica gel (288 mg) in CH_2Cl_2 (1 mL) was added a solution of the alcohol **15a** (133 mg, 0.54 mmol) in CH_2Cl_2 (1 mL) and stirred at rt for 1 h. The reaction mixture was then filtered through a small silica gel column, and the column was eluted with excess CH_2Cl_2. Evaporation of the solvent furnished the enone **16a** (123 mg, 93%) as oil. IR (Neat): ν_{max}/cm^{-1} 1711, 1588; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 8.23 (1H, d, *J* 5.7 Hz), 6.90 and 6.51 (2H, 2×d, *J* 8.4 Hz), 5.93 (1H, d, *J* 5.7 Hz), 3.76 (3H, s), 3.37 (3H, s), 2.65 and 2.53 (2H, 2×d, *J* 18.9 Hz), 2.14 (3H, s), 1.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 208.7 (C), 173.7 (CH), 156.9 (C), 156.1 (C), 129.7 (CH), 127.9 (C), 126.8 (CH), 123.8 (C), 107.5 (CH), 61.0 (CH_3), 55.5 (CH_3), 51.5 (CH_2), 46.8 (C), 27.8 (CH_3), 16.1 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{18}O_3Na$ (M+Na): 247.1334, found: 247.1334.

3.12. 4-(2,6-Dimethoxy-3-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (17a)

A solution of the ketone **16a** (220 mg, 0.894 mmol) in THF (1 mL) was added to a suspension of NaH (180 mg, 60% dispersion in oil, 4.47 mmol, washed with dry hexanes) in THF (2 mL) and DMF (0.2 mL) and stirred at rt for 15 min. Methyl iodide (0.42 mL, 6.7 mmol) was added to the reaction mixture and stirred for 12 h at rt. Water (5 mL) was added to the reaction mixture and extracted with ether (3×5 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the enone **17a** (180 mg, 73%) as oil. IR (Neat): ν_{max}/cm^{-1} 1700, 1593; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 8.17 (1H, d, *J* 5.7 Hz), 6.99 and 6.58 (2H, 2×d, *J* 7.8 Hz), 5.89 (1H, d, *J* 5.7 Hz), 3.83 (3H, s), 3.37 (3H, s), 2.21 (3H, s), 1.53 (3H, s), 1.25 (3H, s), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 214.1 (C), 173.6 (CH), 157.1 (C), 156.8 (C), 129.6 (CH), 126.5 (C), 123.8 (C), 120.6 (CH), 107.0 (CH), 59.9 (CH_3), 54.8 (CH_3), 54.5 (C), 49.5 (C), 25.2 (CH_3), 24.3 (CH_3), 21.6 (CH_3), 16.2 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{22}O_3Na$ (M+Na): 275.1647, found: 275.1651.

3.13. 3-(2,6-Dimethoxy-3-methylphenyl)-2,2,3-trimethylcyclopentanone (18a)

To activated 10% Pd–C (20 mg) was added a solution of the enone **17a** (180 mg, 0.656 mmol) in ethanol (2 mL) and stirred for 1 h at rt in an atmosphere of hydrogen created by evacuative replacement of air (balloon). The catalyst was then filtered off. Evaporation of the solvent under reduced pressure furnished the saturated ketone **18a** (181 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 1734, 1579; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 and 6.51 (2H, 2×d, *J* 8.1 Hz), 3.67 (3H, s), 3.62 (3H, s), 2.45–2.20 (4H, m), 2.22 (3H, s), 1.56 (3H, s), 1.19 (3H, s), 0.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 159.0 (C), 157.4 (C), 129.4 (CH), 124.5 (C), 106.5 (CH), 60.8 (CH_3), 54.0 (CH_3), 34.9 (CH_2), 16.5 (CH_3) (other signals are very broad probably due to fluxional behavior of the molecule); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1610.

3.14. 3-(2,6-Dimethoxy-3-methylphenyl)-2,2,3-trimethylcyclopentanol (19)

To an ice cold magnetically stirred solution of the ketone **18a** (181 mg, 0.66 mmol) in dry methanol (1 mL) was added $NaBH_4$ (47 mg, 1.31 mmol) and stirred for 5 min. The solvent was removed under reduced pressure. Water (3 mL) followed by 3 N aq HCl (4 mL) were added to the reaction mixture and extracted with ether (3×3 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20–1:10) as eluent furnished an epimeric mixture of the alcohol **19** (180 mg, 99%) as oil. IR (Neat): ν_{max}/cm^{-1} 3411, 1591; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 and 6.93 (1H, d, *J* 8.1 Hz), 6.52 (1H, d, *J* 8.1 Hz), 3.89–3.76 (1H, m), 3.73 and 3.71 (3H, s), 3.60 (3H, s), 3.05–2.50 (1H, m), 2.16 (3H, s) 2.20–1.26 (4H, m), 1.50 and 1.48 (3H, s), 1.09 and 1.07 (3H, s), 0.66 (3H, s); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_3Na$ (M+Na): 301.1780, found: 301.1775.

3.15. 4-Methyl-2-(1,2,2-trimethylcyclopentyl)benzene-1,3-diol dimethyl ether (21a)

To a magnetically stirred suspension of NaH (29 mg, 60% dispersion in oil, 0.72 mmol) in dry THF (1 mL) was added a solution of the alcohol **19** (40 mg, 0.144 mmol) in dry THF (0.5 mL) followed by a catalytic amount of imidazole. The reaction mixture was heated to 60 °C for 15 min. It was cooled to rt, added CS_2 (0.09 mL, 1.44 mmol), and refluxed for 15 min. It was cooled to rt, added MeI (0.09 mL, 1.44 mmol), and refluxed for 4 h. It was then cooled to rt, diluted with water (2 mL), and extracted with ether (3× 2 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:10) as eluent furnished the dithiocarbonate **20** (47 mg, 88%) as yellow oil. IR (Neat): ν_{max}/cm^{-1} 1591, 1390, 1375, 1240; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.96 and 6.54 (2H, 2×d, *J* 8.4 Hz), 5.70–5.50 (1H, m), 3.72 (3H, s), 3.63

and 3.61 (3H, s), 3.26 (1H, br s), 2.56 and 2.51 (3H, s), 2.40–2.32 (1H, m), 2.23 (3H, s), 1.92–1.42 (5H, m), 1.19 and 1.16 (3H, s), 0.75 (3H, s). A solution of the dithiocarbonate **20** (47 mg, 0.128 mmol), *n*-Bu_3SnH (0.14 mL, 0.512 mmol), and a catalytic amount of AIBN in dry benzene (2 mL) was refluxed for 3 h. The reaction mixture was cooled, diluted with ether (4 mL), washed successively with 1% aq NH_4OH, water, and brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using hexane as eluent furnished the deoxygenated product **21a** (25 mg, 75%) as colorless oil. IR (Neat): ν_{max}/cm^{-1} 1591; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.91 and 6.50 (2H, 2×d, *J* 8.1 Hz), 3.70 (3H, s), 3.58 (3H, s), 3.13 (1H, br s), 2.21 (3H, s), 2.00–1.90 (1H, m), 1.65–1.40 (4H, m), 1.34 (3H, s), 1.12 (3H, s), 0.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 158.5 (2C, C), 129.0 (C), 128.7 (CH), 124.4 (C), 106.9 (CH), 61.0 (CH_3), 54.5 (CH_3), 52.6 (C), 45.4 (C), 43.6 (CH_2), 40.3 (CH_2), 29.1 (CH_3), 27.3 (CH_3), 24.1 (CH_3), 21.6 (CH_2), 16.8 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_2K$ (M+K): 301.1570, found: 301.1577.

3.16. 4-Methyl-2-(1,2,2-trimethylcyclopentyl)benzene-1,3-diol (herbertene-1,5-diol 22)

Methylmagnesium iodide solution in ether (5 mL) was prepared using Mg (50 mg, 2.1 mmol) and CH_3I (0.16 mL) and the solvent was evaporated under vacuum. A solution of the methyl ether **21a** (14 mg, 0.053 mmol) in dry *p*-cymene (2 mL) was added to MeMgI and refluxed for 8 h. It was then cooled to rt, carefully added to cold saturated aq NH_4Cl solution (5 mL), and extracted with ether (2×2 mL). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the diol **22** (8 mg, 64%). IR (Neat): ν_{max}/cm^{-1} 3606, 3531, 1605; ^1H NMR (300 MHz, $CDCl_3$): δ 6.73 and 6.11 (2H, 2×d, *J* 7.8 Hz), 4.82 (1H, s), 4.57 (1H, br s), 3.31 (1H, br s), 2.13 (3H, s), 1.80–1.50 (5H, m), 1.49 (3H, s), 1.18 (3H, s), 0.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4 (C), 154.8 (C), 128.0 (2C, CH), 115.8 (C), 109.5 (C), 52.3 (C), 46.3 (C), 42.1 (CH_2), 40.8 (CH_2), 27.7 (CH_3), 26.3 (CH_3), 24.8 (CH_2), 21.8 (CH_3), 16.3 (CH_3) (some of the signals are very broad due to fluxional behavior); HRMS: *m*/*z* calcd for $C_{15}H_{22}O_2Na$ (M+Na): 273.1467, found: 273.1479.

3.17. 3-Hydroxy-4-methyl-2-(1,2,2-trimethylcyclopentyl)phenyl acetate (3)

To a magnetically stirred solution of the diol **22** (6 mg, 0.026 mmol) in CH_2Cl_2 (0.3 mL) was added sequentially Ac_2O (5 μL, 0.052 mmol), pyridine (50 μL, 0.615 mmol), and DMAP (1 mg), and stirred at rt for 2 h. Water (1 mL) was added to the reaction mixture and extracted with CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the acetate **3** (5 mg, 71%) as oil. IR (Neat): ν_{max}/cm^{-1} 3516, 1749, 1664, 1587; ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 and 6.33 (2H, 2×d, *J* 7.8 Hz), 4.88 (1H, br s), 2.90–2.80 (1H, m), 2.24 (3H, s), 2.20 (3H, s), 1.74–1.51 (5H, m), 1.42 (3H, s), 1.26 (3H, s), 0.79 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (C), 154.3 (C), 148.7 (C), 128.2 (CH), 126.0 (C), 121.1 (C), 116.3 (CH), 52.2 (C), 45.3 (C), 42.7 (CH_2), 40.3 (CH_2), 28.5 (CH_3), 26.8 (CH_3), 22.9 (CH_3), 21.7 (CH_3), 21.4 (CH_2), 16.3 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1619.

3.18. *Z*-(2-Hydroxy-3-methoxy-4-methylphenyl)but-2-en-1-ol (26)

To a cold (−50 °C) magnetically stirred solution of the coumarin[14] **25** (520 mg, 2.55 mmol) in dry THF (3 mL) was added LAH (93 mg, 2.5 mmol) in portions and stirred for 30 min. Ethyl acetate (2 mL) was added to the reaction mixture to consume the excess LAH. The reaction was then quenched with water (5 mL) and extracted with ether (3×5 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (2:5) as eluent furnished the alcohol **26** (488 mg, 92%). IR (Neat): ν_{max}/cm^{-1} 3398, 1655, 1616, 1575; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.65 (2H, s), 6.23 (1H, br s), 5.81 (1H, td, *J* 7.8 and 1.5 Hz), 3.86 (2H, d, *J* 7.8 Hz), 3.79 (3H, s), 2.28 (3H, s), 2.20 (1H, br s), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 145.6 (C), 145.2 (C), 136.2 (C), 129.6 (C), 127.4 (CH), 126.0 (C), 124.5 (CH), 122.1 (CH), 60.6 (CH_2), 60.5 (CH_3), 25.2 (CH_3), 15.9 (CH_3); HRMS: *m*/*z* calcd for $C_{12}H_{16}O_3Na$ (M+Na): 231.0997, found: 231.1004.

3.19. *Z*-(2,3-Dimethoxy-4-methylphenyl)but-2-en-1-ol (8b)

A solution of the diol **26** (320 mg, 1.54 mmol), anhydrous K_2CO_3 (425 mg, 3.08 mmol), and CH_3I (0.19 mL, 3.08 mmol) in acetone (6 mL) was refluxed for 5 h. Solvent was evaporated under reduced pressure. The residue was taken in water and extracted with ether (3×15 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the cinnamyl alcohol **8b** (520 mg, 97%). IR (Neat): ν_{max}/cm^{-1} 3400; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.85 and 6.67 (2H, 2×d, *J* 8.0 Hz), 5.79 (1H, td, *J* 7.5 and 1.5 Hz), 3.83 (3H, s), 3.79 (2H, d, *J* 7.5 Hz), 3.75 (3H, s), 2.25 (3H, s), 2.05 (3 H, s), 2.00 (1 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 151.5 (C), 149.8 (C), 136.5 (C), 133.3 (C), 131.4 (C), 127.4 (CH), 125.9 (CH), 124.0 (CH), 60.8 (CH_3), 60.6 (CH_2), 60.2 (CH_3), 25.5 (CH_3), 15.9 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154, found: 245.1162.

3.20. Ethyl 3-(2,3-dimethoxy-4-methylphenyl)-3-methylpent-4-enoate (11b)

A solution of the allyl alcohol **8b** (300 mg, 1.35 mmol), triethyl orthoacetate (1.24 mL, 6.76 mmol), and a catalytic amount of propionic acid (10 μL) was placed in a sealed tube and heated to 180 °C for 36 h in an oil bath. Work-up as described for the ester **11a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:40) as eluent furnished the ester **11b** (316 mg, 80%) as oil. IR (Neat): ν_{max}/cm^{-1} 1734, 1635; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.83 and 6.74 (2H, 2×d, *J* 8.1 Hz), 6.25 (1H, dd, *J* 17.4 and 10.8 Hz), 5.02 (1H, dd, *J* 10.8 and 1.2 Hz), 4.94 (1H, dd,

J 17.4 and 0.9 Hz), 3.92 (2H, q, *J* 7.5 Hz), 3.83 (3H, s), 3.74 (3H, s), 3.06 and 2.77 (2H, 2×d, *J* 14.1 Hz), 2.21 (3H, s), 1.53 (3H, s), 1.05 (3H, t, *J* 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.2 (C), 151.9 (C), 151.7 (C), 146.7 (CH), 136.8 (C), 130.8 (C), 124.3 (CH), 122.2 (CH), 111.0 (CH_2), 59.6 (CH_3), 59.4 (CH_2), 59.2 (CH_3), 44.1 (CH_2), 42.7 (C), 25.7 (CH_3), 15.6 (CH_3), 14.1 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_4Na$ (M+Na): 315.1572, found: 315.1586.

3.21. 3-(2,3-Dimethoxy-4-methylphenyl)-3-methylpent-4-en-1-ol (13b)

Reduction of the pentenoate **11b** (316 mg, 1.08 mmol) with LAH (40 mg, 1.08 mmol) in dry ether (3 mL) at 0 °C for 30 min and work-up as described for the alcohol **13a**, followed by purification over silica gel column using ethyl acetate–hexane (3:7) furnished the alcohol **13b** (257 mg, 95%) as oil. IR (Neat): ν_{max}/cm^{-1} 3368; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.82 and 6.75 (2H, 2×d, *J* 8.1 Hz), 6.16 (1H, dd, *J* 17.1 and 10.5 Hz), 5.01 (1H, dd, *J* 10.5 and 0.9 Hz), 4.95 (1H, dd, *J* 17.1 and 0.9 Hz), 3.81 (3H, s), 3.74 (3H, s), 3.60–3.40 (2H, m), 2.42–2.29 (1H, m), 2.21 (3H, s), 2.05–1.96 (1H, m), 1.42 (3H, s), 1.45 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.2 (C), 152.0 (C), 147.9 (CH), 137.7 (C), 130.9 (C), 124.7 (CH), 122.3 (CH), 110.7 (CH_2), 60.2 (CH_2), 59.7 (CH_3), 59.3 (CH_3), 42.8 (C), 42.2 (CH_2), 25.9 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1467, found: 273.1470.

3.22. 3-(2,3-Dimethoxy-4-methylphenyl)-3-methylpent-4-enal (14b)

Oxidation of the alcohol **13b** (250 mg, 1.0 mmol) with PCC (538 mg, 2.5 mmol) and silica gel (540 mg) in CH_2Cl_2 (3 mL) at rt for 15 min and work-up as described for the aldehyde **14a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the aldehyde **14b** (210 mg, 84%) as oil. IR (Neat): ν_{max}/cm^{-1} 2733, 1720, 1681, 1635, 1603; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.46 (1H, t, *J* 2.7 Hz), 6.84 and 6.76 (2H, 2×d, *J* 7.8 Hz), 6.16 (1H, dd, *J* 17.4 and 10.5 Hz), 5.08 (1H, d, *J* 10.5 Hz), 4.98 (1H, d, *J* 17.4 Hz), 3.82 (3H, s), 3.72 (3H, s), 3.07 (1H, dd, *J* 15.3 and 2.7 Hz), 2.76 (1H, dd, *J* 15.3 and 2.7 Hz), 2.20 (3H, s), 1.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.2 (CH), 152.2 (C), 151.9 (C), 146.3 (CH), 136.1 (C), 131.6 (C), 124.9 (CH), 122.2 (CH), 111.8 (CH_2), 59.8 (CH_3), 59.4 (CH_3), 52.2 (CH_2), 42.1 (C), 26.4 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310, found: 271.1324.

3.23. 5-(2,3-Dimethoxy-4-methylphenyl)-5-methylhepta-1,6-dien-3-ol (12b)

Grignard reaction of the aldehyde **14b** (210 mg, 0.847 mmol) in THF with vinylmagnesium bromide [prepared from Mg (41 mg, 1.69 mmol) and vinyl bromide (0.12 mL, 1.69 mmol) in THF (2 mL)] for 10 min at −20 °C and work-up as described for the dienol **12a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished a ≈1:1 diastereomeric mixture of the dienol **12b** (180 mg, 77%) as oil. IR (Neat): ν_{max}/cm^{-1} 3437, 1634, 917; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 6.88 and 6.87 (1H, d, *J* 8.1 Hz), 6.78 and 6.76 (1H, d, *J* 8.1 Hz), 6.25 and 6.24 (1H, dd, *J* 17.7 and 10.8 Hz), 5.84–5.69 (1H, m), 5.12–4.89 (4H, m), 4.04 and 3.96 (1H, m), 3.84 and 3.81 (3H, s), 3.74 and 3.73 (3H, s), 2.38–2.25 (1H, m), 2.22 (3H, s), 1.99–1.89 (1H, m), 1.52 and 1.47 (3H, s), 1.50–1.30 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 152.2 (C), 152.11 and 52.08 (C), 148.6 and 148.2 (CH), 142.3 and 142.2 (CH), 137.7 and 137.6 (C), 131.2 and 131.0 (C), 124.9 and 124.7 (CH), 122.6 and 122.4 (CH), 113.3 and 113.1 (CH_2), 110.8 (CH_2), 70.9 and 70.7 (CH), 59.8 (CH_3), 59.4 and 59.3 (CH_3), 47.0 and 46.5 (CH_2), 43.6 and 43.4 (C), 26.5 and 26.4 (CH_3), 15.8 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1622.

3.24. 4-(2,3-Dimethoxy-4-methylphenyl)-4-methylcyclopent-2-en-1-ol (15b)

RCM reaction of a 1:1 diastereomeric mixture of the diene **12b** (200 mg, 0.72 mmol) with Grubbs' catalyst (30 mg, 5 mol %) in CH_2Cl_2 (30 mL) at rt for 3 h and work-up as described for the cyclopentenol **15a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished a 1:1 diastereomeric mixture of the enol **15b** (180 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3392, 908; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 6.85–6.65 (2H, m), 6.18 and 6.09 (1H, d, *J* 5.4 Hz), 5.82 (1H, t, *J* 5.4 Hz), 4.90–4.75 (1H, m), 3.86 (3H, s), 3.76 (3H, s), 2.58–2.50 (1H, m), 2.21 and 2.20 (3H, s), 1.97 and 1.96 (1H, d, *J* 14.1 Hz), 1.52 and 1.39 (3H, s); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310, found: 271.1313.

3.25. 4-(2,3-Dimethoxy-4-methylphenyl)-4-methylcyclopent-2-enone (16b)

Oxidation of the alcohol **15b** (183 mg, 0.74 mmol) with PCC (397 mg, 1.84 mmol) and silica gel (400 mg) in CH_2Cl_2 (3 mL) at rt for 1 h and work-up as described for the enone **16a**, furnished the enone **16b** (179 mg, 96%) as oil. IR (Neat): ν_{max}/cm^{-1} 1715, 1589; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.73 (1H, d, *J* 5.4 Hz), 6.78 (2H, s), 6.12 (1H, d, *J* 5.4 Hz), 3.82 (3H, s), 3.75 (3H, s), 2.68 and 2.52 (2H, 2×d, *J* 18.3 Hz), 2.22 (3H, s), 1.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 208.6 (C), 170.4 (CH), 152.0 (C), 151.7 (C), 136.4 (C), 131.7 (C), 130.8 (CH), 124.9 (CH), 121.3 (CH), 59.9 (CH_3), 59.4 (CH_3), 51.0 (CH_2), 47.1 (C), 28.4 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{19}O_3$ (M+H): 247.1334, found: 247.1335.

3.26. 4-(2,3-Dimethoxy-4-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (17b)

One-pot dialkylation of the ketone **16b** (100 mg, 0.406 mmol) with NaH (243 mg, 60% dispersion in oil, 6.09 mmol, washed with dry hexanes) and methyl iodide (0.51 mL, 8.12 mmol) in THF (5 mL) and DMF (0.25 mL) for 12 h at rt and work-up as described for the enone **17a**, followed by purification over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the alkylated product **17b** (110 mg, 98%) as oil. IR (Neat): ν_{max}/cm^{-1} 1708, 1600; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.87 (1H, d, *J* 5.7 Hz), 6.80 and 6.70 (2H,

2×d, *J* 7.8 Hz), 6.06 (1H d, *J* 5.7 Hz), 3.87 (3H, s), 3.75 (3H, s), 2.24 (3H, s), 1.47 (3H, s), 1.22 (3H, s), 0.63 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 214.0 (C), 170.7 (CH), 151.9 (2C, C), 134.6 (C), 131.4 (C), 125.0 (CH), 123.0 (2C, CH), 60.0 (CH_3), 59.3 (CH_3), 54.6 (C), 50.9 (C), 26.0 (2C, CH_3), 19.9 (CH_3), 15.7 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{23}O_3$ (M+H): 275.1647, found: 275.1646.

3.27. 3-(2,3-Dimethoxy-4-methylphenyl)-3,4,4-trimethylcyclopentanone (18b)

Hydrogenation of the enone **17b** (110 mg, 0.4 mmol) with 10% Pd–C (20 mg) as the catalyst in ethanol (2 mL) for 1 h and work-up as described for the compound **18a**, furnished the saturated ketone **18b** (111 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 1738; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 and 6.78 (2H, 2×d, *J* 8.4 Hz), 3.84 (3H, s), 3.75 (3H, s), 2.70–2.53 (1 H, m), 2.45–2.35 (2H, m), 2.23 (3H, s), 2.07 (1H, ddd, *J* 12.6, 6.6, and 4.2 Hz), 1.33 (3H, s), 1.23 (3H, s), 0.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 222.1 (C), 152.7 (C), 152.1 (C), 136.8 (C), 130.8 (C), 124.7 (CH), 122.8 (CH), 59.8 (CH_3), 59.4 (CH_3), 53.4 (C), 49.4 (C), 34.1 (CH_2), 32.0 (CH_2), 24.5 (CH_3), 22.3 (CH_3), 20.5 (CH_3), 15.6 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1630.

3.28. 7-(2,3-Dimethoxy-4-methylphenyl)-6,6,7-trimethyl-1,4-dithiaspiro[4.4]nonane (27)

To a magnetically stirred solution of the ketone **18b** (92 mg, 0.34 mmol) in dry CH_2Cl_2 (0.3 mL) was added 1,2-ethanedithiol (0.28 mL, 1.12 mmol) and iodine (16 mg, 20 mol %) and stirred at rt for 30 min. To the reaction mixture 1 M aq $Na_2S_2O_3$ (2 mL) and 10% aq NaOH (10 mL) were added and stirred for 5 min, and extracted with CH_2Cl_2 (2×4 mL). The CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:10) as eluent furnished the thioketal **27** (94 mg, 80%) as oil. IR (Neat): ν_{max}/cm^{-1} 1397, 1277, 1093, 1057, 1021; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.89 and 6.73 (2H, 2×d, *J* 8.1 Hz), 3.86 (3H, s), 3.72 (3H, s), 3.30–3.10 (4H, m), 2.72–2.65 (1H, m), 2.52 (1H, br s), 2.32–2.34 (1H, m), 2.21 (3H, s), 1.76–1.65 (1H, m), 1.54 (3H, s), 1.22 (3H, s), 0.72 (3H, s); HRMS: *m/z* calcd for $C_{19}H_{28}O_2S_2Na$ (M+Na): 375.1428, found: 375.1429.

3.29. 6-Methyl-3-(1,2,2-trimethylcyclopentyl)benzene-1,2-diol dimethyl ether (21b)

To a magnetically stirred solution of the thioketal **27** (94 mg, 0.267 mmol) in dry ethanol (6 mL) was added Raney nickel (200 mg, excess) and refluxed for 3 h. The reaction mixture was cooled and filtered through a short silica gel column using excess CH_2Cl_2. Evaporation of the solvent furnished the deoxygenated product **21b** (70 mg, 100%). IR (Neat): ν_{max}/cm^{-1} 1277, 1094, 1054, 1023; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.91 and 6.73 (2H, 2×d, *J* 8.1 Hz), 3.81 (3H, s), 3.75 (3H, s), 2.57–2.52 (1H, m), 2.21 (3H, s), 1.85–1.40 (5H, m), 1.35 (3H, s), 1.11 (3H, s), 0.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 153.1 (C), 152.1 (C), 138.5 (C), 129.8 (C), 124.2 (CH), 123.6 (CH), 59.9 (CH_3), 59.3 (CH_3), 51.5 (C), 45.0 (C), 41.1 (CH_2), 39.3 (CH_2), 26.9 (CH_3), 25.5 (CH_3), 24.1 (CH_3), 20.5 (CH_2), 15.6 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{26}O_2Na$ (M+Na): 285.1830, found: 285.1838.

3.30. 3-(1,2,2-Trimethylcyclopentyl)-6-methylbenzene-1,2-diol (HM-4 or cuparene-1,2-diol 4)

To a cold (−40 °C) magnetically stirred solution of the dimethyl ether **21b** (40 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was added drop wise a solution of BBr_3 (1 M in CH_2Cl_2, 0.86 mL, 0.86 mmol) and stirred at the same temperature for 4 h. The reaction was then quenched with saturated aq $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished cuparene-1,2-diol **4** (22 mg, 62%). IR (Neat): ν_{max}/cm^{-1} 3613, 3516, 1506; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 and 6.53 (2H, 2×d, *J* 8.4 Hz), 5.52 (1H, br s), 4.87 (1H, br s), 2.65–2.56 (1H, m), 2.20 (3H, s), 1.85–1.40 (5H, m), 1.40 (3H, s), 1.17 (3H, s), 0.75 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2 (C), 141.9 (C), 131.2 (C), 121.2 (C), 120.7 (CH), 120.5 (CH), 50.9 (C), 44.8 (C), 40.8 (CH_2), 39.2 (CH_2), 26.7 (CH_3), 25.3 (CH_3), 22.9 (CH_3), 20.2 (CH_2), 15.3 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 257.1517, found: 257.1512.

3.31. 2-Hydroxy-3-(1,2,2-trimethylcyclopentyl)-6-methylphenyl acetate (HM-3, 28)

Acetylation of the diol **4** (15 mg, 0.064 mmol) with Ac_2O (6 μL, 0.064 mmol) and pyridine (5 μL, 0.064 mmol) in dry CH_2Cl_2 for 3 h at rt and work-up as described for the acetate **3**, followed by purification over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the monoacetate **28** (12 mg, 68%) as oil. IR (Neat): ν_{max}/cm^{-1} 3406, 1770, 1738, 1618; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 and 6.69 (2H, 2×d, *J* 8.4 Hz), 5.18 (1H, s), 2.65–2.44 (1H, m), 2.37 (3H, s), 2.11 (3H, s), 1.82–1.48 (5H, m), 1.40 (3H, s), 1.15 (3H, s), 0.74 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6 (C), 146.4 (C), 137.9 (C), 132.9 (C), 128.2 (C), 126.2 (CH), 121.0 (CH), 51.2 (C), 44.8 (C), 41.1 (CH_2), 39.4 (CH_2), 26.8 (CH_3), 25.5 (CH_3), 22.8 (CH_3), 20.6 (CH_3), 20.4 (CH_2), 16.0 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1636.

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi for the award of a research fellowship to P.C.R.

Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra of cuparene-1,2-diol (**4**), HM-3 (revised) (**28**), and the putative structure of HM-3 (**3**). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.062.

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12. It is worth mentioning that thioketalization reaction of the ketone in **18a** using standard procedure was unsuccessful due to the acid catalyzed cleavage of the cyclopentane moiety from the aromatic part (probably due to the presence of two methoxy groups on the aromatic ring *ortho* to cyclopentane moiety) resulting in the formation of 4-methylresorcinol dimethyl ether. Hence, reductive deoxygenation of the ketone in **18a** was carried out employing Barton's radical protocol.
13. The signals due to three tertiary methyl groups for the synthetic monoacetate **3** appeared at δ 1.42, 1.26, and 0.79, whereas 1.40, 1.15, and 0.74 ppm were reported for HM-3. Similarly, considerable difference is there for the signals due to aromatic protons, e.g., for the two aromatic protons $\Delta\delta$ reported for HM-3 is 0.39, whereas $\Delta\delta$ observed for synthetic **3** is 0.59.
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Tetrahedron 62 (2006) 9403–9409

Palladium-mediated fragmentation reactions of *meta* photocycloadducts to afford arylated or oxidatively cyclised products

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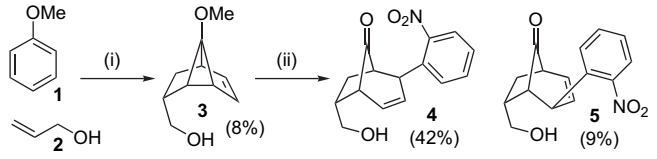
Received 18 May 2006; revised 30 June 2006; accepted 20 July 2006
Available online 10 August 2006

Abstract—Whilst seeking to improve the yield of a Heck-style arylation/fragmentation reaction using a silyloxy substituted *meta* photocycloadduct, an alternative reaction pathway was discovered that led to the formation of the unique oxidatively cyclised compound **8**. This tricyclic ether is believed to form as the result of the *meta* photocycloadduct structure fragmenting to give a π-allyl palladium species and then subsequently being displaced by a neighbouring hydroxyl group. An attempt to develop an enantioselective version of this reaction via the desymmetrisation of a *meso* π-allyl palladium intermediate was made using the *meta* photocycloadduct derived from anisole and *Z*-but-2-ene-1,4-diol, however no enantioenrichment of the products could be detected.

1. Introduction

The diverse reactivity of palladium and its associated compounds has led to the development of many remarkable chemical transformations.[1] We have recently shown[2] how palladium catalysis can be used to promote a fragmentation/arylation process involving a *meta* photocycloadduct and an aryl halide. Hence, when the anisole derived *meta* photocycloadduct **3** was subjected to Heck reaction[3] conditions in the presence of 1-iodo-2-nitrobenzene, compounds **4** and **5** were isolated (Scheme 1).



Scheme 1. Reagents and conditions: (i) h*ν*, cyclohexane; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), NEt_3, DMF, 120 °C, 12 h.

The methoxy-substituted cyclopropylalkene moiety of the photoadduct underwent fragmentation to afford an arylated [3.2.1] bicyclic ketone structure, with the major isomer **4** being isolated in 42% yield. As it was our intention to use compound **4** in a potential synthesis of the alkaloid gelsemine,[4] we investigated the use of alternative substrates to improve the efficiency of its formation. When a similar arylation reaction was performed on the trimethylsilyloxy variant of **3**, an alternative reaction pathway was observed that involved an oxidation process. This publication reports this new mode of reactivity and its further exploitation.

2. Results and discussion

2.1. Arylation and oxidation studies of silyloxy substituted *meta* photoadducts

We wondered if, by replacing the methoxy group of compound **3** with a silyloxy group, the fragmentation and subsequent arylation of the *meta* photoadduct structure would be enhanced by the greater electron releasing power of the silicon group. To investigate this hypothesis the 7-*endo meta* photoadduct isomer **7** was prepared by irradiating a solution of trimethylphenoxysilane and allyl alcohol in cyclohexane with 254 nm UV light. The only photoadduct isomer that could be isolated as a single compound was fortuitously the desired compound **7**. This photoadduct was subjected to the same Heck-style arylation conditions as used on compound **3** in Scheme 1[2] and resulted in the formation of the three major products shown in Scheme 2.

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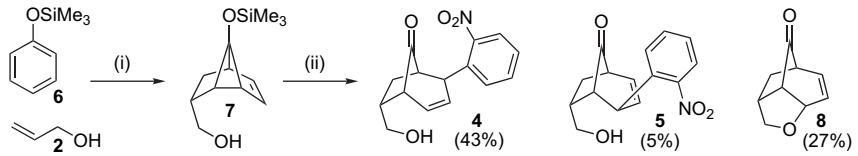
doi:10.1016/j.tet.2006.07.060



Scheme 2. Reagents and conditions: (i) hν, cyclohexane, 4.3%; (ii) 1-iodo-2-nitrobenzene, $Pd(OAc)_2$ (5 mol %), $P(o\text{-Tol})_3$ (10 mol %), NEt_3, DMF, 120 °C, 12 h.

In addition to compounds **4** and **5**, the unique tricyclic ether **8** was obtained, whose structure was confirmed by single crystal X-ray crystallography (Fig. 1).[5]

Compound **8** must have formed as a result of a formal oxidation process via an internal displacement reaction,[6] however as there was only 5 mol % of palladium diacetate present in the mixture and the reaction was performed in a sealed reaction vessel under an atmosphere of nitrogen, we concluded that the 1-iodo-2-nitrobenzene was acting as the reoxidation source for the palladium. If the reaction was repeated in the absence of any 1-iodo-2-nitrobenzene, none of the oxidised compound **8** was detected. We found that upon changing the palladium source from the diacetate to the dichloride, 91% of the compound **7** was converted to products and a highly creditable 63% yield of compound **4** was obtained. The yield of oxidation product **8** could be dramatically improved if copper(II) chloride (200 mol %) was used as the reoxidant[7] such that it was obtained in 69% yield from the silyloxy compound **7** and in 62% yield from the methoxy variant **3**. These results are summarised in Table 1.

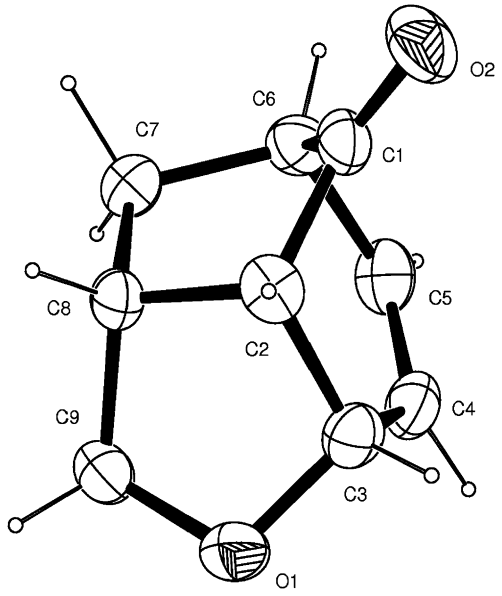


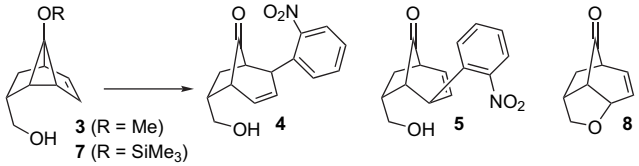
Figure 1. ORTEP drawing of compound **8**.

This unique transformation involving the formation of compound **8** led us to speculate on the nature of the reaction mechanism. Previous results[2] had hinted at the formation of a π-allyl palladium species following initial fragmentation of the *meta* photocycloadduct vinyl-cyclopropane moiety in the presence of a palladium(II) source. In this instance such an intermediate **9** would undergo an internal nucleophilic displacement by the hydroxyl group[6] and subsequently give rise to the heterocycle **8**. In order to maintain the catalytic cycle the reduced palladium[0] species would then need to be reoxidised (Scheme 3).

2.2. Oxidation of diol derived *meta* photoadducts and its implication for asymmetric synthesis

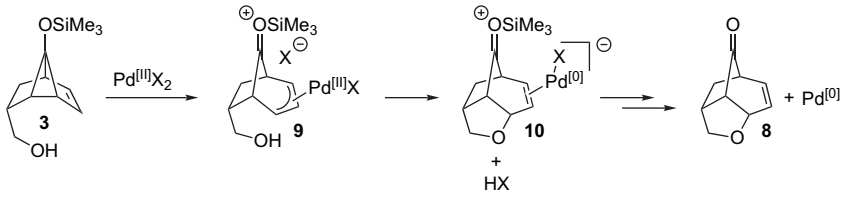
To further extend the application of this reaction, we wondered if an analogue of intermediate **9** that displayed *meso* symmetry could be generated. The attachment of a homochiral ligand to the palladium centre would cause the desymmetrisation of such an intermediate (**14** or **15**), which in turn would kinetically favour a stereoselective displacement process and result in the formation of an enantioenriched product **16**. We reasoned that such a transformation could be achieved starting from the *meta* photocycloadduct derived from *Z*-but-2-ene-1,4-diol **11** and either **1** or **6** (Scheme 4).

Table 1. Arylation and oxidation studies carried out on compounds **3** and **7**

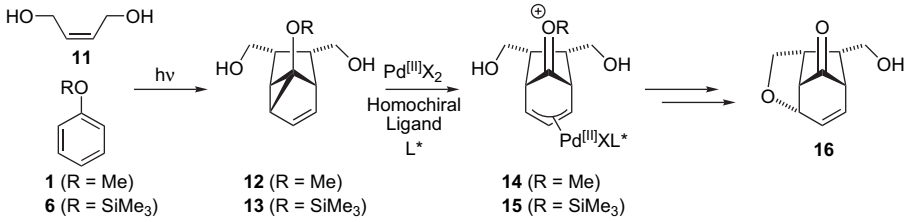


Entry	Starting substrate	Pd source	Aryl halide/oxidising agent	Base (equiv)	Time (h)	Temp (°C)	Yield of **4** (%)	Yield of **5** (%)	Yield of **8** (%)
1	**3**	$Pd(OAc)_2$	1-Iodo-2-nitrobenzene	NEt_3 (1)	12	120	42	9	—
2	**7**	$Pd(OAc)_2$	1-Iodo-2-nitrobenzene	NEt_3 (1)	4	120	43	5	27
3	**7**	$Pd(OAc)_2$	—	NEt_3 (1)	12	120	—	—	—
4	**7**	$PdCl_2$	1-Iodo-2-nitrobenzene	NEt_3 (1)	4	120	63	4	24
5	**7**	$PdCl_2$	$CuCl_2$	NEt_3 (2)	48	20	—	—	69
6	**3**	$PdCl_2$	$CuCl_2$	NEt_3 (2)	48	20	—	—	62

Reagents and conditions: Pd source (5 mol %), $P(o\text{-Tol})_3$ (10 mol %), NEt_3, aryl halide (100 mol %) or $CuCl_2$ (200 mol %), DMF.

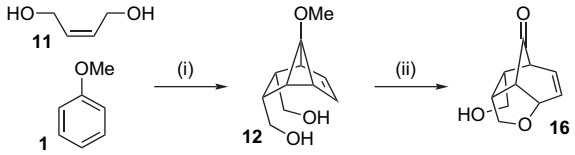


Scheme 3. Proposed reaction mechanism of oxidative cyclisation.



Scheme 4. Proposed reaction scheme for the palladium catalysed oxidative desymmetrisation of a diol photoadduct using a homochiral ligand.

Our initial investigations centred on the preparation of the silyloxy *meta* photocycloadduct **13** derived from **11** and trimethylphenoxysilane **6**, however this proved to be very unstable and rapidly degraded in the presence of silica gel. To get around this problem we reverted to using anisole **1** as the aromatic partner in the photoreaction, as **3** was known to undergo successful conversion to **8** (see Table 1, entry 6). A solution of anisole and *Z*-but-2-ene-1,4-diol in methanol was irradiated with UV light using a quartz immersion-well photoreactor to afford a 14% yield of the desired *endo* photoadduct **12**. When the previously effective conditions for converting **3** to **8** were used to oxidise **12**, only a disappointing 11% yield of **16** was obtained (Scheme 5).

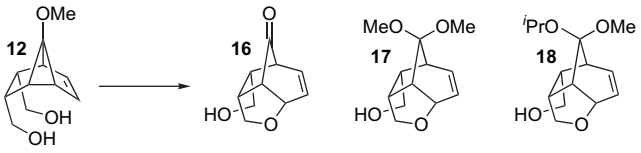


Scheme 5. Reagents and conditions: (i) hν, MeOH, 14%; (ii) $PdCl_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), $CuCl_2$, NEt_3, DMF, 20 °C, 48 h, 11%.

A number of other commonly used solvents were screened to improve the oxidation of **12**, however in each case the diol photoadduct was much less efficiently oxidised than either compounds **3** or **7** (Table 2). Acetonitrile gave a slight improvement in yield, but toluene afforded little and DMSO gave none of the desired ketone **16**. Methanol led to the formation of the oxidised product as its dimethyl acetal **17**[8] in an improved 36% yield, whilst isopropanol gave rise to the mixed acetal **18** in 19% yield. This final transformation for the formation of the mixed acetal **18** was very interesting as it was achieved in a highly stereoselective manner with only a single diastereoisomer being formed.[9]

For our preliminary studies into the formation of enantio-enriched oxidation products, we elected to use methanol as it was the most efficient solvent for oxidising **12** and carried out a series of experiments using the four ligands shown in Figure 2. The BINAP and Trost ligands were chosen as they

Table 2. Solvent optimisation studies for the oxidation of compound **12**



Entry	Solvent	Yield of **16** (%)	Yield of **17** (%)	Yield of **18** (%)
1	DMF	11	—	—
2	MeCN	15	—	—
3	Toluene	5	—	—
4	DMSO	—	—	—
5	MeOH	—	36	—
6	*i*-PrOH	—	—	19

Reagents and conditions: $PdCl_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), $CuCl_2$, NEt_3, solvent, 20 °C, 48 h.

both were good, standard, commercially available ligands for use in allylic alkylation reactions[10] to which this transformation has some similarity. The QUINAP ligand was chosen as it had two different ligating atoms (N and P),[11] whilst sparteine[12] was chosen as it was less prone to oxidation than the phosphine derived ligands.[13]

The palladium complexes were preformed prior to reaction with the photoadduct by stirring the red palladium chloride together with the ligand in methanol overnight under an atmosphere of nitrogen. The methanol was removed in vacuo to leave the various palladium complexes as yellow powders ready for reaction with **12**. In the first series of experiments

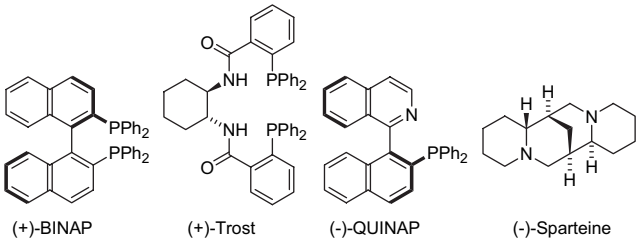
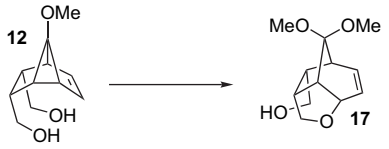


Figure 2. The four homochiral ligands used during the desymmetrisation studies.

Table 3. Oxidation studies involving the diol photoadduct **12** using various ligands and either copper(II) chloride or oxygen as the stoichiometric reoxidant



Entry	Ligand	Stoichiometric reoxidant	Base (mol %)	Time (h)	Yield of **17** (%)
1	(+)-BINAP	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	35
2	(+)-Trost	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	26
3	(−)-QUINAP	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	32
4	(−)-Sparteine	$CuCl_2$ (200 mol %)	NEt_3 (200)	48	25
5	(+)-BINAP	O_2 (1 atm)	—	72	16
6	(+)-Trost	O_2 (1 atm)	—	72	16
7	(−)-QUINAP	O_2 (1 atm)	—	72	10
8	(−)-Sparteine	O_2 (1 atm)	—	48	35

Reagents and conditions: $PdCl_2$ (5 mol %), $CuCl_2$ (5 mol %), stoichiometric reoxidant, ligand, MeOH, 20 °C. Chiral HPLC analysis was carried out on the benzoate ester derivatives of each of the oxidised products and revealed no significant enantiomeric enrichment for any of the products.

(Table 3, entries 1–4) 2 equiv of copper(II) chloride were used as the reoxidant along with 2 equiv of triethylamine to neutralise the hydrogen chloride that was formed during the course of the reaction. Each reaction was carried out in a sealed reaction vessel under an atmosphere of nitrogen and left to stir for two days to allow complete consumption of starting material. In a second series of experiments (Table 3, entries 5–8) Wacker conditions were employed to achieve the desired oxidation reaction.[14] In these circumstances a catalytic quantity of copper(II) chloride was used to aid reoxidation of the palladium complex, but the stoichiometric oxidant was a balloon of oxygen gas. To establish if enantioselectivity had been achieved, the free hydroxyl group on each of the products was converted to a benzoate ester and each of these was submitted for chiral HPLC analysis.

Disappointingly no evidence of any enantioenrichment of the oxidised products could be detected for any of the entries in Table 3. In the best cases (entries 1 and 8) the oxidised product **17** was obtained in a similar yield to that observed when the tri-*ortho*-tolylphosphine ligand was used. On the whole the anaerobic conditions afforded a greater yield of **17**, whilst the Wacker conditions usually required longer reaction times for complete consumption of starting material and led to a reduced yield of product. The exception to this was when sparteine was used as the ligand and this may be related to the phosphine ligands being prone to oxidation under the aerobic conditions.[13] Stoltz et. al.[15] had shown how sparteine could be used very effectively to carry out asymmetric oxidative Wacker cyclisation reactions. The reaction involved heating a solution of the substrate in toluene at 80 °C under an oxygen atmosphere in the presence of 10 mol % palladium bis(trifluoroacetate), 40 mol % sparteine and molecular sieves. Unfortunately when analogous conditions were used to oxidise compound **12**, the reaction failed to afford any of the desired ketone **16**.

3. Conclusion

Whilst attempting to improve the yield of a palladium-mediated Heck-style arylation/fragmentation reaction of the 7-*endo meta* photocycloadduct compound **3** derived from anisole and allyl alcohol, the reaction was repeated with the equivalent photoadduct isomer **7** derived from trimethylphenoxysilane and allyl alcohol. In addition to isolating the expected arylated products **4** and **5**, an alternative mode of reactivity involving an oxidation process was observed, which resulted in the formation of the unique tricyclic ether **8**. The efficiency of the Heck reaction of photoadduct **7** to produce the arylated product **4** was significantly improved when palladium(II) chloride was used instead of palladium(II) acetate and the oxidation process to form **8** was also dramatically improved when palladium(II) chloride and copper(II) chloride were used as the oxidants. A similar oxidative cyclisation reaction could be induced using the *meta* photocycloadduct **12** derived from anisole and *Z*-but-2-ene-1,4-diol. The products from this process could be obtained either as a ketone (**16**) or an acetal (**17** or **18**) depending upon the nature of the solvent with methanol being the solvent of choice. Unfortunately attempts to induce the reaction asymmetrically via the desymmetrisation of a proposed π-allyl palladium intermediate **14** with the aid of various homochiral ligands failed to yield any enantioenriched products.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Bruker DPX300 or Bruker AMX500 Fourier transform spectrometers at 300 or 500 MHz, respectively. Chemical shifts (δ) are quoted in parts per million using tetramethylsilane or residual chloroform as internal reference (δ=0.00 ppm) and coupling constants (J) are quoted in hertz. ^{13}C NMR spectra were recorded using the same instruments and chemical shifts (δ) are quoted in parts per million using $CDCl_3$ as internal reference (δ=77.0 ppm).

IR spectra were recorded on Perkin–Elmer Spectrum One Fourier transform instruments and frequencies (ν_{max}) are quoted in wavenumbers (cm^{-1}).

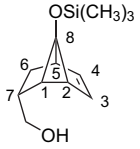
Low- and high-resolution electron impact (EI) and chemical impact (CI) mass spectra were recorded using a Fisons Autospec instrument. High-resolution electrospray ionisation

(ESI) mass spectra were recorded using a Bruker Daltonics APEXIII instrument.

The starting materials for the synthesis of the compounds were obtained from the usual suppliers (Sigma–Aldrich–Fluka, Lancaster, Fisher etc.) unless otherwise stated. The anhydrous solvents were obtained from Aldrich Chemicals in Sure/Seal™ bottles and were used without further purification. Petrol refers to petroleum ether with a boiling range of 40–60 °C. Flash column chromatography was performed using Fisher Matrex 60 (35–70 μm) silica. Analytical thin layer chromatography (TLC) was performed using Whatman K6F silica gel plates (60 Å porosity).

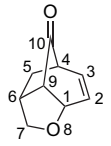
Irradiations were carried out in quartz immersion-well reactors fitted with 6 or 16 W low-pressure mercury vapour lamps or 125 or 400 W medium-pressure mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen-free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through a sintered glass tube into the solvent at room temperature. Experiments were conducted with gentle stirring of the reaction solution under an atmosphere of nitrogen and with cold-water cooling of the lamp and vessel contents throughout.

4.1.1. *rac*-(1*S*,2*R*,5*R*,7*R*,8*S*)-7-Hydroxymethyl-8-trimethylsilyloxytricyclo[3.2.1.0^{2,8}]oct-3-ene 7. A solution of trimethylphenoxysilane (33.4 g, 201 mmol) and allyl alcohol (23.3 g, 402 mmol) in cyclohexane (400 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with UV light for 120 h using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials and solvent were removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/Et_2O 2:1) to obtain the 7-*endo* isomer **7** (1.93 g, 4.3%) as a viscous, pale yellow oil.



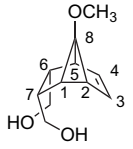
^{1}H NMR (500 MHz, C_6D_6) δ 0.12 (9H, s, $OSi(CH_3)_3$), 1.40 (1H, dd, J=1.4, 12.8 Hz, H-6a), 1.95 (1H, br d, J=8.4 Hz, H-2), 2.02 (1H, dd, J=6.3, 8.4 Hz, H-1), 2.08 (1H, br s, –OH), 2.37 (1H, ddd, J=6.6, 11.4, 12.8 Hz, H-6b), 2.70 (1H, m, H-7b), 2.96 (1H, ddd, J=1.2, 2.7, 6.4 Hz, H-5), 3.48 (1H, dd, J=7.5, 10.2 Hz, –C*H*HOH), 3.54 (1H, dd, J=8.0, 10.2 Hz, –CH*H*OH), 5.37 (1H, dddd, J=0.6, 1.3, 2.7, 5.6 Hz, H-4), 5.49 (1H, dd, J=2.3, 5.6 Hz, H-3); ^{13}C NMR (125 MHz, C_6D_6) δ 0.85, 38.3, 39.3, 39.9, 45.6, 56.2, 66.0, 86.4, 129.1, 136.5; IR 1646, 3370 cm^{-1}; HRMS (ESI) *m*/*z* calcd $C_{12}H_{20}NaO_2Si$ $[M+Na]^+$ 247.1130, found 247.1126.

4.1.2. *rac*-(1*S*,4*R*,6*R*,9*S*)-8-Oxatricyclo[4.2.1.1^{4,9}]dec-2-ene-10-one 8. A mixture of the 7-*endo* photoadduct **7** (130 mg, 0.58 mmol), palladium(II) chloride (10 mg, 0.06 mmol), copper(II) chloride (156 mg, 1.16 mmol), triethylamine (118 mg, 1.16 mmol), tri-*ortho*-tolylphosphine (36 mg, 0.06 mmol) and dry DMF (5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into 2 M hydrochloric acid (50 ml) and diethyl ether (50 ml). The resulting heavy emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×50 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/Et_2O 2:1) to afford **8** (60 mg, 69%) as a colourless solid of prism crystals (for crystallographic details see Ref. 5) mp 87.8–89.5 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (1H, dd, J=1.6, 13.0 Hz, H-5a), 2.33 (1H, ddd, J=6.0, 9.4, 13.0 Hz, H-5b), 2.68 (1H, ddd, J=2.0, 6.0, 7.7 Hz, H-4), 2.88 (1H, ddd, J=2.0, 6.8, 7.6 Hz, H-9), 2.97–3.03 (1H, m, H-6b), 3.68 (1H, dd, J=4.0, 8.7 Hz, H-7a), 4.36 (1H, t, J=8.5 Hz, H-7b), 5.12 (1H, dd, J=3.8, 7.0 Hz, H-1), 5.64 (1H, dddd, J=0.5, 0.9, 3.6, 9.0 Hz, H-2), 6.22 (1H, dd, J=7.5, 9.0 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.4, 37.2, 44.2, 53.3, 75.9, 85.8, 125.5, 134.6, 209.9; IR 1626, 1764 cm^{-1}; HRMS (EI) *m*/*z* calcd $C_9H_{10}O_2$ $[M]^+$ 150.0681, found 150.0688.

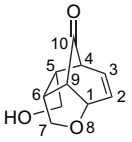
4.1.3. *rac*-(1*S*,2*R*,5*S*,6*S*,7*R*,8*S*)-6,7-Dihydroxymethyl-8-methoxytricyclo[3.2.1.0^{2,8}]oct-3-ene 12. A solution of anisole (43.2 g, 400 mmol) and *Z*-but-2-ene-1,4-diol (70.4 g, 800 mmol) in methanol (350 ml) was added to a quartz immersion-well photoreactor and degassed by passing a stream of nitrogen through it for 20 min. This solution was then irradiated with UV light for 120 h using a 16 W low-pressure mercury vapour lamp. The unreacted starting materials and solvent were removed by distillation and the residue was subjected to column chromatography (silica, eluting with Et_2O/MeOH 100:1, then CH_2Cl_2/MeOH 20:1) to obtain the *endo* isomer **12** (11.3 g, 14%) as a viscous, pale green oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (1H, ddd, J=1.2, 2.4, 8.4 Hz, H-2), 2.26 (1H, dd, J=6.7, 8.4 Hz, H-1), 2.80–2.88 (1H, br s, –OH), 2.87–2.94 (1H, m, H-7b), 3.03–3.09 (1H, m, H-6b), 3.14 (1H, ddd, J=1.3, 2.6, 5.7 Hz, H-5), 3.38 (3H, s, $-OCH_3$), 3.48–3.60 (1H, br s, –OH), 3.50 (1H, dd, J=3.7, 10.7 Hz, –C*H*HOH), 3.57 (1H, dd, J=4.5, 11.4 Hz, –C*H*HOH), 3.67 (1H, t, J=11.2 Hz, –CH*H*OH), 3.98 (1H, t, J=10.3 Hz, –CH*H*OH), 5.63 (1H, ddd, J=1.2, 2.6, 5.8 Hz, H-4), 5.73 (1H, dd, J=2.4, 5.8 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.2, 39.0, 44.7, 53.4, 55.4, 56.4, 60.9, 62.8, 90.6, 131.3, 133.0; IR 1592, 1656, 3306 cm^{-1};

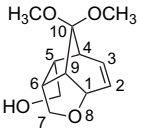
HRMS (ESI) *m/z* calcd $C_{11}H_{16}NaO_3$ $[M+Na]^+$ 219.0997, found 219.0998.

4.1.4. *rac*-(1*S*,4*S*,5*S*,6*R*,9*S*)-8-Oxa-5-hydroxymethyltricyclo[4.2.1.1^{4,9}]dec-2-ene-10-one 16. A mixture of the diol photoadduct **12** (210 mg, 1.07 mmol), palladium(II) chloride (10 mg, 0.054 mmol), copper(II) chloride (317 mg, 2.36 mmol), triethylamine (238 mg, 2.36 mmol), tri-*ortho*-tolylphosphine (35 mg, 0.12 mmol) and isopropanol (5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into water (50 ml) and diethyl ether (100 ml). The resulting emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×100 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with CH_2Cl_2/EtOAc 1:1) to afford **16** (29 mg, 15%) as a pale amber, viscous oil.



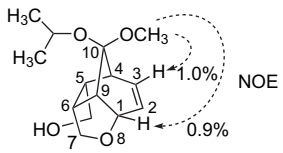
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (1H, br s, –OH), 2.72 (1H, dddd, *J*=5.2, 7.9, 7.9, 9.4 Hz, H-5b), 2.80 (1H, ddd, *J*=1.9, 5.2, 7.2 Hz, H-4), 2.97 (1H, dddd, *J*=0.7, 1.9, 6.9, 7.8 Hz, H-9), 3.11–3.17 (1H, m, H-6b), 3.77 (1H, dd, *J*=7.9, 10.4 Hz, –C*H*HOH), 3.82 (1H, dd, *J*=4.1, 9.5 Hz, H-7), 3.87 (1H, dd, *J*=7.9, 10.4 Hz, –CH*H*OH), 4.07 (1H, dd, *J*=8.5, 9.5 Hz, H-7), 5.04 (1H, dd, *J*=3.7, 6.7 Hz, H-1), 5.77 (1H, ddd, *J*=0.8, 3.7, 9.1 Hz, H-2), 6.06 (1H, dd, *J*=7.3, 9.1 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.8, 44.5, 46.9, 54.6, 60.0, 67.8, 85.2, 128.1, 131.5, 208.3; IR 1626, 1755, 3436 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{10}H_{12}NaO_3$ $[M+Na]^+$ 203.0684, found 203.0682.

4.1.5. *rac*-(1*S*,4*S*,5*S*,6*R*,9*S*)-8-Oxa-5-hydroxymethyltricyclo-10,10-dimethoxy[4.2.1.1^{4,9}]dec-2-ene 17. A mixture of the diol photoadduct **12** (435 mg, 2.22 mmol), palladium(II) chloride (20 mg, 0.11 mmol), copper(II) chloride (657 mg, 4.88 mmol), triethylamine (493 mg, 4.88 mmol) and tri-*ortho*-tolylphosphine (74 mg, 2.44 mmol) and MeOH (8 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into water (50 ml) and diethyl ether (100 ml). The resulting emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×100 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 4:1) to afford **17** (182 mg, 36%) as a colourless solid of plate crystals (for crystallographic details see Ref. 15) mp 90.4–91.8 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (1H, br s, –OH), 2.63 (1H, ddd, *J*=2.1, 5.1, 7.0 Hz, H-4), 2.76 (1H, dddd, *J*=5.1, 7.9, 7.9, 9.0 Hz, H-5b), 2.82–2.88 (1H, m, H-6b), 2.89–2.92 (1H, m, H-9), 3.18 (3H, s, –OCH_3), 3.27 (3H, s, –OCH_3), 3.66 (1H, dd, *J*=3.8, 9.3 Hz, H-7), 3.67 (1H, dd, *J*=8.0, 10.4 Hz, –C*H*HOH), 3.74 (1H, dd, *J*=8.0, 10.4 Hz, –CH*H*OH), 3.91 (1H, dd, *J*=8.0, 9.4 Hz, H-7), 4.70 (1H, dd, *J*=3.6, 6.2 Hz, H-1), 5.73 (1H, ddd, *J*=1.0, 3.6, 9.4 Hz, H-2), 5.89 (1H, dd, *J*=7.0, 9.4 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.3, 41.3, 47.0, 48.3, 49.2, 51.0, 61.2, 67.0, 79.1, 110.0, 128.5, 129.3; IR 1641, 3400 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{12}H_{18}NaO_4$ $[M+Na]^+$ 249.1103, found 249.1101.

4.1.6. *rac*-(1*S*,4*S*,5*S*,6*R*,9*S*,10*R*)-8-Oxa-5-hydroxymethyltricyclo-10-isopropoxy-10-methoxy[4.2.1.1^{4,9}]dec-2-ene 18. A mixture of the diol photoadduct **12** (200 mg, 1.02 mmol), palladium(II) chloride (9 mg, 0.05 mmol), copper(II) chloride (275 mg, 2.04 mmol), triethylamine (206 mg, 2.04 mmol) and tri-*ortho*-tolylphosphine (31 mg, 0.10 mmol) and isopropanol (5 ml) was added to a re-sealable reaction tube. The tube was flushed with a stream of dry nitrogen, sealed and stirred at room temperature for 48 h. The reaction mixture was poured into water (50 ml) and diethyl ether (100 ml). The resulting emulsion was filtered through Celite and washed through with diethyl ether (100 ml). The biphasic mixture was partitioned and the aqueous phase was further extracted with diethyl ether (2×100 ml). The combined organic portions were washed with brine (50 ml), water (50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue subjected to column chromatography (silica, eluting with petrol/EtOAc 4:1) to afford **18** (49 mg, 19%) as a pale green, viscous oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, d, *J*=6.2 Hz, –OCH(CH_3)CH_3), 1.21 (3H, d, *J*=6.2 Hz, –OCH(CH_3)CH_3), 1.36 (1H, br s, –OH), 2.54–2.57 (1H, m, H-4), 2.83–2.88 (2H, m, H-5b, H-6b), 2.91 (1H, m, H-9), 3.17 (3H, s, –OCH_3), 3.66 (1H, dd, *J*=3.3, 9.3 Hz, H-7), 3.69 (1H, dd, *J*=7.7, 10.3 Hz, –C*H*HOH), 3.76 (1H, dd, *J*=7.4, 10.4 Hz, –CH*H*OH), 3.92 (1H, dd, *J*=8.5, 9.5 Hz, H-7), 4.17 (1H, sept, *J*=6.2 Hz, –OC*H*(CH_3)CH_3), 4.71 (1H, dd, *J*=3.6, 6.4 Hz, H-1), 5.73 (1H, ddd, *J*=1.0, 3.6, 9.3 Hz, H-2), 5.88 (1H, dd, *J*=6.9, 9.4 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 40.4, 42.6, 47.4, 50.9, 51.5, 61.3, 64.3, 67.0, 79.5, 110.4, 128.6, 128.9; IR 1641, 3434 cm^{-1}; HRMS (ESI) *m/z* calcd $C_{14}H_{22}NaO_4$ $[M+Na]^+$ 277.1416, found 277.1413.

Acknowledgements

We gratefully acknowledge funding from Tocris–Cookson Ltd and the EPSRC (GR/T08807/01) for this research and have appreciated the opportunity to discuss this chemistry with Professor P. J. Parsons and Professor P. A. Wender. We would also like to thank Dr. A. Abdul Sada for mass spectroscopy studies along with Anna Thom and Louise Argent for chiral HPLC studies.

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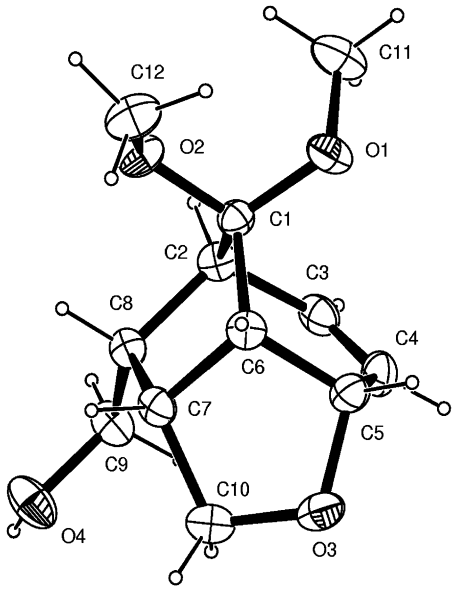
8. The crystallographic data for compound **17** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 607018. Formula: $C_{12}H_{18}O_4$ Unit cell parameters: *a* 8.5840(5) *b* 11.6522(8) *c* 11.9274(6) β 108.976(4) space group P21/n.



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Tetrahedron 62 (2006) 9410–9416
Tetrahedron

Structure, reactivity, and application of some triketone derivatives

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Received 6 May 2006; revised 17 July 2006; accepted 19 July 2006
Available online 9 August 2006

Abstract—The major tautomer of several triketone derivatives in organic and aqueous solutions has been determined. Their solvent- and base-sensitive properties have been applied in the design of a polarity-sensitive fluorescent probe and an acidichromic colorant, respectively. The regioselective acetylation and methylation of 2-acyldimedone, 3-acyl-4-hydroxycoumarin, and 2-acyl-1,3-indandione have also been investigated. The results indicated that acetylation and methylation of the first two occurred specifically at endocyclic enolic oxygens, whereas for the latter they occurred at exocyclic enolic oxygen.

1. Introduction

Triketones and their derivatives have long been known for their extensive application as biologically active substances. For instance, nitisinone has been used as a therapeutic agent for the treatment of tyrosinaemia type I disease;[1] sethoxydim, an oxime derivative of triketone, is a herbicide that is used for the control of grasses in broadleaf crops (Fig. 1).[2] Therefore, understanding the structure and reactivity of triketone derivatives is crucial for further developments of other important biologically active molecules. While up to five tautomers are possible for a single triketone compound, the distributions of these tautomers are highly dependent on both molecular structures and surrounding solvent systems. For instance, although previous studies have demonstrated that both 2-acyldimedone and 2-acyl-4-hydroxycoumarin mainly exist in endocyclic enol forms in solid states,[3] the major tautomer of these triketones present in solution is highly dependent on solvent polarity, that is, the major tautomer of 2-acetyldimedone in relatively nonpolar organic solvents such as hexane and chloroform is in the endocyclic enol form, and the major tautomer in polar protic solvents like methanol or aqueous solution mainly presents in the exocyclic enol form.[4] A similar observation is also made of 2-acetyl-4-hydroxycoumarin,[5] as indicated in Scheme 1. Here we report the determination of major tautomers of several triketone derivatives in organic and aqueous solutions. Both solvent- and base-sensitive properties of these triketones have been applied in the design and synthesis of a potential polarity-sensitive fluorescent probe and an acidichromic colorant, respectively. Furthermore, the regioselective reactions of some triketones i.e. 2-acyldimedone, 3-acyl-4-hydroxycoumarin, and 2-acyl-1,3-indandione toward acetylation and methylation have also been investigated. Some of the results have been previously communicated.[6,11]

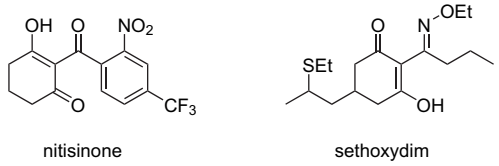
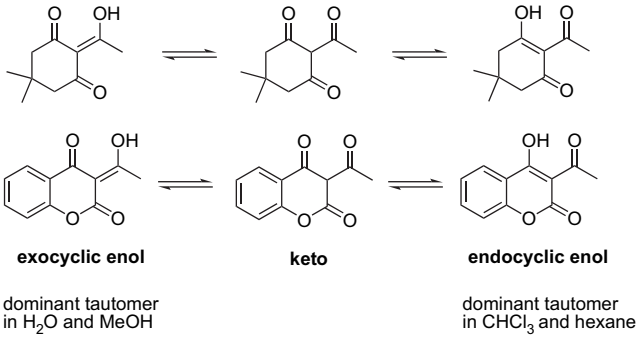


Figure 1. The structures of two biologically active triketone derivatives.



Scheme 1. The major tautomer of 2-acetyldimedone and 2-acetyl-4-hydroxycoumarin exists in polar protic and nonpolar solvents.

Keywords: Triketone; Polarity-sensitive fluorescent probe; Acidichromic colorant.
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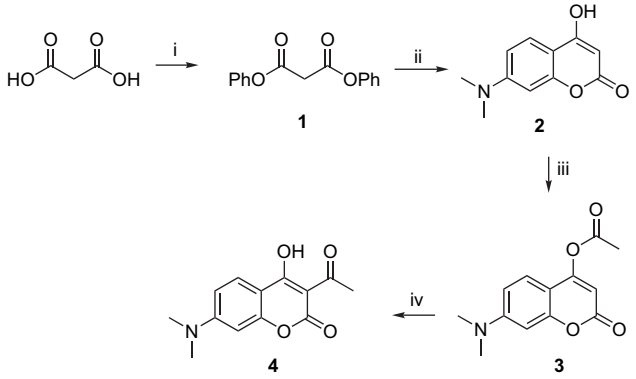
doi:10.1016/j.tet.2006.07.053

2. Results and discussion

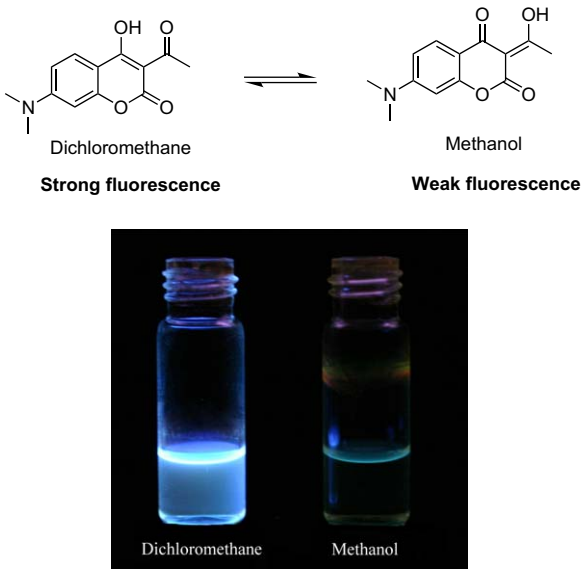
Since 2-acetyl-4-hydroxycoumarin itself is weakly fluorescent, an *N*,*N*-dimethylamino group was incorporated at 7-position of the coumarin moiety in an effort to enhance its fluorescence property. The proposed compound **4** was prepared in four steps as outlined in Scheme 2. It started with esterification of malonic acid with phenol in the presence of phosphorus oxychloride to give the diester **1**.[7] The diester **1** was then coupled with 3-*N*,*N*-dimethylaminophenol in toluene to afford 7-*N*,*N*-dimethylamino-4-hydroxycoumarin **2**.[8] Esterification of **2** with acetyl chloride in the presence of triethylamine as a base yielded ester **3**. Final isomerization was achieved by treating **3** with a catalytic amount of potassium cyanide and 18-crown-6 in methylene chloride to afford the target molecule **4**.



Scheme 2. Reagents and conditions: (i) $POCl_3$, phenol, 115 °C, 1.5 h; (ii) 3-dimethylaminophenol, toluene, reflux, 7 h; (iii) acetyl chloride, Et_3N, CH_2Cl_2, 0 °C, 0.5 h; (iv) KCN, Et_3N, 18-crown-6, CH_2Cl_2, rt, 72 h.

The synthesized compound **4** exists mainly in the endocyclic enol form in organic solvents like methylene chloride and is highly fluorescent due to the presence of an *N*,*N*-dimethylamino group. Essentially no fluorescence was detected when **4** was dissolved in protic solvents like methanol, where it exists mainly in the exocyclic enol form (Scheme 3). Figure 2 shows the UV absorption spectra of **4** in various compositions of methanol and methylene chloride. Two isosbestic points were observed at 300 and 350 nm, which suggest interconversion of two different tautomeric forms. The fluorescence quantum yield of **4** in various solvents was also determined as indicated in Table 1. Up to 30 times difference between the highest fluorescence quantum yield of **4** in benzene (Φ_f=0.91) and the lowest fluorescence quantum yield in water (Φ_f=0.03) was observed.

Since the energy difference between exocyclic and endocyclic enols of 2-acetyl-4-hydroxycoumarin has been calculated to be merely 1 kcal/mol,[5] we speculated that the major tautomer of 2-acyldimedone in nonpolar organic solutions can be switched from the endocyclic enol form to the exocyclic enol one by a simple conjugation extension of the triketone moiety. The extension of conjugation was easily accomplished by a base-catalyzed condensation of 2-acetyldimedone with 4-*N*,*N*-dimethylaminobenzaldehyde to yield compound **5** (Scheme 4). The observation of a long range coupling with a coupling constant of 0.9 Hz between the enolic hydrogen and the adjacent vinyl hydrogen on



Scheme 3. The major tautomers of compound **4** in CH_2Cl_2 and CH_3OH, and their fluorescence difference.

proton NMR spectra in deuterated chloroform confirmed that **5** exists in the more conjugated exocyclic enol form in nonpolar organic solvents. This result suggested that the dominant tautomer of triketone derivatives can be easily shifted from one to the other by introducing an extra functional group adjacent to it. A similar extension of conjugation of 2-acetyl-4-hydroxycoumarin also switched the major tautomer to the expected exocyclic enol **6** (Scheme 4).

In addition to possessing polarity-sensitive property, some triketones are also sensitive to bases. For instance, the triketone functional group in 2-acyl-1,3-cyclohexanedione is coplanar,[3a] owing to the conjugation of C-2 carbonyl moiety with the cyclohexene ring system by an intramolecular hydrogen bond between the C-3 hydroxyl hydrogen and the oxygen atom of C-2 carbonyl group. After deprotonation of C-3 hydroxyl group by a base, however, the intramolecular hydrogen bond is disrupted. The subsequent intrinsic electrostatic repulsion between the 2-acyl oxygen atom and the two 1,3-diketone oxygens causes deformation of the molecule from planarity. This base-sensitive property of triketones has been recently applied in the design and synthesis of an acidichromic colorant, which can undergo two distinct and reversible color changes under both strongly acidic and basic conditions (Scheme 5).[6]

In the case of 2-acyl-1,3-indandione, three tautomers are also possible for this benzene-fused triketone (Scheme 6). The crystal structure of 2-acetyl-1,3-indandione[9] has been determined to be in the exocyclic enol form in the solid state, with the enolic hydrogen external to the indan system, thus the indan portion is essentially planar. This exocyclic enol form is also the major tautomer in solutions and is not solvent-sensitive. The reason why this particular configuration is favored over the other possible endocyclic enol tautomer is currently not clear, presumably due to the antiaromatic nature of the latter.[10]

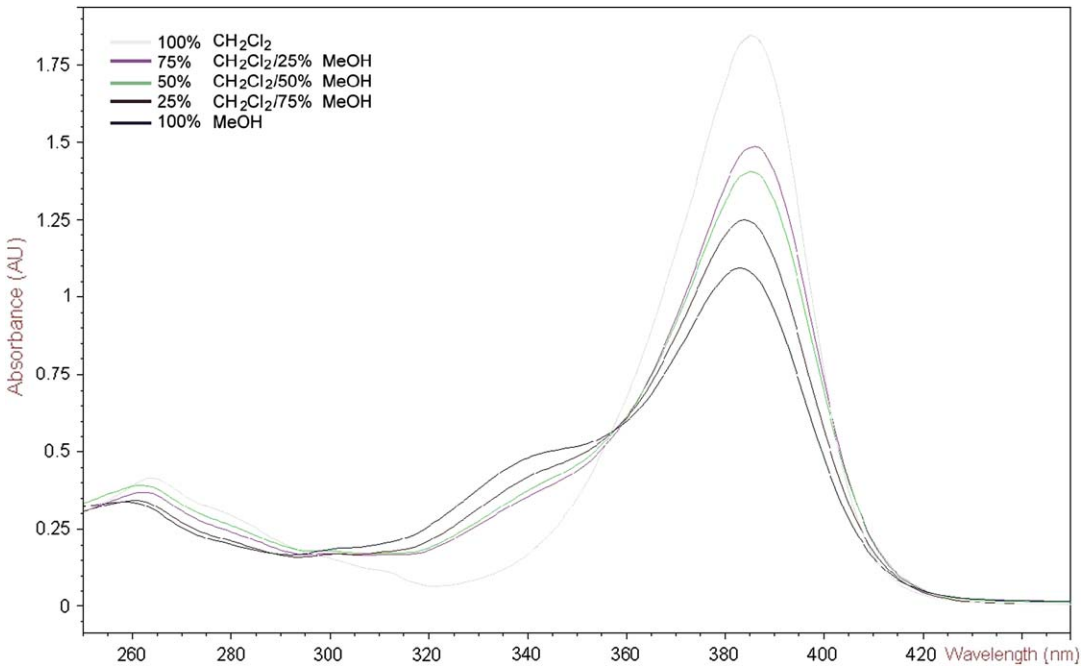


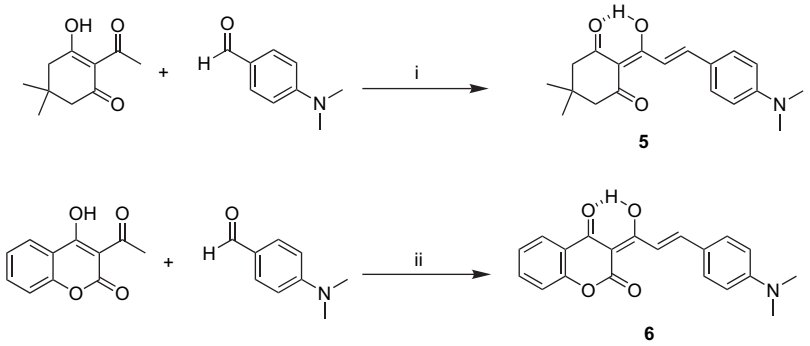
Figure 2. UV absorption spectra of **4** in various compositions of methanol and methylene chloride.

Table 1. The fluorescence quantum yield of **4** in various solvents

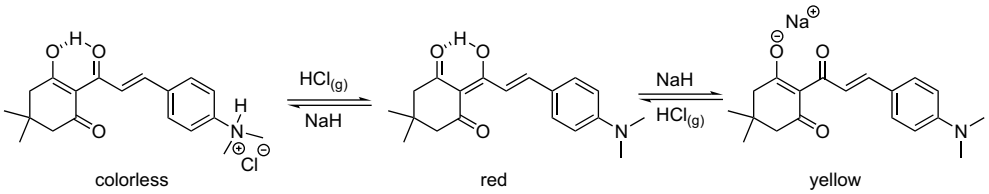
Solvent	λ_{ex} (nm)	λ_{em} (nm)	Quantum yield (Φ_f)
Benzene	385	407	0.91
Hexane	375	384	0.90
Toluene	385	405	0.86
CH_2Cl_2	385	418	0.85
$CHCl_3$	385	414	0.82
EtOAc	385	418	0.41
THF	385	420	0.31
Acetone	385	429	0.04
EtOH	385	424	0.04
CH_3CN	385	433	0.03
CH_3OH	345	421	0.03
DMF	389	418	0.03
H_2O	345	427	0.03

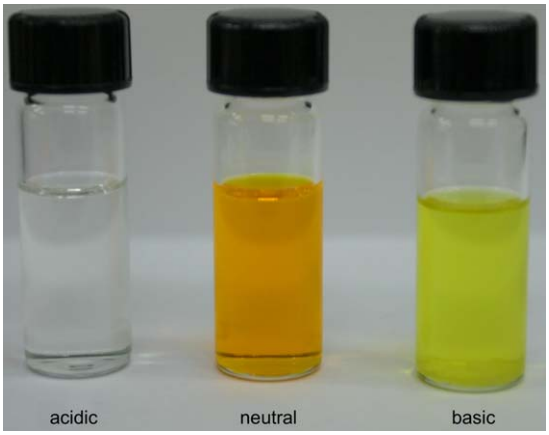
Acetylation of 2-acetyl-1,3-cyclohexanedione with acetyl chloride under basic conditions occurs specifically at 3-enolic oxygen to give the enol ester **7**. The electrostatic repulsion between the 2-acyl oxygen atom and the two 1,3-diketone oxygens of the resulting enol ester caused deformation of the triketone functional group from planarity. This repulsion can be easily relieved via enolization of the 2-acyl group of **7**, followed by a 1,5-acyl transfer reaction to afford enol acetate **8**. The resulting **8** can then undergo esterification again to obtain enol diacetate **9**. Thus, with available α-hydrogens on the 2-acyl group, this intrinsic repulsion presumably provides a driving force for enol ester **7** to undergo enolization and subsequent isomerization.[11] A similar rearrangement was also observed for 3-acyl-4-hydroxycoumarin to afford **12**, as shown in Scheme 7.

Acetylation of 2-acyl-1,3-indandione by ketene[12] or acetyl chloride, however, occurred selectively at C-2 hydroxyl group to give the only product **13** quantitatively (Scheme 8). The enol ester **13** is unstable and prone to be hydrolyzed in the aqueous solution due to the previously described electrostatic repulsion between the two oxygens. It, however, has lower energy than the undetected enol ester **14**, presumably because **14** is further destabilized by the proposed antiaromatic nature. No further rearrangement of **13** was observed.

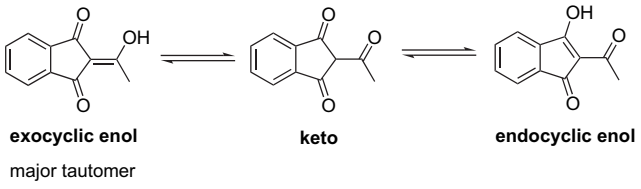


Scheme 4. Shifting the endocyclic enol tautomer to exocyclic enol tautomer by extension of conjugation. Reagents and conditions: (i) NaOH, MeOH, 80 °C, 24 h; (ii) piperidine, benzene, reflux, Dean–Stark trap.



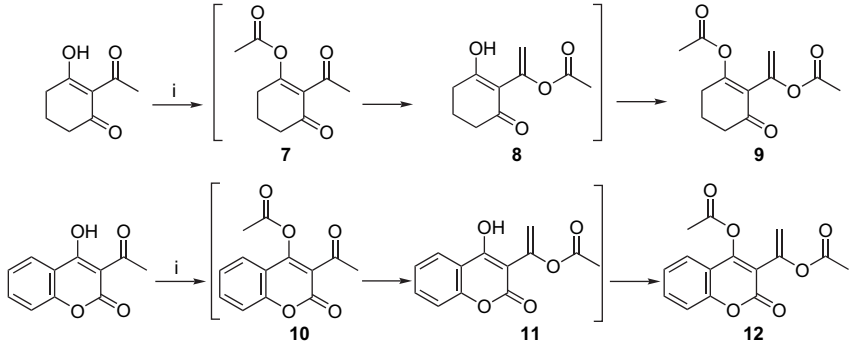


Scheme 5. The acidichromic switch of **5** and the corresponding colors in acidic, neutral, and basic conditions.

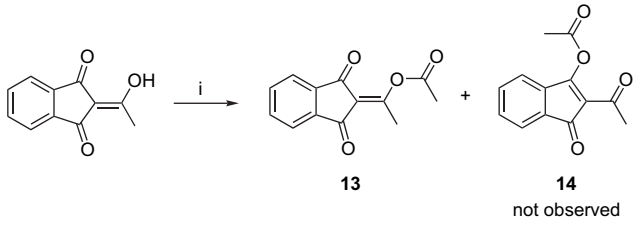


Scheme 6. Three possible tautomers of 2-acetyl-1,3-indandione.

Similar to the acylation reaction, alkylation of 2-acetyl-1,3-cyclohexanedione and 3-acyl-4-hydroxycoumarin has been found to occur specifically at endocyclic enolic oxygen to give the corresponding enol ether, whereas alkylation of 2-acyl-1,3-indandione occurred specifically at exocyclic enolic oxygen. Interestingly, reactions of 3-acetyl-4-hydroxy-7-*N*,*N*-dimethylaminocoumarin with excess diazomethane in methylene chloride generated the expected methylated compound **15** along with a minor ring cyclization

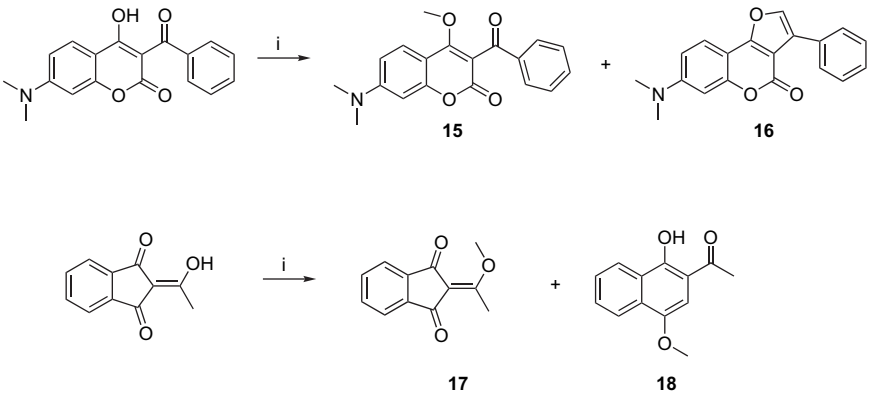


Scheme 7. Acetylation and subsequent 1,5-acyl transfer reaction of 2-acetyl-1,3-cyclohexanedione and 3-acetyl-4-hydroxycoumarin. Reagents and conditions: (i) acetyl chloride, Et_3N, CH_2Cl_2, rt.



Scheme 8. Acetylation of 2-acetyl-1,3-indandione. Reagents and conditions: (i) acetyl chloride, Et_3N, CH_2Cl_2, rt.

product **16**. Reaction of 2-acetyl-1,3-indandione with excess diazomethane under the same conditions, on the other hand, gave the ring expansion product **18**, in addition to methyl enol ether **17** (Scheme 9). Although these methylation and ring expansion reactions have been described in the literature a quarter of a century ago,[13] the X-ray structure of **17** was not provided. Thus, the real structure of **17** remains unclear. Here we present the crystal structures of **16**, **17**, and **18**, as shown in Figure 3.[14] The X-ray structure of **17** confirmed unambiguously that the methylation of 2-acyl-1,3-indandione did occur



Scheme 9. Methylation products of two triketone derivatives with excess diazomethane. Reagents and conditions: (i) CH_2N_2, CH_2Cl_2, 0 °C.

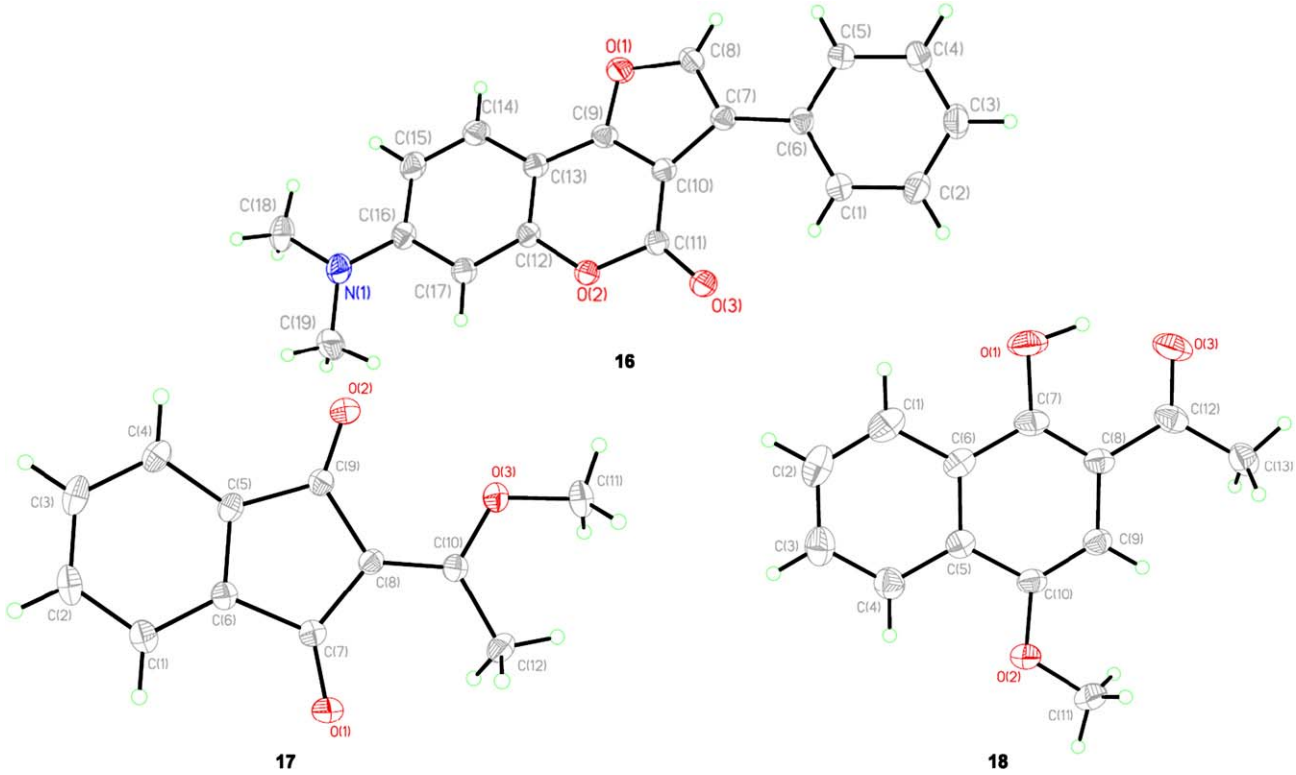


Figure 3. X-ray crystal structures of compounds **16**, **17**, and **18**.

at exocyclic enolic oxygen instead of the previously reported endocyclic enolic one. The favored stabilization energy gained after aromatization seems to be the major driving force for the formation of cyclization product **16** and ring expansion product **18**.

3. Conclusions

The solvent-sensitive property of the triketones has been successfully applied in the design and synthesis of a polarity-sensitive fluorescent probe. Additionally, we have demonstrated that the major tautomer of the triketone derivatives in organic solvents can be easily switched from endocyclic enol form to the exocyclic enol one by a simple conjugation extension. The resulting conjugated system, together with its base-sensitive property, has been applied to develop an acidichromic colorant. Moreover, acylation of 2-acyl-1,3-dimedone and 2-acyl-4-hydroxycoumarin was found to occur specifically at endocyclic enolic oxygen followed by a subsequent 1,5-acyl transfer reaction, while acylation of 2-acyl-1,3-indandione occurred at exocyclic enolic oxygen to give the corresponding enol ester without further rearrangement. Similarly, alkylation of 2-acetyl-1,3-cyclohexanedione and 3-acyl-4-hydroxycoumarin has been found to occur specifically at endocyclic enolic oxygen, whereas alkylation of 2-acyl-1,3-indandione occurred at exocyclic enolic oxygen. Finally, the structures of cyclization and ring expansion products of methylation of 3-acetyl-4-hydroxy-7-*N*,*N*-dimethylaminocoumarin and 2-acetyl-1,3-indandione, respectively, with excess diazomethane have also been characterized by X-ray crystallography.

4. Experimental

4.1. General

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian VXR300 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data. Preparation of compounds **5** and **6** has been previously reported.[6]

4.2. UV and fluorescence measurements

Absorption spectra were acquired using an HP8453 spectrophotometer and emission spectra were obtained on a Hitachi F-4500 fluorospectrometer.

4.3. Calculation of fluorescence quantum yield

UV–vis spectra were measured on an HP8453 spectrometer with a 1 cm path length quartz cell. Fluorescence spectra were measured on a Hitachi F-4500 fluorescence spectrophotometer. Coumarin 1 (Φ_f=0.99, λ_{max}=374 nm in CH_2Cl_2) was used as an external standard for the measurement of fluorescence quantum yields of **4**. Fluorescence quantum yields were measured by comparing the integrated area under the fluorescence curve for the compound **4** and coumarin 1 at equal absorbance at the same excitation wavelength. The quantum yields were corrected for the refractive index of the solvent.

4.3.1. 7-(*N*,*N*-Dimethylamino)-4-hydroxycoumarin (2). To a solution of compound **1** (0.1 g, 0.5 mmol) in toluene (20 mL) was added 3-*N*,*N*-dimethylaminophenol (0.4 g, 0.5 mmol). The reaction mixture was refluxed for 7 h. After completion of the reaction, the cake was filtered and washed with hexanes. The crude product was dried under vacuum to give a gray solid in an 85% yield. Mp 261–262 °C (lit.[7] 260–262 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, J=8.7 Hz, 1H), 6.68 (dd, J=8.7, 2.4 Hz, 1H), 6.48 (d, J=2.4 Hz, 1H), 5.27 (s, 1H), 2.99 (s, 6H).

4.3.2. 7-(*N*,*N*-Dimethylamino)-2-oxo-2*H*-chromen-4-yl acetate (3). To a stirred mixture of 7-*N*,*N*-dimethylamino-4-hydroxycoumarin **2** (1.0 g, 4.9 mmol) and triethylamine (0.5 g, 4.9 mmol) in methylene chloride (20 mL) was added acetyl chloride (0.4 g, 4.9 mmol) at 0 °C for 30 min. After completion of the reaction, the solvent was concentrated in vacuo. This mixture was poured into water. The solution was then extracted with dichloromethane twice. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes = 1:9) to give a brown solid in a 95% yield. Mp 110–111 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (d, J=9.0 Hz, 1H), 6.57 (dd, J=9.0, 2.4 Hz, 1H), 6.43 (d, J=2.4 Hz, 1H), 6.08 (s, 1H), 3.03 (s, 6H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 162.6, 159.4, 155.7, 153.3, 123.2, 108.8, 103.9, 99.0, 97.6, 77.4, 77.0, 76.6, 40.0, 21.1. HRMS (EI) *m*/*z* calcd for $C_{13}H_{13}NO_4$ 247.0846, found 247.0845 (M^+). IR ν (KBr) 3346, 1608, 893, 796 cm^{-1}.

4.3.3. 3-Acetyl-7-(dimethylamino)-4-hydroxy-2*H*-chromen-2-one (4). To a solution of compound **3** (3.2 g, 12.9 mmol) in methylene chloride (20 mL) were added KCN (1.6 g, 24.6 mmol) and a catalytic amount of 18-crown-6 at room temperature for three days. After completion of the reaction, the solvent was concentrated in vacuo. This mixture was poured into water. The solution was then extracted with dichloromethane twice. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes = 1:6) to give a red solid in an 85% yield. Mp 169–170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 17.64 (s, 1H), 7.82 (d, J=9.3 Hz, 1H), 6.63 (dd, J=9.3, 2.4 Hz, 1H), 6.37 (d, J=2.4 Hz, 1H), 3.12 (s, 6H), 2.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4, 177.9, 161.1, 157.0, 155.7, 126.7, 109.2, 103.2, 98.6, 96.8, 77.4, 77.0, 76.6, 40.1, 29.8. HRMS (EI) *m*/*z* calcd for $C_{13}H_{13}NO_4$ 247.0845, found 247.0853 (M^+). IR ν (KBr) 3406, 1726, 1619, 1423, 823, 768 cm^{-1}.

4.3.4. 2-(1-Acetoxyethylidene)-1,3-indandione (13). To a solution of 2-acyl-1,3-indandiones (500 mg, 2.66 mmol) and triethylamine (200 mg, 2.66 mmol) in dichloromethane (5 mL) was added acetyl chloride (270 mg, 2.66 mmol) at room temperature for 1 h. After completion of the reaction, the solvent was concentrated in vacuo. This mixture was poured into water. The solution was then extracted with dichloromethane twice. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes = 1:9) to give a yellow solid in a 90% yield. Mp 94–95 °C (lit.[15] 93–95 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95–7.94 (m, 1H), 7.89–7.88 (m, 1H), 7.79–7.76 (m, 2H), 2.63 (s, 3H), 2.41 (s, 3H).

4.4. General procedure for preparation of compounds 9 and 12

To a solution of 2-acetyl-3-hydroxycyclohex-2-enone (0.1 g, 0.65 mmol) and triethylamine (0.2 g, 1.75 mmol) in methylene chloride (5 mL) was added acetyl chloride (0.1 g, 1.62 mmol) at room temperature for three days. After completion of the reaction, the solvent was concentrated in vacuo. This mixture was poured into water. The solution was then extracted with dichloromethane twice. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography to give the desired product.

4.4.1. Acetic acid 2-(1-acetoxyvinyl)-3-oxo-cyclohex-1-enyl ester (9). Brown liquid. Yield 95%. ^{1}H NMR

($CDCl_3$, 300 MHz) δ 5.20 (d, J=1.8 Hz, 1H), 4.94 (d, J=1.8 Hz, 1H), 2.64 (t, J=6.3 Hz, 2H), 2.50 (t, J=6.3 Hz, 2H), 2.22 (s, 3H), 2.08 (s, 3H), 2.05 (quintet, J=6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.0, 168.4, 167.6, 167.0, 143.8, 125.4, 108.4, 37.1, 28.9, 20.8, 20.8, 20.2. HRMS (EI) *m/z* calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0849 (M^+). IR ν (KBr) 1763, 1685, 1368, 1204, 1011, 889 cm^{-1}.

4.4.2. Acetic acid 1-(4-hydroxy-2-oxo-2*H*-1-benzopyran-3-yl)vinyl ester (12). White solid. Yield 88%. Mp 109–110 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.48 (dd, J=7.8, 1.2 Hz, 1H), 7.36–7.28 (m, 2H), 5.42 (d, J=4.8 Hz, 1H), 5.41 (d, J=4.8 Hz, 1H), 2.45 (s, 3H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2, 166.6, 159.3, 156.0, 152.5, 143.1, 133.0, 124.5, 123.4, 116.7, 115.6, 114.6, 110.6, 20.6. HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_6$ 288.0634, found 288.0640 (M^+). IR ν (KBr) 1757, 1612, 1363, 1194, 1084, 765 cm^{-1}.

4.5. General procedure for preparation of compounds 15–18

To a solution of 2-acetyl-1,3-indandione (0.5 g, 2.7 mmol) in dichloromethane (5 mL) was added excess diazomethane at 0 °C. After completion of the reaction (monitored by TLC), the solvent was concentrated in vacuo. The crude product was purified by column chromatography to give the desired product.

4.5.1. 3-Benzoyl-7-dimethylamino-4-methoxy-4a,8a-dihydro-1-benzopyran-2-one (15). Yellow solid. Yield 75%. Mp 132–133 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J=8.1 Hz, 2H), 7.63 (d, J=9.0 Hz, 1H), 7.60–7.40 (m, 3H), 6.58 (dd, J=9.0, 2.1 Hz, 1H), 6.39 (s, 1H), 3.81 (s, 3H), 2.99 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.0, 165.0, 154.5, 153.2, 137.4, 133.2, 129.1, 128.3, 124.6, 108.7, 104.1, 96.6, 60.2, 39.6. HRMS (EI) *m/z* calcd for $C_{19}H_{17}NO_4$ 323.1158, found 323.1163 (M^+). IR ν (KBr) 1617, 1583, 1250, 833, 766 cm^{-1}.

4.5.2. 7-Dimethylamino-3-phenyl-5a,9a-dihydrofuro[3,2-*c*][1]benzopyran-4-one (16). Yellow solid. Yield 8%. Mp 187–188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.68 (dd, J=7.2, 1.5 Hz, 2H), 7.68 (d, J=8.7 Hz, 1H), 7.61 (s, 1H), 7.46–7.36 (m, 3H), 6.68 (dd, J=9.0, 2.4 Hz, 1H), 6.62 (d, J=2.4 Hz, 1H), 3.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 158.6, 154.8, 152.3, 139.4, 129.6, 128.5, 128.4, 127.9, 126.2, 121.6, 109.2, 104.2, 101.7, 98.3, 40.2. HRMS (EI) *m/z* calcd for $C_{19}H_{15}NO_3$ 305.1052, found 305.1047 (M^+). IR ν (KBr) 1711, 1376, 1113, 815, 755 cm^{-1}.

4.5.3. 2-(1-Methoxyethylidene)-1,3-indandione (17). White solid. Yield 15%. Mp 161–163 °C (lit.[13] 163–165 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83–7.79 (m, 2H), 7.67–7.64 (m, 2H), 4.08 (s, 3H), 2.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.0, 188.6, 179.0, 140.3, 139.4, 133.8, 133.5, 121.9, 121.8, 111.2, 56.2, 14.5.

4.5.4. 1-(1-Hydroxy-4-methoxynaphthalen-2-yl)ethanone (18). Yellow solid. Yield 40%. Mp 116–117 °C (lit.,[13] 118–120 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.75 (s, 1H), 8.45 (d, J=8.3 Hz, 1H), 8.19 (d, J=8.3 Hz, 1H), 7.69–7.55 (m, 2H), 6.80 (s, 1H), 3.97 (s, 3H), 2.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.7, 157.4, 147.4, 130.3, 129.7, 126.6, 125.9, 124.4, 121.9, 112.0, 100.9, 55.7, 27.0.

Acknowledgements

The authors would like to thank the National Science Council of Republic of China, Taiwan for financially supporting this research under contract no. NSC 93-2113-M-029-002.

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Tetrahedron 62 (2006) 9417–9422

[1,5]-Silatropic shifts in disilyl substituted indenes: an NMR spectroscopic and computational study

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Received 9 May 2006; revised 28 June 2006; accepted 13 July 2006
Available online 10 August 2006

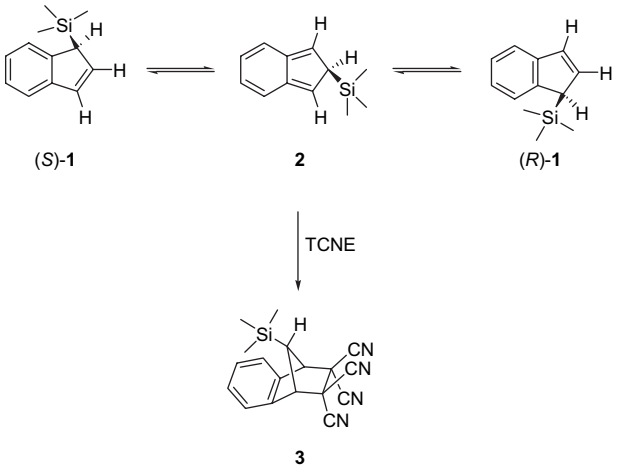
Abstract—The equilibrium profiles for [1,5]-silatropic shifts in a series of 1,3-/1,1-disilyl substituted indenes were studied by NMR and computational methods based on density functional theory. Both methods indicate higher activation parameters for the [1,5]-shifts than observed in monosilyl substituted indene analogues.

1. Introduction

In main group chemistry, migrations of R_3E substituents (E=Si, Ge, Sn) in organic molecules have been studied for several years.[1] Such substituents, especially when E=Si, often form essential parts of group 4 metallocene catalysts utilized for stereoselective polymerization of α-olefins.[2] Accordingly, there is considerable recent interest in the study of the dynamic and migratory processes in these compounds.

The migration of σ-bonded silyl fragments over indenyl surfaces was first reported over three decades ago.[3] The mechanism of this silicon migration can be explained by two successive [1,5]-sigmatropic shifts; molecule (*S*)-**1** interconverts to its enantiomer (*R*)-**1** via the *iso*-indene intermediate **2** (Scheme 1).[4] The aromaticity is lost in **2** and this highly reactive non-aromatic intermediate rapidly isomerizes to the more stable structure. While this intermediate is unstable it can be trapped with tetracyanoethylene as the Diels–Alder adduct **3**.[5]

The experimentally determined barrier energy for [1,5]-shifts in **1** is ~25 kcal mol^{-1}.[3a,c] In earlier work it has been demonstrated that the activation energy for the [1,5]-silatropic shifts in indenyl moieties can be decreased by 3–7 kcal mol^{-1} by fusing aromatic rings to the system.[6] Likewise, the activation energies for the [1,5]-silatropic shifts in several monosilyl substituted indene derivatives have been determined previously,[7] while just in few cases the corresponding shifts in disubstituted indenes have been studied. Davison and Rakita reported the activation energy



Scheme 1. [1,5]-Sigmatropic shifts in silyl substituted indenes.

for such [1,5]-silatropic shifts in 1,2-bis(trimethylsilyl)-indene (26 kcal mol^{-1})[3c] and 1-trimethyl-2-methylindene (26.5 kcal mol^{-1}),[3d,e] whereas the activation energy for silicon migration in 1,3-dimethyl-1-(trimethylsilyl)indene was reported by Stradiotto et al. (23 kcal mol^{-1}).[8] In the previous work, attempts have been made to determine the activation energies for the corresponding shifts in both 1,3-bis(trimethylsilyl)indene [(*R*/*S*)-**9**, vide infra][3c] and bis(trimethylsilyl)benz[*e*]indene[6a] by variable temperature or single selective inversion NMR technique. However, in neither of the cases could the coalescence temperature or the exchange of protons be observed.

In the context of our recent studies on the synthesis and functionalization of alkenyl substituted indenes[9] we have prepared the racemic bis(silyl)indenes (*R*/*S*)-**4** and (*R*/*S*)-**7**

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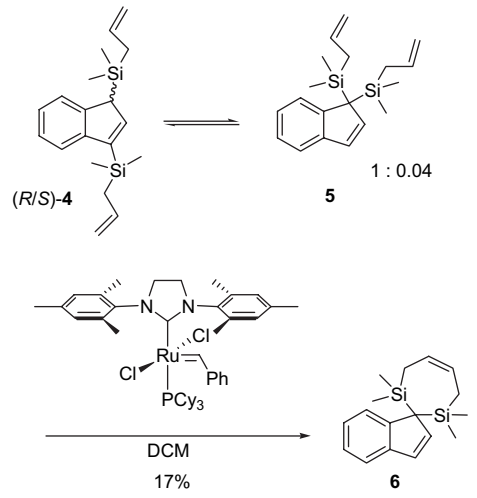
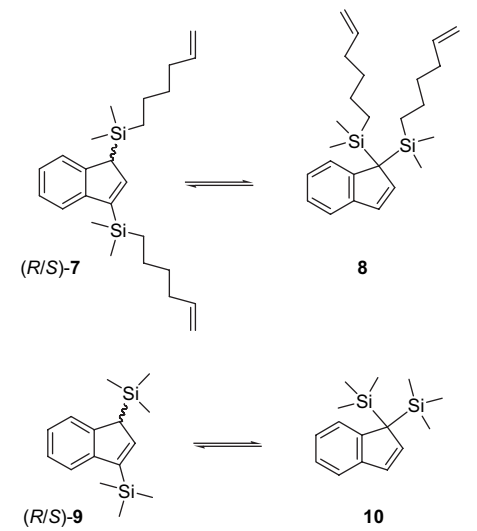
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.040

as displayed in Schemes 2 and 3, respectively.[9b] In both the cases, the initially formed, geminally substituted compounds **5** and **8** are expected to rearrange to their predominant 1,3-disubstituted analogues via [1,5]-silatropic shifts. When, however, the isolated 1:0.04 mixture from the synthesis of (*R*/*S*)-**4** and **5** was subjected to the Grubbs' second generation ruthenium metathesis catalyst (NHC)(PCy_3)Cl_2Ru=CHR,[10] instead of the expected 1,3-ring bridged product, the only ring-closure product spirocyclic 1,1-substituted indene **6** was isolated and obtained in fair yield (17%) (Scheme 2).[9b] Thus, during the course of the ring-closure, the amount of the 1,1-substituted compound must have been enriched. An alternative driving-force is that the seven-membered ring is more easily formed than the corresponding nine-membered ring, as only a slight bias in product stability would be required, even if the equilibrium is in favor of the 1,3-substituted form of (*R*/*S*)-**4**. It could also be considered that the 1,3-substituted isomer ring closes directly followed by the silatropic shifts, although this can be considered highly unlikely due to the imminent strain in the hypothetical nine-membered ring formed at first.[9b]



Scheme 2. [1,5]-Silatropic shifts in (*R*/*S*)-**4/5** and the corresponding ring-closing metathesis reaction with Grubbs' second generation catalyst.



Scheme 3. [1,5]-Silatropic shifts in (*R*/*S*)-**7/8** and (*R*/*S*)-**9/10**.

Considering the scarce amount of reports on silyl migration in disilylindenes[3c,6a] prompted us to study the energy and equilibrium profiles of the (*R*/*S*)-**4/5** mixture. By evaluation of the activation energy for the silyl migration in this system, we wished to determine whether the second silyl group facilitates the conversion between the two isomers by decreasing the activation energy for migration. This, in turn, could be the facilitating factor for the formation of the 1,1-spiro product in the metathesis reaction.[11] Studies of the equilibrium between (*R*/*S*)-**4** and **5** should also give more insights into the concentration of the geminal form, which is a precursor to the spiro compound **6**.

We present here a detailed study on the [1,5]-silatropic shifts in (*R*/*S*)-**4/5**, as well as its close analogues 1,3-/1,1-bis(hexenyldimethyl)silylindenes (*R*/*S*)-**7/8** and 1,3-/1,1-bis(trimethylsilyl)indenes (*R*/*S*)-**9/10**. The equilibria between the geminally and 1,3-substituted forms were studied with advanced NMR spectroscopic techniques and the connection between the equilibrium constant and free-energy was used to determine the direction of the reaction and the energetic difference between the equilibrating isomers. In addition, changes in enthalpy and entropy in the equilibria were determined. The activation parameters and thermodynamical equilibria were also obtained computationally by using density functional theory.

2. Results and discussion

2.1. NMR spectroscopic studies

The equilibrium constant at a given temperature was determined by dissolving the compound in question in 1,1,2,2-tetrachloroethane-d_2, letting the sample reach the thermal equilibrium and integrating the peaks corresponding to olefinic CH-resonances in the five-membered rings of both isomers. The equilibrium constants for dialkenylsilylindenes (*R*/*S*)-**4/5** and (*R*/*S*)-**7/8**, and for 1,3-/1,1-bis(trimethylsilyl)-indene (*R*/*S*)-**9/10** were measured at several temperatures between 64.5 (337.7 K) and 108.4 °C (381.6 K). By utilizing the basic equations of thermodynamics, the enthalpy change for the equilibrium was calculated from the slope of the straight line obtained by plotting ln K versus $1/T$ (Table 1). In addition, the changes in free-energy and entropy for the (*R*/*S*)-**4/5**, (*R*/*S*)-**7/8**, and (*R*/*S*)-**9/10** equilibria were calculated at 64.5 °C (337.7 K) (Table 1).

As expected, the enthalpy changes for (*R*/*S*)-**4/5**, (*R*/*S*)-**7/8**, and (*R*/*S*)-**9/10** were of the same order of magnitude. The ΔH obtained for the 1,3-/1,1-bis(trimethylsilyl)indene (*R*/*S*)-**9/10** equilibrium (0.44 kcal mol^{-1}) differs from the value reported earlier (2.1 kcal mol^{-1}).[3c] However, in contrast to

Table 1. Equilibrium parameters for (*R*/*S*)-**4/5**, (*R*/*S*)-**7/8**, and (*R*/*S*)-**9/10**

Equilibrating isomers	ΔH (cal mol^{-1})[a]	ΔG (kcal mol^{-1})[b]	ΔS (cal mol^{-1} K^{-1})[b]
(*R*/*S*)-**4/5**	−465	1.1	−4.5
(*R*/*S*)-**7/8**	−402	1.3	−5.0
(*R*/*S*)-**9/10**	−436	0.4	−2.4

[a] Error limit for $\Delta H \pm 1$ cal mol^{-1} based on linear regression analyses.
[b] Determined at 64.5 °C (337.7 K).

the earlier report, we observed that the rate of the [1,5]-silatropic shifts in these disilylindenes is *very low*, taking hours to reach the thermal equilibrium at low temperatures. The earlier work by Davison and Rakita reports that the equilibrium for (*R*/*S*)-**9**/**10** was reached in approximately 5 min.[3c] The difference in ΔH reported for this compound by us and Davison and Rakita most likely stems from the fact that in the earlier work the thermal equilibrium had not been reached at the time the equilibrium constants were measured.

All the values of free-energy were positive indicating that the reaction is favored toward the 1,3-disubstituted product (Schemes 2 and 3). This verifies the assumption that the initially formed, geminally substituted disilylindene rearranges to the 1,3-substituted analogue.[9b] By comparing the ΔG values for (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8** with the value obtained for (*R*/*S*)-**9**/**10** it can be observed that ΔG for (*R*/*S*)-**9**/**10** is approximately three times smaller than the values for (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8** (Table 1). Thus, the energy difference between the geminally substituted compound and its 1,3-substituted analogue is much larger for (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8** than in (*R*/*S*)-**9**/**10**. Consequently, the equilibrium concentration of the geminally substituted form is much larger in the case of 1,3-/1,1-bis(trimethylsilyl)indene (*R*/*S*)-**9**/**10** than in the cases of the dialkenylsilylindenes (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8**.

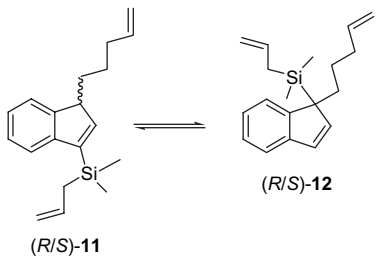
According to Davison and Rakita the (*R*/*S*)-**9**/**10** ratio at ambient temperature is approximately 1:1 whereas at higher temperatures the 1,3-isomer predominates.[3c] Our NMR studies show that in the case of (*R*/*S*)-**9**/**10**, the equilibrium concentration of the geminally substituted isomer indeed decreases on increasing the temperature but the ratio of **10** at ambient temperature is less than 50%, being approximately 38%.

The same trend was observed for the dialkenylsilylindenes (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8**; the equilibrium is driven toward the direction of the 1,3-substituted isomer at higher temperatures. When (*R*/*S*)-**4**/**5** is treated with the Grubbs' second generation Ru catalyst at ambient temperature, the formation of the spiro compound **6** (Scheme 2) can be explained as follows. While the initial mixture of (*R*/*S*)-**4**/**5** only contains 4% of compound **5**, a slow rearrangement toward the equilibrium containing approximately 19% of **5** takes place. Compound **5** then directly cyclizes to form **6** in the presence of the Grubbs' catalysts.

The dynamic processes can also be investigated by 2D EXSY NMR where the chemical exchange is detected before the occurrence of line broadening.[12] While the activation energies for the [1,5]-silatropic shifts in (*R*/*S*)-**4**/**5**, (*R*/*S*)-**7**/**8**, and (*R*/*S*)-**9**/**10** are far too high for reaching the coalescence points within the operational temperature limits of the NMR probe employed ($T \leq 134$ °C, 407 K), the occurrence of the [1,5]-silatropic shifts could nevertheless be demonstrated by exchange spectroscopy (EXSY). Thus, we investigated the dynamic behavior of (*R*/*S*)-**4**/**5**, (*R*/*S*)-**7**/**8**, and (*R*/*S*)-**9**/**10** by 2D EXSY NMR at several temperatures. In the cases of (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8**, the corresponding cross-signals could not be observed at temperatures below 134 °C (407 K) indicating that the exchange rate is slower than what is observable on the NMR time scale. The rate of exchange can be increased by raising the observation temperature, and for both compounds (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8** cross-signals between the exchanging C(1) and C(3) protons were detected by 2D EXSY NMR at 134 °C (407 K) with 0.5 s mixing time. For (*R*/*S*)-**9**/**10**, however, the exchange rate is faster and can be detected at lower temperatures providing cross-peaks between the exchanging C(1) and C(3) protons at 110 °C (383 K). For comparison with the results reported earlier, we measured the 2D EXSY spectrum for trimethylsilylindene (*R*/*S*)-**1** at 110 °C (383 K) and obtained clear cross-peaks between the exchanging C(1) and C(3) protons. Obviously, [1,5]-silatropic shifts take place in disilyl substituted indenes such as (*R*/*S*)-**4**/**5**, (*R*/*S*)-**7**/**8**, and (*R*/*S*)-**9**/**10**, but the rates of the rearrangements are slow, especially in the case of (*R*/*S*)-**4**/**5** and (*R*/*S*)-**7**/**8**. The results obtained indicate that the activation energy for the silicon migration in disilylindenes is higher than ~25 kcal mol^{-1}, which is the experimentally determined barrier for [1,5]-silatropic shifts in (*R*/*S*)-**1**.[3a,b] Corresponding results were obtained computationally, as described below.

As a further proof for the silatropic shifts, we attempted to trap the presumed *iso*-indene intermediates as Diels–Alder adducts in analogy to Scheme 1 by using the methods described earlier.[5b,7a,b] After five days of reaction time, only marginal amounts of the Diels–Alder products were formed as verified by mass spectrometry.[13] This may be due to the slow rates of the [1,5]-shifts in these compounds at ambient temperature, or simply the low stabilities of the corresponding *iso*-indene intermediates.

In the previous synthetic study, we also prepared the 1,3-disubstituted indene (*R*/*S*)-**11** having one alkyl and one silyl substituent (Scheme 4).[9b] Consequently, it was of interest to investigate the activation energy for the potential silyl migration in this compound as well. This could provide further information on whether the hypothetical equilibrium and silyl migration between (*R*/*S*)-**11** and (*R*/*S*)-**12** are either facilitated or slowed down by replacing one silyl group in the indenyl five-membered ring with an alkyl chain. Accordingly, 2D EXSY experiments were carried out at temperatures ranging from 100 to 134 °C (373–407 K) yielding no observable cross-peaks, most likely due to the slow reaction rates for [1,5]-shifts in these compounds. Thus, the activation barrier for [1,5]-silatropic shifts in (*R*/*S*)-**11** is much higher than in (*R*/*S*)-**4**/**5**, (*R*/*S*)-**7**/**8**, and (*R*/*S*)-**9**/**10**, which all bear in common two silyl subsituents. A possible contributing factor for the higher activation energy in (*R*/*S*)-**11** is the increased steric crowding in the 1,1-substituted analogue



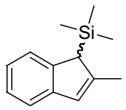
Scheme 4. Potential [1,5]-Silatropic shifts between (*R*/*S*)-**11** and (*R*/*S*)-**12**.

(*R*/*S*)-**12** resulting from the shorter bond length of the C–C (approx. 1.53 Å) bond as compared to the corresponding C–Si (approx. 1.87 Å) bond in compounds **5**, **8**, and **10**. This in turn could somewhat increase the energy difference and barrier for migration between the positional isomers (*R*/*S*)-**11** and (*R*/*S*)-**12**.

2.2. Computational studies

Theoretical calculations of some silyl shifts were carried out for comparison with the experiments. The transition state energies, enthalpies, entropies, and the reaction Gibb's energies ($\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, and ΔG, respectively) were calculated at 1 bar and 51.9 °C (325 K) for (*R*/*S*)-**1**, (*R*/*S*)-**4/5**, (*R*/*S*)-**9/10**, and 1-trimethylsilyl-2-methylindene (*R*/*S*)-**13** (Fig. 1). The results are given in Table 2. The earlier published activation energies for the [1,5]-silatropic shifts in (*R*/*S*)-**1** and (*R*/*S*)-**13**, determined using the variable temperature NMR technique, are well in line with our computational results.[3a,c–e] However, the theoretical calculations predicted rather different thermodynamic equilibria for (*R*/*S*)-**4/5** and (*R*/*S*)-**9/10** (ΔG=8.9 and 4.1 kcal mol^{-1}, respectively) compared to the results obtained experimentally.[14]

The transition state energy $\Delta G^{\ddagger}$ increases with the number or bulkiness of the substituents. The transition state energies for the [1,5]-silicon shifts are comparable to the experiment's, varying from 25.8 for (*R*/*S*)-**1** to 30.1 kcal mol^{-1} for (*R*/*S*)-**4/5**. The *iso*-indene intermediate structures resulting from [1,5]-silicon shifts in (*R*/*S*)-**9/10** and (*R*/*S*)-**4/5** are very unstable with ΔG being at 51.9 °C (325 K) and 1 bar, 21.1 and 28.2 kcal mol^{-1} compared to **9** and **4**, respectively. The corresponding ΔG for the equilibria between (*R*/*S*)-**1** and (*R*/*S*)-**13** is also high, being 17.3 and 26.0 kcal mol^{-1}, respectively. This is understandable, since the aromatic nature of the indene structure is lost in the *iso*-indene intermediates. As there exists two energetically different [1,5]-silatropic shifts in (*R*/*S*)-**9/10** and (*R*/*S*)-**4/5**, there are also two different transition states. The second transition state between the *iso*-indene intermediate and the geminal isomer is always the rate determining step being approximately 4 kcal mol^{-1} higher than the first transition state in (*R*/*S*)-**9/10** and (*R*/*S*)-**4/5**.



(*R*/*S*)-**13**

Figure 1. 1-Trimethylsilyl-2-methylindene (*R*/*S*)-**13**.

Table 2. Activation parameters for the [1,5]-silatropic shifts in (*R*/*S*)-**1**, (*R*/*S*)-**4/5**, (*R*/*S*)-**9/10**, and (*R*/*S*)-**13** calculated at the B3LYP/cc-pVDZ level

Equilibrating isomers	$\Delta G^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})
(*R*/*S*)-**1**	25.8	−4.2	24.4
(*R*/*S*)-**13**	28.0	−6.2	26.0
(*R*/*S*)-**9/10**	29.6	−6.3	27.6
(*R*/*S*)-**4/5**	30.1	−5.7	28.2

3. Summary and conclusions

We have presented here the equilibrium profiles for [1,5]-silatropic shifts in a series of disilyl substituted indenes by determining the equilibrium constants for these migrations at several temperatures. The equilibrium parameters for bis-(trimethylsilyl)indene (*R*/*S*)-**9/10** are well in line with the results published earlier.[3c] For the di(alkenylsilyl)indenes, however, the activation energies were higher than what we expected at the outset of this study, based on purely sterical arguments. In the cases of (*R*/*S*)-**4/5** and (*R*/*S*)-**7/8**, both of which contained silyl substituents larger than TMS, the geminally substituted 1,1-isomer became considerably more unfavorable than in the case of the 1,1-TMS-substituted analogue **10**. The equilibrium amounts of the 1,1-substituted compounds **5** and **8** at ambient temperature were under 20% compared to 38% of **10** under the same migratory conditions. The larger substituents at silicon thus bear a considerable effect on both the equilibrium and the energetic differences between the exchanging isomers. Additionally, we studied the [1,5]-silatropic shifts in (*R*/*S*)-**4/5**, (*R*/*S*)-**7/8**, and (*R*/*S*)-**9/10** by utilizing 2D EXSY NMR techniques. It can be concluded that the activation energies for (*R*/*S*)-**4/5**, (*R*/*S*)-**7/8**, and (*R*/*S*)-**9/10** were higher than the activation energy for 1-(trimethylsilyl)indene (*R*/*S*)-**1**. A similar trend was also observed computationally. The additional silyl substituent in position C(3) of the indene increases the barrier for silicon migration. The activation barrier for migration is further increased by replacing one of the silyl substituents with an alkyl group as in (*R*/*S*)-**11**. In this case, the rate of the [1,5]-silatropic shifts was lower than could be detected with the NMR techniques available. The computational studies verify the conclusions made from the 2D EXSY experiments. The additional silyl substituent at C(3) position possibly unstablilizes the *iso*-indene intermediate leading to an increase in the activation energy for the [1,5]-silatropic shift in disilylindenes. The substituents on the silicon do not significantly affect the activation energy, the difference in activation energy of (*R*/*S*)-**4/5** and (*R*/*S*)-**9/10** being only 0.5 kcal mol^{-1}, as determined by the calculations.

4. Experimental

4.1. General considerations

The compounds investigated, (*R*/*S*)-**4/5**,[9b] (*R*/*S*)-**7/8**,[9b] (*R*/*S*)-**9/10**,[3c] (*R*/*S*)-**11/12**,[9b] and 1*H*-inden-1-yltrimethylsilane (*R*/*S*)-**1**,[15] were prepared as previously described. NMR spectra were recorded using a Bruker Avance 600 (^{1}H NMR 600 MHz) spectrometer equipped with Magnex 14.1 T standard bore superconducting magnet and Bruker Avance 400 (^{1}H NMR 400 MHz) spectrometer equipped with Oxford 9.4 T standard bore superconducting magnet. The probe used in all the experiments was Bruker 5 mm straight broad band BBO-probe with *z*-gradient. In all the cases, NMR spectra were referenced against residual ^{1}H-impurities in the solvent. The NMR spectra were recorded in δ values with 1,1,2,2-tetrachloroethane-d_2 as the solvent. Sample temperatures were maintained throughout the measurements by using the Bruker BVT-3000 temperature controlling unit with BCU-05 precooling unit. The temperature calibration of the instrument was performed externally by using 80%

ethylene glycol in DMSO. The mass spectrometric analyses of the Diels–Alder products were performed on an Agilent 1100 Series LC/MSD SL Trap Instrument. The compounds were analyzed by direct inlet infusion to the source by a syringe pump at a rate of 5 μL min^{-1} and at a concentration of about 10 mg mL^{-1}. The operation parameters were as follows: drying gas temperature, 325 °C (598 K); drying gas flow rate, 5 L min^{-1}; nebulizer gas pressure, 15 psi. The instrument was operated in positive mode.

4.2. 2D EXSY measurements

2D EXSY spectra were recorded in the phase-sensitive mode using the pulse sequence for NOESY (90°–t_1–90°–t_m–90°–ACQ).[12] In a typical experiment, 256 increments were recorded in the f_2 dimension in 2K data points. Each increment was acquired in 8–16 scans over a 6.8 kHz spectral width. The acquired data were Fourier transformed with qsine window function in both f_1 and f_2. The relaxation delay was set to 2 s. Experiments were carried out at temperatures ranging from 100 to134 °C (373–407 K) using 1,1,2,2-tetrachloroethane-d_2 as the solvent. Mixing times ranging from 0.3 to 3 s were used. The best results were obtained with a 0.5 s mixing time.

4.3. Computational details

All of the stationary points on the potential energy surfaces were optimized at the DFT level of the theory. The Becke three-parameter hybrid method[16] with the Lee–Yang–Parr correlation functional approximation (B3LYP)[17] and the Dunning correlation consistent polarized valence double-ξ (cc-pVDZ) basis set were used.[18,19] All the calculations were carried out spin restricted. Vibrational analyses were carried out at the same level of theory to prove that the optimized structures are true minima (as no negative frequencies were found) or transition states (when only one negative frequency was found relevant to the silicon shift). Vibrational analysis (scaled by 0.9806,[20] 1 bar, 325 K) provided also thermodynamic contributions to the electronic energies to obtain $\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, and ΔG. In the case of (*R*/*S*)-**4**/**5**, potential minima conformations with respect to the allyl substituents were optimized by a grid search using Sybyl 7.1 software[21] and Tripos force field as implemented in the software. Found minima structures were used as starting geometries for the DFT optimization. All calculations were done with the Gaussian98/03 software.[22]

Acknowledgements

Financial support to S.S. from the Swedish Academy of Engineering Sciences in Finland is gratefully acknowledged. The computational studies reported in this work are part of the activities at the Åbo Akademi Process Chemistry Centre within the Finnish Centre of Excellence Programme (2000–2011) by the Academy of Finland. Financial support from the Academy of Finland is gratefully acknowledged by V.N. (project no. 212620). We also thank Prof. Jorma Mattinen, M.Sc. Lotta Salste, and Mrs. Päivi Pennanen for their assistance with the thermodynamic calculations, NMR, and MS analyses. Resources provided by CSC, the Finnish IT Center for science, are also kindly acknowledged.

Supplementary data

Plots of ln *K* versus 1/*T* for (*R*/*S*)-**4**/**5**, (*R*/*S*)-**7**/**8**, and (*R*/*S*)-**9**/**10** and 2D EXSY spectra for (*R*/*S*)-**4**/**5**, (*R*/*S*)-**7**/**8**, (*R*/*S*)-**9**/**10**, and 1*H*-inden-1-yltrimethylsilane (*R*/*S*)-**1** as well as a table reporting the ΔG for (*R*/*S*)-**9**/**10** obtained with various computational methods are available from the authors as supplementary material free of charge. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.040.

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14. It is notable that the calculated Gibb's free energies defining the equilibrium for the [1,5]-silatropic shifts in (*R*/*S*)-**9/10** as well as in (*R*/*S*)-**4/5** are far too high compared to the experimentally obtained values reported in Table 1. The ΔG and difference in the electronic energy ΔE were therefore calculated for (*R*/*S*)-**9/10** with several methods and are tabulated in Supplementary data with related discussion.
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Regio- and stereoselective double alkylation of β-enamino esters with organolithium reagents followed by *one-pot* reduction: convenient method for the synthesis of tertiary γ-amino alcohols

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Received 6 April 2006; revised 26 June 2006; accepted 13 July 2006
Available online 10 August 2006

Abstract—An easy, high yielding and stereoselective procedure for the preparation of tertiary γ-amino alcohols starting from β-enamino esters is presented. In this procedure, the double alkylation of β-enamino esters with organolithium reagents is followed by *one-pot* reduction with sodium borohydride in methanol/acetic acid. A hypothesis of mechanism is given, explaining the observed diastereoselectivity through molecular modeling. The configuration of the products was determined by ^{1}H NMR spectroscopy coupled with conformational analysis.

1. Introduction

A field of great interest in modern organic chemistry is the development of efficient enantioselective catalysts applicable to a wide range of reactions.[1–3] In previous studies[4,5] we have found that a substoichiometric amount of enantiopure aminoalkyl phenols and aminoalkyl naphthols accelerates the alkylation of aldehydes with alkylzincs, affording the corresponding alcohols in good enantiomeric purity. These chiral ligands are stable and highly accessible compounds, obtained by stereoselective reduction[6] or alkylation[7,8] of the corresponding 2-imidoyl phenols, or by aminoalkylation of naphthols.[9,10] Similarly to amino phenols, γ-amino alcohols are efficient chelating agents applicable in asymmetric synthesis promoted by chiral metallic catalyst. In addition γ-amino alcohols are useful building blocks in the synthesis of many natural products, pharmaceuticals, and compounds of biological interest.[11–17] Known procedures for the synthesis of γ-amino alcohols include reduction of isoxazoles and isoxazolines,[18] β-amino carbonyl compounds[19,20] or enaminones,[21,22] reductive amination of β-hydroxy ketones via Schiff bases,[23] or by in situ reduction of the lithiated β-hydroxy imine obtained by directed aldol condensation developed by Wittig.[24–28] All these reductive methods produce only secondary or primary γ-amino alcohols.

The preparation of tertiary γ-amino alcohols is known within the literature but the number of reports are limited.[29–35] We have proposed a general procedure for the preparation of tertiary γ-amino alcohols starting from β-enamino ketones,[36] and to the best of our knowledge other procedures starting from β-enamino esters are not known. In this paper, the scope and limitations of alkylation of β-enamino esters with organolithium compounds are presented as a method for the efficient and diastereoselective preparation of tertiary γ-amino alcohols.

2. Results and discussion

A mild and general method for the regio- and stereoselective synthesis of functionalized tertiary γ-amino alcohols (**2**) proceeds through the double alkylation of β-enamino esters (**1**) with alkyllithium reagents, followed by one-pot reduction of the intermediate dilithium β-hydroxy imines. This double alkylation works well with organolithium reagents in toluene at 0 °C or at room temperature, without the assistance of a Lewis acid. Grignard reagents under these conditions were unreactive. A number of examples were carried out using various organolithium reagents with differently functionalized β-enamino esters and the results are summarized in Table 1. The addition of organolithium reagents to enamino esters under these conditions is regioselective: the double alkylation occurs exclusively to the carbonyl group and not to the imine function.[37,38]

As shown in Table 1, the reduction occurs generally with good yields and *syn* diastereoselectivity in the case of compounds **2k–p**. The overall yields are very good when the R^3 substituent is a phenyl group (Table 1, entries 1–4) while

Keywords: β-Enamino esters; γ-Amino alcohols; Alkylation; Reduction.
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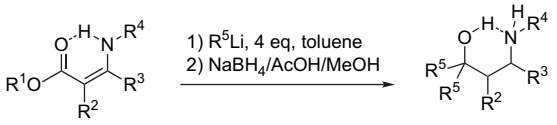
doi:10.1016/j.tet.2006.07.044

Table 1



1a-i **2a-p**

Entry	1	R^1O	R^2	R^3	R^4	2	R^5	T (°C)	Time (h)	Yield (%)[a]	d.r. (*syn*/*anti*)
1	**1a**	EtO	H	Ph	Ph	**2a**	Me	20	2	90	—
2	**1a**	EtO	H	Ph	Ph	**2b**	Bu	0	1	88	—
3	**1a**	EtO	H	Ph	Ph	**2c**	*i*-Pr	0	1	88 (42)[b]	—
4	**1a**	EtO	H	Ph	Ph	**2d**	Ph	20	1	91	—
5	**1b**	BnO	H	Me	Ph	**2e**	Bu	0	1	49	—
6	**1b**	BnO	H	Me	Ph	**2f**	*i*-Pr	0	1	59	—
7	**1c**	EtO	H	Pr	Ph	**2g**	Bu	0	1	57	—
8	**1d**	EtO	H	Ph	Bn	**2h**	Bu	0	1	65	—
9	**1e**	EtO	H	Ph	R*[c]	**2i**	Bu	20	1	47	73/27[d]
10	**1f**	EtO	Me	Me	Ph	**2j**	Bu	0	1	55	32/68
11	**1g**	EtO	$(CH_2)_3$		Ph	**2k**	Me	50	5	62	64/36
12	**1g**	EtO	$(CH_2)_3$		Ph	**2l**	Bu	0	1	72 (55)[b]	64/36 (76/24)[b]
13	**1h**	EtO	$(CH_2)_3$		Bn	**2m**	Bu	0	1	52	87/13
14	**1i**	EtO	$(CH_2)_4$		Ph	**2n**	Me	20	3	68	69/31
15	**1i**	EtO	$(CH_2)_4$		Ph	**2o**	Bu	0	1	89	65/35
16	**1i**	EtO	$(CH_2)_4$		Ph	**2p**	*i*-Pr	0	1	85	51/49

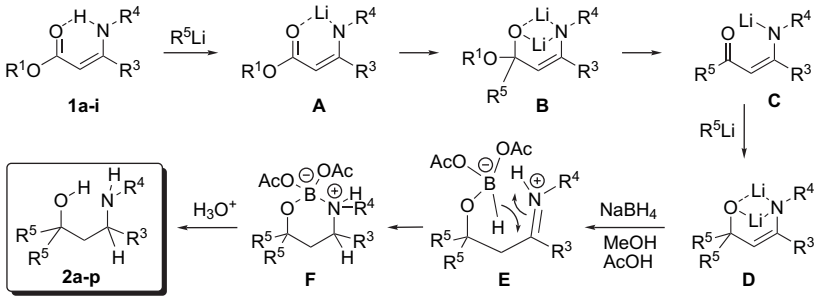
[a] Combined yields of the two isolated diastereomers.
[b] Reduction performed in absence of acetic acid.
[c] R*-NH_2=(*R*)-1-phenylethylamine.
[d] (2*S*,1′*R*)/(*R*,*R*) d.r.

they decreases in the presence of aliphatic groups (entries 5–7). β-Enamino esters derived from aniline (R^4=Ph) present a more electrophile ester function toward the organolithium reagents. Starting from β-enamino ester **1e**, that contains the chiral auxiliary (*R*)-(+)-phenylethylamino group, the reaction affords the amino alcohol (2*S*,1′*R*)-**2i** with reasonable diastereoisomeric excess, and the pure diastereomer can be obtained by flash chromatography. β-Enamino esters **1g–i** afford the amino alcohols *syn*-**2k–p** as major diastereomers (see Table 1).

In the hypothesized mechanism, depicted in Scheme 1, the first metalation of β-enamino esters **1a–i** affords the intermediate **A**, in which the chelated lithium atom enhances the electrophilicity of the ester function, making the addition of a second alkyllithium molecule easier. The dilithiated intermediate **B** eliminates lithium alkoxide with formation of the lithiated enamino ketone **C**. β-Enamino ketones **3** (see Scheme 3) can be isolated in some cases, when only 2.5 equiv of alkyllithium are used.[36] Generally, the lithiated β-enamino ketone **C** is more reactive with respect to the intermediate **A** and adds an organolithium molecule again, forming the intermediate **D**.[17] The *one-pot* reduction of **D** to the γ-amino alcohol **2a–p** occurs intramolecularly through the intermediate **E**.

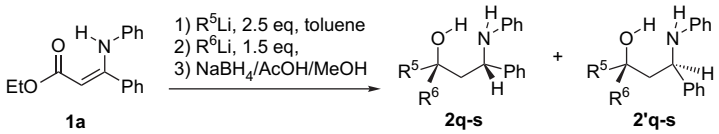
The presence of acetic acid in the reaction mixture in the reduction stage is important, because it allows a faster reduction and better yields in the final γ-amino alcohol **2** than the reduction conducted only in methanol. Anyway in this second case a higher diastereomeric excess is observed (see Table 1, entries 3 and 13 and Table 2, entry 3). After quenching the intermediate lithium alkoxide (**D**) with acid (saturated aqueous NH_4Cl), the free hydroxy imine (**4**) can be isolated (see Scheme 3), but its reduction with sodium borohydride in methanol resulted in lower yields of the γ-amino alcohol (**2**) because the free β-hydroxy imine (**4**) is unstable and dissociates spontaneously into the ketone **10** and imine **11** through a retroaldolic type process, as described in Scheme 2.[39]

On the other hand, the *one-pot* reduction of the reaction mixture with sodium borohydride, after methanol quenching only, does not take place. On the basis of these observations,



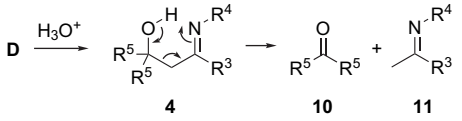
Scheme 1.

Table 2



Entry	1	Step 1			Step 2			2	Yield (%)[a]	d.r. (**2**/**2′**)
		R^5	T (°C)	Time (min)	R^6	T (°C)	Time (min)			
1	**1a**	Ph	0	30	Bu	0	60	**2q**	49	73/27
2	**1a**	Ph	0	30	*i*-Pr	0	60	**2r**	64	86/14
3	**1a**	*t*-Bu	0	60	Bu	20	60	**2s**	77 (41)[b]	84/16 (93/7)[b]

[a] Combined yields of the two diastereomers isolated.
[b] Reduction performed in absence of acetic acid.

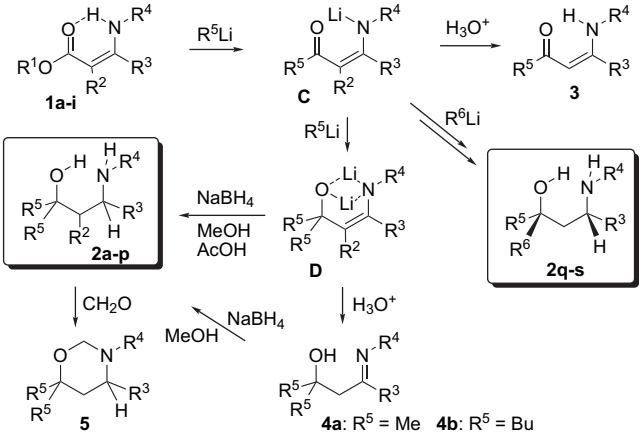


Scheme 2.

the more convenient *one-pot* reduction with sodium borohydride in methanol and acetic acid was chosen.

The *syn* stereochemistry of the hydride transfer can be explained by considering that the aminoborane complex *syn*-**F** is more stable than the corresponding *anti*-**F** (see the PM3 semiempirical level optimized geometries and the relative formation enthalpies in Figure 1).[40] The proposed mechanism is consistent with literature reports[41,42] and the *anti* stereochemistry of the products obtained reflects the intramolecular nature of the reaction. *syn* Products are generally obtained by intermolecular processes.[43]

Generally, the addition of the organometallic reagents to the intermediate lithium enamino ketones (**C**) is faster than the first addition. The intermediate enamino ketones are not isolable even with the use of a stoichiometric amount (2.5 equiv) of the organolithium reagent. Only when phenyllithium or *tert*-butyllithium is used, the preparation of the intermediate β-enamino ketones is possible with good yields[44] (see Scheme 3). This chemoselectivity was utilized for the stereoselective formation of a new stereogenic center at the quaternary carbinolic atom by the addition of a second different organolithium reagent on the intermediate enamino ketone (see Table 2). From the reduction step γ-amino alcohols **2q–s** as major diastereomers were obtained, resulting from the attack of the hydride from the same side of the less bulky group, that is, the R^6 substituent.



Scheme 3.

In the early phase of this research, the possibility of the synthesis of the γ-amino alcohol **2** by inverting the alkylation–reduction sequence was evaluated. As shown in Scheme 4, the β-amino esters **6a**,**b**, obtained by the reduction of the β-enamino esters **1a**,**d**,[45] were treated with *n*-butyllithium. From this sequence, the γ-amino alcohols **2b**,**h** are obtained

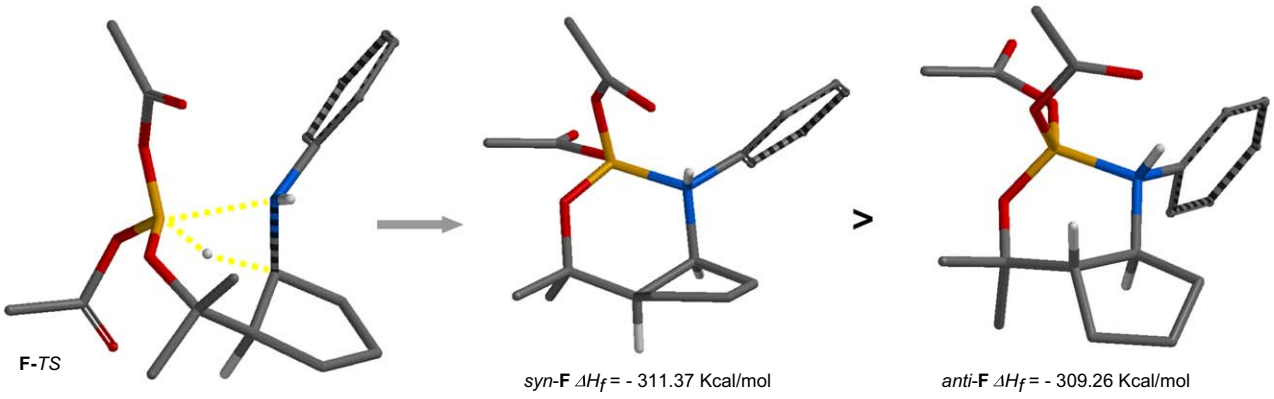
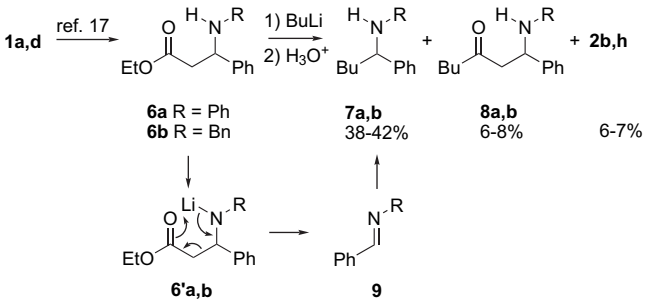


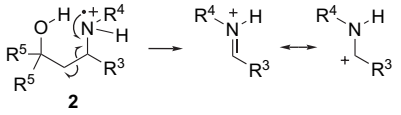
Figure 1. Transition structure for the intramolecular reduction of the β-hydroxy imine through the intermediate **E** with the formation of the thermodynamically more stable aminoborane complex *syn*-**F**.

in very low yields (6–7%). The amines **7a**,**b**, obtained as the main product, are formed by alkylation of the imine **9a**,**b**, derived by the decomposition of the lithiated β-amino ester **6′a**,**b** through a retroaldol pathway, as depicted in Scheme 4.



Scheme 4.

The molecular ion peak in the EI Mass Spectrometry of the β-amino alcohols (**2**) is usually quite weak. The base peak frequently results from C–C cleavage of α–β bond next to the nitrogen atom (see Scheme 5 and Section 5). This preferential fragmentation pathway is useful and routinely used to distinguish the possible regioisomers.



Scheme 5.

3. Stereochemistry

The diastereoisomeric ratio was calculated by integration of the ^{1}H and ^{13}C NMR data from the crude reaction mixture. Separation of pure diastereoisomers was carried out by fractional crystallization or by flash column chromatography.

The configuration of the stereogenic centers of the γ-amino alcohols **2** was assigned by interpreting the chemical shifts' general trend observed in ^{1}H NMR spectra of the isolated isomers on the basis of the more stable conformations calculated by molecular modeling.[40]

In the γ-amino alcohols **2**, an intramolecular hydrogen bond between the proton of the hydroxy group and the nitrogen atom was observed, which makes the cyclic chair conformation rigid and stabilizes the molecule in a conformation similar to that of the corresponding 1,3-tetrahydro oxazine (**5**), as reported also in literature.[22,46]

The attribution of the relative *syn*/*anti* configuration for products **2k**–**p** was made on the basis of N-C*H* signals in ^{1}H NMR for both diastereomers. In the major diastereomers *syn*-**2k**–**p** this proton results in a broad singlet with $W_{1/2}$=8.5–5.3 Hz. In the minor *anti*-**2k**–**m**, the same proton results upshifted by about 0.05–0.19 ppm with a $^{3}J_{ax-ax}$ of 7.2–8.0 Hz. Analogously in the minus diastereomers, *anti*-**2n**–**p**, the N-C*H* proton is upshifted by about 0.47–0.71 ppm with a $^{3}J_{ax-ax}$ of 10.3–10.7 Hz.

In the case of the products (*R**,*R**)-**2q** and (*R**,*S**)-**2q**, the relative configuration of the chiral centers was assigned on the basis of NOE experiments on the corresponding 1,3-tetrahydro oxazine derivative **5q**. The (*R**,*S**) relative configuration was attributed to the diastereomer that showed a strong NOE effect exerted by H-4 (geminal to the phenyl group) on the three nearer methylene protons H-2 and H-5 of the oxazine ring and H-1′ in the lateral butyl chain. Molecular modeling confirmed that in the more stable conformation all these protons are very close to each other, as shown in Figure 2. The (*R**,*R**) relative configuration was attributed to the other diastereomer that presented, instead of the NOE effect, a strong upshift of 0.55 ppm for the H-4 signal with respect to the corresponding proton of the (*R**,*S**) diastereomer. In the more stable conformation the phenyl ring in 6 assumes a position such as to exert a shielding effect on H-4, as shown in Figure 2.

In addition, the absolute configurations of both diastereomers of γ-amino alcohols **2i** were attributed through 1,3-tetrahydro oxazine derivatives **5i**, whose more stable conformations are depicted in Figure 3 and are in agreement with the ^{1}H NMR spectra. In these spectra the H-4 presents ^{3}J values of 11.0 and 11.5 Hz, typical of a *trans*-diaxial coupling, and an axial–equatorial ^{3}J values of 4.0 and 4.2 Hz, respectively. The (*R*,*R*) absolute configuration was attributed to the diastereomer that showed H-2 and H-4 upshifted

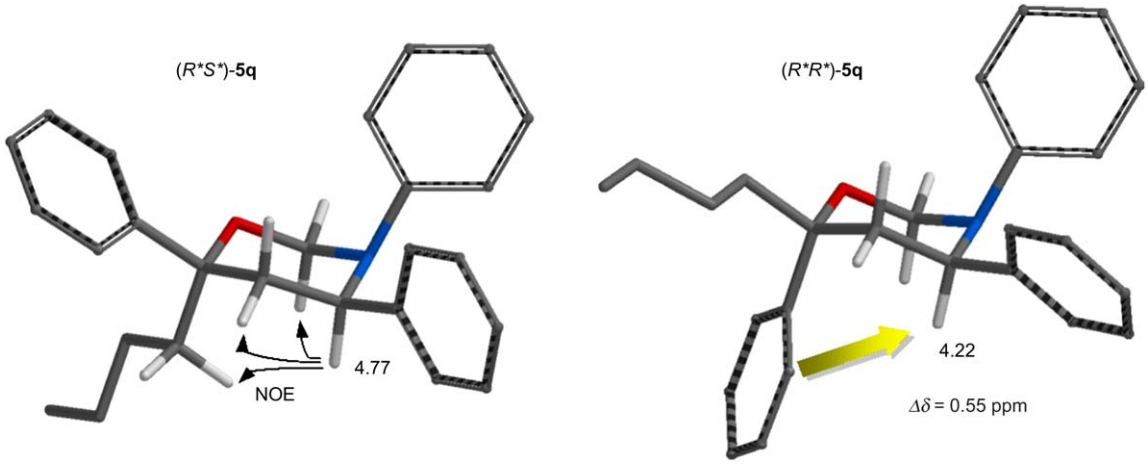


Figure 2. Models for the more stable conformation of **5q** diastereomers.

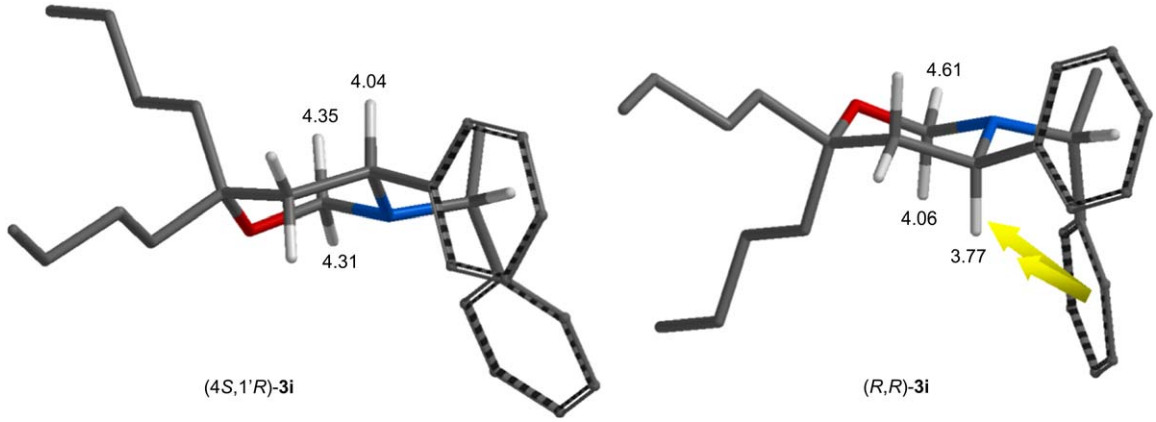


Figure 3. Models for the more stable conformation of **3i** diastereomers.

signals, of 0.25 and 0.27 ppm, respectively, due to the 1′-phenyl group arranged in the position depicted in Figure 3.

The relative trans configuration of (*R**,*R**)-**5j** is attributed on the basis of N-C*H* proton at 3.34 ppm with a $^{3}J_{ax-ax}$ value of 10.2 Hz, that is upshifted by 0.35 ppm with respect to the corresponding proton of *cis*-(*R**,*S**)-**5j**, at 3.69 ppm, with a ^{3}J value of 5.7 Hz.

4. Conclusion

In summary, an easy, general and stereoselective method for the direct preparation of tertiary γ-amino alcohols from β-enamino esters in good yields and satisfactory diastereomeric excess has been developed. The methodology consists of the double alkylation of β-enamino esters **1** with organolithium reagents followed by the *one-pot* reduction of the reaction mixture with sodium borohydride in methanol/acetic acid. The opportune choice of the reaction conditions and reagents enables the generation of a quaternary chiral center on the carbon atom bonded to the hydroxy function. Easily available starting materials and practical experimental conditions allow the facile preparation of these chiral pre-catalysts.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated using residual unadulterated solvents as the internal reference. Coupling constants are given in hertz. IR spectra were recorded using FTIR apparatus.

5.2. Materials and solvents

All reagents were commercially available, were purchased at the highest quality, and were purified by distillation when necessary. Hexane and toluene were distilled and stored on sodium wires before use. The following organolithium reagents were used: MeLi (1.6 M solution in diethylether), BuLi (2.5 M solution in hexane), PhLi (1.8 M solution in cyclohexane/diethylether 70:30), *i*-PrLi (1.7 M solution in pentane).

5.3. Synthesis of β-enamino esters 1a–i

β-Enamino esters **1** were prepared by condensation of β-ketoesters with amines according to standard literature methods.[47] β-Enamino esters **1b**,**c**,**g–i** were prepared in solventless way by mixing the β-ketoester and the amine in equimolecular amounts and stirring the mixture for 2–18 h at room temperature until TLC or GC analysis of the mixture revealed the complete consumption of the starting materials. After this time the reaction mixture was dissolved in *n*-hexane, dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the resulting crude β-enamino ester was purified by crystallization or filtration on SiO_2 with a 97:3 cyclohexane/ethyl acetate mixture as eluent.

5.4. General procedure for the alkylation and *one-pot* reduction of β-enamino esters 1: synthesis of γ-amino alcohols 2a–p

The β-enamino esters **1a–i** (1 mmol) were dissolved in toluene (3 mL), under nitrogen atmosphere, then was added the organolithium reagent (4.0 mmol); according to the reaction conditions and reagents reported in Table 1. Then the reaction mixture was quenched with methanol (1 mL) and concentrated under reduced pressure. The crude mixture was dissolved again in methanol (4 mL) at 0 °C and acetic acid (3 mL) and then $NaBH_4$ (4 mmol) were added in portions. After 1 h the mixture was treated with Na_2CO_3, until basic pH was reached, and extracted with dichloromethane (2×20 mL). The organic layer was dried with anhydrous Na_2SO_4, then filtered and the solvent was removed under reduced pressure. Chromatographic separation of the crude oil on silica gel with AcOEt/cyclohexane (3:97–20:80 v/v) afforded the pure γ-amino alcohols. Spectral data of products **2a–p** are as follow.

5.4.1. 4-Anilino-2-methyl-4-phenylbutan-2-ol [2a]. Colorless oil; IR (Neat) ν 3368, 1602, 1500, 1314, 1269, 751, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H, *Me*), 1.42 (s, 3H, *Me*), 1.84 (dd, 1H, J=14.8, 3.3 Hz, H'_b), 2.01 (dd, 1H, J=14.8, 10.9 Hz, H_b), 2.85 (br s, 1H, N*H*), 4.30 (br s, 1H), 4.62 (dd, 1H, J=10.9, 3.3 Hz, H_c), 6.50–6.70 (m, 3H),

7.05–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 28.2, 32.3, 50.9, 56.7, 71.6, 114.8, 118.3, 126.2, 127.2, 129.0, 129.3, 144.8, 147.4; MS (EI, 70 eV): *m/z* 255 (M^+, 14), 182 (100), 104 (14), 93 (22), 77 (22). Anal. Calcd for $C_{17}H_{21}NO$ (255.4): C 79.96; H 8.29; N 5.49. Found: C 79.74; H 8.13; N 5.56.

5.4.2. 1-Anilino-3-butyl-1-phenylheptan-3-ol [2b]. Colorless oil; IR (Neat) ν 3370, 1602, 1500, 1317, 1268, 750, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J=6.8 Hz, *Me*), 0.96 (t, 3H, J=6.6 Hz, *Me*), 1.20–1.53 (m, 10H), 1.58–1.75 (m, 2H), 1.81 (dd, 1H, J=15.0, 3.7 Hz, H'_b), 1.93 (dd, 1H, J=15.0, 10.1 Hz, H_b), 2.60 (br s, 1H, N*H*), 4.55 (dd, 1H, J=10.1, 3.7 Hz, H_c), 4.95 (br s, 1H, O*H*), 6.50–6.70 (m, 3H, Ar-*H*), 7.00–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 23.5, 23.6, 25.6, 26.9, 38.0, 40.9, 47.5, 56.1, 75.4, 114.7, 118.1, 126.2, 127.1, 128.9, 129.2, 145.1, 147.5; MS (EI, 70 eV): *m/z* (%) 339 (M^+, 9), 282 (2), 182 (100), 104 (8), 93 (12), 77 (10). Anal. Calcd for $C_{23}H_{33}NO$ (339.5): C 81.37; H 9.80; N 4.13. Found: C 81.21; H 9.89; N 4.01.

5.4.3. 1-Anilino-3-isopropyl-4-methyl-1-phenylpentan-3-ol [2c]. Colorless oil; IR (Neat) ν 3366, 1602, 1499, 1308, 1265, 752, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J=7.0 Hz, *Me*), 1.01 (d, 3H, J=7.0 Hz, *Me*), 1.10 (d, 3H, J=7.0 Hz, *Me*), 1.15 (d, 3H, J=7.0 Hz, *Me*), 1.80–2.16 (m, 4H), 3.41 (br s, 1H, N*H*), 4.66 (br s, 1H, O*H*), 4.71 (dd, 1H, J=9.5, 4.4 Hz, H_c), 6.60–6.80 (m, 3H, Ar-*H*), 7.05–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 17.5, 17.7, 18.0, 18.6, 35.2, 36.2, 40.8, 56.6, 77.7, 115.6, 119.0, 126.1, 127.3, 129.0, 129.3, 114.8, 147.0; MS (EI, 70 eV): *m/z* (%) 311 (M^+, 4), 268 (2), 182 (100), 114 (6), 104 (8), 93 (20), 77 (22), 43 (15). Anal. Calcd for $C_{21}H_{29}NO$ (311.5): C 80.98; H 9.38; N 4.50. Found: C 81.13; H 9.49; N 4.31.

5.4.4. 3-Anilino-1,1,3-triphenylpropan-1-ol [2d]. White crystals; mp 128–130 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3325, 1601, 1496, 1308, 1260, 753, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.66 (dd, 1H, J=14.8, 11.0 Hz, H_b), 2.86 (dd, 1H, J=14.8, 2.0 Hz, H'_b), 4.46 (dd, 1H, J=11.0, 2.0 Hz, H_c), 4.50 (br s, 1H, N*H*), 5.35 (br s, 1H, O*H*), 6.40–6.80 (m, 3H, Ar-*H*), 7.00–7.60 (m, 17H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 49.1, 57.2, 78.9, 116.4, 119.9, 125.9, 126.1, 126.5, 127.1, 127.2, 127.5, 128.5, 128.6, 129.0, 129.3, 143.6, 146.3, 146.6, 147.8; MS (EI, 70 eV): *m/z* (%) 379 (M^+, 3), 269 (6), 180 (100), 165 (35), 77 (44). Anal. Calcd for $C_{27}H_{25}NO$ (379.5): C 85.45; H 6.64; N 3.69. Found: C 85.43; H 6.73; N 3.64.

5.4.5. 5-(2-Anilinopropyl)nonan-5-ol [2e]. Colorless oil; IR (Neat) ν 3368, 1602, 1498, 1320, 1252, 1151, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=6.6 Hz, *Me*), 0.96 (t, 3H, J=6.6 Hz, *Me*), 2.29 (d, 3H, J=6.2 Hz, *Me*), 1.15–1.50 (m, 10H), 1.55–1.75 (m, 4H), 3.67 (br s, 2H), 3.70–3.90 (m, 1H), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 22.3, 23.5, 23.6, 25.6, 26.8, 38.9, 40.3, 45.3, 47.2, 74.5, 115.7, 119.4, 129.5, 147.0; MS (EI, 70 eV): *m/z* (%) 277 (M^+, 4), 220 (2), 202 (4), 120 (100), 93 (6), 77 (6). Anal. Calcd for $C_{18}H_{31}NO$ (277.4): C 77.92; H 11.26; N 5.05. Found: C 78.12; H 11.44; N 5.11.

5.4.6. 5-Anilino-3-isopropyl-2-methylhexan-3-ol [2f]. Colorless oil; IR (Neat) ν 3350, 1601, 1498, 1381, 1255, 1137, 753, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J=6.6 Hz, *Me*), 0.95 (d, 3H, J=7.0 Hz, *Me*), 1.01 (d, 3H, J=7.0 Hz, *Me*), 1.02 (d, 3H, J=7.0 Hz, *Me*), 1.13 (d, 3H, J=6.2 Hz, *Me*), 1.51 (dd, 1H, J=15.0, 10.6 Hz, H_b), 1.67 (dd, 1H, J=15.0, 5.9 Hz, H'_b), 1.85 (hept, 1 H, J=6.8 Hz, Me_2CH), 1.94 (hept, 1H, J=7.0 Hz, Me_2CH), 3.10 (br s, 1H, N*H*), 3.75–3.95 (m, 1H, H_c), 4.40 (br s, 1H, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 17.3, 17.4, 17.8, 18.1, 21.8, 34.8, 36.5, 38.2, 48.6, 76.7, 116.4, 119.9, 129.5, 146.8; MS (EI, 70 eV): *m/z* (%) 249 (M^+, 4), 206 (2), 120 (100), 93 (5), 77 (5). Anal. Calcd for $C_{16}H_{27}NO$ (249.4): C 77.06; H 10.91; N 5.62. Found: C 77.31; H 10.76; N 5.86.

5.4.7. 7-Anilino-5-butyldecan-5-ol [2g]. Colorless oil; IR (Neat) ν 3364, 1602, 1498, 1319, 1253, 1146, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7.3 Hz, *Me*), 0.91 (t, 3H, J=6.6 Hz, *Me*), 0.92 (t, 3H, J=6.6 Hz, *Me*), 1.10–1.65 (m, 17H), 1.72 (dd, 1H, J=15.0, 2.2 Hz, H'_b), 3.55 (br s, 1H, N*H*), 3.55–3.75 (m, 1H, H_c), 3.95 (br s, 1H, O*H*), 6.65 (m, 3H, Ar-*H*), 7.10–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 14.4, 19.2, 23.5, 23.6, 25.6, 26.7, 38.4, 38.8, 40.4, 42.3, 51.0, 74.4, 115.5, 119.1, 129.5, 147.0; MS (EI, 70 eV): *m/z* (%) 305 (M^+, 4), 262 (1), 230 (5), 148 (100), 120 (53), 106 (22), 77 (9). Anal. Calcd for $C_{20}H_{35}NO$ (305.5): C 78.63; H 11.55; N 4.58. Found: C 78.79; H 11.41; N 4.75.

5.4.8. 5-(2-Benzylamino-2-phenylethyl)nonan-5-ol [2h]. Colorless oil; IR (Neat) ν 3291, 1602, 1205, 1027, 744, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H, J=7.0 Hz, 2*Me*), 1.05–1.18 (m, 1H), 1.20–1.45 (m, 10H), 1.50–1.57 (m, 1H), 1.62 (dd, 1H, J=14.6, 2.4 Hz, H'_b), 1.78 (dd, 1H, J=14.6, 11.9 Hz, H_b), 3.48 (d, 1H, J=12.8 Hz, *Bn*), 3.66 (d, 1H, J=12.8 Hz, *Bn*), 3.20 (br s, 2H, N*H*, O*H*), 3.86 (dd, 1H, J=11.9, 2.4 Hz, H_c), 7.20–7.50 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 23.5, 23.6, 25.6, 26.9, 38.5, 40.6, 45.5, 51.1, 58.9, 74.3, 126.6, 127.5, 127.6, 128.7, 128.9, 129.1, 139.2, 143.7; MS (EI, 70 eV): *m/z* (%) 296 (M^+−57, 4), 278 (3), 196 (70), 106 (16), 91 (100). Anal. Calcd for $C_{24}H_{35}NO$ (353.4): C 81.53; H 9.98; N 3.96. Found: C 81.38; H 10.13; N 3.75.

5.4.9. 5-{(2*S*)-2-[(1′*R*)-1′-Phenylethyl]amino-2-phenylethyl}nonan-5-ol [(2*S*,1′*R*)-2i]. Colorless oil $[\alpha]_D^{20}$ −10.8 (*c* 1.9, $CHCl_3$); IR (Neat) ν 3293, 1601, 1375, 1141, 1028, 759, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.8 Hz, *Me*), 1.01 (t, 3H, J=7.0 Hz, *Me*), 1.18–1.55 (m, 10H), 1.40 (d, 3H, J=6.2 Hz, *Me*-CH), 1.62–1.85 (m, 4H), 3.20 (br s, 1H, N*H*), 3.55 (q, 1H, J=6.3 Hz, Me-C*H*), 4.17 (t, 1H, J=7.0 Hz, H_c), 4.40 (br s, 1H, O*H*), 7.10–7.40 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 21.3, 23.6, 23.7, 25.5, 27.2, 38.6, 40.6, 45.9, 54.6, 57.0, 74.3, 126.3, 126.7, 127.5, 127.6, 128.8, 129.1, 143.5, 145.4; MS (EI, 70 eV): *m/z* (%) 352 (M^+−15, 3), 310 (7), 210 (78), 106 (96), 105 (100). Anal. Calcd for $C_{25}H_{37}NO$ (367.6): C 81.70; H 10.15; N 3.81. Found: C 81.86; H 10.28; N 3.67.

5.4.10. 5-{(2*R*)-2-[(1′*R*)-1′-Phenylethyl]amino-2-phenylethyl}nonan-5-ol [(*R*,*R*)-2i]. Colorless oil; IR (Neat) ν 3297, 1599, 1378, 1140, 1034, 759, 700 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 0.76 (t, 3H, J=7.0 Hz, *Me*), 0.88 (t, 3H, J=6.2 Hz, *Me*), 0.90–1.40 (m, 12H), 1.28 (d, 3H, J=6.6 Hz, *Me*-CH), 1.50 (dd, 1H, J=14.6, 2.6 Hz, H'_b), 1.75 (dd, 1H, J=14.6, 11.7 Hz, H_b), 3.20 (br s, 1H, N*H*), 3.47 (q, 1H, J=6.6 Hz, Me-C*H*), 3.57 (dd, 1H, J=11.7, 2.6 Hz, H_c), 4.00 (br s, 1H, O*H*), 7.10–7.45 (m, 10H, Ar-*H*); MS (EI, 70 eV): *m*/*z* (%) 352 (M^+-15, 1), 310 (5), 210 (85), 106 (87), 105 (100). Anal. Calcd for $C_{25}H_{37}NO$ (367.6): C 81.7; H 10.15; N 3.81. Found: C 81.61; H 10.29; N 3.62.

5.4.11. 5-[(*R,*R**)-2-Anilino-1-methylpropyl]nonan-5-ol [*trans*-2j].** Oil; ^1H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H), 1.05–1.18 (m, 6H), 1.20–1.70 (m, 12H), 1.80 (dq, 1H, J=8.8, 7.0 Hz, H_b), 3.65 (br s, 2H, N*H*, O*H*), 3.70 (dq, 1H, J=8.8, 6.3 Hz, H_c), 6.70–7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 13.2, 14.4, 14.5, 19.8, 23.7, 23.9, 25.3, 25.7, 36.9, 37.6, 44.4, 52.3, 77.1, 116.0, 119.6, 129.6, 146.8; MS (EI, 70 eV): *m*/*z* (%) 291 (M^+, 2), 120 (100), 93 (9), 77 (6). Anal. Calcd for $C_{19}H_{33}NO$ (291.5): C 78.29; H 11.41; N 4.81. Found: C 78.48; H 11.32; N 4.63.

5.4.12. 5-[(1*R,2*S**)-2-Anilino-1-methylpropyl]nonan-5-ol [*cis*-2j].** Oil; ^1H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H), 1.05–1.18 (m, 6H), 1.20–1.75 (m, 13H), 3.65 (br s, 2H, N*H*, O*H*), 4.08 (qd, 1H, J=6.3, 2.3 Hz, H_c), 6.70–7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 6.6, 14.3, 14.4, 19.3, 23.6, 23.8, 25.9, 26.4, 36.0, 37.9, 41.9, 49.1, 77.7, 115.9, 119.6, 129.6, 146.8; MS (EI, 70 eV): *m*/*z* (%) 291 (M^+, 2), 120 (100), 93 (8), 77 (8). Anal. Calcd for $C_{19}H_{33}NO$ (291.5): C 78.29; H 11.41; N 4.81. Found: C 78.52; H 11.57; N 4.59.

5.4.13. 2-[(1*R,2*S**)-2-Anilinocyclopentyl]propan-2-ol [*cis*-2k].** Colorless oil; IR (Neat) ν 3371, 1601, 1505, 1322, 1190, 748, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3H, *Me*), 1.34 (s, 3H, *Me*), 1.60–2.00 (m, 7H, N*H*), 3.00 (br s, 1H), 3.65 (br s, 1H), 3.90–3.98 (m, 1H, H_c), 6.60–6.80 (m, 3H, Ar-*H*), 7.10–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.4, 29.9, 30.8, 32.5, 52.7, 57.3, 72.1, 114.4, 117.8, 129.4, 147.9; MS (EI, 70 eV): *m*/*z* (%) 219 (M^+, 34), 204 (6), 186 (6), 132 (84), 119 (100), 106 (14), 93 (39). Anal. Calcd for $C_{14}H_{21}NO$ (219.3): C 76.67; H 9.65; N 6.39. Found: C 76.49; H 9.84; N 6.24.

5.4.14. 2-[(*R,*R**)-2-Anilinocyclopentyl]propan-2-ol [*trans*-2k].** Colorless oil; IR (Neat) ν 3400, 1602, 1503, 1320, 1180, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 6H, 2*Me*), 1.30–1.54 (m, 2H), 1.60–1.88 (m, 4H), 2.02–2.22 (m, 1H), 3.00 (br s, 1H, N*H*), 3.60 (br s, 1H, O*H*) 3.75 (q, 1H, J=7.2 Hz, H_c), 6.60–6.90 (m, 3H, Ar-*H*), 7.10–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 22.9, 25.6, 27.3, 29.8, 33.5, 56.6, 57.4, 72.8, 114.6, 118.3, 129.4, 147.8; MS (EI, 70 eV): *m*/*z* (%) 219 (M^+, 40), 204 (7), 186 (6), 132 (81), 119 (100), 106 (13), 93 (29). Anal. Calcd for $C_{14}H_{21}NO$ (219.3): C 76.67; H 9.65; N 6.29. Found: C 76.72; H 9.58; N 6.46.

5.4.15. 5-[(1*R,2*S**)-2-Anilinocyclopentyl]nonan-5-ol [*cis*-2l].** Colorless oil; IR (Neat) ν 3378, 1601, 1508, 1321, 1269, 747, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86–0.98 (m, 6H, 2*Me*), 1.10–2.00 (m, 21H), 3.85–3.95 (m, 1H, H_c), 6.80–6.90 (m, 3H, Ar-*H*), 7.10–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 21.1, 22.7, 23.5, 25.9, 26.3, 32.3, 37.8, 38.4, 39.2, 49.7, 56.7, 76.0, 114.4, 117.6, 129.4, 147.9; MS (EI, 70 eV): *m*/*z* (%) 303 (M^+, 11), 285 (3), 246 (14), 228 (16), 132 (74), 119 (100), 106 (13), 93 (32). Anal. Calcd for $C_{20}H_{33}NO$ (303.5): C 79.15; H 10.96; N 4.62. Found: C 79.32; H 10.79; N 4.39.

5.4.16. 5-[(*R,*R**)-2-Anilinocyclopentyl]nonan-5-ol [*trans*-2l].** ^1H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H, 2*Me*), 1.20–2.05 (m, 20H), 3.60 (br s, 1H, N*H*), 3.85 (td, 1H, J=7.3, 2.2 Hz, H_c), 6.60–7.30 (m, 5H, Ar-*H*).

5.4.17. 5-[(1*R,2*S**)-2-(Benzylamino)cyclopentyl]nonan-5-ol [*cis*-2m].** Colorless oil; IR (Neat) ν 3271, 1605, 1260, 1169, 745, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7.0 Hz, *Me*), 0.90 (t, 3H, J=7.0 Hz, *Me*), 1.05–1.55 (m, 13H), 1.60–1.82 (m, 8H), 3.18–3.26 (m, 1H, H_c), 3.84 (d, 1H, J=12.4 Hz, *Bn*), 3.66 (d, 1H, J=12.4 Hz, *Bn*), 7.20–7.35 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 20.8, 22.1, 23.6, 23.7, 25.7, 26.3, 31.0, 37.3, 39.4, 49.4, 52.4, 60.3, 74.9, 127.5, 128.6, 128.8, 139.6; MS (EI, 70 eV): *m*/*z* (%) 298 (M^+-19, 2), 277 (4), 260 (44), 146 (43), 106 (26), 91 (100). Anal. Calcd for $C_{21}H_{35}NO$ (317.5): C 79.44; H 11.11; N 4.41. Found: C 79.27; H 11.18; N 4.24.

5.4.18. 5-[(*R,*R**)-2-(Benzylamino)cyclopentyl]nonan-5-ol [*trans*-2m].** ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7.0 Hz, *Me*), 0.91 (t, 3H, J=6.6 Hz, *Me*), 1.10–1.90 (m, 20H), 2.05–2.25 (m, 1H), 3.00–3.15 (m, 1H, H_c), 3.72 (d, 1H, J=12.8 Hz, *Bn*), 3.91 (d, 1H, J=12.8 Hz, *Bn*), 7.20–7.40 (m, 5H, Ar-*H*).

5.4.19. 2-[(1*R,2*S**)-2-Anilinocyclohexyl]propan-2-ol [*cis*-2n].** White crystals; mp 64–66 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3367, 1601, 1504, 1243, 1169, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.70 (m, 6H, 2*Me*), 1.22 (s, 3H), 1.34 (s, 3H), 1.80–2.00 (m, 3H), 3.45 (br s, 1H, N*H*), 3.95 (br s, 1H, O*H*), 4.03–4.12 (m, 1H, H_c), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 20.1, 21.2, 26.1, 28.6, 29.3, 29.5, 48.6, 50.1, 72.8, 115.7, 119.2, 129.6, 147.0; MS (EI, 70 eV): *m*/*z* (%) 233 (M^+, 31), 218 (9), 200 (6), 132 (100), 119 (26), 106 (20), 93 (42). Anal. Calcd for $C_{15}H_{23}NO$ (233.3): C 77.21; H 9.93; N 6.00. Found: C 77.36; H 10.19; N 5.81.

5.4.20. 2-[(*R,*R**)-2-Anilinocyclohexyl]propan-2-ol [*trans*-2n].** White crystals; mp 122–124 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3363, 1598, 1505, 1239, 1167, 745, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.16 (m, 2H), 1.18–1.40 (m, 2H), 1.21 (s, 3H, *Me*), 1.26 (s, 3H, *Me*), 1.52 (td, 1H, J=11.2, 3.3 Hz), 1.64–1.84 (m, 2H), 1.85–2.00 (m, 1H), 2.06–2.20 (m, 1H), 3.36 (td, 1H, J=10.7, 3.9 Hz, H_c), 4.15 (br s, 2H, N*H*, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.8, 26.3, 29.0, 29.5, 34.6, 52.8, 57.0, 74.2, 116.4, 120.2, 129.5, 146.5; MS (EI, 70 eV): *m*/*z* (%) 233 (M^+, 29), 218 (6), 200 (6), 132 (100), 119 (28), 106 (22), 93 (54). Anal. Calcd for $C_{15}H_{23}NO$ (233.3): C 77.21; H 9.93; N 6.00. Found: C 77.37; H 9.82; N 6.18.

5.4.21. 5-[(1*R,2*S**)-2-Anilinocyclohexyl]nonan-5-ol [*cis*-2o].** Colorless oil; IR (Neat) ν 3366, 1601, 1504, 1242, 1153, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 6H, 2*Me*), 1.10–

1.75 (m, 17H), 1.80–2.00 (m, 4H), 3.80 (br s, 2H, N*H*, O*H*), 3.95–4.05 (m, 1H, H_c), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 20.2, 20.6, 23.6, 23.7, 25.9, 26.2, 26.4, 29.3, 35.4, 37.3, 44.8, 49.8, 77.7, 115.8, 119.3, 129.6, 146.9; MS (EI, 70 eV): *m*/*z* (%) 317 (M^+, 13), 299 (3), 260 (24), 242 (21), 132 (100), 119 (36), 106 (42), 93 (85). Anal. Calcd for $C_{21}H_{35}NO$ (317.5): C 79.44; H 11.11; N 4.41. Found: C 79.53; H 11.02; N 4.60.

5.4.22. 5-[(*R,*R**)-2-Anilinocyclohexyl]nonan-5-ol [*trans*-2o].** Colorless oil; IR (Neat) ν 3359, 1603, 1500, 1245, 1151, 748, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H, 2*Me*), 1.15–1.85 (m, 20H), 2.05–2.20 (m, 1H), 3.46 (td, 1H, *J*=10.3, 3.8 Hz, H_c), 4.00 (br s, 2H, N*H*, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.25 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.5, 23.8, 24.1, 25.0, 25.6, 26.0, 26.6, 28.6, 35.1, 36.9, 37.3, 49.2, 56.4, 77.0, 116.5, 120.2, 129.6, 146.7; MS (EI, 70 eV): *m*/*z* (%) 317 (M^+, 20), 299 (4), 260 (49), 242 (18), 132 (100), 119 (32), 106 (36), 93 (78). Anal. Calcd for $C_{21}H_{35}NO$ (317.5): C 79.44; H 11.11; N 4.41. Found: C 79.40; H 11.16; N 4.54.

5.4.23. 3-[(1*R,2*S**)-2-Anilinocyclohexyl]-2,4-dimethylpentan-3-ol [*cis*-2p].** Colorless oil; IR (Neat) ν 3369, 1602, 1498, 1242, 1057, 751, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 12H, *J*=7.0 Hz, 4*Me*), 1.25–2.25 (m, 11H), 3.89 (br s, 2H, N*H*, O*H*), 4.04 (s, 1H, H_c), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 18.4, 19.1, 19.3, 19.4, 20.2, 22.5, 26.3, 30.0, 32.2, 35.2, 42.4, 50.2, 78.8, 115.9, 119.4, 129.6, 146.6; MS (EI, 70 eV): *m*/*z* (%) 289 (M^+, 30), 271 (8), 246 (100), 228 (14), 132 (99), 106 (48), 93 (97). Anal. Calcd for $C_{19}H_{31}NO$ (289.5): C 78.84; H 10.79; N 4.84. Found: C 78.97; H 10.55; N 4.97.

5.4.24. 3-[(*R,*R**)-2-Anilinocyclohexyl]-2,4-dimethylpentan-3-ol [*trans*-2p].** Colorless oil; IR (Neat) ν 3279, 1602, 1498, 1242, 1060, 994, 754, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J*=7.0 Hz, *Me*), 0.99 (d, 3H, *J*=7.0 Hz, *Me*), 1.05 (d, 3H, *J*=7.0 Hz, *Me*), 1.12 (d, 3H, *J*=7.0 Hz, *Me*), 1.12–1.42 (m, 4H), 1.63–1.95 (m, 4H), 1.96–2.30 (m, 3H), 3.57 (td, 1 H, *J*=10.3, 3.9 Hz, H_c), 4.50 (br s, 2H, N*H*, O*H*), 6.70–6.90 (m, 3H, Ar-*H*), 7.15–7.30 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.1, 19.4, 20.2, 25.8, 27.0, 29.2, 33.0, 33.8, 36.0, 48.2, 58.1, 79.4, 116.9, 120.4, 129.5, 146.4; MS (EI, 70 eV): *m*/*z* (%) 289 (M^+, 19), 271 (17), 246 (97), 228 (17), 132 (93), 106 (43), 93 (100). Anal. Calcd for $C_{19}H_{31}NO$ (289.5): C 78.84; H 10.79; N 4.84. Found: C 78.71; H 10.96; N 4.63.

5.5. General procedure for the alkylation and *one-pot* reduction for the synthesis of γ-amino alcohols 2q–s

The β-enamino ester **1a** (1 mmol) was dissolved in toluene (3 mL), under nitrogen atmosphere at 0 °C, then was added the first organolithium reagent (2.5 mmol), according to the reaction conditions and reagents reported in Table 2. After the reaction time (see Table 2) the second organolithium reagent was added (1.5 mmol). After 1 h the reduction procedure was performed (see above). Spectral data of products **2q–s** are as follow.

5.5.1. (1*R,3*S**)-1-Anilino-1,3-diphenylheptan-3-ol [(1*R**,3*S**)-2q].** Colorless oil; IR (Neat) ν 3419, 1601, 1504, 1314, 1266, 751, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, *J*=6.6 Hz, *Me*), 0.90–1.10 (m, 1H), 1.15–1.45 (m, 3H), 1.98 (t, 2H, *J*=7.7 Hz), 2.15–2.40 (m, 2H, H_b, H'_b), 2.95 (br s, 1H, N*H*), 4.30 (br s, 1H, O*H*), 4.68 (t, 1H, *J*=7.0 Hz, H_c), 6.30–6.75 (m, 3H, Ar-*H*), 7.00–7.50 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.8, 42.1, 51.6, 55.9, 76.8, 114.6, 118.3, 125.2, 126.4, 126.8, 127.3, 128.2, 128.6, 129.0, 129.2, 144.5, 147.1; MS (EI, 70 eV): *m*/*z* (%) 359 (M^+, 3), 284 (1), 182 (100), 118 (56), 104 (18), 77 (49). Anal. Calcd for $C_{25}H_{29}NO$ (359.5): C 83.52; H 8.13; N 3.90. Found: C 83.47; H 7.92; N 3.68.

5.5.2. (1*R,3*R**)-1-Anilino-1,3-diphenylheptan-3-ol [(1*R**,3*R**)-2q].** Colorless oil; IR (Neat) ν 3425, 1600, 1505, 1312, 1261, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J*=7.1 Hz, *Me*), 1.00–1.50 (m, 4H), 1.75–1.90 (m, 2H), 2.20–2.40 (m, 2H, H_b, H'_b), 4.18 (t, 1H, *J*=6.8 Hz, H_c), 4.55 (br s, 2H, N*H*, O*H*), 6.40–6.70 (m, 3H, Ar-*H*), 7.00–7.60 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.5, 44.5, 50.0, 56.8, 78.0, 116.2, 119.7, 125.1, 125.7, 125.9, 126.7, 127.2, 128.5, 128.9, 129.2, 143.7, 146.5; MS (EI, 70 eV): *m*/*z* (%) 359 (M^+, 5), 284 (2), 182 (100), 118 (51), 105 (15), 77 (43). Anal. Calcd for $C_{25}H_{29}NO$ (359.5): C 83.52; H 8.13; N 3.90. Found: C 83.73; H 8.01; N 3.73.

5.5.3. (1*R,3*R**)-1-Anilino-4-methyl-1,3-diphenylpentan-3-ol [(1*R**,3*R**)-2r].** Colorless oil; IR (Neat) ν 3418, 1601, 1505, 1316, 1266, 1026, 752, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, 3H, *J*=7.0 Hz, *Me*), 0.91 (d, 3H, *J*=6.6 Hz, *Me*), 2.11 (sept, 1H, *J*=6.7 Hz, Me_2CH), 2.31 (dd, 1H, *J*=14.8, 8.8 Hz, H_b), 2.50 (dd, 1H, *J*=14.8, 4.8 Hz, H'_b), 2.77 (br s, 1H, N*H*), 4.02 (br s, 1H, O*H*), 4.55 (dd, 1H, *J*=8.8, 4.8 Hz, H_c), 6.20–6.30 (m, 2H, Ar-*H*), 6.54–6.66 (m, 1H, Ar-*H*), 6.94–7.08 (m, 2H, Ar-*H*), 7.20–7.40 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 16.9, 17.7, 38.4, 47.9, 55.5, 78.2, 114.1, 117.9, 125.9, 126.5, 126.7, 127.3, 128.2, 128.9, 129.0, 144.4, 145.5, 146.8; MS (EI, 70 eV): *m*/*z* (%) 345 (M^+, 7), 182 (100), 105 (20), 77 (29). Anal. Calcd for $C_{24}H_{27}NO$ (345.8): C 83.44; H 7.88; N 4.05. Found: C 83.28; H 8.08; N 4.22.

5.5.4. (1*R,3*S**)-1-Anilino-4-methyl-1,3-diphenylpentan-3-ol [(1*R**,3*S**)-2r].** Colorless oil; IR (Neat) ν 3379, 1601, 1500, 1314, 1265, 752, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 3H, *J*=6.6 Hz, *Me*), 1.06 (d, 3H, *J*=6.6 Hz, *Me*), 2.02 (sept, 1H, *J*=6.8 Hz, Me_2CH), 2.26 (dd, 1H, *J*=14.7, 3.3 Hz, H'_b), 2.37 (dd, 1H, *J*=14.7, 10.1 Hz, H_b), 3.88 (br s, 2H, N*H*, O*H*), 4.14 (dd, 1H, *J*=10.1, 3.3 Hz, H_c), 6.15–6.20 (m, 2H, Ar-*H*), 6.60–6.80 (m, 1H, Ar-*H*), 7.00–7.50 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 16.9, 17.5, 39.2, 47.4, 57.2, 80.0, 116.2, 119.7, 126.2, 126.7, 127.3, 127.7, 128.4, 128.9, 129.2, 143.9, 146.3, 146.5; MS (EI, 70 eV): *m*/*z* (%) 345 (M^+, 7), 182 (100), 105 (20), 77 (33). Anal. Calcd for $C_{24}H_{27}NO$ (345.8): C 83.44; H, 7.88; N 4.05. Found: C 83.66; H, 7.63; N 4.31.

5.5.5. (1*S,3*R**)-1-Anilino-3-(*tert*-butyl)-1-phenylheptan-3-ol [(1*S**,3*R**)-2s].** White crystals; mp 81–83 °C (*n*-hexane/CH_2Cl_2); IR (Nujol) ν 3369, 1602, 1503, 1312,

1266, 751, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, J=6.8 Hz), 1.06 (s, 9H, *t-Bu*), 1.30–1.75 (m, 6H), 1.86 (dd, 1H, J=15.4, 10.6 Hz, H_b), 2.08 (dd, 1H, J=15.4, 2.6 Hz, H'_b), 3.47 (br s, 1H, N*H*), 4.40 (br s, 1H, O*H*), 4.75 (dd, 1H, J=10.6, 2.6 Hz, H_c), 6.60–6.80 (m, 3H, Ar-*H*), 7.05–7.40 (m, 7H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.5, 23.8, 26.0, 26.7, 37.8, 39.0, 42.7, 57.0, 77.2, 115.6, 119.1, 126.2, 127.2, 129.0, 129.3, 144.6, 146.8; MS (EI, 70 eV): *m/z* (%) 339 (M^+, 5), 282 (2), 182 (100), 104 (14), 93 (16), 77 (14), 57 (11). Anal. Calcd for $C_{23}H_{33}NO$ (339.5): C 81.37; H 9.80; N 4.13. Found: C 81.46; H 9.64; N 4.26.

5.5.6. (1*R,3*R**)-1-Anilino-3-(*tert*-butyl)-1-phenylheptan-3-ol [(1*R**,3*R**)-2s].** MS (EI, 70 eV): *m/z* (%) 339 (M^+, 6), 278 (11), 182 (100), 104 (15), 93 (17), 77 (22), 57 (17).

5.6. General procedure for the synthesis of β-hydroxy imines 4

The β-enamino ester **1a** (1 mmol) was dissolved in toluene (3 mL), at 0 °C and was added alkyllithium reagent (methyllithium or butyllithium, 4 mmol) according to the reaction conditions and reagents reported in Table 1, entries 1 and 2. The reaction mixture was then quenched with aqueous saturated NH_4Cl (5 mL) and extracted with dichloromethane (2×10 mL). The organic layer was dried with anhydrous Na_2SO_4, then filtered, and the solvent was removed under reduced pressure. Spectral characterization of the β-hydroxy imines **4** was done by analysis of the crude reaction mixture. Spectral data of β-hydroxy imines **4a** and **4b** are as follows.

5.6.1. 2-Methyl-4-phenyl-4-(phenylimino)butan-2-ol [4a]. Yield 58%; Oil; IR (liquid film) ν_{max} 3392, 1630, 1594, 1212, 761, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 6H, 2*Me*), 2.92 (s, 2H, CH_2), 5.93 (s, 1H, O*H*), 6.60–7.30 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$): δ 29.8, 50.5, 70.6, 121.4, 123.9, 127.7, 128.4, 128.8, 129.1, 138.2, 149.3, 172.6. Anal. Calcd for $C_{17}H_{19}NO$ (253.3): C 80.60; H 7.56; N 5.53%. Found: C 81.74; H 7.79; N 5.29%.

5.6.2. 3-Butyl-1-phenyl-1-(phenylimino)heptan-3-ol [4b]. Yield 63%; Oil; ^1H NMR ($CDCl_3$) δ 0.91 (t, 6H J=6.8 Hz, 2*Me*), 1.25–1.50 (m, 8H), 1.61–1.73 (m, 4H), 2.89 (s, 2H, CH_2), 5.79 (s, 1H, O*H*), 6.65–7.35 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.4, 23.6, 26.4, 39.5, 47.2, 74.8, 121.4, 123.8, 127.7, 128.4, 128.8, 129.0, 138.4, 149.4, 172.8. Anal. Calcd for $C_{23}H_{31}NO$ (337.5): C 81.85; H 9.26; N 4.15%. Found: C 81.07; H 9.38; N 3.91%.

5.7. General procedure for the synthesis of 1,3-tetrahydro oxazines 5

The γ-amino alcohols **2i**,**j**,**q** (0.5 mmol) were dissolved in THF (1 mL), and was added aqueous formaldehyde 35% (0.085 mL, 1 mmol). After 6 h the solvent was removed under reduced pressure and the crude tetrahydro oxazines purified by short filtration on a thin pad of silica gel with cyclohexane/AcOEt (97:3 v/v) or CH_2Cl_2/*n*-hexane (50:50 v/v) as eluent. Spectral data of tetrahydro oxazines **5** are as follow.

5.7.1. (*R,*R**)-6,6-Dibutyl-4,5-dimethyl-3-phenyl-1,3-oxazinane [(*R**,*R**)-5j].** White crystals; mp 50–52 °C (*n*-esano); IR (Nujol) ν_{max} 1600, 1503, 1379, 1247, 1020, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (t, 3H, J=7.0 Hz, *Me*), 0.90 (d, 3H, J=7.0 Hz, *Me*), 0.94 (t, 3H, J=6.6 Hz, *Me*), 1.00–1.70 (m, 12H), 1.28 (d, 3H, J=6.2 Hz, *Me*), 2.08 (dq, 1H, J=7.0, 10.2 Hz, H_b), 3.34 (dq, 1H, J=6.2, 10.2 Hz, H_c), 4.83 (d, 1H, J=11.0 Hz, O-CH_2-N), 4.89 (d, 1H, J=11.0 Hz, O-CH_2-N), 6.80–7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 14.5, 19.3, 23.5, 23.6, 24.4, 25.4, 33.0, 37.2, 39.7, 56.7, 72.4, 78.4, 117.3, 120.1, 129.2, 149.2. Anal. Calcd for $C_{20}H_{33}NO$ (303.5): C 79.15; H 10.96; N 4.62. Found: C 79.23; H 10.79; N 4.81.

5.7.2. (4*S,5*R**)-6,6-Dibutyl-4,5-dimethyl-3-phenyl-1,3-oxazinane [(4*S**,5*R**)-5j].** Colorless oil; IR (Neat) ν_{max} 1598, 1379, 1252, 1188, 1018, 756, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, J=7.3 Hz, *Me*), 0.88 (t, 3H, J=7.0 Hz, *Me*), 0.96 (t, 3H, J=6.4 Hz), 1.08–1.42 (m, 9H), 1.40 (d, 3H, J=7.3 Hz, *Me*), 1.47–1.63 (m, 2H), 1.92–2.10 (m, 1H), 2.19 (dq, 1H, J=7.3, 5.7 Hz, H_b), 3.69 (dq, 1H, J=7.3, 5.7 Hz, H_c), 4.83 (s, 2H, O-CH_2-N), 6.85–7.35 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 13.0, 14.3, 14.4, 15.9, 23.6, 23.8, 25.2, 25.4, 32.7, 35.3, 36.8, 57.9, 70.3, 78.7, 119.4, 120.6, 129.1, 150.6. Anal. Calcd for $C_{20}H_{33}NO$ (303.5): C 79.15; H 10.96; N 4.62. Found: C 79.34; H 10.84; N 4.48.

5.7.3. (4*S*)-6,6-Dibutyl-4-phenyl-3-[(1′*R*)-1′-phenylethyl]-1,3-oxazinane [(4*S*,1′*R*)-5i]. Oil; $[\alpha]_D^{20}$ +1.4 (*c* 1.6, $CHCl_3$); IR (liquid film) ν_{max} 1595, 1498, 1374, 1013, 753, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=6.9 Hz, *Me*), 0.98 (t, 3H, J=7.0 Hz, *Me*), 1.12–1.44 (m, 9H), 1.38 (d, 3H, J=7.0 Hz, *Me*-CH), 1.47–1.60 (m, 2H), 1.75 (dd, 1H, J=13.7, 3.9 Hz, H'_b), 1.82–1.94 (m, 1H), 1.85 (dd, 1H, J=13.7, 11.0 Hz, H_b), 3.94 (q, 1H, J=7.0 Hz, Me-C*H*), 4.04 (dd, 1H, J=11.0, 3.9 Hz, H_c), 4.31 (d, 1H, J=10.0 Hz, O-CH_2-N), 4.35 (d, 1H, J=10.0 Hz, O-CH_2-N), 7.15–7.50 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.2, 14.4, 23.4, 23.6, 25.3, 25.6, 33.1, 38.5, 42.5, 55.4, 58.0, 72.1, 75.8, 126.7, 127.2, 127.6, 127.7, 128.2, 128.7, 143.9, 144.4. Anal. Calcd for $C_{26}H_{37}NO$ (379.6): C 82.27; H 9.83; N 3.69. Found: C 82.45; H 9.61; N 3.52.

5.7.4. (*R*)-6,6-Dibutyl-4-phenyl-3-[(*R*)-1′-phenylethyl]-1,3-oxazinane [(*R*,*R*)-5i]. Oil; $[\alpha]_D^{20}$ +96.6 (*c* 1.1, $CHCl_3$); IR (liquid film) ν_{max} 1596, 1501, 1374, 1245, 1016, 748, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, J=6.8 Hz, *Me*), 0.86 (t, 3H, J=6.6 Hz, *Me*), 1.05–1.35 (m, 9H), 1.35 (d, 3H, J=7.0 Hz, *Me*-CH), 1.40–1.65 (m, 3H), 1.61 (dd, 1H, J=13.9, 4.0 Hz, H'_b), 1.77 (dd, 1H, J=13.9, 11.5 Hz, H_b), 3.77 (dd, 1H, J=11.5, 4.2 Hz, H_c), 3.95 (q, 1H, J=7.0 Hz, Me-C*H*), 4.06 (d, 1H, J=9.9 Hz, O-CH_2-N), 4.61 (d, 1H, J=9.9 Hz, O-CH_2-N), 7.10–7.50 (m, 10H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 20.4, 23.4, 23.5, 25.2, 25.5, 32.4, 39.2, 43.6, 57.6, 58.6, 73.2, 75.8, 127.0, 127.1, 127.5, 128.2, 128.3, 128.8, 141.4, 145.4. Anal. Calcd for $C_{26}H_{37}NO$ (379.6): C 82.27; H 9.83; N 3.69. Found: C 82.43; H 9.60; N 3.88.

5.7.5. (4*S,6*R**)-6-Butyl-3,4,6-triphenyl-1,3-oxazinane [(4*S**,6*R**)-5q].** Colorless oil; IR (Neat) ν_{max} 1600, 1505, 1249, 1026, 753, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (t, 3H, J=7.0 Hz, *Me*), 0.86–1.04 (m, 1H), 1.10–1.42 (m, 3H), 1.78 (ddd, 1H, J=11.6, 4.5, 1.6 Hz), 2.14 (ddd, 1H, J=11.8, 4.1, 1.5 Hz), 2.34 (dd, 1H, J=14.5, 11.8 Hz, H_b),

2.49 (dd, 1H, J=14.5, 5.5 Hz, H'_b), 4.77 (dd, 1H, J=11.8, 5.5 Hz, H_c), 5.14 (d, 1H, J=10.6 Hz, O-CH_2-N), 5.33 (d, 1H, J=10.6 Hz, O-CH_2-N), 6.80–6.95 (m, 3H, Ar-*H*), 7.15–7.45 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.8, 40.3, 44.3, 58.2, 75.2, 78.3, 117.2, 120.1, 125.3, 126.4, 126.8, 127.2, 128.3, 128.9, 129.1, 144.1, 146.7, 149.7. Anal. Calcd for $C_{26}H_{29}NO$ (371.5): C 84.06; H 7.87; N 3.77. Found: C 83.87; H 7.73; N 3.59.

5.7.6. (4*R,6*R**)-6-Butyl-3,4,6-triphenyl-1,3-oxazinane [(4*R**,6*R**)-5q].** Colorless oil; IR (neat) ν_{max} 1597, 1505, 1023, 755, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J=7.0 Hz, *Me*), 1.10–1.35 (m, 4H), 1.80 (t, 2H, J=7.7 Hz), 2.38 (dd, 1H, J=14.3, 11.7 Hz, H_b), 2.57 (dd, 1H, J=14.3, 4.4 Hz, H'_b), 4.22 (dd, 1H, J=11.7, 4.4 Hz, H_c), 5.02 (d, 1H, J=10.3 Hz, O-CH_2-N), 5.12 (d, 1H, J=10.3 Hz, O-CH_2-N), 6.70–6.85 (m, 3H, Ar-*H*), 7.00–7.50 (m, 12H, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 25.5, 42.8, 44.5, 58.5, 76.9, 79.3, 119.3, 120.9, 126.5, 126.6, 126.9, 127.2, 128.5, 128.8, 128.9, 143.7, 143.8, 148.2. Anal. Calcd for $C_{26}H_{29}NO$ (371.5): C 84.06; H 7.87; N 3.77. Found: C 84.27; H 7.99; N 3.58.

Acknowledgements

The financial support of this research by grant from University of Camerino and from MIUR-PRIN (contract no. 2005037725_001) is gratefully acknowledged.

Supplementary data

The computational results (Cartesian coordinates of the optimized geometries and semiempirical PM3 level enthalpies of formation) for *cis*-**2k–F**, *trans*-**2k–F**, (*R**,*S**)-**5q**, (*R**,*R**)-**5q**, (4*S*,1′*R*)-**3i**, (*R*,*R*)-**3i** are given. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.044.

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Tetrahedron 62 (2006) 9433–9439

Synthesis of new axially-disubstituted silicon-phthalocyanine derivatives: optical and structural characterisation

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Received 17 March 2006; revised 27 June 2006; accepted 13 July 2006
Available online 9 August 2006

Abstract—This paper describes the synthesis of a range of new axially-disubstituted silicon-phthalocyanines with several ester and ether derivatives as axial ligands, including phenyl, terphenyl, thienyl and pyrenyl systems. Their absorption and emission spectra are reported and fluorescence lifetimes and quantum yields are correlated with the ligand structures. The X-ray crystal structure of a new polymorph of silicon-phthalocyanine bis(3-thienyl)acetate **7** is described.

1. Introduction

Phthalocyanines (Pcs) and related macrocycles are of great interest due to the array of interesting optoelectronic and coordination properties, which they display.[1] They serve as active components in such diverse fields as media for optical data storage,[2] electrochromic[3] and optical limiting devices,[4] multistage-redox-dependent fluorophores,[5] photosensitisers,[6] and medicinal therapeutic agents.[7] Many of the properties of Pcs are highly dependent on the extent of intermolecular π–π stacking interactions between the planar faces of the macrocycles. For example, dimerisation or aggregation (i.e., strong interactions) between neighbouring Pc molecules generally leads to fluorescence quenching and a broadened, blue-shifted principle Q-band due to exciton coupling[8] and can normally be observed even in very dilute solutions. One topic of current interest is the study of Pc derivatives which are not able to aggregate due to special structural features, thereby giving rise to sharply defined UV–vis absorption and emission peaks and higher photoluminescence quantum yields at high concentrations. Examples are provided by axially-substituted metallo-Pcs[9] and derivatives with bulky peripheral substituents, e.g., with rigid spirocyclic fused rings.[10]

Axially-substituted silicon-Pcs have higher quantum yields and longer fluorescence lifetimes than zinc- and aluminium-Pcs, and are therefore more suited to fluorescence studies.[11] We have previously described the synthesis of symmetrical silicon-Pc bis-esters, e.g., compounds **4** and **7**,[12] and analogues containing electroactive tetrathiafulvalene groups.[13] We have now extended this methodology to produce a series of new Si-Pc derivatives, comprising symmetrically- and unsymmetrically-substituted esters and a related bis-ether derivative, **1**–**11**. The photophysical properties of compounds **1**–**11** are discussed, along with the X-ray crystal structure of a new polymorph of silicon-phthalocyanine bis(3-thienyl)acetate **7** obtained during the course of this work.

2. Results and discussion

2.1. Synthesis

The synthesis of the target compounds involved the nucleophilic displacement of one or two chloride substituents from either PhSi(Pc)Cl or $Si(Pc)Cl_2$, respectively, by reaction with the acid or alkoxide derivative of the ligand in 2-methoxyethyl ether or dioxane at high temperature. The structures of compounds **1**–**11** thereby obtained are shown in Chart 1. The substituent ligands were chosen to probe the effects on the optical properties of the system by varying the aryl substituents and their mode of linkage to the central Si atom. In compounds **1**–**3**, a phenyl substituent is attached directly to the silicon; compounds **3** and **9** contained phenoxide substituents; all other aryl groups are attached through ester linkages. The aryl groups used in this study are: phenyl (**1**–**3**, **9**), thienyl (**2**, **5**–**7**), terphenyl (**8**) and pyrenyl (**10** and **11**). Flexibility was introduced into the ligand structure in compounds **2**, **7**, **10** and **11** by incorporating additional alkyl

Keywords: Phthalocyanine; Axial ligands; Fluorescence; Crystal structure; Pyrene.
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doi:10.1016/j.tet.2006.07.046

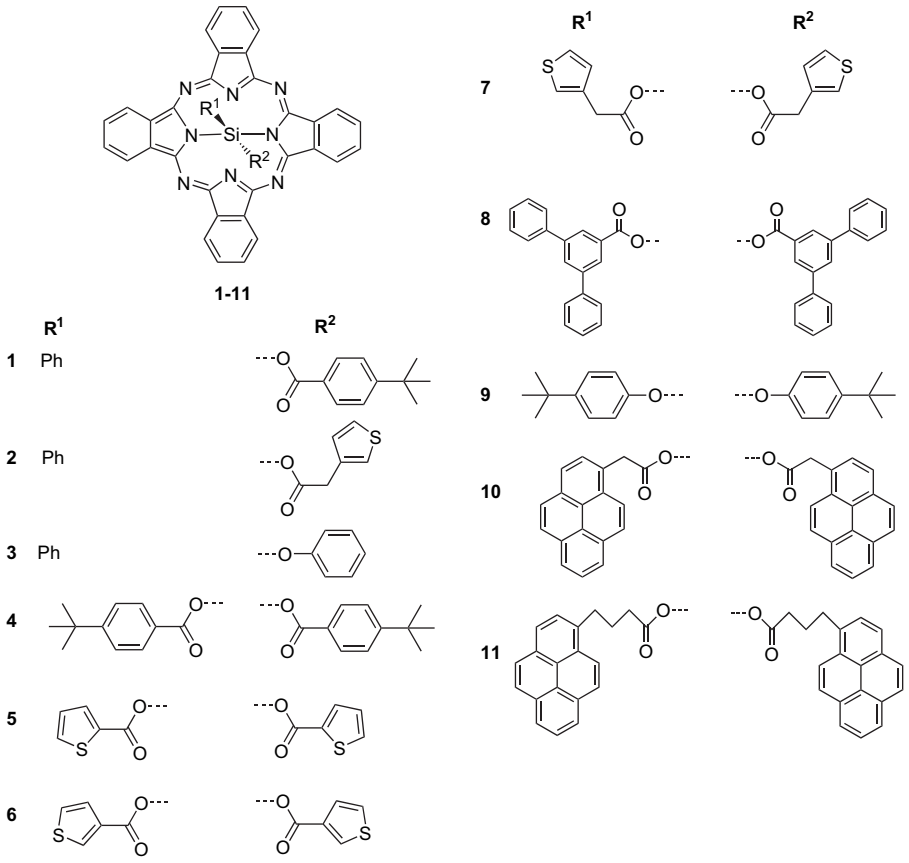

Chart 1. Structures of the axial Pc derivatives studied in this work.

spacers. Compounds **4** and **7** have been reported by us previously[12] and serve as reference materials in the present work.

All the new Pc derivatives were characterised by ^{1}H NMR, solution-state UV–vis absorption and emission spectra, and electrospray ionisation or MALDI-ToF mass spectrometry, with additional ^{13}C NMR spectra and elemental analysis for some compounds; all these data are consistent with the predicted structures. The limited solubility meant that some carbon atoms (especially of the Pc unit) were not observed in the ^{13}C NMR spectra of some of the derivatives even after long acquisition times.

The axially-substituted Pcs have characteristic ^{1}H NMR spectra: the close proximity of the ligand to the large macrocyclic ring current induces a large upfield shift (i.e., to low frequency) in the ligand proton resonances. Thus the five ligand hydrogen atoms of PhSi(Pc)Cl give a doublet at δ 1.56 (2H) and triplets at δ 5.13 (2H) and 5.53 (1H) ppm from the *o*-, *m*- and *p*-Ph protons, respectively. For compound **1** the corresponding resonances are seen at δ 1.82, 5.16 and 5.60 ppm, with two additional doublets from the 4-*tert*-butylbenzoate ligand at δ 4.96 and 6.21 ppm. A comparison of the bis(3-thienyl) derivatives **6** and **7** shows that the additional methylene spacer in the latter has a relatively small effect on the chemical shift of the thienyl ring protons (**6**: δ 4.98, 5.14, 6.12; **7**[12]: 4.41, 4.94, 6.06 ppm).

Within the series (Chart 1), compound **10** gave clear and well-resolved ^{1}H and ^{13}C NMR spectra (Fig. 1). In particular, strong orbital interactions of the pyrene fragments with the Si-Pc core result in pronounced upfield shifts of some of the pyrene protons, which range from δ 8.31 to 5.38 ppm (one proton is overlapped with a Pc signal). For the bis(pyrene) analogue **11** with a longer spacer, the pyrene–Pc orbital overlap is reduced and the furthest upfield pyrene protons are at δ 6.57 ppm.

2.2. X-ray crystal structure of 7

Recrystallisation of **7** by slow diffusion of hexane into a DCM solution of **7** unexpectedly yielded a different polymorph (β-**7**) from the α-**7** polymorph we had obtained previously[12] from the same solvent. Both structures are monoclinic. In α-**7** the Si atom lies at a crystallographic inversion centre in the space group $P2_1/c$, whereas in β-**7** the molecule occupies a general position in the space group $C2/c$ (Fig. 2). The coordination polyhedron of the Si atom is an octahedron compressed along an O···O axis. The mean Si–N distance of 1.904(5) Å is the same as in α-**7** [1.909(3) Å] and other $SiPc(O_2CR)_2$ compounds[12,14–16] (1.900–1.914 Å) but shorter than in Si-Pc without axial ligands (1.946 and 1.965 Å).[17] The SiN_4 coordination is perfectly planar, but the Si-Pc system as a whole is puckered: the average deviation of the 41 non-H atoms from their mean plane is 0.11 Å and the maximum deviation is 0.28 Å (cf. 0.06 and 0.14 Å, respectively, in α-**7**), interplanar angles between the four 'isoindole' moieties vary from 5 to 12° (cf. 0–6° in α-**7**). The carboxy moieties O(1)O(2)C(33)C(34) and O(3)O(4)C(39)C(40) are inclined to the SiN_4 plane by 73 and 83° (cf. 75° in α-**7**), which is rather usual for $SiPc(O_2CR)_2$

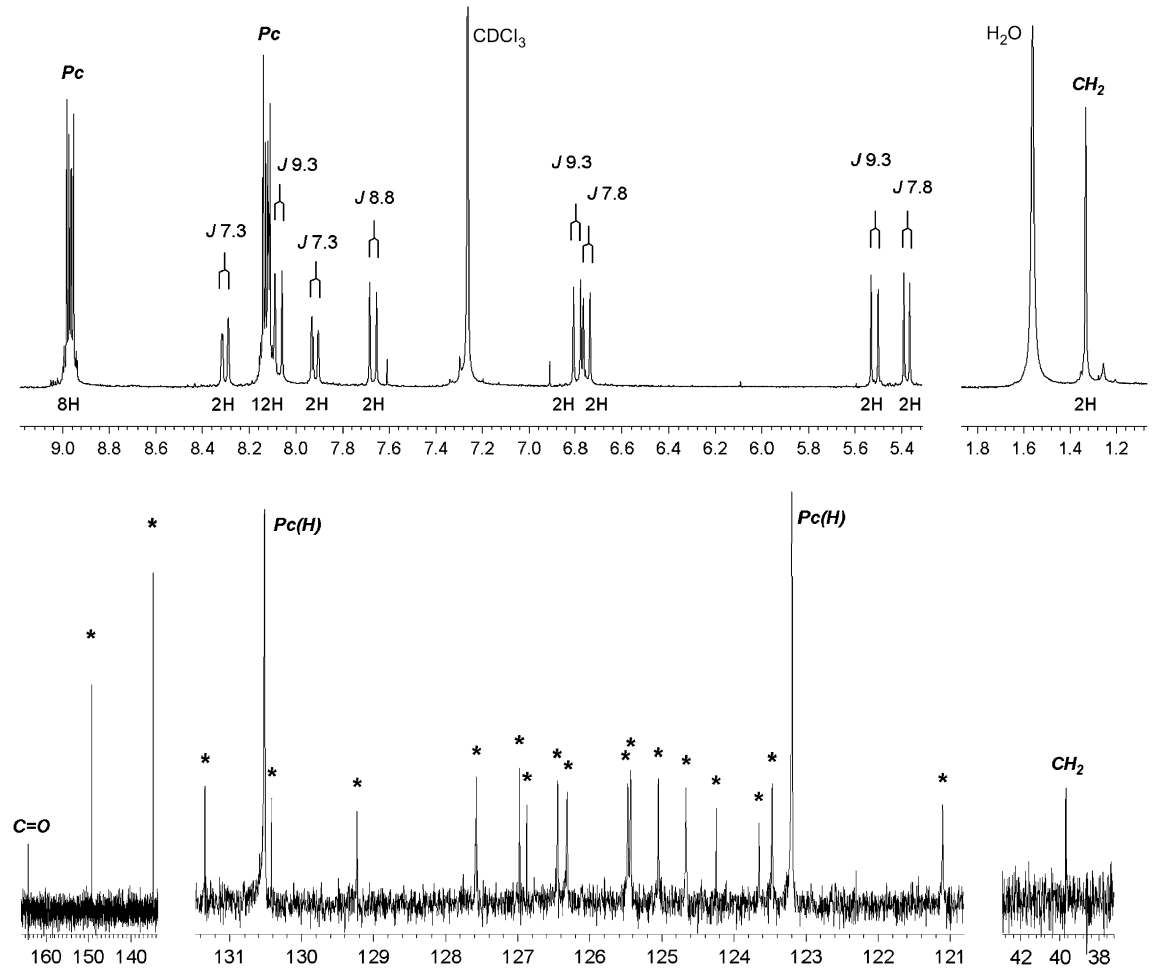

Figure 1. ^{1}H (top) and ^{13}C (bottom) NMR spectra of compound **10** in $CDCl_3$.

molecules. However, in other respects the molecular conformations in α-**7** and β-**7** are quite different. In α-**7**, and all other $SiPc(O_2CR)_2$ structures, the carboxy groups have a trans orientation with respect to the O–Si–O axis, whether or not the Si atom occupies an inversion centre. In β-**7** the carboxy groups are in a *gauche* orientation, with the O(2)···O(1)···O(3)···O(4) torsion angle of 92°. In α-**7** the thienyl rings are stacked to the phthalocyanine moiety (interplanar angle 11°).

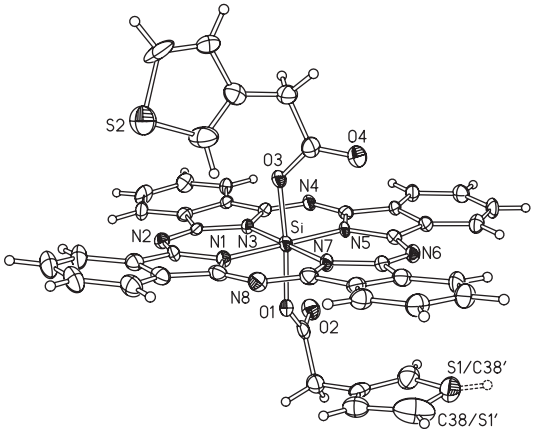

Figure 2. Molecule of **7** in the β polymorph. Selected bond distances (Å): Si–N(1) 1.911(3), Si–N(3) 1.899(3), Si–N(5) 1.900(3), Si–N(7) 1.907(3), Si–O(1) 1.756(3), Si–O(3) 1.778(3).

Such a conformation has been observed previously in all $SiPc(O_2CR)_2$ molecules, which had the rotational freedom to adopt it. In β-**7**, one thienyl ring is near-parallel and the other near-perpendicular to the phthalocyanine moiety; the dihedral angles to the SiN_4 plane being 8 and 82°, respectively. The Si–O bond lengths in β-**7** differ by 0.02 Å, whereas in its analogues these distances are equal within experimental error, if not symmetrically equal (in the range 1.742–1.758 Å). The 'parallel' thienyl ring in β-**7** (as in α-**7**) is disordered by a 180° rotation around the C(34)–C(36) bond, with S and C atoms statistically mixed in a 3:2 ratio.

2.3. Absorption and fluorescence spectroscopy

The photophysical data for compounds **1**–**11** in dichloromethane (DCM) are collated in Table 1.

All of the Si-Pcs show very sharp electronic absorption transitions in the concentration range 10^{-4}–10^{-7} M (Table 1 and Figs. 3 and 4 for compound **3** and **11** in DCM), which are characteristic of monomeric Si-Pc derivatives.[18] The retention of monomeric behaviour even at 10^{-4} M demonstrates that the axial ligands are very effective in sterically isolating

Table 1. Photophysical data for Si-Pc compounds **1–11**

Compound	λ_{max}^{abs}/nm	λ_{max}^{PL}/nm	Φ_f[a]	τ_{f1}/ns[b]	τ_{f2}/ns[b]
1	685	691	0.55	7.1 (99%)	1.1 (1%)
2	688	696	0.52	6.9 (99%)	1.0 (1%)
3	685	692	0.31	5.8	—
4[12]	685	691	0.62	6.7	—
5	686	689	0.48	6.2 (88%)	2.1 (12%)
6	684	689	0.58	6.3 (86%)	2.4 (14%)
7[12]	685	691	0.39	6.7	—
8	685	691	0.69	6.4 (96.4%)	1.7 (4.6%)
9	680	683	0.06	0.5 (94.7%)	5.4 (5.3%)
10	691	696	0.84	6.9 (99.6%)	0.1 (0.4%)
11	684	691	0.81	6.4 (99.6%)	1.9 (0.4%)

[a] ±10%, λ_{ex}=615 nm, λ_{em}=630–850 nm, 293 K, in DCM.
[b] ±0.1 ns, λ_{ex}=635 nm, λ_{em}=690 nm, 293 K, in DCM.

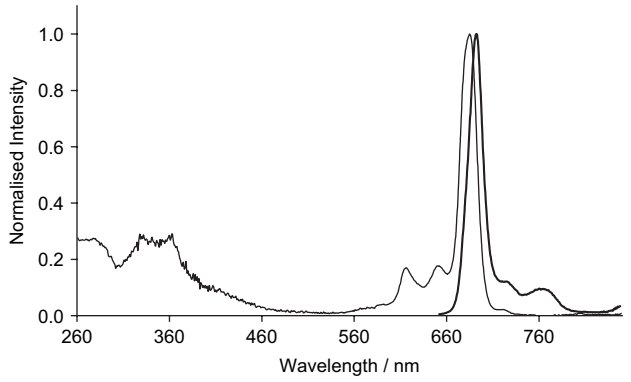

Figure 3. Normalised absorption (thin line) and emission spectra (thick line) of compound **3** in DCM (λ_{ex}=615 nm, same conditions as stated in Table 1).

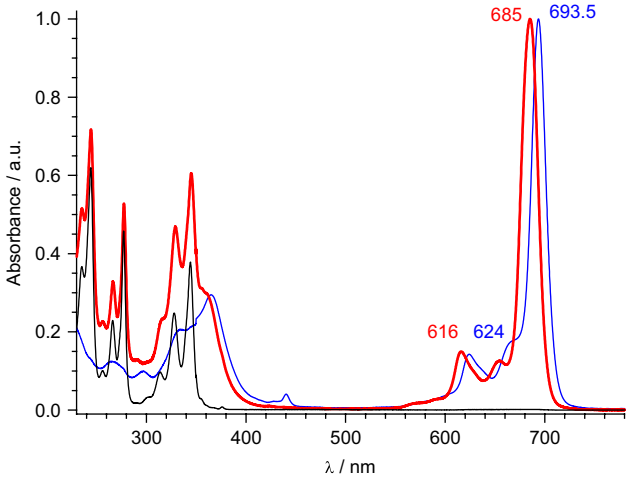

Figure 4. Normalised absorption spectra of compound **11** (thick red line), $Si(Pc)Cl_2$ (thin blue line) and 1-pyrenebutyric acid (thin black line) in DCM.

the chromophoric Pc rings, by preventing intermolecular interactions between the macrocycles. All the derivatives, **1–11**, show small hypsochromic shifts of their long-wavelength maxima compared to $Si(Pc)Cl_2$ (by 2–14 nm, Table 1, and Fig. 3). As an example, Figure 4 compares the electron absorption spectra of compound **11** with $Si(Pc)Cl_2$ and 1-pyrenebutyric acid, demonstrating that the spectrum of **11** combines the spectral features of both the silicon-phthalocyanine and the ligand. The molar extinction coefficients determined for compounds **4**, **8** and **10** in DCM are of the order of $\sim 2\times10^5$ mol dm^{-3} cm^{-1} at λ_{max} and are consistent with those values found for monomeric phthalocyanines.

Analysis of the emission data in Table 1 shows that the electronic energy levels are relatively unaltered by changing the axial substituents and all of the compounds have a very small Stokes shift of less than 10 nm. In general, the fluorescence quantum yield (Φ_f) and fluorescence lifetime (τ_{f1}) values are high, with the exception of compounds **3**, **5**, **7** and **9**, and are typical of silicon-phthalocyanines.[1] The presence of the lighter Si atom in the macrocycle leads to lower rates of inter-system crossing (ISC) than those observed in other metallo-Pcs, e.g., zinc derivatives.[19] The high Φ_f (>0.5) and long lifetimes (>6 ns) are indicative of efficient fluorescent emission and a fairly small non-radiative decay constant. Compounds **8**, **10** and **11** have the most bulky substituents and possess the highest Φ_f values due to their ability to prevent intermolecular interactions and show no evidence of ligand-macrocycle quenching.

The axial ligands in compounds **5** and **7** contain thiophene and also possess significantly lower Φ_f values. The electron-rich thiophene group may quench the excited state by an electron transfer mechanism resulting in a lower value for Φ_f.[20–24] As shown in Figure 2, if a thiophene ring is allowed to lie close (i.e., parallel) to the Pc macrocycle then electron transfer is more facile. Unusually the lifetimes of **5** and **7** are not reduced by this quenching. The calculated rate constants of fluorescence k_f ($=\Phi_f/\tau_f$) are 7.7×10^7 and 5.8×10^7 s^{-1} for compounds **5** and **7**, respectively, in comparison to that of 7.7×10^7 s^{-1} for compound **1**.

Compounds **3** and **9** also have low Φ_f and τ_f values. The axial phenoxy substituents lead to significant quenching of the phthalocyanine fluorescence, again possibly via an electron transfer process.

3. Conclusions

We have synthesised a range of new silicon-Pc derivatives possessing axial substituents, which effectively prevent aggregation of the Pc chromophores as shown by the very sharp transition in their visible absorption and emission spectra. Altering the axial substituents does not significantly change the λ_{max} values. The luminescence properties are characterised by long lifetimes and high quantum yields, except for compound **9** where the two axial phenoxy substituents lead to significant quenching of the Pc fluorescence, possibly via an electron transfer process. Future work will address new functionalisation modes at the silicon centre and at the periphery of the Pc platform to enable further tuning of the optoelectronic and structural properties of these interesting materials.

4. Experimental

4.1. General

General details of equipment and procedures are the same as those we have reported previously.[12] All synthetic reagents were used as supplied. Solvents were dried and distilled using standard procedures.

4.2. Synthesis

Compounds **4** and **7** were prepared as described previously.[12] Crystals of **7** were obtained by a slow diffusion of hexane into a DCM solution containing **7**.

4.2.1. Phenyl silicon-phthalocyanine chloride [PhSi(Pc)Cl].[25] 1,3-Diiminoisoindoline (10.0 g, 68.9 mmol) and phenyltrichlorosilane (17.5 mL, 109 mmol) were stirred in a mixture of tetrahydronaphthalene (175 mL) and tributylamine (75 mL) at 215 °C for 20 h. The resultant mixture was allowed to cool and then methanol (100 mL) was added. Filtration of the precipitate followed by copious washing with methanol and diethyl ether gave phenyl silicon-phthalocyanine chloride as a purple solid (6.1 g, 54%) after recrystallisation from toluene; mp>400 °C (Found: C, 69.90%; H, 3.25%; N, 17.16%. $C_{38}H_{21}N_8ClSi$ requires: C, 69.88%; H, 3.24%; N, 17.16%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.56 (2H, d, ^3J=7.8 Hz, *o*-Ph), 5.13 (2H, dd, ^3J=7.5, 7.5 Hz, *m*-Ph), 5.53 (1H, t, ^3J=7.5 Hz, *p*-Ph), 8.53 (8H, m, PcH), 9.68 (8H, m, PcH); IR (Nujol): ν_{max} 2926, 2856, 1464, 1380, 1336, 1286, 1164, 1124, 1080, 908, 727 cm^{-1}; MS (ES$^+$): *m*/*z* 652, 653, 654 [M]$^+$, 617, 618, 619 [M−Cl]$^+$.

4.2.2. Phenyl silicon-phthalocyanine 4-*tert*-butylbenzoate (1). A mixture of 4-*tert*-butylbenzoic acid (0.055 g, 0.31 mmol) and PhSi(Pc)Cl (0.20 g, 0.31 mmol) was stirred in 2-methoxyethyl ether (8 mL) at 160 °C for 3 h. Quenching of the reaction mixture in water (25 mL), followed by filtration of the resulting precipitate gave a green solid. Unreacted PhSi(Pc)Cl was removed by recrystallisation from toluene, and the filtrate was added to a 5% NaOH solution (150 cm^3). After separation of the layers and washing of the organic layer with water, evaporation of the organic layer to dryness gave **1** as a green solid (0.19 g, 78%); mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (9H, s, CH_3), 1.82 (2H, d, ^3J=6.9 Hz, *o*-PhH), 4.96 (2H, d, ^3J=8.7 Hz, ArH), 5.16 (2H, dd, ^3J=7.2, 7.2 Hz, *m*-PhH), 5.60 (1H, t, ^3J=7.0 Hz, *p*-PhH), 6.21 (2H, d, ^3J=8.7 Hz, ArH), 8.35 (8H, m, PcH), 9.66 (8H, m, PcH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.06 (CH_3), 41.30 (*C*Me$_3$), 124.36, 131.51, 133.33, 136.35, 150.32, 172.63 (CO_2) [some Pc and Ph peaks were not seen in ^{13}C NMR spectrum]; IR (DCM): ν_{max} 3054, 2988, 2367, 2340, 1420, 1270, 900, 742, 711 cm^{-1}; MS (ES$^+$): *m*/*z* 817, 818, 819 [M+Na]$^+$; HRMS found: 794.2573, calcd for $C_{49}H_{34}N_8O_2Si$: 794.2574.

4.2.3. Phenyl silicon-phthalocyanine 3-thienylacetate (2). A mixture of thiophene-3-acetic acid (0.044 g, 0.31 mmol) and PhSi(Pc)Cl (0.20 g, 0.31 mmol) was stirred in 2-methoxyethyl ether (8 mL) at 160 °C for 3 h. Workup as described for **1**, gave **2** as a blue solid (0.16 g, 69%); mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (2H, s, CH_2), 1.73 (2H, d, ^3J=8.1 Hz, *o*-Ph), 4.43 (1H, d, ^3J=3.6 Hz, thiophene-5H), 4.96 (1H, s, thiophene-2H), 5.10 (2H, dd, ^3J=8.3, 7.0 Hz, *m*-Ph), 5.56 (1H, t, ^3J=7.2 Hz, *p*-Ph), 6.11 (1H, d, ^3J=3.7 Hz, thiophene-4H), 8.35 (8H, m, PcH), 9.63 (8H, m, PcH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.34 (CH_2), 112.59, 120.31, 123.60, 124.30, 126.41, 128.78, 131.50, 132.86, 135.88, 136.34, 150.20, 164.54 (CO_2) [one peak was not seen in ^{13}C NMR spectrum]; MS (MALDI-ToF): *m*/*z* 781, 782, 783 [M+Na]$^+$.

4.2.4. Phenyl silicon-phthalocyanine phenoxide (3). Sodium phenoxide (0.036 g, 0.31 mmol) and PhSi(Pc)Cl (0.20 g, 0.31 mmol) were stirred in 1,4-dioxane (25 mL) at 102 °C for 19 h. Quenching of the reaction mixture in water (25 mL), followed by filtration of the resulting precipitate gave **3** as a dark blue solid (0.15 g, 71%) after recrystallisation from 1,2-dichlorobenzene; mp>400 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.55 (2H, d, ^3J=8.1 Hz, *o*-PhH), 5.13 (2H, dd, ^3J=7.8, 6.9 Hz, *m*-PhH), 5.52 (1H, t, ^3J=6.8 Hz, *p*-PhH), 6.78 (2H, d, ^3J=7.8 Hz, ArH), 7.19 (1H, t, ^3J=7.9 Hz, ArH), 8.53 (8H, m, PcH), 9.68 (8H, m, PcH) (2H, ArH, obscured by DMSO peaks); IR (DCM): ν_{max} 3058, 2992, 2367, 2310, 1389, 1270, 900, 746, 711 cm^{-1}; MS (MALDI-ToF): *m*/*z* 710, 711, 712 [M]$^+$, 633, 634, 635 [M−Ph]$^+$). HRMS found: 710.1997, calcd for $C_{44}H_{26}N_8OSi$: 710.1999.

4.2.5. Silicon-phthalocyanine bis-thiophene-2-carboxylate (5). 2-Thiophene-carboxylic acid (0.21 g, 1.64 mmol) and $Si(Pc)Cl_2$ (0.20 g, 0.33 mmol) were stirred together in 2-methoxyethyl ether (20 mL) at 160 °C for 15 h. Workup as described for **1** gave **5** as a blue solid (0.068 g, 26%); mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (2H, d, ^3J=3.0 Hz, thiophene-3H), 5.94 (2H, dd, ^3J=4.4, 4.4 Hz, thiophene-4H), 6.37 (2H, d, ^3J=4.2, thiophene-5H), 8.39 (8H, m, PcH), 9.71 (8H, m, PcH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 124.45, 130.45, 131.73, 135.85, 150.57 [no Pc peaks were seen in ^{13}C NMR spectrum]; IR (DCM): ν_{max} 3054, 1592, 1527, 1389, 1336, 1270, 1068, 817, 746, 707 cm^{-1}; MS (MALDI-ToF): *m*/*z* 794, 795, 796 [M$^+$], 667, 668, 669 [M−ThCO$_2$]$^+$; HRMS found: 794.0976, calcd for $C_{42}H_{22}N_8O_4S_2Si$: 794.0975.

4.2.6. Silicon-phthalocyanine bis-thiophene-3-carboxylate (6). Following the procedure for **5**, 3-thiophene-carboxylic acid (0.21 g, 0.33 mmol) and $Si(Pc)Cl_2$ (0.2 g, 0.33 mmol) gave **6** (0.045 g, 17%); mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.98 (2H, m, thiophene-5H), 5.14 (2H, s, thiophene-2H), 6.12 (2H, m, thiophene-4H), 8.40 (8H, m, PcH), 9.71 (8H, m, PcH) [thienyl-2,4 proton peaks could not be cleanly resolved and are listed as multiplets]; MS (ES$^+$): *m*/*z* 794, 795, 796 ([M]$^+$), 667, 668, 669 [M−ThCO$_2$]$^+$; HRMS found: 794.0975, calcd for $C_{42}H_{22}N_8O_4S_2Si$: 794.0975.

4.2.7. 3,5-Diphenylbenzoic acid. Benzeneboronic acid (1.00 g, 8.20 mmol), 3,5-dibromobenzoic acid (1.10 g, 3.92 mmol), $Pd(PPh_3)_2Cl_2$ (0.58 g, 0.83 mmol) and degassed THF (100 mL) were stirred at room temperature for ca. 30 min. Degassed aqueous Na_2CO_3 solution (15 mL) was added and the mixture was stirred for 96 h at 100 °C. The solvent was evaporated in vacuo, ethyl acetate (100 mL) was added and the reaction was washed twice with water (100 mL). The layers were separated and the aqueous layer was acidified with concd HCl to pH 1. The resultant brown precipitate was filtered and placed in a Soxhlet extractor for 95 h (solvent: ethyl acetate). Evaporation of the solvent in vacuo gave 3,5-diphenylbenzoic acid as a light brown solid (0.512 g, 47%); mp 246 °C (Found: C, 82.92%, H, 5.11%. $C_{19}H_{14}O_2$ requires: C, 83.19%, H, 5.14%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44 (2H, m, ArH), 7.50 (4H, m, ArH), 7.67 (4H, m, ArH), 8.05 (1H, t, ^4J=1.8 Hz, ArH), 8.32 (2H, d, ^4J=1.8 Hz, ArH), 11.24

(1H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.63, 128.03, 128.33, 129.34, 130.47, 131.52, 140.32, 142.63, 170.50 (CO_2); IR (DCM): ν_{max} 3062, 2820, 2658, 2592, 2520, 1694, 1597, 1504, 1468, 1437, 1402, 1339, 1292, 1265, 1243, 948, 894, 738, 699, 643 cm^{-1}; MS (MALDI-ToF): *m/z* 274 $[M]^+$, 229 $[M-CO_2H]^+$.

4.2.8. Silicon-phthalocyanine bis(3,5-diphenylbenzoate) (8). A mixture of 3,5-diphenylbenzoic acid (0.40 g, 1.64 mmol) and Si(Pc)Cl_2 (0.20 g, 0.33 mmol) was stirred in 2-methoxyethyl ether (20 mL) at 160 °C for 20 h. Workup as described for **1** gave **8** (0.10 g, 28%) as a bright blue solid; mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 6.68 (8H, m, ArH), 7.07 (12H, m, ArH), 7.54 (2H, m, ArH), 7.72 (2H, m, ArH), 8.28 (2H, m, ArH), 8.41 (8H, m, PcH), 9.74 (8H, m, PcH); ^{13}C NMR (125 MHz, $CDCl_3$) 124.55, 125.77, 126.65, 127.50, 128.75, 131.81, 135.89, 139.60, 140.44, 150.62, 159.70, 168.07 [all the Pc peaks and one ligand peak were not seen in ^{13}C NMR spectrum]; IR (DCM): ν_{max} 3050, 2362, 2340, 1390, 1270, 896, 746, 711 cm^{-1}; MS (MALDI-ToF): *m/z* 1086, 1087, 1088 $[M]^+$; HRMS found: 1086.3099, calcd for $C_{70}H_{42}N_8O_4Si$: 1086.3098.

4.2.9. Silicon-phthalocyanine bis(4-*tert*-butylphenoxide) (9). Sodium (4-*tert*-butyl)phenoxide (0.22 g, 1.27 mmol) and Si(Pc)Cl_2 (0.20 g, 0.33 mmol) were stirred together in 2-methoxyethyl ether (20 mL) at 160 °C for 11 h. Quenching of the reaction mixture in water (75 mL) followed by filtration of the resulting precipitate gave **9** as a blue solid (0.056 g, 20%); mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.56 (18H, s, CH_3), 2.35 (4H, d, ^3J=8.4 Hz, ArH), 5.53 (4H, d, ^3J=8.7 Hz, ArH), 8.32 (8H, m, PcH), 9.60 (8H, m, PcH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.88 (CH_3), 34.42 (CCH_3), 115.06 (ArH), 126.78 (ArH), 143.86 (ArH), 153.46 (ArH) [all the Pc peaks were not seen in the ^{13}C NMR spectrum]; IR (DCM): ν_{max} 3054, 2988, 2305, 1389, 1266, 896, 751, 707 cm^{-1}; MS (MALDI-ToF): *m/z* 838, 839, 840 $[M]^+$, 781, 782, 783 $M-{}^tBu]^+$; HRMS found: 838.3200, calcd for $C_{52}H_{42}N_8O_2Si$: 838.3200.

4.2.10. Silicon-phthalocyanine bis(1-pyreneacetate) (10). 1-Pyreneacetic acid (510 mg, 1.96 mmol) and Si(Pc)Cl_2 (300 mg, 0.49 mmol) were stirred together in 2-methoxymethyl ether (3.0 mL) at 160 °C for 4 h. The solvent was removed in vacuo and the residue was filtered through a short silica gel column by eluting with DCM. The solvent was evaporated and the residue was chromatographed on silica gel using DCM as the eluent to afford compound **10** as a dark blue solid (160 mg, 32%); mp>400 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (4H, s, CH_2), 5.38 (2H, d, ^3J=7.8 Hz, pyrene), 5.52 (2H, d, ^3J=9.3 Hz, pyrene), 6.75 (2H, d, ^3J=7.8 Hz, pyrene), 6.79 (2H, d, ^3J=9.3 Hz, pyrene), 7.67 (2H, d, ^3J=8.8 Hz, pyrene), 7.92 (2H, d, ^3J=7.3 Hz, pyrene), 8.07 (2H, d, ^3J=9.3 Hz, pyrene), 8.09–8.16 (10H, m, PcH+pyrene), 8.31 (2H, d, ^3J=7.3 Hz, pyrene), 8.97 (8H, m, PcH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.68 (CH_2), 123.20 (PcH), 123.48, 123.66, 124.26, 124.67, 125.06, 125.45, 125.48, 126.32, 126.45, 126.89, 126.98, 127.58, 129.24, 130.43, 130.53, 131.35, 134.70, 149.12, 164.14 (CO_2); MS (MALDI-ToF): *m/z* 1058, 799.1, 800.1, 801.1 ($[M-$pyrene-$CH_2CO_2]^+$); HRMS found: 1058.2785, calcd for $C_{68}H_{38}N_8O_4Si$: 1058.2785.

4.2.11. Silicon-phthalocyanine bis(1-pyrenebutanoate) (11). 1-Pyrenebutyric acid (950 mg, 3.29 mmol) and Si(Pc)Cl_2 (500 mg, 0.82 mmol) were stirred together in 2-methoxymethyl ether (3.0 mL) under argon at 160 °C for 3 h. The solvent was removed in vacuo and the residue was filtered through a short silica gel column by eluting with DCM. The solvent was evaporated and the residue was chromatographed on a preparative silica gel TLC plate (2 mm thickness) using DCM as eluent to afford compound **11** (30 mg, 3%) as a dark blue solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.50 (4H, t, ^3J=6.8 Hz, $CH_2CH_2CH_2CO_2$), −0.30 (4H, m, $CH_2CH_2CH_2CO_2$), 0.88 (4H, m, $CH_2CH_2CH_2CO_2$), 6.57 (2H, d, ^3J=7.8 Hz, pyrene), 7.12 (2H, d, ^3J=9.2 Hz, pyrene), 7.62 (2H, d, ^3J=7.8 Hz, pyrene), 7.68 (2H, d, ^3J=9.2 Hz, pyrene), 7.97 (2H, d, ^3J=7.8 Hz, pyrene), 7.99–8.18 (6H, m, pyrene), 8.24 (8H, m, PcH), 8.31 (2H, d, ^3J=7.8 Hz, pyrene), 9.56 (8H, m, PcH); MS (ES^+): *m/z* 1114.3, 1115.3, 1116.3 $[M]^+$; HRMS found: 1114.3412, calcd for $C_{72}H_{46}N_8O_4Si$: 1114.3411.

4.3. X-ray crystallography

The X-ray diffraction experiment was carried out on a Bruker SMART 3-circle diffractometer with an APEX CCD area detector, using a 60 W Mo-target microfocus Bede Microsource® X-ray generator with glass polycapillary X-ray optics (Mo Kα radiation, graphite monochromator, $\bar{\lambda}$=0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structure was solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL software (version 6.12, Bruker AXS, Madison WI, USA, 2001). Crystal data: $C_{44}H_{26}N_8O_4S_2Si$, **7**, M=822.94, T=120 K, monoclinic, space group $C2/c$ (no. 15), a=23.306(4), b=8.718(2), c=36.791(7) Å, β=107.98(1)°, V=7110(2) Å^3, Z=8, D_c=1.538 g cm^{-3}, μ=0.25 mm^{-1}, 22,658 reflections with $2\theta \leq 50°$, R_{int}=0.129, final R=0.059 on 3556 reflections with $I \geq 2\sigma(I)$, $wR(F^2)$=0.147 on all 6216 unique reflections. CCDC-290547.

4.4. UV–vis absorption and fluorescence

Background corrected UV–vis absorption spectra were recorded on a Unicam UV2 UV–vis spectrometer controlled by a PC using Vision 3.50 software. Fluorescence spectra were recorded on either a Spex Fluorolog 3-22 spectrofluorimeter or a Spex Fluoromax 2 spectrofluorimeter and were corrected for the spectral response of the machine. Lifetimes were recorded using the technique of time correlated single photon counting.[19,26] Quantum yields were determined by the comparative method of Williams et al.,[27] measurements being taken using several dilutions of each sample to negate concentration effects. Disulfonated aluminium Pc (Φ_f=0.40) was used as the standard.

Acknowledgements

We thank EPSRC for funding (C.A.B.).

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Tetrahedron 62 (2006) 9440–9445

Microwave induced thermal gradients in solventless reaction systems

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Received 13 April 2006; revised 8 July 2006; accepted 11 July 2006
Available online 10 August 2006

Abstract—Development of thermal heterogeneity under microwave irradiation for solventless solid–liquid phase-transfer catalytic (PTC) reactions has been studied by means of a thermovision camera and fiber-optics thermometer.

1. Introduction

Recently, microwave irradiation has been found to be a very efficient tool to improve yields of a great number of chemical transformations.[1–3] Many authors suppose that it might be a result of specific microwave interaction with reagents on molecular scale when the reaction system's polarity is increased from a ground state to a transition state[4] or on macromolecular scale, which in turn influences yield[5] as well as selectivity.[6] Most recent critical reviews concerned with these effects were published by Perreux and Loupy,[4] Nuchter et al.,[5] and de la Hoz et al.[6]

The most successful examples of microwave applications were found to be related to the use of heterogeneous solvent-free systems, in which microwaves interact directly with reagents and, therefore, can more efficiently drive chemical reactions. The possible accelerations of such reactions are expected to be optimal since they are not moderate or impeded by solvents.[7] On the other hand, in diluted homogenous chemical systems in which it is possible to obtain a good thermal homogeneity by use of an effective mechanical stirring or/and boiling chips, it was proved that acceleration of microwave-assisted reactions was rather negligible;[8,9] however, it could be also dependent on the mechanism of the reaction.[10]

Temperature measurement during microwave irradiation of materials is the major problem in microwave-enhanced processing of materials. However, there is a general agreement that the application of fiber-optics thermometers is the only reliable way to determine temperature under microwave conditions; using a thermovision camera, we reported that the application of a pyrometer and fiber-optics thermometer did not give correct values while high temperature gradients were developed within reaction mixtures.[11–13] For example, it was shown that heterogeneous support like Magtrieve, which is a strong microwave absorber, could reach higher temperature than the boiling point of a solvent applied in the synthesis, but a pyrometer and fiber-optics thermometer did not show this effect.[11,12] In another example, in the case of viscous homogenous reaction media like epoxy resins, a thermovision camera showed high temperature gradients on the surface of the reaction mixtures. Since in some parts of the sample local temperatures under microwave irradiation can be different, pyrometers as well as fiber-optics thermometers gave only information about the local temperatures but bulk temperature of the reaction mixture was hard to estimate.[13]

2. Results and discussion

In the present study, we decided to apply the microwave protocol to investigate the reaction of salicylaldehyde with ethyl ester of chloroacetic acid under solid–liquid PTC conditions in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB) as a catalyst. The reaction resulted in the formation of (2-formylphenoxy)acetic acid ethyl ester (**1**), which after further intermolecular condensation gave benzofuran-2-carboxylic acid ethyl ester (**2**)—the final product (Scheme 1).

Keywords: Microwave irradiation; Benzofuran; Solventless solid–liquid reaction.
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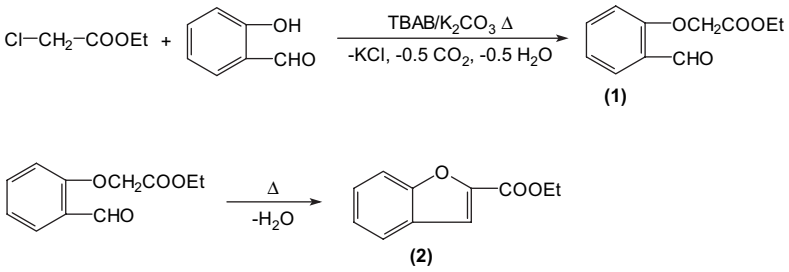
doi:10.1016/j.tet.2006.07.038



Scheme 1. Preparation of benzofuran-2-carboxylic acid ethyl ester.

This reaction was chosen as the test reaction because in our previous study we had found that it was an effective way for the synthesis of a number of benzofuran derivatives.[14] When the reaction was run with the same reaction temperature profiles under both conventional (oil bath) and microwave conditions, different distributions of the intermediate (**1**) and final product (**2**) were determined (Table 1). It is worth stressing that the product distribution was much strongly affected by the microwaves, and the yield of **2** was higher in comparison with conventional experiments when the reaction was run at lower temperatures; for example, 85 °C (Table 1, entries 4 and 5) versus 110 °C (Table 1, entries 2 and 3). Thus, in order to observe the influence of microwave irradiation on chemical reactions if the yields were high under both microwave and conventional conditions it was required not to increase but decrease the reaction temperatures, which have been shown in previous reports.[15] In our case, it allowed finding a temperature range where yields or/and product distributions were different for both protocols (Table 1). Furthermore, the addition of a small amount of polar or non-polar solvents also influences the product distribution. In this case, two solvents were applied: one capable of strongly coupling and the second not coupling with microwaves, i.e., ethanol and cyclohexane, respectively. The addition of ethanol strongly shifted the product distribution toward the final product (**2**), whereas the addition of cyclohexane resulted in much lower yield of **2**.[16] The extensive discussion on the influence of reaction medium, reaction mechanism, temperature, temperature measurement method, and stirring on the reaction yield and selectivity under microwave irradiation in comparison with conventional thermal heating can be found in the literature.[17,18]

For the purpose of the present investigation on thermal gradients in heterogeneous systems in which the development of such gradients has been confirmed by both theoretical calculations as well as experimental results,[19–21] we decided to repeat our previous experiments[14] under slightly modified conditions so that it was possible to use a thermovision camera. The development of a temperature gradient (superheating) within a cross-section of alumina within a Petri dish has been already presented by means of a thermovision camera. Then kinetic calculations of a theoretical reaction indicated that the yield of this reaction might be higher because of the development of temperature gradients under microwave irradiation.[20] In this paper, we were able to prove these conclusions experimentally.

First of all, we have observed that crude compounds **1** and **2** adsorbed on the surface of K_2CO_3 gave different colors (i.e., yellow (**1**) and brown (**2**)), which were utmost of importance and permitted to visually follow the progress of the reaction (Figs. 1 and 2). At the same time, temperature of the reaction mixtures and temperature of the surface were determined by fiber-optics thermometer (ReFlex, Nortech) and thermovision camera (V-20, VigoSystem), respectively. The results of the experiments under conventional conditions that were run in order to find optimal conditions for microwave experiments are shown in Table 2. Obviously, the reactions were carried out without a mechanical stirring of the reaction mixtures in order to monitor them with the thermovision camera.

Table 1. The distribution of the intermediate (**1**) and the final product (**2**) in the synthesis of benzo[*b*]furans under both conventional (Δ) and microwave (MW) conditions

No.	Temperature (°C)	Time (min)	Solvent (ml)	Yield (%)	
				1	**2**
1	110	10/MW	—	12	66
2	110	20/MW	—	—	100
3	110	20/Δ	—	4	96
4	85	20/MW	—	15	85
5	85	20/Δ	—	90	10
6	85	30/MW	Cyclohexane (1.5)	62	38
7	85	30/MW	EtOH (100%) (1.5)	0	100
8	85	30/MW	EtOH (96%) (1.5)	0	100
9	85	30/Δ	EtOH (100%) (1.5)	47	53

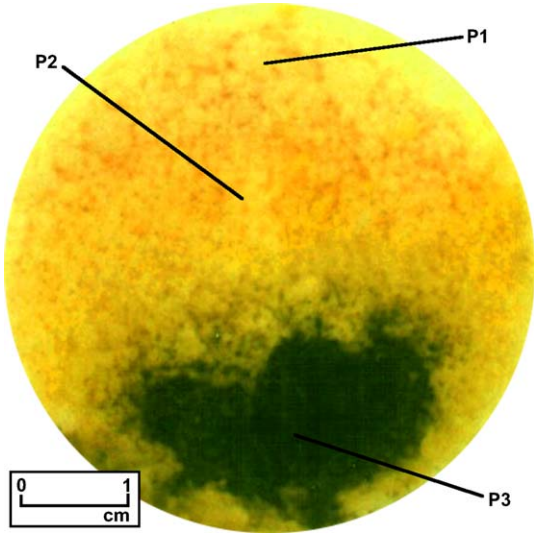


Figure 1. Photograph of the surface of the reaction mixture (Table 3, entry 1).

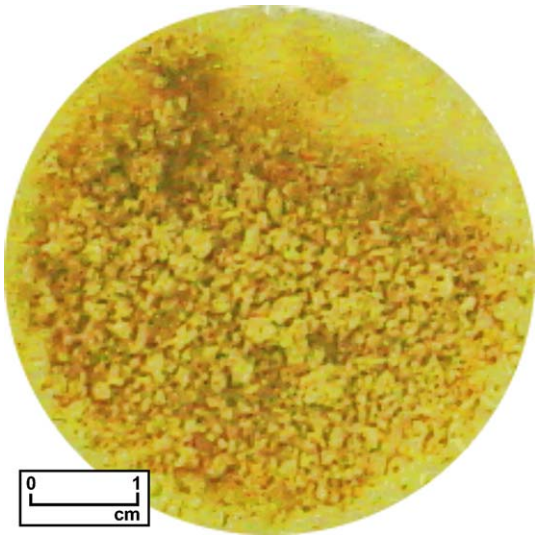


Figure 2. Photograph of the surface of the reaction mixture (Table 3, entry 2).

Table 2. The influence of temperature on the product selectivity of **1** and **2** in the synthesis of benzo[*b*]furans under conventional conditions (5 min)

No.	Temperature (°C)	Catalyst (0.5 mmol)	Selectivity[a] (%)	
			1	**2**
1	70	TBAB	100	0
2	95	TBAB	48	52
3	115	TBAB	12	88
4	135	TBAB	0	100
5	145	TBAB	0	100
6	95	—	100	0
7	110	—	74	26
8	150	—	11	89
9	80[b]	TBAB	0	0
10	80[b]	—	0	0
11	90[c]	TBAB	0	0
12	90[c]	—	0	0
13	110[d]	TBAB	3	97
14	85[d]	TBAB	71	29

[a] The reaction's selectivity is determined by GC/MS.
[b] Al_2O_3 was used instead of K_2CO_3.
[c] Without any solid support.
[d] The reaction time was 20 min.

However, the addition of the catalyst (i.e., TBAB) strongly increased the yield of the final product (**2**) (Table 2, entries 1–5), it was also possible to carry out the reaction without the catalyst at elevated temperatures (Table 2, entries 6–8). Moreover, the use of TBAB resulted in the release of volatile products of its decomposition upon the surface of the reaction mixtures that in turn strongly influenced the temperature measurements by means of the thermovision camera (i.e., release of any vapor within the reaction vessel immediately leads to disability of the thermovision camera).

It was also found that the reaction did not occur when K_2CO_3 was substituted with another commonly used mineral support, i.e., Al_2O_3 or when the reagents were applied without any support (Table 2, entries 9 and 10, respectively). Finally, for the purpose of microwave investigation with the thermovision camera it was decided to carry out the reaction on K_2CO_3 support at 110 °C without the catalyst. The results of the microwave experiments are presented in Table 3.

Table 3. Average[a] reaction selectivity depending on experimental mode

No.	Selectivity[a] (%)		Description
	1	**2**	
1	33	67	No stirring
2	70	30	Vessel rotation
3	84	16	Vessel rotation and stirring
4	100	0	No stirring, addition of 6 ml of decane
5	67	33	No stirring, vessel rotation
6	77	23	No stirring, vessel rotation

[a] Average selectivity determined by GC/MS from entire reaction mixture. All microwave experiments were carried out in the same condition: maximal microwave power 240 W, maximal temperature 110 °C.

The first three experiments (Table 3, entries 1–3) were carried out in order to check the influence of the rotation of the reaction vessels and stirring of the reaction mixture on process selectivity. In the case of the first experiment (entry 1), the reaction mixture was placed in the microwave reactor without any rotation of the reaction vessel. In the second case (entry 2), there was only applied a vessel rotation, while in the third case (entry 3) there was used the vessel rotation and mechanical stirring by immobilizing the quartz spatula inside the reaction vessel.

At the beginning, the development of thermal gradients during microwave experiments on the surface of reaction mixtures was confirmed visually, i.e., it was possible to observe the formation of brown spots in all the places where the compound **1** was converted to **2** (Figs. 1 and 2). These observations were later proved by the analysis of the samples taken from different places from the surface of the reaction mixtures. Also, thermal gradients were revealed by means of the thermovision camera, which detected strong temperature increase in the central part (on the side of the microwave waveguide in the reactor) of the reaction mixture in comparison to outer regions (Fig. 4).

Eventually, the existence of thermal gradient was proved by the quantitative analysis by taking samples from different places of reaction mixtures that exhibited different temperatures during the reactions (Figs. 1 and 4, entries P1, P2, and P3). The results are summarized in Table 4. It can be seen that the highest conversion of **1** to **2** was found for the sample P3, which exhibited the highest temperature (ca. 200 °C) during the microwave experiment (Table 4, entry 3). Then the conversions of **1** to **2** 45% and 0% were observed for the samples P2 and P1, which gained lower temperatures than P3, i.e., 125 °C (Table 4, entry 2) and 70 °C (Table 4, entry 1), respectively. These results are in good agreement with the experiments under conventional conditions (Table 1), in which it was shown that only the samples that reached higher temperature (more than 150 °C) can give high

Table 4. Local composition of the reaction mixture (Figs. 1 and 4)

Sample	Color	Temperature (°C)	Yield (%)	
			1	**2**
P1	Light	70	100	0
P2	Brown	125	55	45
P3	Dark	200	0	100

conversion of **1** to **2** (Table 1, entry 8) without a catalyst. For the samples that reached temperatures lower than 100 °C (Table 1, entry 6), no conversion of **1** to **2** was observed at all.

It has been shown that the investigated reaction system is characterized by the strong interaction with microwaves, which results in very high heating rates. Therefore, a lot of heat can be generated within a small amount of the material in a relatively short time (3 min). This behavior leads to overheating and difficulties in proper temperature measurement. The investigation has proved the existence of thermal heterogeneity in microwave irradiated reaction mixtures without rotation, occurring as a result of significant differences in intensity of microwave field in a reactor cavity.

The rotation of the reaction vessel within the microwave cavity decreases substantially the temperature gradient; however, still the regions are characterized by different colors, i.e., different concentrations of **1** and **2** in the reaction mixture (Fig. 2). In fact, the rotation of reaction vessels reduced overheating, the reaction mixture was exposed to more homogenous microwave field, and, in turn, the yield of **2** was lower (Table 3, entry 2) than for the experiments without rotation (Table 3, entry 1) but much closer (i.e., comparable) to the yield of the reaction under conventional conditions (Table 2, entry 7).

The mechanical stirring with a quartz spatula placed within the reaction mixture improved the thermal homogeneity of the reaction mixture to a greater extent than the rotation of the reaction vessels (Table 3, entry 3); the results are comparable to those obtained under conventional conditions (Table 2, entry 7). Although, it is hard to jump to further conclusions since we did not run conventional protocol with the stirring of reaction mixtures, it can be seen (Fig. 3) that the surface of the reaction mixture was more homogenous in comparison with the experiments with vessel rotation (Fig. 2) and, in particular, without rotation (Fig. 1). Two additional experiments (Table 3, entries 5 and 6) were performed in order to observe the repeatability of the microwave protocol and they gave satisfactory results. It was also shown that the addition of an inert liquid, *n*-decane (Table 3, entry 4), which was added in such an amount that it formed 1–2 mm layer over the top of the reaction mixture, improved temperature homogeneity too; however, it was a bit difficult to observe with the thermovision camera and visually, but the fiber-optics thermometer showed the same temperature (i.e., ca. 110 °C) at every region of the reaction mixture.

Figure 3. Photograph of the surface of the reaction mixture (Table 3, entry 3).

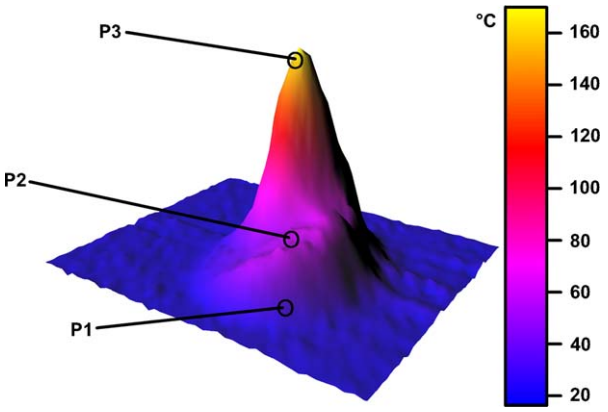


Figure 4. Thermovision photograph of the surface of the reaction mixture during the experiment (Table 3, entry 1).

The results presented above are important because one can expect that overall reaction yields given in Table 3 should be similar for all the experiments and do not show significant differences during additional rotation of the vessels and/or stirring of the reaction mixtures. It can be assumed that the overall energy input given by microwaves is similar in all the cases, thus the reaction rate can be different in different regions of the reaction mixture because temperature is different but overall reaction rates should be comparable. In fact, we observed an opposite situation, the increase in temperature homogeneity caused a decrease of the overall reaction yields and made them comparable to those obtained under conventional conditions.

Eventually, Figure 5 illustrates the relation between temperature measured by the fiber-optics thermometer and thermovision camera versus reaction time for the two experiments without and with an inert solvent (Table 3, entries 1 and 4, respectively). In all the cases, temperatures measured by the thermovision camera were lower than those measured by the fiber-optics thermometer. It can be also seen that the temperature differences between the fiber-optics thermometer and thermovision camera were higher for the experiment with the inert solvent (Table 3, entry 4) in comparison with the experiments without the solvent (Table 3, entry 1). It can be explained by the difficulties in temperature measurements by the thermovision camera in the presence of solvent, which was mentioned earlier, as well as heat transfer process of non-polar liquids that proceeds only via conventional heat transport (i.e., thermal conduction) that is slower than microwave heating. Thus, in such a case temperature measurements under microwave irradiation were inaccurate for two possible reasons. First, the rate of heating is so high and measurement devices have some specific thermal inertia during temperature measurements. Second, there

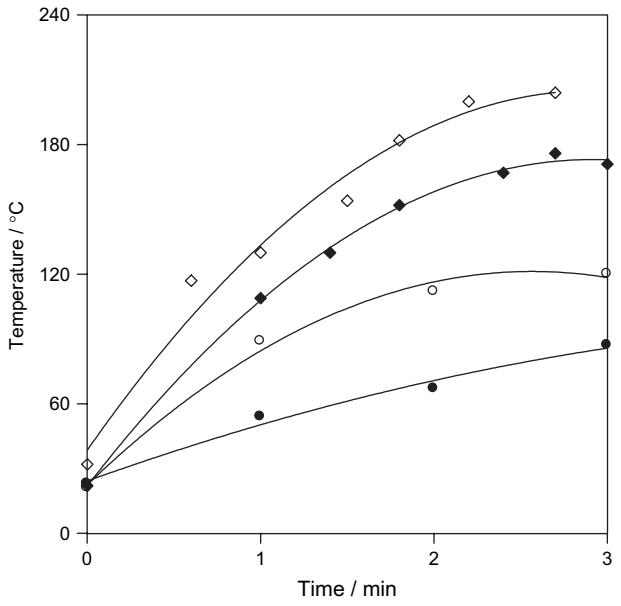


Figure 5. Relation between time and temperature, during reaction progress, measured by fiber-optics thermometer in the hot zone—P3 (◇) and shown by thermovision camera as maximal (◆) (Table 3, entry 1). For the sake of comparison two curves were added: temperature measured by the fiber-optics thermometer placed in the position identified as the hot zone (○) and the camera (●) for the experiments with an inert solvent (Table 3, entry 4).

are only appointed local temperatures (fiber-optics thermometer) or average temperatures (thermovision camera) that in the latter case correspond only to the temperature of surface, which is lower than the bulk temperature.

3. Conclusion

In conclusion, a proper temperature measurement in case of heterogeneous reaction mixture is very difficult. In order to maintain a good temperature homogeneity and make some comparison with the experiments under conventional conditions, an effective stirring has to be provided, perhaps, together with a small amount of an inert solvent. There is a general agreement that the application of fiber-optics thermometers is the reliable way to determine temperature under microwave conditions. Applying the thermovision camera, we found that for the reactions in heterogeneous systems under microwave irradiation, the temperature measurement with a fiber-optics thermometer can lead to serious errors like pyrometry; in particular for those experiments that are planned without any attention being paid to temperature homogeneity of the reaction mixture. In the latter case, a high temperature gradient within the reaction mixture generated by the microwaves leads to a higher conversion of reactants or/and reaction rates, which in turn might be a reasonable explanation to the so-called non-thermal microwave effects, i.e., an increase of reaction rates that is inadequate to the temperature of reaction medium. Therefore, before considering the increase of reaction rates by special microwave effects (thermal or non-thermal), first, we need to consider all the factors that might influence chemical reactions under microwave conditions like a reaction mechanism, temperature profiles (gradients), and, in particular, proper design of our experiments.

4. Experimental

All chemicals were purchased from Aldrich and used as received. The reactions were carried out in a single-mode microwave reactor with a continuous power regulation (SynthWave 402, Prolabo). The inlet at the top of the reactor allowed the application of the thermovision camera (Vigo V-20E2) and the introduction of the fiber-optics thermometer (ReFlex, Nortech), which was used to control the temperature during microwave experiments. GC/MS spectra were determined on GC/MS 5890 SERIES II HEWLETT–PACKARD gas chromatograph equipped with Ultra 2 (25 m×0.25 mm×0.25 μm) column with HEWLETT–PACKARD 5971 Series Mass Detector.

In a typical experiment, the reactions were carried out by simply mixing K_2CO_3 (2.70 g, 20 mmol), salicylaldehyde (0.61 g, 5 mmol), chloroacetic acid ethyl ester (1.22 g, 10 mmol), and a catalyst (TBAB 0.16 g, 0.50 mmol). Then the mixtures were irradiated for 3 min in an open quartz vessel (4 cm of diameter) in the microwave reactor or heated for 5 min in a thermostated oil bath (2 min were added in comparison to microwave experiments because of a thermal inertia of the vessel). Finally, the reaction mixtures were extracted with 20 ml of acetone to estimate overall yields by means of GC/MS.

Acknowledgements

This work was undertaken as part of the EU sponsored D32 COST Program (Chemistry in High-Energy Microenvironments).

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Tetrahedron 62 (2006) 9446–9455
Tetrahedron

A general approach to crinine-type *Amaryllidaceae* alkaloids: total syntheses of (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine

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Received 14 June 2006; revised 6 July 2006; accepted 7 July 2006
Available online 10 August 2006

Abstract—A general strategy for synthesizing the crinine-type *Amaryllidaceae* alkaloids was developed. And total syntheses of four representative crinine-type *Amaryllidaceae* alkaloids: (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine, were accomplished via a common intermediate **17**. This crucial precursor was achieved on the basis of the NBS-promoted semipinacol rearrangement recently developed by our group and an intramolecular Michael addition, which efficiently constructed the sterically congested quaternary carbon center and the hydroindole skeleton of the crinine-type alkaloids, respectively.

1. Introduction

The crinine-type *Amaryllidaceae* alkaloids possess a wide range of biological activities.[1,2] For example, (±)-haemanthidine (**1**),[3] (±)-tazettine (**3**),[4] and (±)-crinamine (**4**)[5] show high analgesic, mild anticancer, and cytotoxic activities, respectively. In particular, (±)-pretazettine (**2**),[3] which exhibits high anticancer activity, has recently stimulated extremely the interest of chemists.[3,6] The important structural features of these alkaloids include an arylhydroindole core and a *cis* or *trans* hydroxyl group in the pyrrolidine ring, which represent central synthetic challenges. To date, several creative strategies had emerged to address these problems.[3–5,7] Despite the availability of many synthetic methods, it is necessary to develop more general procedures.

As a part of our ongoing research program for synthesizing *Amaryllidaceae* alkaloids,[8] we report herein a new general approach to the more complex crinine-type alkaloid members **1**–**4** (Fig. 1).

Our retrosynthetic analysis is shown in Scheme 1. We envisioned that all four target molecules could be synthesized from the same crucial arylhydroindole enone **5**, which might be prepared from **6** through an intramolecular Michael addition. The requisite double bond and 1,2-amino alcohol unit of intermediate **6** would be derived from the bromine and aldehyde functions in compound **7**, respectively. The key sterically congested quaternary carbon center in **7** could be constructed by the NBS-promoted semipinacol rearrangement of allylic alcohol **8**.

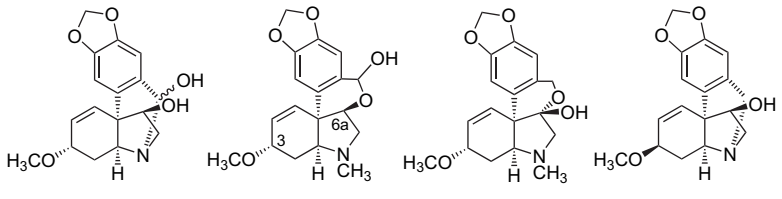

Figure 1. Representative member of the crinine-type *Amaryllidaceae* alkaloids.

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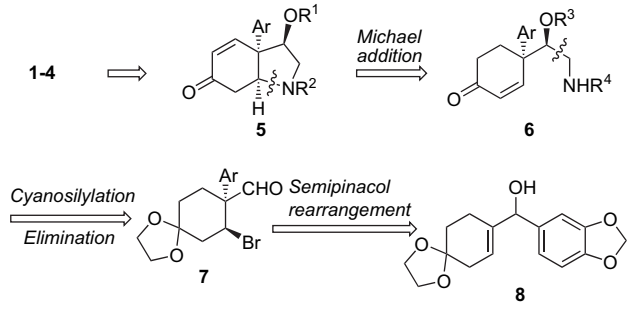
doi:10.1016/j.tet.2006.07.027

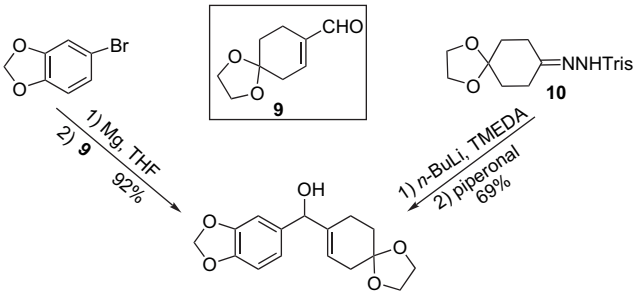


Scheme 1. Retrosynthetic analysis of target molecules **1**–**4**; Ar=3,4-methylenedioxyphenyl.

2. Results and discussion

2.1. Preparation of allylic alcohol 8

The starting allylic alcohol **8** was prepared by two means. One was the addition of aldehyde **9**[9] to the Grignard reagent of 4-bromo-1,2-(methylenedioxy)benzene, the other was the Shapiro reaction between **10**[8d] and piperonal (Scheme 2).



Scheme 2. Preparation of allylic alcohol **8**.

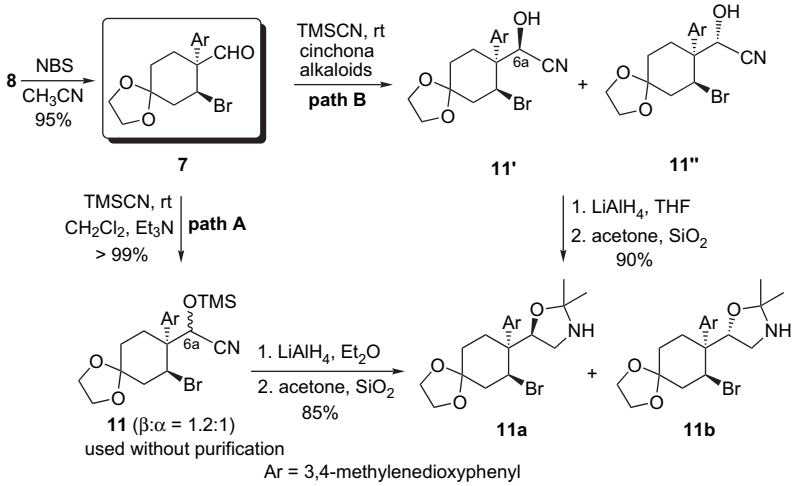
2.2. Preparation of aldehyde 7 and compounds 11a and 11b

By utilizing the work recently developed by our group on the use of *N*-bromosuccinimide (NBS)-promoted semipinacol rearrangement to build the quaternary carbon center,[8b] the aldehyde **7** was easily prepared from the alcohol **8** in excellent yield (95%) and with high diastereoselectivity (d.r.>99:1). In order to introduce the hydroxyl group at C-6a position and extend a nitrogen-containing carbon chain, the cyanation method was applied. The addition of trimethylsilylcyanide (TMSCN) to the aldehyde **7** set the hydroxyl group at C-6a position, and the corresponding trimethylsilyl ether adducts (**11**, a mixture of two isomers), which could not be separated by silica gel chromatography, were then reduced with $LiAlH_4$. After protection of the amino alcohol with acetone, two separable diastereoisomers (**11a** and **11b**) were obtained in 85% yield over three steps (path A in Scheme 3). However, the diastereoselectivity was very low (**11a/11b**=1.2:1) when triethylamine (Et_3N) was used as a base. To increase the diastereoselectivity of the initial addition reaction, other conditions were investigated (Table 1). The cinchona alkaloids were selected as the base in place of Et_3N. Notably, in all tests with different cinchona alkaloids, only the cyanohydrin products, but none of the corresponding TMS adduct were isolated (Scheme 3). The use of a stoichiometric quantity of the hydroquinine was necessary (entries 9–11, Table 1). Evaluation of bases and solvents showed that the best conditions for the reaction,

Table 1. Preparation of cyanohydrin in different conditions[a]

Entry	Solvent	Base/equiv	Time	Ratio[b] **11′**/**11″**	Yield[c] (%)
1	Et_2O	Quinine/1	2 d	—[d]	Trace
2	THF	Quinine/1	2 d	—[d]	Trace
3	Toluene	Quinine/1	2 d	2.1:1	62
4	CH_2Cl_2	Quinine/1	2 d	2.8:1	83
5	CH_2Cl_2	Quinidine/1	2 d	2.3:1	81
6	CH_2Cl_2	Cinchonine/1	2 d	2.0:1	78
7	CH_2Cl_2	Cinchonidine/1	2 d	2.6:1	76
8	CH_2Cl_2	Hydroquinidine/1	2 d	3.28:1	79
9	CH_2Cl_2	Hydroquinine/0.1	4 d	1.61:1	56
10	CH_2Cl_2	Hydroquinine/0.5	3 d	1.88:1	63
11	CH_2Cl_2	Hydroquinine/1	2 d	3.5:1	82
12	CH_2Cl_2	Hydroquinine/2	10 h	2.7:1	90

[a] Reaction was carried out on a 0.1 mmol scale with 1.2 equiv of TMSCN in 2 mL of solvent for 2 d, unless noted otherwise.
[b] Determined by ^1H NMR.
[c] The yield was overall yields of **11′** and **11″**, based on the recovered material.
[d] Not determined.

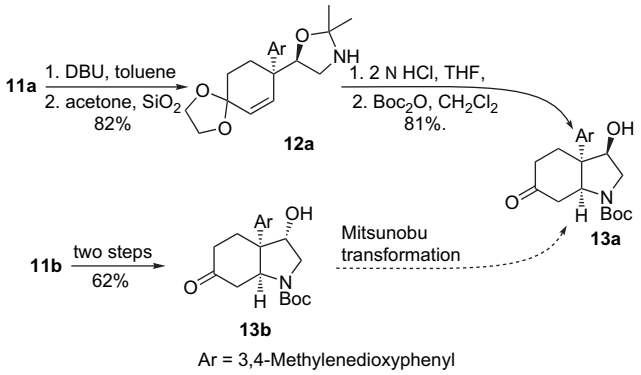


Scheme 3. Preparation of aldehyde **7** and compounds **11a** and **11b**.

which provided product **11′** and **11″** (ratio=3.5:1), were hydroquinine as base and CH_2Cl_2 as solvent (entry 11, Table 1). Interestingly, the decrease in diastereoselectivity was observed when a twofold hydroquinine was employed (entry 12, Table 1). As shown in Scheme 3, **11a** and **11b** were also obtained from **11′** and **11″** under the similar reaction conditions. The major isomer **11a** was identified to be the desired intermediate (as will be discussed below).

2.3. Construction of arylhydroindole framework 13a

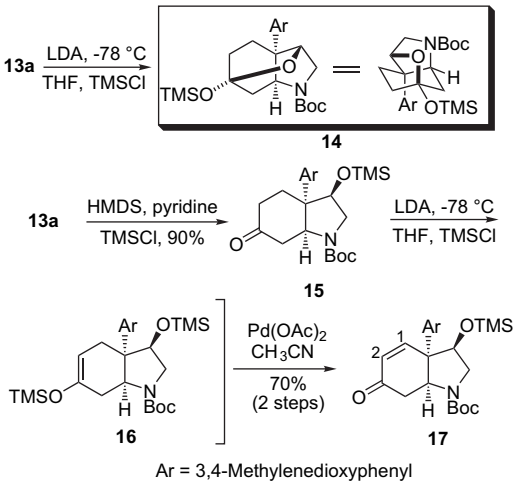
The major isomer **11a** was dehydrobrominated by treatment with 1,8-diazabicyclo[5.4.0]under-7-ene (DBU) in refluxing toluene, and the requisite double bond of **12a** was introduced in 82% yield. Under acidic condition, **12a** was deprotected and transformed into the corresponding secondary amine in nearly quantitative yield,[4c] and without purification this Michael addition product was treated with di-*tert*-butyl dicarbonate (Boc_2O) to provide the crucial intermediate **13a** in 81% yield (Scheme 4).[10] Successively, the transformation of the minor isomer **11b** into the intermediate **13a** was also investigated (Scheme 4). The diastereoisomer **13b** (6a-*epi*-**13a**) was prepared in the same fashion from **11b** in 62% yield (two steps). With the isomer **13b** in hand, we next focused on the inversion of the configuration at C-6a position. Under the standard Mitsunobu conditions,[11] the reactions did not provide the expected product **13a**, but resulted only in the decomposition of the starting material.



Scheme 4. Construction of the arylhydroindole framework (**13a** and **13b**).

2.4. Preparation of enone 17 and determination of β-OH at C-6a position

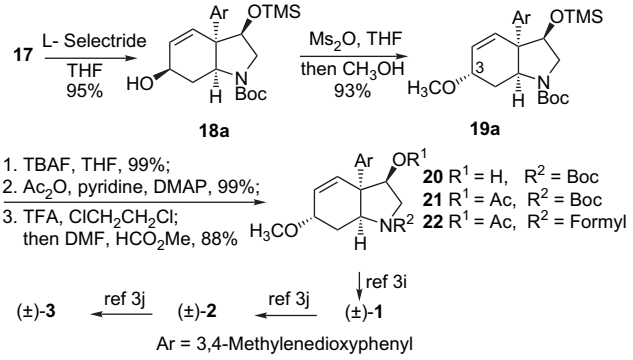
With the rapid construction of the arylhydroindole framework **13a**, installation of the C1–C2 double bond was investigated. Initially we anticipated that the silyl enol ether **16** could be synthesized from **13a** by silylation of the hydroxyl group and enolization of the carbonyl group in a one-pot process (Scheme 5). However, unexpected compound **14** was isolated in excellent yield under the conditions of lithium diisopropylamine (LDA) and chlorotrimethylsilane (TMSCl). The formation of **14** is a fortuitous proof of the relative stereochemistry of the hydroxyl group at C-6a position, since the secondary alcohol of opposite configuration cannot form an oxygen bridge at C-3 position.[12] To our knowledge, as an efficient chemical method to determine the key hydroxyl group configuration at C-6a position in this hydroindoline system, this conversion is first reported by our group.[13] Due to the failure of the one-pot operation, the hydroxyl of **13a** was first protected as the silyl ether under the Sweeley's condition,[14] giving compound **15** in excellent yield. Enolization of **15** and trapping with TMSCl afforded the silyl enol ether **16**, which was oxidized directly by $Pd(OAc)_2$[15] to furnish the desired enone **17** in 70% yield (Scheme 5).



Scheme 5. Determination of β-OH at C-6a position and preparation of enone **17**.

2.5. Total syntheses of haemanthidine (1), pretazettine (2), and tazettine (3)

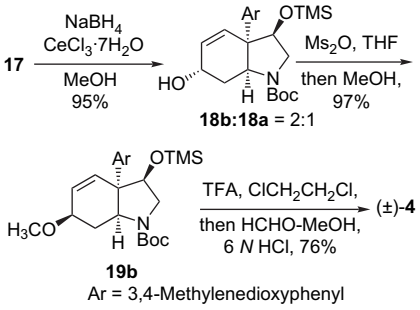
Having introduced the correct C1–C2 double bond, we then proceeded to set the methyloxy group at the C-3 position in stereoselective manner. Enone **17** was reduced with L-Selectride in THF at −78 °C to afford allylic alcohol **18a** as a single diastereoisomer in excellent yield, whose formation arose from the attack of hydride on the *exo* face of the hydroindole system. Using Whitlock's method,[16] we inverted the β-hydroxyl group of **18a** into the required α-methoxy derivative **19a** in 93% yield. The alcohol **20** was easily prepared from compound **19a** and converted into the *N*-formyl derivative **22** via acetate **21** (86% yield for four steps). Following the known procedures,[3i,3j] we achieved the total syntheses of **1**, **2**, and **3** from derivative **22** (Scheme 6), whose spectral data were identical to those reported in the literature.[3i,3j]



Scheme 6. Total syntheses of haemanthidine (**1**), pretazettine (**2**), and tazettine (**3**).

2.6. Total synthesis of crinamine (4)

Additionally, enone **17** was reduced under Luche condition[17] at room temperature to afford allylic alcohol **18** in 95% yield (**18b**/**18a**=2:1), albeit with disappointing diastereoselectivity. Allylic ether **19b** was obtained from **18b** using the same method as in the preparation of **19a**. After removal of the Boc and TMS protecting groups of **19b** with CF_3COOH, the followed Pictet–Spengler reaction in a one-pot procedure readily gave crinamine **4** in 76% yield, whose spectral data were agreed with those reported in the literature (Scheme 7).[3i,2b]



Scheme 7. Total synthesis of crinamine (**4**).

3. Conclusion

In summary, we successfully synthesized the crinine-type *Amaryllidaceae* alkaloids including (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine using an NBS-promoted semipinacol rearrangement developed by our group and a Michael addition as the key steps, and disclosed a general strategy for synthesizing the crinine-type *Amaryllidaceae* alkaloids.

4. Experimental

4.1. General

Melting points were measured on X-4 melting point apparatus and are uncorrected. IR spectra were measured on KBr disks by using a Nicolet NEXUS 670 FTIR spectrometer. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Mercury-plus 300BB spectrometer (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR spectra), a Brucker AM-400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR spectra). The EIMS spectra were recorded on a HP5988A mass spectrometer, and the high-resolution mass spectra were recorded on Brucker Daltonics APEX II 49e spectrometer by means of the ESI technique. Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Qingdao Marine Chemical Company (China). Solvents for reaction were distilled prior to use: THF and Et_2O from Na and benzophenone, MeOH from Mg and I_2, CH_2Cl_2, Et_3N, and DMF from CaH_2, and toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under an argon atmosphere.

4.1.1. Benzo[1,3]dioxol-5-yl-(1,4-dioxa-spiro[4.5]dec-7-en-8-yl)-methanol (8).

Process A: to a stirred suspension of magnesium turnings 240 mg (10 mmol) in dry THF (20 mL) was added 1.2 mL 4-bromo-1,2-(methylenedioxyl)benzene (10 mmol) in 10 mL THF at room temperature. The reaction mixture was stirred for 2 h until the magnesium turnings had disappeared. Then a solution of aldehyde **9**[9] 1.7 g (10 mmol) in THF (20 mL) was added to the above mixed solution at 0 °C. After 30 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (30 mL) and allowed to stir for another 1 h. The aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with water, brine, and dried over Na_2SO_4, then concentrated under reduced pressure. Recrystallization from petroleum/EtOAc afforded the allylic alcohol **8** (2.67 g, 92%) as a white crystal. Mp 104–106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.86–6.75 (m, 3H), 5.95 (d, J=2.7 Hz, 2H), 5.77 (s, 1H), 5.05 (s, 1H), 3.98–3.95 (m, 4H), 2.35 (br s, 2H), 2.10–2.08 (m, 2H), 1.71 (t, J=6.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 146.8, 139.3, 136.2, 120.1, 119.9, 108.0, 107.9, 107.0, 100.9, 77.0, 64.3, 35.4, 30.8, 23.5 ppm; IR (KBr): ν 3418, 1500, 1488, 1442, 1251, 1231, 1115, 1051, 1037, 938, 926 cm^{-1}; MS (70 eV, EI): *m/z* (%) 290 (M^+, 12), 272 (1), 226 (3), 151 (23), 122 (24), 99 (16), 93 (15), 86 (100), 77(11); HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$: 313.1046 $[M+Na]^+$; found: 313.1044.

Process B: to a cold (−78 °C) suspension of **10** (4.36 g, 10 mmol) in dried tetramethylethylenediamine (TMEDA, 30 mL) was added dropwise *n*-BuLi (2.0 M in hexane, 12.0 mL, 24 mmol) under an argon atmosphere (10 min). The reaction mixture was stirred at room temperature for 4 h, and then cooled to −78 °C again. The solution of piperonal (3.0 g, 20 mmol) in dried TMEDA (15 mL) was added dropwise. After 1 h, the mixture was poured into saturated aqueous solution of NH_4Cl (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum/EtOAc=5:1) provided the allylic alcohol **8** (2.0 g, 69%).

4.1.2. 8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-carbaldehyde (7).

To a solution of allylic alcohol **8** (290 mg, 1 mmol) in CH_3CN (15 mL) was added NBS (196 mg, 1.1 mmol) at room temperature. The reaction mixture was stirred for 6 h until the allylic alcohol had disappeared completely as monitored by TLC. The solution was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=6:1) to give the aldehyde **7** as a white crystal (350 mg, 95%). Mp 84–86 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 6.80–6.75 (m, 2H), 6.63 (dd, J=8.3, 2.3 Hz, 1H), 5.96 (s, 2H), 4.71 (dd, J=12.9, 4.2 Hz, 1H), 3.99–3.90 (m, 4H), 2.52–2.47 (m, 1H), 2.35–2.31 (m, 1H), 2.22 (t, J=12.9 Hz, 1H), 1.84 (dd, J=12.9, 9.9 Hz, 2H), 1.67–1.64 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 148.3, 147.0, 132.1, 120.3, 108.4, 108.0, 107.0, 101.3, 64.6, 64.4, 56.5, 51.0, 43.6, 32.1, 31.8 ppm; IR (KBr): ν 3405, 1712, 1501, 1439, 1241, 1150, 1093, 1036, 938, 622 cm^{-1}; MS (70 eV, EI): *m/z* (%) 370 (M^+, 3), 368

(M^+, 3), 289 (9), 260 (41), 259 (34), 215 (37), 187 (57), 174 (100), 157 (26), 128 (43), 115 (63), 108 (52), 99 (70), 80 (93), 63 (33); HRMS (ESI) calcd for $C_{16}H_{17}O_5BrNa$: 391.0152 $[M+Na]^+$; found: 391.0158.

4.1.3. 5-(8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-yl)-2,2-dimethyl-oxazolidine (11a and 11b). *Path A*: to a solution of the above aldehyde **7** (1.11 g, 3 mmol) in CH_2Cl_2 (30 mL) was added dropwise TMSCN (0.48 mL, 3.6 mmol) at room temperature, and then Et_3N (0.52 mL, 3.8 mmol) was added. The mixture was stirred and the reaction was monitored by ^1H NMR. After the material had disappeared completely, the reaction mixture was concentrated in vacuo. The solution of the residue in Et_2O (30 mL) was added dropwise to a solution of $LiAlH_4$ (228 mg, 6 mmol) in dry Et_2O (50 mL) at 0 °C. After the mixture was stirred for 2 h at room temperature, the reaction mixture was quenched with H_2O, 15% NaOH, and H_2O, and the resulting mixture was filtered. The solid residue was washed well with $CHCl_3$, and the combined organic phases were concentrated. The residue was purified by flash column chromatography silica gel (petroleum/acetone=5:1) to give white gem **11a** (612 mg, 46.4%) and **11b** (510 mg, 38.6%). Compound **11a**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (br, 2H), 6.79 (d, J=8.0 Hz, 1H), 5.96 (d, J=3.6 Hz, 2H), 5.22 (s, 1H), 4.26 (dd, J=7.4, 4.2 Hz, 1H), 4.05–3.98 (m, 2H), 3.82–3.78 (m, 2H), 3.03 (dd, J=12.6, 7.4 Hz, 1H), 2.70 (dd, J=12.4, 4.4 Hz, 1H), 2.15 (dd, J=11.4, 3.0 Hz, 2H), 2.05–2.01 (m, 1H), 1.92–1.81 (m, 2H), 1.74 (d, J=14 Hz, 1H), 1.20 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.4, 129.6, 122.4, 109.6, 107.7, 107.3, 101.1, 95.5, 82.1, 77.2, 64.4, 63.4, 56.6, 47.5, 47.0, 37.9, 30.7, 26.5, 25.3 ppm; IR (KBr): ν 3304, 1491, 1434, 1374, 1243, 1093, 1040, 933, 911, 732, 644 cm^{-1}; MS (70 eV, EI): m/z (%) 360 (1), 260 (23), 174 (41), 115 (8), 100 (100), 71 (25), 70 (16), 43 (15); HRMS (ESI) calcd for $C_{20}H_{27}NBrO_5$: 440.1067 $[M+H]^+$; found: 440.1073. Compound **11b**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J=1.8 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 5.94–5.93 (m, 2H), 4.85 (t, J=7.3 Hz, 1H), 4.33 (dd, J=7.4, 5.0 Hz, 1H), 4.02–3.94 (m, 2H), 3.87–3.83 (m, 2H), 3.21 (dd, J=12.5, 7.7 Hz, 1H), 2.79 (dd, J=12.6, 5.1 Hz, 1H), 2.40–2.31 (m, 3H), 2.16 (br, 1H), 1.83–1.80 (m, 1H), 1.61–1.54 (m, 2H), 1.51 and 1.11 (2s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.1, 133.5, 120.6, 108.9, 107.8, 107.6, 101.0, 95.1, 80.1, 65.8, 64.5, 63.8, 54.4, 47.9, 47.5, 41.1, 31.0, 26.6, 25.0 ppm; IR (KBr): ν 3307, 1712, 1490, 1435, 1240, 1038, 940, 827, 662 cm^{-1}; MS (70 eV, EI): m/z (%) 360 (1), 292 (1), 260 (24), 174 (42), 115 (9), 100 (100), 71 (26), 70 (16), 55 (9), 43 (13).

4.1.4. (8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-yl)-hydroxy-acetonitrile (11′ and 11″). To a solution of the above aldehyde **7** (312 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added dropwise TMSCN (0.14 mL, 1.05 mmol) at room temperature, and then hydroquinine (278 mg, 0.85 mmol) was added. The mixture was stirred for 2 d at room temperature, and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=5:1) to give 263 mg white solid (**11′** and **11″**, ratio=3.5:1) and recovered the starting material 12 mg. ^1H NMR (300 MHz, $CDCl_3$): δ 6.85–6.78 (m, 3H), 6.01 and 6.00 (2s, 2H), 5.20 (m, 1H), 4.96 (d, J=11.4 Hz, 0.67H), 4.76 (d, J=10.8 Hz, 0.19H), 4.07–4.00 (m, 2H), 3.85–3.81 (m, 2H), 2.27–2.09 (m, 4H), 1.83–1.79 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 148.5, 147.8, 147.6, 127.0, 121.7, 117.9, 117.6, 108.9, 108.6, 107.0, 101.6, 101.5, 70.2, 69.7, 64.5, 63.6, 60.5, 53.2, 52.7, 48.9, 48.8, 38.4, 38.0, 31.0, 30.5, 24.8, 24.3 ppm; IR (KBr): ν 3389, 1710, 1506, 1437, 1244, 1091, 1039, 940, 845 cm^{-1}; MS (70 eV, EI): m/z (%) 259 (1), 174 (1), 88 (11), 86 (69), 84 (100), 82 (15), 80 (13), 49 (16), 47 (18), 43 (13).

4.1.5. 5-(8-Benzo[1,3]dioxol-5-yl-7β-bromo-1,4-dioxa-spiro[4.5]decane-8-yl)-2,2-dimethyl-oxazolidine (11a and 11b). *Path B*: to a solution of $LiAlH_4$ (32 mg, 0.84 mmol) in THF (10 mL) was added dropwise a solution of the mixtures of **11′** and **11″** (160 mg, 0.4 mmol) in THF (10 mL) at 0 °C. After 20 min, the reaction was quenched with H_2O, 15% NaOH, and H_2O, and the resulting mixture was filtered. The solid residue was washed well with $CHCl_3$, the combined organic phases were concentrated, and the residue was purified by silica gel (petroleum/acetone=5:1) to give white gem **11a** (124 mg, 70%) and **11b** (35 mg, 20%).

4.1.6. 5-(8-Benzo[1,3]dioxol-5-yl-1,4-dioxa-spiro[4,5]-dec-6-en-8-yl)-2,2-dimethyl-oxazolidine (12a). A mixture of **11a** (516 mg, 1.18 mmol) and DBU (1.8 mL, 11.8 mmol) in toluene (20 mL) was refluxed for 2 d. The mixture was concentrated in vacuo. The residue was purified directly by flash column chromatography on silica gel (petroleum/acetone=3:1) to afford compound **12a** (347 mg, 82%, two steps) as a white gum. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.80 (dd, J=8.2, 3.0 Hz, 1H), 6.69 (dd, J=8.2, 3.0 Hz, 1H), 6.02 (dd, J=11.2, 2.4 Hz, 1H), 5.90 (t, J=2.8 Hz, 2H), 5.75 (d, J=10.8 Hz, 1H), 4.04–3.83 (m, 5H), 3.01–2.95 (m, 1H), 2.89–2.83 (m, 1H), 2.00–1.95 (m, 2H), 1.78–1.75 (m, 1H), 1.65–1.58 (m, 2H), 1.28 (s, 3H), 1.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 145.9, 136.9, 135.3, 128.6, 120.9, 108.6, 107.5, 105.4, 100.8, 95.8, 83.1, 64.6, 64.3, 47.7, 45.8, 30.0, 29.8, 27.1, 25.7 ppm; IR (KBr): ν 3313, 1487, 1434, 1240, 1099, 1038, 936, 814 cm^{-1}; MS (70 eV, EI): m/z (%) 260 (3), 187 (2), 128 (3), 115 (3), 100 (100); HRMS (ESI) calcd for $C_{20}H_{26}NO_5$: 360.1805 $[M+H]^+$; found: 360.1801.

4.1.7. 5-(8-Benzo[1,3]dioxol-5-yl-1,4-dioxa-spiro[4,5]-dec-6-en-8-yl)-2,2-dimethyl-oxazolidine (12b). The same method was applied to the preparation of compound **12b** (79%, two steps). ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J=1.6 Hz, 1H), 6.80 (dd, J=8.2, 1.4 Hz, 1H), 6.70 (dd, J=7.8, 3.0 Hz, 1H), 5.99 (d, J=10.0 Hz, 1H), 5.90 (s, 2H), 5.86 (d, J=10.0 Hz, 1H), 4.15–4.12 (m, 1H), 4.00–3.94 (m, 3H), 3.86 (dd, J=6.4, 5.8 Hz, 1H), 3.16 (dd, J=12.0, 7.2 Hz, 1H), 2.91 (dd, J=12.0, 5.4 Hz, 1H), 2.00–1.92 (m, 2H), 1.69–1.65 (m, 2H), 1.58–1.52 (m, 1H), 1.33 (s, 3H), 1.27 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 145.9, 136.4, 134.3, 130.3, 121.1, 108.3, 107.5, 105.3, 100.8, 95.6, 82.3, 64.7, 64.3, 47.8, 46.1, 31.9, 29.5, 26.8, 25.2 ppm; IR (KBr): ν 3313, 1653, 1610, 1487, 1434, 1240, 1038, 936, 814 cm^{-1}; MS (70 eV, EI): m/z (%) 360 (M^+, 1), 260 (23), 174 (41), 115 (8), 100 (100), 71 (25), 70

(16), 43 (15); HRMS (ESI) calcd for $C_{20}H_{26}NO_5$: 360.1805 $[M+H]^+$; found: 360.1801.

4.1.8. 3a-Benzo[1,3]dioxol-5-yl-3β-hydroxy-6-oxo-octahydro-indole-1-carboxylic acid *tert*-butyl ester (13a). A solution of the above protected amino alcohol **12a** (277 mg, 0.77 mmol), THF (15 mL), and 2 N HCl (2.2 mL) was heated at reflux for 6 h. After cooled to room temperature, the reaction was quenched by addition solid of K_2CO_3 until pH=8. The resulting layers were separated and the aqueous layer was extracted with $CHCl_3$ (5×10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), and triethylamine (0.33 mL, 2.4 mmol) was added to the solution. The solution was stirred for 10 min, then added $(Boc)_2O$ 252 mg (1.16 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, whereupon H_2O (3 mL) was added and the organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=1:1) to give **13a** as a white gum (234 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (br, 0.64H), 6.78 (br, 2.30H), 5.96 (s, 2H), 4.64–4.58 (br, 0.74H), 4.46 (br, 0.60H), 4.28 (br, 0.64H), 3.67 (br, 0.56H), 3.34 (d, J=10.4 Hz, 1H), 3.06–2.85 (br, 2H), 2.60 (br, 0.77H), 2.38 (br, 1H), 2.23–1.85 (br, 3H), 1.15 and 1.42 (2s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.1, 154.4, 148.3, 148.0, 146.5, 137.1, 134.8, 119.1, 118.9, 108.2, 106.9, 106.5, 106.3, 101.2, 94.9, 94.6, 81.0, 80.1, 79.7, 77.2, 59.4, 56.9, 56.2, 53.0, 52.5, 52.2, 51.6, 51.1, 45.6, 45.1, 43.5, 43.0, 42.7, 42.1, 36.5, 33.3, 33.2, 28.4, 26.4 ppm; IR (KBr): ν 3405, 1689, 1506, 1488, 1402, 1237, 1167, 1039, 932, 732 cm^{-1}; MS (70 eV, EI): *m/z* (%) 375 (M^+, 3), 319 (3), 229 (4), 216 (8), 188 (9), 174 (14), 115 (11), 77 (10), 57 (100); HRMS (ESI) calcd for $C_{20}H_{25}NO_6Na$: 398.1574 $[M+Na]^+$; found: 398.1580.

4.1.9. 3a-Benzo[1,3]dioxol-5-yl-3α-hydroxy-6-oxo-octahydro-indole-1-carboxylic acid *tert*-butyl ester (13b). The same method was applied to the preparation of compound **13b** (yield: 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86–6.79 (m, 3H), 5.99 (s, 2H), 4.62 (br, 1H), 4.13 (br, 1H), 3.70 (br, 2H), 3.26 (br, 0.5H), 2.99 (br, 0.5H), 2.81 (br, 1H), 2.25–2.00 (m, 4H), 1.48 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.9, 155.4, 148.9, 147.1, 131.7, 120.8, 108.9, 107.4, 101.4, 80.6, 77.4, 57.8, 54.2, 53.2, 43.1, 41.4, 36.2, 31.4, 28.4 ppm; IR (KBr): ν 3426, 1711, 1690, 1490, 1396, 1235, 1037, 931 cm^{-1}; MS (70 eV, EI): *m/z* (%) 375 (M^+, 1), 229 (4), 216 (40), 174 (14), 115 (5), 70 (8), 57 (84), 43 (100).

4.1.10. 7-Benzo[1,3]dioxol-5-yl-1β-trimethylsilanyloxy-2-oxa-5-aza-tricyclo[4.3.1.0^{3,7}]decane-5-carboxylic acid *tert*-butyl ester (14). A solution of *n*-butyllithium (2 M solution in hexane, 0.3 mL) was added dropwise to a solution of diisopropylamine (0.084 mL, 0.6 mmol) in THF (5 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 45 min before being cooled to −78 °C and treated with a solution of **13a** (101 mg, 0.27 mmol) in THF (2 mL). After 30 min, TMSCl (0.080 mL, 0.63 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min, then slowly warmed to −20 °C, and quenched after 1 h with saturated $NaHCO_3$ solution (2 mL). After dilution with ether (30 mL), the organic layer was separated, and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated in vacuum. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=10:1) provided the acetal **14** (109 mg, 90%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73–6.63 (m, 3H), 5.90 (s, 2H), 4.60 (dd, J=3.6, 1.6 Hz, 1H), 4.52 (d, J=6.8 Hz, 0.59H), 4.39 (d, J=7.6 Hz, 0.42H), 3.31 (d, J=11.4 Hz, 0.5H), 3.26 (d, J=11.6 Hz, 0.5H), 2.95–2.87 (m, 1H), 2.28–2.24 (m, 1H), 2.16–2.13 (m, 1H), 2.10–2.02 (m, 1H), 1.98–1.86 (m, 2H), 1.79–1.72 (m, 1H), 1.48 (s, 4H), 1.39 (s, 5H), 0.14 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 154.0, 147.9, 146.3, 135.2, 118.8, 108.2, 106.5, 106.3, 101.0, 96.4, 96.2, 80.6, 79.9, 79.5, 79.4, 60.2, 57.0, 56.5, 52.9, 52.4, 45.4, 44.9, 43.7, 43.2, 34.8, 34.7, 28.5, 28.3, 1.89 ppm; IR (KBr): ν 1693, 1402, 1245, 1174, 1041, 923, 873, 844 cm^{-1}; MS (70 eV, EI): *m/z* (%) 447 (M^+, 1), 288 (14), 246 (19), 202 (22), 73 (49), 57 (100); HRMS (ESI) calcd for $C_{23}H_{34}NSiO_6$: 448.2150 $[M+H]^+$; found: 448.2150.

4.1.11. 3a-Benzo[1,3]dioxol-5-yl-6-oxo-3β-trimethylsilanyloxy-octahydro-indole-1-carboxylic acid *tert*-butyl ester (15). To a solution of **13a** (107 mg, 0.29 mmol) in dried pyridine (1.5 mL) were added hexamethyl disilazane (HMDS) (0.4 mL, 1.92 mmol) and TMSCl (0.3 mL, 2.36 mmol) subsequently. The reaction mixture was stirred for 30 min and H_2O (0.5 mL) was added carefully. After dilution with CH_2Cl_2 (30 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with saturated $CuSO_4$ solution, water, brine, dried over Na_2SO_4, and concentrated in vacuum. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=12:1) provided **15** (115 mg, 90%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81–6.74 (m, 3H), 5.95 (s, 2H), 4.68–4.59 (br, 1H), 3.99 (s, 1H), 3.67 (br, 1H), 3.41–3.34 (br, 1H), 3.21 (br, 0.4H), 3.04 (br, 0.5H), 2.68 (dd, J=16.8, 5.2 Hz, 1H), 2.23–2.09 (m, 4H), 1.49 (s, 9H), −0.10 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 155.9, 148.1, 146.5, 133.4, 121.0, 108.4, 108.2, 101.3, 80.6, 77.4, 59.1, 55.1, 53.7, 42.6, 41.4, 36.9, 31.0, 28.7, 0.00 ppm; IR (KBr): ν 1693, 1491, 1393, 1250, 1167, 936, 845 cm^{-1}; MS (70 eV, EI): *m/z* (%) 447 (M^+, 0.5), 216 (100), 174 (16), 73 (30), 57 (50); HRMS (ESI) calcd for $C_{23}H_{33}NSiO_6Na$: 470.1969 $[M+Na]^+$; found: 470.1960.

4.1.12. 3a-Benzo[1,3]dioxol-5-yl-6-oxo-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (17). A solution of *n*-butyllithium (2 M solution in hexane, 0.23 mL) was added dropwise to a solution of diisopropylamine (0.065 mL, 0.46 mmol) in THF (5 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 45 min before being cooled to −78 °C and treated with a solution of silyl ether **15** (195 mg, 0.44 mmol) in THF (2 mL). After 30 min, TMSCl (0.07 mL, 0.55 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min, slowly warmed to −20 °C, and quenched with saturated $NaHCO_3$ solution (2 mL) after 1 h. After diluting with

ether (30 mL), the organic layer was separated, and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated in vacuum to give the silyl enol ether **16**, which was used in the next reaction without further purification. A mixture of this residue, $Pd(OAc)_2$ (160 mg, 0.71 mmol) in CH_3CN (20 mL) was stirred at room temperature overnight. The mixture was then concentrated and the brown residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to afford enone **17** as a white foamy solid (137 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, J=10.5 Hz, 1H), 6.84 (s, 1H), 6.78 (s, 2H), 6.29 (d, J=10.8 Hz, 1H), 5.95 (s, 2H), 4.51–4.46 (m, 1H), 4.24 (br, 0.45H), 4.11 (br, 0.76H), 3.89–3.81 (m, 1H), 3.67 (br, 0.44H), 3.30–3.24 (br, 0.61H), 3.09–2.94 (m, 1H), 2.45–2.30 (br, 1H), 1.44 (s, 9H), 0.05 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 197.4, 154.4, 148.3, 147.7, 147.4, 147.0, 132.2, 132.0, 130.8, 120.5, 108.3, 107.1, 101.3, 80.7, 80.1, 76.6, 75.7, 61.7, 54.0, 52.9, 52.3, 52.0, 37.8, 36.4, 28.3, −0.23 ppm; IR (KBr): ν 1697, 1504, 1488, 1394, 1250, 1164, 1113, 1040, 934, 912, 844, 733 cm^{-1}; MS (70 eV, EI): m/z (%) 215 (14), 214 (100), 73 (27), 57 (43), 41 (13); HRMS (ESI) calcd for $C_{23}H_{31}NSiO_6Na$: 468.1813 $[M+Na]^+$; found: 468.1817.

4.1.13. 3a-Benzo[1,3]dioxol-5-yl-6β-hydroxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (18a). To a well-stirred solution of enone **17** (24 mg, 0.054 mmol) in THF (2 mL) at −78 °C under argon atmosphere was added dropwise a solution of L-Selectride (1.0 M solution in THF, 0.07 mL, 0.07 mmol) by syringe and the resulting solution was stirred for 15 min at this temperature. The reaction mixture was quenched by the addition of CH_3OH (0.2 mL) over 1 min. The resulting slurry was allowed to warm to room temperature slowly, and H_2O (3 mL) was added. The aqueous layer was extracted with $CHCl_3$ (3×20 mL), and the combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc 10:1) afforded the allylic alcohol **18a** as white crystal (24 mg, 95%). Mp 168–170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.75 (s, 2H), 6.26 (dd, J=9.9, 3.6 Hz, 1H), 6.20 (d, J=9.9 Hz, 1H), 5.94 (s, 2H), 4.40 (t, J=10.0 Hz, 1H), 4.10 (br, 1H), 3.94 (br, 1H), 3.73 (br, 1H), 3.07 (dd, J=13.6, 8.4 Hz, 1H), 2.60 (br, 0.7H), 1.84 (br, 0.6H), 1.68–1.47 (m, 1H), 1.48 (s, 9H), −0.02 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 148.0, 146.5, 135.1, 131.8, 128.3, 120.5, 108.1, 107.6, 101.1, 80.3, 77.3, 63.6, 60.3, 52.9, 51.8, 29.7, 28.5, −0.11 ppm; IR (KBr): ν 3424, 1690, 1399, 1248, 1111, 1037, 936, 844 cm^{-1}; MS (70 eV, EI): m/z (%) 447 (M^+, 0.2), 198 (100), 199 (14), 73 (21), 57 (31), 41 (10); HRMS (ESI) calcd for $C_{23}H_{33}NSiO_6Na$: 470.1969 $[M+Na]^+$; found: 470.1974.

4.1.14. 3a-Benzo[1,3]dioxol-5-yl-6α-methoxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (19a). To a solution of allylic alcohol **18a** (22 mg, 0.049 mmol) and NEt_3 (0.10 mL, 0.72 mmol) in THF (2 mL) was added Ms_2O (54 mg, 0.31 mmol) at 0 °C and the solution was stirred for 1 h. To this solution was added MeOH (2 mL) and the solution was stirred at 0 °C for 3 d. Ethyl acetate (30 mL) was added to this solution, and the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **19a** as a colorless amorphous (21 mg, 93%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, J=1.6 Hz, 1H), 6.63 (dd, J=10.0, 1.8 Hz, 1H), 6.76 (d, J=7.2 Hz, 1H), 6.20 (d, J=10.5 Hz, 1H), 5.95 (d, J=10.5 Hz, 1H), 5.95 (s, 2H), 4.49–4.44 (m, 1H), 4.05 (br, 0.4H), 3.88–3.78 (m, 2.3H), 3.68–3.61 (m, 0.4H), 3.38–3.32 (m, 3H), 2.98 (t, J=10.0 Hz, 1H), 2.85 (br, 0.33H), 2.60 (br, 0.64H), 1.48 (s, 9H), 0.067 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 154.3, 147.8, 146.3, 135.3, 131.7, 131.3, 128.3, 127.9, 120.9, 108.0, 107.8, 101.1, 80.0, 79.6, 76.1, 75.3, 72.6, 61.5, 56.0, 53.4, 52.5, 51.9, 51.3, 28.5, 27.2, 25.8, −0.11 ppm; IR (KBr): ν 1694, 1488, 1395, 1249, 1101, 936, 879, 843 cm^{-1}; MS (70 eV, EI): m/z (%) 231 (9), 199 (13), 198 (51), 73 (48), 57 (100), 41 (27); HRMS (ESI) calcd for $C_{24}H_{35}O_6NSiNa$: 484.2126 $[M+Na]^+$; found: 484.2129.

4.1.15. 3a-Benzo[1,3]dioxol-5-yl-3β-hydroxy-6α-methoxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (20). To a solution of silyl ether **19a** (43 mg, 0.095 mmol) in THF (3 mL) was added dropwise a solution of Bu_4NF (1 M solution in THF, 0.1 mL, 0.10 mmol) at room temperature. After 10 min, the solution was concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=1:1) afforded the alcohol **20** (36.5 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.88 (d, J=8.1 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.26 (d, J=10.5 Hz, 1H), 5.96 (s, 2H), 5.92 (d, J=11.1 Hz, 1H), 4.60 (br, 1H), 4.06 (br, 0.7H), 3.93–3.86 (br, 2.73H), 3.40 (s, 3H), 3.13 (t, J=9.3 Hz, 1H), 2.77 (br, 0.6H), 2.57 (br, 0.8H), 1.76 (br, 1H), 1.54 (s, 1H), 1.48 (s, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 148.1, 146.7, 134.8, 132.4, 127.6, 120.7, 109.8, 108.3, 107.6, 101.2, 80.1, 74.7, 72.4, 61.2, 56.1, 53.6, 50.8, 28.5, 27.6 ppm; IR (KBr): ν 3404, 1674, 1605, 1487, 1409, 1320, 1132, 930 cm^{-1}; MS (70 eV, EI): m/z (%) 389 (M^+, 1), 259 (1), 249 (21), 230 (19), 199 (10), 198 (13), 115 (10), 57 (100), 41 (26); HRMS (ESI) calcd for $C_{21}H_{31}N_2O_6$: 407.2177 $[M+NH_4]^+$; found: 407.2174.

4.1.16. 3β-Acetoxy-3a-benzo[1,3]dioxol-5-yl-6α-methoxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (21). A solution of alcohol **20** (30 mg, 0.077 mmol), DMAP (2 mg), pyridine (0.03 mL), and Ac_2O (0.04 mL) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 2 h. Ethyl acetate (20 mL) was added to the solution and the organic phase was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography on silica gel (petroleum/EtOAc=2:1) provided **21** (33 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J=1.6 Hz, 1H), 6.87 (dd, J=8.2, 1.8 Hz, 1H), 6.77 (d, J=8.2 Hz, 1H), 6.17 (dd, J=10.2, 2.8 Hz, 1H), 5.96 (s, 2H), 5.86 (d, J=10.2 Hz, 1H), 5.59 (t, J=6.4 Hz, 0.5H), 5.52 (t, J=6.4 Hz, 0.5H), 4.12 (d, J=3.6 Hz, 0.5H), 4.05 (d, J=4.4 Hz, 0.5H), 3.98–3.92 (m, 1H), 3.85 (br, 1H), 3.40 (s, 3H), 3.17 (dd, J=11.2, 6.0 Hz, 0.5H), 3.08 (dd, J=10.8, 7.2 Hz, 0.5H), 2.61 (t, J=6.0 Hz, 0.5H),

2.40–2.33 (m, 0.5H), 2.02 (s, 3H), 1.86–1.81 (m, 0.5H), 1.76–1.71 (m, 0.5H), 1.47 and 1.25 (2s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 154.2, 148.1, 146.8, 134.5, 131.3, 130.5, 129.3, 128.5, 120.4, 108.2, 107.6, 101.2, 80.2, 75.8, 75.1, 72.0, 59.8, 56.2, 49.3, 49.1, 28.5, 27.8, 26.5, 20.9 ppm; IR (KBr): ν 2975, 1744, 1694, 1489, 1392, 1238, 1039, 935 cm^{-1}; MS (70 eV, EI): *m/z* (%) 431 (M^+, 1), 291 (13), 198 (20), 71 (20), 57 (100), 43 (54), 41 (26); HRMS (ESI) calcd for $C_{23}H_{33}N_2O_7$: 449.2282 $[M+NH_4]^+$; found: 449.2276.

4.1.17. 3β-Acetic acid-3a-benzo[1,3]dioxol-5-yl-1-formyl-6α-methoxy-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3-yl ester (22). To a solution of **21** (26 mg, 0.06 mmol) in $ClCH_2CH_2Cl$ (2 mL) was added CF_3COOH (0.1 mL, 1.3 mmol) at room temperature. After 3 h, solid K_2CO_3 (ca. 200 mg) was added to the solution, and a small amount of Na_2SO_4 was also added. The undissolved material was filtered off and the solvent was removed. DMF (1 mL) and HCO_2Me (2 mL) were added to this crude amine and the solution was warmed at 90 °C for 6 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **22** as a white film (19 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 0.62H), 8.25 (s, 0.46H), 6.89 (dd, *J*=4.8, 1.6 Hz, 1H), 6.86–6.83 (m, 1H), 6.77 (dd, *J*=8.4, 2.8 Hz, 1H), 6.24–6.19 (m, 1H), 5.96 (s, 2H), 5.88 (d, *J*=10.4 Hz, 1H), 5.67 (t, *J*=6.0 Hz, 0.63H), 5.50 (t, *J*=7.2 Hz, 0.5H), 4.22 (dd, *J*=8.0, 3.4 Hz, 1H), 4.09–4.02 (m, 1H), 3.89 (dd, *J*=12.4, 4.0 Hz, 1H), 3.40 (s, 1.35H), 3.39 (s, 1.70H), 3.31–3.25 (m, 1H), 2.75 (t, *J*=8.4 Hz, 0.48H), 2.31–2.24 (m, 0.56H), 2.03 (s, 1.75H), 1.99 (s, 1.35H), 1.99–1.95 (m, 0.64H), 1.69–1.65 (m, 0.68H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.0, 161.6, 160.6, 148.3, 147.0, 133.9, 133.6, 132.3, 129.6, 129.3, 127.7, 120.3, 120.0, 108.4, 108.3, 107.4, 101.3, 75.0, 74.9, 71.6, 71.1, 59.5, 59.4, 56.5, 56.3, 52.8, 51.5, 48.5, 47.3, 30.9, 26.1, 20.9, 20.8 ppm; IR (KBr): ν 3385, 2922, 1741, 1668, 1378, 1237, 1069, 1037 cm^{-1}; MS (70 eV, EI): *m/z* (%) 359 (M^+, 2), 198 (8), 115 (8), 84 (67), 49 (35), 47 (42), 43 (100); HRMS (ESI) calcd for $C_{19}H_{22}NO_6$: 360.1442 $[M+H]^+$; found: 360.1437.

4.1.18. (±)-Haemanthidine (1). A solution of formamide **22** (15 mg, 0.042 mmol) in freshly distilled $POCl_3$ (0.5 mL) was stirred at 80 °C under sealed tube. After 4 h, the mixture was cooled to room temperature and the excess $POCl_3$ was removed in vacuum. Aqueous THF (1:1, 1.0 mL) was added and the solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (1.0 mL), and K_2CO_3 (50 mg, 0.36 mmol) was added to the solution. The mixture was stirred at room temperature for additional 1 h, and filtered. The filtrate was removed under vacuum and the resulted crude product was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH=6:1) to give **1** (10 mg, 76%) as an opaque film. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 0.40H), 6.83 (s, 0.50H), 6.81 (s, 0.41H), 6.78 (s, 0.48H), 6.44–6.35 (m, 2H), 5.94–5.92 (m, 2H), 5.76 (s, 0.42H), 5.11 (s, 0.47H), 4.24 (dd, *J*=14.4, 7.0 Hz, 0.43H), 3.95–3.90 (m, 2.5H), 3.66 (dd, *J*=12.8, 4.4 Hz, 0.5H), 3.40 and 3.39 (2s, 3H), 3.42–3.38 (m, 0.5H), 3.28 (dd, *J*=12.4, 2.8 Hz, 0.5H), 3.03 (dd, *J*=13.6, 2.0 Hz, 0.5H), 2.36 (td, *J*=13.6, 4.4 Hz, 0.6H), 2.24 (td, *J*=13.6, 4.4 Hz, 1H), 2.05 (dd, *J*=13.6, 4.0 Hz, 1H), 2.02 (br, 0.5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.8, 146.9, 146.6, 135.7, 134.1, 132.9, 132.5, 128.0, 127.3, 126.2, 126.0, 109.5, 108.4, 102.9, 102.8, 101.1, 88.4, 85.8, 78.6, 78.1, 72.4, 72.1, 62.0, 58.0, 56.9, 56.6, 56.5, 51.9, 50.7, 50.3, 27.7, 27.4 ppm; IR (KBr): ν 3383, 2924, 1482, 1246, 1087, 1036, 933, 732 cm^{-1}; MS (70 eV, EI): *m/z* (%) 317 (M^+, 9), 284 (14), 268 (16), 227 (11), 209 (17), 201 (11), 200 (13), 199 (11), 103 (12), 102 (11), 88 (28), 73 (38), 71 (44), 47 (55), 41 (71), 39 (24); HRMS (ESI) calcd for $C_{17}H_{20}NO_5$: 318.1337 $[M+H]^+$; found: 318.1334.

4.1.19. (±)-Pretazettine (2). To a well-stirred solution of **1** (7.0 mg, 0.022 mmol) in MeOH (3 mL) was added methyl iodine (0.38 mL, 6.2 mmol). The reaction mixture was stirred for 6 h before removing the methanol in vacuum. The residue was treated with aqueous hydrochloric acid (2 mL, 0.01 M) for 1 min and the pH of the solution was adjusted to 8 with saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ (6×5 mL), and the organic portions were combined, dried, and concentrated. The crude product was purified by flash column chromatography on silica gel ($MeOH/Et_3N/CHCl_3$=10:3:87) to afford **2** as a white film (6.9 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.77 (s, 1H), 6.13 (s, 1H), 5.93 (s, 2H), 5.89 (d, *J*=10.8 Hz, 1H), 5.52 (d, *J*=10.4 Hz, 1H), 4.34 (dd, *J*=11.2, 7.2 Hz, 1H), 4.18–4.14 (m, 1H), 3.44 (s, 3H), 3.01–2.96 (m, 2H), 2.67 (dd, *J*=9.6, 8.0 Hz, 1H), 2.55–2.48 (m, 1H), 2.50 (s, 3H), 1.77 (dd, *J*=11.2, 10.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 146.5, 135.4, 129.1, 128.9, 127.4, 108.1, 104.9, 101.2, 93.9, 73.9, 73.1, 64.1, 56.1, 54.1, 46.2, 43.3, 30.2 ppm; IR (KBr): ν 3350, 1482, 1254, 1089, 1036, 934 cm^{-1}; MS (70 eV, EI): *m/z* (%) 331 (M^+, 4), 316 (3), 247 (25), 225 (7), 201 (9), 139 (8), 128 (9), 115 (18), 85 (60), 83 (100), 82 (10), 77 (12), 74 (18), 70 (27), 57 (16), 55 (16), 44 (37), 42 (31); HRMS (ESI) calcd for $C_{18}H_{22}NO_5$: 332.1492 $[M+H]^+$; found: 332.1486.

4.1.20. (±)-Tazettine (3). To a well-stirred solution of **2** (6.9 mg, 0.0208 mmol) in MeOH (1.0 mL) was added 0.1 M NaOH (0.7 mL, 0.07 mmol), and the reaction mixture was stirred for 30 min before removing the MeOH in vacuum. The aqueous layer was extracted with $CHCl_3$ (7×5 mL), and the organic portions were combined, dried, and concentrated. The crude product was purified by flash column chromatography on silica gel ($MeOH/CHCl_3$=1:9) to afford **3** as a white film (6.3 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.51 (s, 1H), 6.16 (d, *J*=10.2 Hz, 1H), 5.91 (s, 2H), 5.62 (d, *J*=10.2 Hz, 1H), 4.97 (d, *J*=15.0 Hz, 1H), 4.65 (d, *J*=15.0 Hz, 1H), 4.16–4.13 (m, 1H), 3.47 (s, 3H), 3.32 (d, *J*=10.2 Hz, 1H), 2.88 (br, 1H), 2.70 (d, *J*=10.2 Hz, 1H), 2.42 (s, 3H), 2.28–2.22 (m, 1H), 1.67–1.60 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 146.5, 130.8, 128.6, 128.1, 125.5, 109.3, 104.0, 102.1, 101.0, 72.9, 70.1, 65.6, 62.1, 56.1, 49.9, 41.9, 26.8 ppm; IR (KBr): ν 3196, 1475, 1453, 1380, 1127, 883, 706 cm^{-1}; MS (70 eV, EI): *m/z* (%) 331 (M^+, 6), 316 (3), 298 (5), 247 (56), 201 (13), 199 (15), 185 (10), 152 (20), 113 (12), 112 (11), 97 (23), 71 (64), 57 (87), 55 (51), 49 (60), 43 (100), 42 (95), 41 (80); HRMS (ESI) calcd for $C_{18}H_{22}NO_5$: 332.1492 $[M+H]^+$; found: 332.1490.

4.1.21. 3a-Benzo[1,3]dioxol-5-yl-6α-hydroxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (18b). To a solution of **17** (150 mg, 0.52 mmol) in methanol (10 mL) was added $CeCl_3 \cdot 7H_2O$ (193 mg, 0.52 mmol) at room temperature and then $NaBH_4$ (49 mg, 1.3 mmol) was added. After stirring for 5 min, the reaction mixture was quenched with H_2O (0.5 mL). The solution was concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (10 mL) back extracting the aqueous phase with CH_2Cl_2 (50 mL). The combined organic portions were concentrated and the residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **18b** as a white amorphous (90 mg, 63%) and **18a** as white crystal (46 mg, 32%). Compound **18b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, J=1.6 Hz, 1H), 6.85 (dd, J=8.0, 2.0 Hz, 1H), 6.78 (br, 1H), 6.11 (d, J=10.8 Hz, 1H), 5.92 (d, J=10.0 Hz, 1H), 5.92 (s, 2H), 4.41 (br, 1H), 4.28 (br, 1H), 3.99 (br, 0.5H), 3.88 (br, 0.5H), 3.81 (dd, J=10.0, 7.2 Hz, 1H), 3.63 (br, 0.5H), 2.95 (t, J=10.0 Hz, 1H), 2.79 (br, 0.5H), 2.57 (d, J=12.4 Hz, 0.5H), 1.62 (br, 1H), 1.46 (s, 9H), −0.08 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 147.9, 146.4, 135.5, 133.9, 128.0, 127.7, 120.8, 118.9, 108.0, 107.7, 106.8, 101.1, 80.1, 79.6, 76.2, 75.5, 61.6, 53.1, 53.0, 52.3, 51.9, 51.4, 28.54, 28.46, −0.12 ppm; IR (KBr): ν 3405, 1690, 1488, 1397, 1250, 879, 843 cm^{-1}; MS (70 eV, EI): m/z (%) 447 (M^+, 0.3), 216 (100), 198 (37), 73 (45), 57 (78); HRMS (ESI) calcd for $C_{23}H_{33}NSiO_6Na$: 470.1969 $[M+Na]^+$; found: 470.1977.

4.1.22. 3a-Benzo[1,3]dioxol-5-yl-6β-methoxy-3β-trimethylsilanyloxy-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid *tert*-butyl ester (19b). To a solution of **18b** (34 mg, 0.076 mmol) and NEt_3 (0.15 mL, 1.08 mmol) in THF (2 mL) was added Ms_2O (92 mg, 0.53 mmol) at 0 °C and the solution was stirred for 1 h. To this solution was added MeOH (2 mL) and the solution was stirred at 0 °C for 3 d. Ethyl acetate (50 mL) was added to this solution, and the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum/EtOAc=3:1) to give **19b** as a colorless amorphous (34 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (d, J=8.1 Hz, 1H), 6.76 (s, 2H), 6.16 (dd, J=12.3, 4.2 Hz, 1H), 6.01 (d, J=11.7 Hz, 1H), 5.95 (s, 2H), 4.34 (t, J=6.3 Hz, 1H), 4.05–3.96 (br, 1H), 3.71–3.66 (m, 2H), 3.55 (dd, J=10.5, 6.3 Hz, 0.5H), 3.38–3.34 (m, 0.32H), 3.34 (s, 3H), 3.19–3.06 (m, 1H), 2.83–2.78 (m, 0.55H), 2.50–2.45 (m, 0.33H), 1.49 and 1.46 (2s, 9H), −0.01 (s, 5H), −0.04 (s, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.32, 154.26, 147.9, 146.2, 136.4, 136.0, 130.0, 129.7, 129.6, 129.3, 120.2, 120.0, 108.0, 107.8, 107.6, 107.4, 101.1, 79.5, 79.1, 72.6, 72.4, 72.3, 61.5, 59.8, 59.4, 56.4, 55.9, 53.8, 52.7, 52.0, 28.5, 27.2, −0.07 ppm; IR (KBr): ν 1693, 1399, 1249, 1107, 1038, 936, 843 cm^{-1}; MS (70 eV, EI): m/z (%) 461 (M^+, 0.1), 230 (12), 199 (15), 198 (100), 73 (20), 57 (29), 41 (8); HRMS (ESI) calcd for $C_{24}H_{36}NSiO_6$: 462.2306 $[M+H]^+$; found: 462.2302.

4.1.23. (±)-Crinamine (4). To a solution of compound **19b** (20 mg, 0.043 mmol) in dry $ClCH_2CH_2Cl$ (2 mL) was added trifluoroacetic acid (0.1 mL, 1.3 mmol) at 0 °C. After the mixture was stirred for 8 h at room temperature, saturated aqueous $NaHCO_3$ (1 mL) was added, and the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give crude amine. A solution of formalin (0.05 mL) in MeOH (0.1 mL) was added to this amine. After the solution was stirred for 10 min, 6 M aqueous hydrochloric acid (2.5 mL) was added. The mixture was warmed to 40 °C for 10 h, cooled to room temperature, and then basified by the dropwise addition of $NH_3 \cdot H_2O$. The resultant mixture was extracted with $CHCl_3$ (5×10 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=10:1) to afford **4** (10 mg, 76%, two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.49 (s, 1H), 6.27 (s, 2H), 5.91 (d, J=2.0 Hz, 2H), 4.34 (d, J=17.0 Hz, 1H), 4.02 (dd, J=10.0, 6.0 Hz, 1H), 3.98–3.97 (m, 1H), 3.72 (d, J=17.0 Hz, 1H), 3.41 (s, 3H), 3.39–3.37 (m, 2H), 3.23 (dd, J=13.2, 4.4 Hz, 1H), 2.15–2.05 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 146.3, 136.2, 135.5, 126.8, 123.6, 106.9, 103.2, 100.9, 80.1, 76.1, 66.2, 63.6, 61.3, 55.8, 50.3, 30.3 ppm; IR (KBr): ν 3363, 2920, 1654, 1481, 1238, 1036, 935 cm^{-1}; MS (70 eV, EI): m/z (%) 270 (17), 269 (87), 268 (30), 240 (40), 224 (27), 211 (19), 181 (84), 153 (26), 115 (47), 77 (31), 71 (40), 69 (44), 57 (59), 55 (63), 43 (100), 41 (48); HRMS (ESI) calcd for $C_{17}H_{20}NO_4$: 302.1387 $[M+H]^+$; found: 302.1382.

Acknowledgements

This work was financially supported by the NSFC (No. 20021001, 203900501) and Chang Jiang Scholars of Program of China.

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Tetrahedron 62 (2006) 9456–9466
Tetrahedron

Tautomeric equilibria in the reaction products of asymmetric 1,3-diamines with β-dicarbonyl compounds

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Received 18 April 2006; revised 19 June 2006; accepted 6 July 2006
Available online 14 August 2006

Dedicated to the late Professor Kirill N. Zelenin

Abstract—The reaction products of 1,3-butanediamine and 2-methyl-2,4-pentanediamine with β-keto aldehydes were shown by ^{1}H and ^{13}C NMR spectroscopy to exist as tautomeric mixtures in solutions, comprising one cyclic and two open-chain forms due to the non-equivalence of the amino groups. The chain products exist as *Z*- and *E*-isomers. After equilibration, the products from 1,3-butanediamine contain relatively less of the cyclic form than those from 2-methyl-2,4-pentanediamine. The products of 2-methyl-2,4-pentanediamine with *p*-substituted aroylacetaldehydes, exhibit a linear correlation between log *K* of the ring–chain equilibria and Hammett's σ values of the aromatic ring substituents. α-Substitution of β-keto aldehydes notably increased the relative amounts of the chain *E*-isomers in their condensation products and also resulted in the formation of two diastereomers for each of the cyclic products. No ring–chain equilibria were observed in the products of 1,3-butanediamine and 2-methyl-2,4-pentanediamine with β-diketones, β-keto esters, or β-keto amides.

1. Introduction

Various ring–chain, ring–ring, and ring–chain–ring tautomeric equilibria have been discussed in recent years.[1–3] In particular, ring–chain equilibria were observed in solutions of hexahydropyrimidines, where only one open-chain tautomer (the diamine Schiff base) could be formed in each system, either because of substitution at the other amino group[4,5] or because of molecular symmetry.[6] For tetrahydroquinazolines derived from 2-aminomethylaniline and aromatic aldehydes, only one of the two possible open-chain forms was observed.[7]

We have observed for the first time chain–ring–chain tautomerism[8] in 2-aryl-4-methylhexahydropyrimidines obtained from 1,3-diaminobutane and aromatic aldehydes. However, the reaction mixtures frequently contained bis-imino products, which were inseparable from the target products of 1:1 condensation. A similar difficulty for other compounds was previously mentioned in the literature.[9]

In search for a suitable alternative to aromatic aldehydes in condensations with asymmetric 1,3-diamines, we turned to β-dicarbonyl compounds. Tautomerism in their various nitrogen derivatives is well described.[10] Moreover, their reaction products with diamines were expected to contain considerable amounts of the keto enamine tautomers, similarly to the previously observed cases of ring–chain tautomerism in their condensation products with aminoamides[11,12] and 2-aminomethylaniline.[13] In the latter case, similarly to the aromatic aldehyde derivatives,[7] only one of two possible chain (keto enamine) tautomers was observed.

In the present work, effects of the electronic factors on the tautomeric equilibria were probed by preparing derivatives of *p*-substituted benzoylacetic aldehydes. Steric effects of a bulky substituent in the β-dicarbonyl reaction component were studied using derivatives of pivaloylacetic aldehyde. Derivatives of propionylpropionaldehyde and its alicyclic analogs, 2-formylcyclopentanone and 2-formylcyclohexanone, were used to clarify the effects of α-substitution in the dicarbonyl component. Finally, derivatives of β-diketones, β-keto esters, and β-keto amides were approached, where we expected increased amounts of the imine tautomers to be observed.

2. Results and discussion

2.1. Reactions of 1,3-butanediamine and 2-methyl-2,4-pentanediamine with β-keto aldehydes

The 1:1 condensation products existed in solutions as tautomeric mixtures of one cyclic tautomer (**B**) and two chain

Keywords: Ring–chain tautomerism; Hexahydropyrimidines; β-Dicarbonyl compounds; 1,3-Diamines.
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✠ Deceased.

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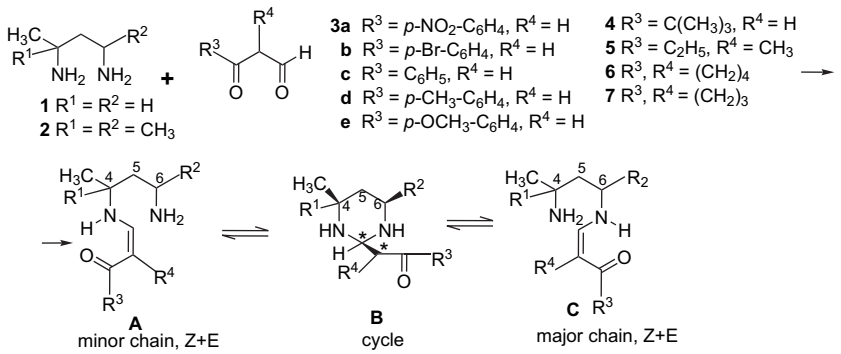
doi:10.1016/j.tet.2006.07.033



8 $R^1 = R^2 = R^4 = H$, $R^3 = Ph$, **9** $R^1 = R^2 = R^4 = H$, $R^3 = C(CH_3)_3$, **10** $R^1 = R^2 = H$, $R^3 = C_2H_5$, $R^4 = CH_3$.
11a-e $R^1 = R^2 = CH_3$, R^3 = *p*-substituted Ph, $R^4 = H$, **12** $R^1 = R^2 = CH_3$, $R^3 = C(CH_3)_3$, $R^4 = H$
13 $R^1 = R^2 = R^4 = CH_3$, $R^3 = C_2H_5$, **14** $R^1 = R^2 = CH_3$, $R^3, R^4 = (CH_2)_4$, **15** $R^1 = R^2 = CH_3$, $R^3, R^4 = (CH_2)_3$

Scheme 1.

ene–amines (**A** and **C**) formed due to the non-equivalent amino groups (Scheme 1). The tautomeric mixtures reached equilibria after 10–15 h standing. Their ^1H and ^{13}C NMR spectra were assigned using DEPT 135, COSY, HSQC, and HMBC.

The presence of two chain tautomers was confirmed by pairwise =C*H*–NH signals at 6.5–7.0 and 7.2–7.9 ppm for the *Z*- and *E*-isomers, respectively; N*H*–CH= signals at 9.0–10.7 (*Z*-isomers, intramolecular hydrogen bonding) and 6.4–8.4 ppm (*E*-isomers); and the carbon signals at 186.5–206.2 (conjugated C=O), 139.5–154.3 (*C*H–NH), and 89.8–105.9 ppm (=*C*–C=O). These two open-chain forms were confirmed as **A** and **C** by HMBC spectra. To simplify the following discussion, the numbering of atoms in the hexahydropyrimidine ring was preserved in the open-chain forms.

For example, in the HMBC spectra of compound **8** there were observed correlations between =C*H*–NH (6.96 ppm, dd) and *C*H_2NH (C-6, 46.7 ppm) indicating the **C** tautomer, and between =C*H*–NH (7.00 ppm, dd) and *C*H–CH_3 (C-4, 52.3 ppm) indicating the **A** tautomer. Similar HMBC correlations were also observed for all the compounds **8**–**10**. Signals originating from the vicinity of the amino groups further confirmed the presence of **A** and **C** tautomers. In the NMR spectra of **8**–**10** (R^1=R^2=H), the **A** tautomer gave the signals of H-4 at 3.36–3.47 and those of C-4 at 51.6–52.6 ppm, whereas the tautomer **C** gave the respective signals at 2.81–3.02 and 44.0–44.5 ppm. For the **A** tautomers, the H-6 signals were found at 2.57–2.80 and those of C-6 at 38.3–38.7 ppm, whereas the **C** tautomer gave the respective signals at 3.24–3.36 and 45.2–46.7 ppm.

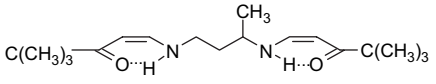
Similarly, the presence of **A** and **C** forms in the substituted diamine derivatives (**11**–**15**, R^1=R^2=CH_3) was confirmed by HMBC spectra. Thus, for compound **11c** cross-peaks indicating **C** form were observed between =C*H*–NH (7.01 ppm) and *C*H–CH_3 (C-6, 52.2 ppm), and those indicating **A** form between =C*H*–NH (7.11 ppm) and *C*$(CH_3)_2$ (C-4, 54.4 ppm). Furthermore, compounds **11**–**15** gave signals for the **A** tautomer at 3.00–3.19 (H-6) and at 43.6–44.6 ppm (C-6) as compared to those of the **C** tautomer at 3.46–3.62 (H-6) and 49.7–52.1 ppm (C-6). The signals of C-4 for the **A** and **C** tautomers were found at 53.84–54.63 and 49.2–50.0 ppm, respectively. Notably, the NH signal for **A** was a broadened doublet (*J*=12–14 Hz) due to a coupling to =CH, whereas that of **C** gave a broadened triplet (or rather dd, due to a coupling to both =CH and C*H*–CH_3, see Scheme 1).

Diastereomers of the cyclic structures **B** were identified from the signals at 3.6–4.2 (H-2) and at 61.8–73.4 (C-2), 198.7–220.9 (unconjugated C=O), and 43.7–51.5 ppm (*C*H–CO).

Generally, for all of compounds **8**–**15** the **A** tautomers (produced by condensation to the sterically more hindered amino group) were less abundant than the **C** tautomers. As to the cyclic tautomers, they were less abundant for the 1,3-butanediamine (**8**–**10**) than for the 2-methyl-2,4-pentanediamine derivatives **11**–**13**. A similar tendency was previously observed for the condensation products of **1** and **2** with aromatic aldehydes.[8] These observations are in line with the well-known rule for ring–chain tautomeric equilibria that highly substituted ring tautomers are relatively more stable (i.e., they predominate over the open-chain forms in equilibrated mixtures).[14] Also, the relative stability of the cyclic tautomers derived from diamines **1** and **2** conforms to the so-called *gem*-dimethyl effect:[14] the presence of geminal methyl substituents in cyclic tautomers usually increases their relative stability in ring–chain equilibria.

Compositions of the equilibrated tautomeric mixtures are listed in Table 1 (note that some of the isomers gave indistinguishably overlapping signals).

Upon storing (2–15 days, depending on the starting ketoaldehyde), the 1:1 condensation products partially disproportionated into free diamines and bis-imines. The latter were also formed as by-products of the main reaction, but was successfully removed by column chromatography. One of the bis-imino products (**16**, Fig. 1) was purposefully synthesized as a reference compound and characterized by NMR spectroscopy. In chloroform solution it existed in the



16

Figure 1.

Table 1. Compositions of equilibrium mixtures (% of the total)

Compd	DMSO-d_6					$CDCl_3$				
	E_{major}	E_{minor}	Z_{major}	Z_{minor}	Cyclic	E_{major}	E_{minor}	Z_{major}	Z_{minor}	Cyclic
8	Σ52		Σ48		—	—	—	63	33	4
9	Σ42		37	19	2	—	—	59	27	14
10	57	34	5	4	—	22	8	41	20	4+5
11c	Σ35		45	8	12	—	—	42	11	47
12	21	1	35	6	36	—	—	16	4	80
13	61	11	4	—	Σ24	26	9	23	5	22+15
14	Overlapping signals					20	7	34	8	13+18
15	65	18	7	2	4+4	38	18	20	5	9+10

Quantitative data were obtained by integration of ═C*H*–NH (linear forms) and H-2 (cyclic forms) signals.

Z-configuration ($J_{CH=CH}$=8.0) stabilized by intramolecular hydrogen bonding (IMHB).

2.1.1. Reactions with pivaloylacetic and *p*-substituted benzoylacetic aldehydes. The derivatives of aroylacetic aldehydes (**8**, **11a–e**) and pivaloylacetic aldehyde (**9**, **12**) in chloroform solutions exist as mixtures of two chain tautomers **A** and **C** (*Z*-isomers, $J_{CH=CH}$=7.4–8.0 stabilized by IMHB) and cyclic tautomers **B**. For the latter, only one diastereomeric form was observed, in which the substituents of the hexahydropyrimidine ring are equatorial, so there is no *syn*-axial interactions between R^3COCH_2 and R^1 (Fig. 2). For example, in the NOESY spectrum of **12** (R^1=R^2=CH_3, R^3=*t*-Bu), a correlation was observed between H-2 (4.02 ppm, dd, J_1=4.75, J_2=6.0 Hz) and H-6 (2.97 ppm, m). Similarly, only one of the two possible diastereomers was previously detected for the analogous hexahydropyrimidines derived from diamine **2**.[8] Cyclic forms of diamine **1** derivatives were observed as a mixture of both possible diastereomers, but the concentration of one of them was very low (ratio approx. 1:10).[8]

When dissolved in DMSO-d_6, which is a highly polar solvent, compounds **8**, **9**, **11**, and **12** gave a smaller amount of cyclic **B** tautomer than when dissolved in chloroform, and also *E*-forms of the chain tautomers could be observed in DMSO-d_6. Being more polar than the corresponding *Z*-isomers, the *E*-isomers are better stabilized by non-specific solvation, e.g., intermolecular hydrogen bonding between the solvent and the NH groups.[14] Formation of the *E*-isomers in DMSO-d_6 was confirmed by the proton signals of –CH═C*H*–CO (5.3–6.0 ppm, d, $J_{CH=CH}$=12.5–12.8 Hz). We noted that the *E*-isomers produced broadened signals, especially in the carbon spectra of **11** and **12**, although the corresponding C–H correlations were clearly observed in the HSQC spectra. However, the signals for *Z*-isomers were sharp. This indicates that some dynamic processes, which are slow in NMR time scale, take place in the case of *E*-isomers. The cause for the broadening is most likely hindered rotation at the N–C bond (in –HN–CH═C– moiety), which has a partial double bond character. This has been previously observed for secondary enaminones by Kozerski et al.[15] Also the observation that N*H* and C*H* protons (in the moiety above) exhibit the most broadened signals, is in harmony with the hindered rotation at N–C bond.

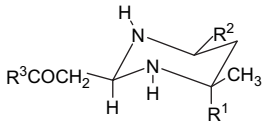


Figure 2.

As the temperature was increased from room temperature to 57 °C, the signals for *E*-isomers sharpened, but were still rather broad. The decomposition of the structure inhibited extensive measurements at higher temperatures. The lowering of temperature was unfortunately not possible because of the melting point of DMSO-d_6 (and *E*-isomers were not observed in $CDCl_3$). We also noted that the relative amounts of *E*- and *Z*-isomers changed as the temperature was changed. This further proves the existence of ring–chain tautomeric equilibrium system as presented in Scheme 1.

Upon equilibration, the relative content of the linear tautomers (sum total of [**A**]+[**C**]) is higher for the aroylacetaldehyde derivatives (i.e., [**8A+C**]>[**9A+C**], [**11A+C**]>[**12A+C**]), probably due to stabilizing effect of conjugation between the aromatic ring and C═C–C═O fragments in **8A**, **8C** and **11A**, **11C**, which cannot be achieved in the pivaloylacetaldehyde derivatives **9** and **12**.

For the series **11a–e**, in which substantial amounts of the tautomers **B** were observed, the ring–chain equilibrium constants in $CDCl_3$ correlated closely with the electronic properties of the substituents on the aromatic rings (Table 2,

Table 2. Compositions of equilibrium mixtures (% relative to the major chain tautomer) for the condensation products of 2-methyl-2,4-pentanediamine with *p*-substituted benzoylacetaldehydes in $CDCl_3$ solutions

Compd	Substituent	σ	Chain tautomer **C** (major)	Chain tautomer **A** (minor)	Cyclic tautomer **B**	*K*=[A+C]/[B]
11a	NO_2	0.78	100	25	11	0.088
11b	Br	0.23	100	24	54	0.435
11c	H	0	100	25	116	0.928
11d	CH_3	−0.17	100	22	173	1.430
11e	OCH_3	−0.27	100	24	240	1.927

Eq. 1). In DMSO-d_6, the equilibrium constants of **11a–e** could not be determined with a sufficient precision because of the interference with broadened signals of the *E*-isomers.

$$\log K_{eq}(CDCl_3) = -(0.0558 \pm 0.007) - (1.282 \pm 0.019)\sigma, \quad r = -0.999 \qquad (1)$$

Apart from this, the aromatic ring substituents were expected to affect the IMHB strength and, thereby, the chemical shifts of the NH protons. Indeed, linear correlations between their chemical shifts and the σ constants were observed (Eqs. 2 and 3). Compounds **11a–e** were dissolved in similar concentrations:

$$\delta_{NH\ major} = (0.34 \pm 0.03)\sigma + (10.43 \pm 0.01), \quad r = 0.982 \qquad (2)$$

$$\delta_{NH\ minor} = (0.38 \pm 0.03)\sigma + (10.86 \pm 0.01), \quad r = 0.987 \qquad (3)$$

The yields and properties of **11a–e** are listed in Table 3. The ^{1}H and ^{13}C NMR parameters for their major (**C**) and minor chain tautomers (**A**), and cyclic tautomers (**B**) are shown in Tables 4–9.

2.1.2. Reaction with propionylpropionaldehyde. Substitution at the α-position in the dicarbonyl component (compounds **10** and **13**, R^4=CH_3) resulted in the formation of *E*-isomers of their chain tautomers already in chloroform solutions (see Table 1). Also, *Z*-isomers and cyclic tautomers were detected, although open-chain forms of **10** and **13** in DMSO solutions exist exclusively as *E*-isomers. It has been noted previously[16] that the presence of R^4 substituent greatly affects *Z*/*E* equilibria in enaminones.

The cyclic tautomers **B** can in principle exist in four diastereomeric forms of which only two were actually detected in ca. 1:1 ratio. The same ratio of diastereomers was observed for the cyclic reaction product of propionylpropionaldehyde with 2-aminobenzenesulfonamide,[12] which had only two chiral centers, the C-2 of the ring and C-1′ of the side chain. So it can be concluded that the two diastereomers of **10B** and **13B** are due to the chiral center at C-1′ since only one diastereomer was detected when R^4=H (compare **8** and **9** with **11** and **12**, respectively). The cyclic forms are relatively less stable in **10** (derived from the less substituted diamine **1**) than in **13** (derived from **2**), similarly to the derivatives of **1** and **2** with other aldehydes (see Table 1). Also, cyclic tautomers are generally less stable in DMSO than in $CDCl_3$.

The presence of both *Z*- and *E*-isomers of **10** and **13** was confirmed by the NOE spectra. Thus, the spectrum of **13** in $CDCl_3$ showed correlations between the C*H*═ (6.72 and 6.61 ppm) and ═C–CH_3 (1.81 and 1.83 ppm) of the *Z*-isomers and the absence of such correlation for the corresponding signals of the *E*-isomers. Moreover, the presence of the *E*,*E*′-conformation (Fig. 3) of the latter was proved by NOE correlations observed between the C*H*═ signals and CH_2–CH_3 (2.40–2.50 ppm, m). It is known from the literature on the geometrical isomerism of enaminones[16] that NH signals of their *Z*-forms are shifted downfield from the corresponding *E*-form signals due to IMHB. Indeed, we observed the NH signals of the *Z*- and *E*-isomers at 9.07–10.86 and 6.48–8.48 ppm, respectively. Moreover,

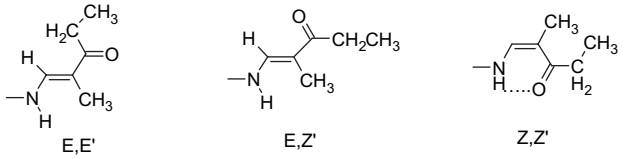


Figure 3.

the carbon signals of ═C*H*–NH (*E*-) and ═*C*–C═O (*E*-) were shifted by 2–3 ppm to higher field than the corresponding *Z*-form signals.

The *Z*-isomers are destabilized by steric interactions involving the methyl substituent, which are minimized in the *E*,*E*′-conformation (Fig. 3). In DMSO-d_6 solutions, the chain tautomers of **10** and **13** predominantly existed in the *E*,*E*′-conformation, similarly to the analogous derivatives of 2-aminobenzenesulfonamide.[12]

2.1.3. Reactions with 2-formylcyclohexanone and 2-formylcyclopentanone. In these compounds, an additional structural constraint is introduced apart from the α-substitution, which could be expected to affect the tautomeric equilibria. Unfortunately, the condensation products of **1** with the title ketoaldehydes were unstable, and rapidly decomposed.

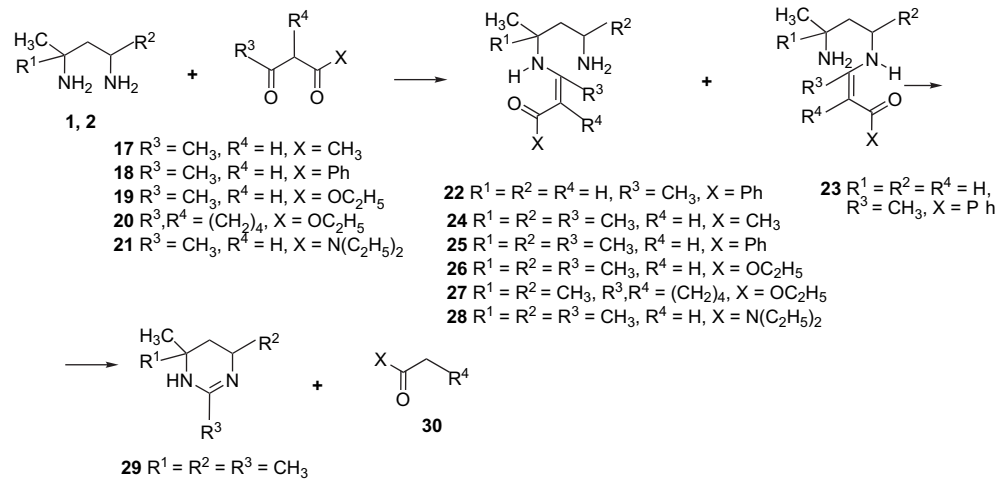
Derivatives of the substituted diamine **2** (**14** and **15**) were more stable, and their behavior resembled that of **13**. The *E*-isomers of the chain forms were observed even in chloroform solutions, and two diastereomers of each cyclic tautomer were detected (Table 1). In principle, the compositions of equilibrium mixtures should not differ much for the structurally very similar compounds **13** (R^3=Et, R^4=Me) and **14** [R^3R^4=–$(CH_2)_4$–]. The slightly decreased stability of **14B** relative to **13B** may be explained by the presence of alicyclic substructure, as noted in the literature.[14] The presence of a cyclic moiety usually decreases the fraction of a ring tautomer.[14]

For the 2-formylcyclopentanone derivative **15** in $CDCl_3$, the total content of the *E*-isomers (38%+18%) is higher than for the 2-formylcyclohexanone derivative **14** (20%+7%). Moreover, the size of the aliphatic carbocycle seems to affect the total content of the heterocyclic tautomers (19% for **15** vs 31% for **14**), a trend also observed in the previous study.[12]

2.2. Reactions of 1,3-butanediamine and 2-methyl-2,4-pentanediamine with β-diketones, β-keto esters, and β-keto amides

As shown in Scheme 2, the reactions always occurred at the more reactive acetylic carbonyl (as in **18**) or, in general, at the keto group of keto esters and keto amides **19–21**.

Unlike the ketoaldehyde derivatives (where R^3=H), reaction products **22–28** do not form cyclic tautomers at all. Inspection of the conformations of the possible cyclic isomers shows that the destabilizing interactions of CH_3 and $XCOCH_2$ groups with *syn*-axial H or CH_3 cannot be avoided in any of the conformers as shown in Figure 4.



Scheme 2.

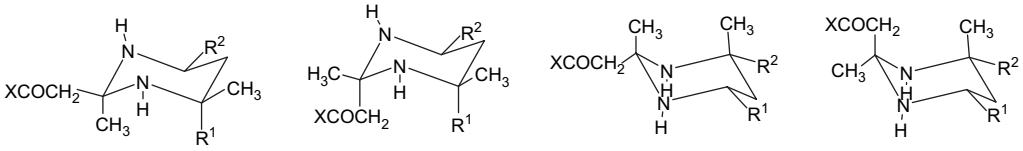


Figure 4.

The derivatives of diamine **1** invariably contained considerable amounts of the bis-condensation products, which could not be removed by column chromatography except the benzoylacetone derivative, which was obtained as a 4:1 mixture of regioisomers **22** and **23**. Their ratio remained constant in different solvents, indicating the absence of chain–chain tautomerism.

Condensations with the substituted diamine **2** occurring to the less hindered amino group produced a single regioisomer in each case (**24**–**28**), all of which were pure *Z*-isomers except the acetoacetic ester derivative **26** (*Z*/*E*=100:16). Possible effects of α-substitution (R^4=CH_3) in the dicarbonyl component on the *Z*/*E* isomerism could not be studied because the condensation products of α-substituted acetylacetone and acetoacetic ester (R^3=R^4=X=CH_3 and R^3=R^4=CH_3, X=OC_2H_5) were unstable.

Upon prolonged storage in solutions, compounds **24**–**28** decomposed to form **29** (Scheme 2) which, according to the ^{13}C NMR spectra, does not contain a carbonyl group. The double bond position in **29** was determined by comparing the chemical shifts of C-4 (49.3 ppm) and C-6 (43.4 ppm) with the corresponding signals for **12B** (C-4, 49.2 and C-6, 46.5 ppm) and with the previously reported[8] spectrum of 4,4,6-trimethyl-2-phenylhexahydropyrimidine (C-4, 49.5 and C-6, 46.9 ppm). The high-field shift of C-6 signal in **29** indicates a double bond between N-1 and C-2.

3. Conclusion

Ring–chain tautomerism involving two open-chain regioisomers is for the first time reported for the 1:1 condensation products of β-keto aldehydes with substituted aliphatic 1,3-diamines possessing non-equivalent amino groups. The equilibrium mixtures contained relatively higher amounts of the cyclic tautomers in the case of the more substituted diamine **2**.

For a series of condensations products of diamine **2** with *para*-substituted benzoylacetic aldehydes, the ring–chain equilibrium constants correlated closely with the Hammett σ constants for the aromatic substituents.

Increasing the solvent polarity (i.e., $CDCl_3$ vs DMSO-d_6) decreased the equilibrium content of the cyclic tautomers.

In addition to the ring–chain tautomerism, *Z*- and *E*-forms of the chain tautomers were also observed. In $CDCl_3$, *Z*-isomers prevail, whereas in DMSO-d_6 the amounts of *E*-isomers become much higher. Substitution at the α-position of the starting ketoaldehyde increased the amounts of the *E*-forms in the equilibria and resulted in the formation of diastereomeric mixtures of the cyclic tautomers.

The condensation products of **1** and **2** with β-diketones, β-keto esters, and β-keto amides did not exhibit any ring–chain tautomerism. No imine structures could be observed for any of the reaction products.

4. Experimental

4.1. General

In general, the ring–chain equilibria were reached in NMR tubes at 10–15 h after dissolving the compound. The equilibria were considered to be settled when two consecutive measurements at 2 h intervals indicated no change in the ratio of the chain and cyclic forms.

4.2. Spectrometry

NMR spectra were acquired using Bruker Avance 500 and 600 spectrometers (equipped with BBI-5mm-Zgrad-ATM and BBO-5mm-Zgrad probes) operating at 500.13 and 600.13 MHz for ^{1}H and 125.77 and 150.90 MHz for ^{13}C, respectively. Spectra were recorded at 25 °C using DMSO-d_6 and $CDCl_3$ as a solvent with a non-spinning sample in 5 mm NMR tubes. Spectra were processed by a PC with Windows XP operating system and XWin-NMR software. Proton and carbon spectra were referenced internally to TMS signal using value 0.00 ppm. ^{1}H NMR spectra and ^{13}C NMR proton-decoupled spectra were acquired with single-pulse excitation and 30° flip angle. Exponential weighting (1 Hz) was applied prior to Fourier transformation (in carbon spectra). Gradient selected DQF-COSY spectra were acquired with cosygpmfqf pulse program (pulse programs refer to original ones installed by Bruker). Gradient selected NOESY spectra were acquired with noesygpph pulse program. Gradient selected ^{1}H–^{13}C HSQC spectra were acquired with hsqcetgpsisp.2 pulse program (using shaped pulses). Gradient selected ^{1}H–^{13}C HMBC spectra were acquired with hmbcgplpndqf pulse program.

Mass-spectral measurements of the $M^{+\bullet}$ compositions were obtained in the EI ionization mode, direct insertion probe, on a VG ZABSpec instrument at a resolving power of 7000–8000 (10% valley definition).

4.3. General synthetic procedures

The starting keto aldehydes were prepared according to the standard methods[17] and used immediately for condensations with the diamines.

4.3.1. Reaction of 1,3-diamines with β-keto aldehydes (procedure A, substances 8–15, 22, 23, 25). To a solution of diamine (2–3 mmol) in 10 mL of dry ether stirred and cooled on an ice bath, a solution of equimolar amount of β-keto aldehyde (2–3 mmol) in 10 mL of dry ether was slowly added. In the course of addition, ammonium salt of the keto aldehyde precipitated. The reaction mixture was stirred at a room temperature overnight, concentrated in vacuo, and chromatographed on silica gel (100–250 mesh, elution with ether/methanol 2:1).

4.3.1.1. 1-(3-Phenyl-3-oxoprop-1-enylamino)-3-aminobutane (8). Yield 37% (220 mg), yellowish oil. HRMS: $C_{13}H_{18}N_2O$ $M^{+\bullet}$ calcd 218.1419; obsd 218.1411. Compound *Z*-**8C** (major chain): δ_H ($CDCl_3$): 1.11 (3H, d, J_{CH_3CH}=6.4, CH_3), 1.57 (1H, m, H-a from CH_2–CH), 1.67 (1H, m, H-b from CH_2–CH), 3.02 (1H, m, CHCH$_3$), 3.36 (2H, m, CH_2NH), 5.69 (1H, d, $J_{CH=CH}$=7.6, =CH–CO), 6.96 (1H, dd, $J_{CH=CH}$=7.6, J_{CH-NH}=12.8, =CH–NH), 7.41 (3H, m, H-3′, H-4′, H-5′), 7.87 (2H, d, J=7.8, H-2′, H-6′), 10.38 (1H, br s, NH). δ_C ($CDCl_3$): 24.8 (CH_3), 40.6 (CH_2CH), 44.5 (CH–CH_3), 46.7 (CH_2–NH), 90.1 (CH–CO), 127.0 (C-2′, C-6′), 128.2 (C-3′, C-5′), 130.8 or 130.9 (C-4′), 139.8 (C-1′), 154.3 (CHNH), 189.8 (CO). Compound *Z*-**8A** (minor chain): δ_H ($CDCl_3$): 1.29 (3H, d, J_{CH-CH_3}=6.8, CH_3), 1.67 (2H, m, CH_2CH), 2.79 (2H, m, CH_2NH$_2$), 3.46 (1H, m, CHCH$_3$), 5.69 (1H, d, $J_{CH=CH}$=7.6, =CH–CO), 7.00 (1H, dd, $J_{CH=CH}$=7.2, J_{CH-NH}=12.8, =CH–NH), 7.41 (3H, m, H-3′, H-4′, H-5′), 7.86 (2H, d, J=7.8, H-2′, H-6′), 10.38 (1H, br s, NH). δ_C ($CDCl_3$): 22.3 (CH_3), 38.7 (CH_2NH_2), 41.3 (CH_2CH), 52.3 (CH_3CH), 89.8 (CHCO), 127.0 (C-2′, C-6′), 128.2 (C-3′, C-5′), 130.8 or 130.9 (C-4′), 139.8 (C-1′), 154.2 (CHNH), 189.7 (CO). Compound **8B** (cyclic), observed signals: δ_H ($CDCl_3$): 4.04 (1H, t, J_{CH-CH_2}=5.6, H-2). δ_C ($CDCl_3$): 23.0 (CH_3), 35.0 (C-5), 45.7 (C-6), 51.3 (C-4), 68.3 (C-2), 133.4 (C-4′), 136.8 (C-1′), 198.8 (CO).

4.3.1.2. 1-(4.4-Dimethyl-3-oxopent-1-enyl)amino-3-aminobutane (9). Yield 46% (210 mg), yellowish oil. HRMS: $C_{11}H_{22}N_2O$ $M^{+\bullet}$ calcd 198.1732; obsd 198.1739. Compound *Z*-**9C** (major chain): δ_H ($CDCl_3$): 1.10 (3H, d, J_{CH_3CH}=6.5, CH_3), 1.14 (9H, s, (CH_3)$_3$C), 1.53 (1H, m, H-a from CH_2–CH), 1.63 (1H, m, H-b from CH_2–CH), 3.00 (1H, m, CHCH$_3$), 3.28 (2H, m, CH_2NH), 5.15 (1H, d, $J_{CH=CH}$=8.0, =CH–CO), 6.76 (1H, dd, $J_{CH=CH}$=7.5, J_{CH-NH}=12.5, =CH–NH), 9.90 (1H, br s, NH). δ_C ($CDCl_3$): 24.7 (CH_3), 27.7 ((CH_3)$_3$C), 40.6 (CH_2CH), 41.5 (C(CH$_3$)$_3$), 44.4 (CH–CH_3), 46.4 (CH_2–NH), 88.9 (CH–CO), 153.3 (=CHNH), 206.1 (CO). Compound *Z*-**9A** (minor chain): δ_H ($CDCl_3$): 1.14 (9H, s, (CH_3)$_3$C), 1.24 (3H, d, J_{CH-CH_3}=6.5, CH_3), 1.62 (2H, m, CH_2CH), 2.70–2.80 (2H, m, CH_2NH$_2$), 3.36 (1H, m, CHCH$_3$), 5.14 (1H, d, $J_{CH=CH}$=7.5, =CH–CO), 6.80 (1H, dd, $J_{CH=CH}$=7.5, J_{CH-NH}=13.0, =CH–NH), 9.84 (1H, br s, NH). δ_C ($CDCl_3$): 22.3 (CH_3), 27.7 ((CH_3)$_3$C), 38.7 (CH_2NH_2), 41.4 (CH_2CH), 41.5 (C(CH$_3$)$_3$), 52.6 (CH_3CH), 88.6 (=CHCO), 151.9 (=CHNH), 206.1 (CO). Compound **9B** (cyclic): δ_H ($CDCl_3$): 1.08 (3H, d, J_{CH_3CH}=6.5, CH_3), 1.14 (9H, s, (CH_3)$_3$C), 1.25 (1H, m, H-5ax), 1.60 (1H, m, H-5eq), 2.70–2.85 (3H, m, CH_2CO, CH–CH_3), 3.00 (2H, m, H-4ax, H-6ax), 3.13 (1H, ddd, J_{6eq6ax}=13.0, J_{6eq5ax}=4.4, J_{6eq5eq}=1.9, H-6eq), 3.81 (1H, t, J_{CH-CH_2}=5.7, H-2). δ_C ($CDCl_3$): 23.0 (CH_3), 26.7 ((CH_3)$_3$C), 35.0 (C-5), 41.6 (C(CH$_3$)$_3$), 43.6 (CH_2CO), 45.7 (C-6), 51.3 (C-4), 68.1 (C-2), 215.4 (CO).

4.3.1.3. 1-(2-Methyl-3-oxopent-1-enyl)amino-3-aminobutane (10). Yield 42% (150 mg), yellowish oil. HRMS: $C_{10}H_{20}N_2O$ $M^{+\bullet}$ calcd 184.1576; obsd 184.1574. Compound *E*-**10C** (trans-major chain): δ_H (DMSO-d_6): 0.95 (3H, t,

Table 3. *p*-Substituted 4-(3-aryl-3-oxoprop-1-enyl)amino-2-amino-2-methylpentanes **11a–e**

Compd	Yield, %	Yield, mg	Appearance	$M^{+\bullet}$	HRMS	
					Calculated	Observed
11a	27	80	Yellow oil	$C_{15}H_{21}N_3O_3$	291.1583	291.1582
11b	50	330	Yellow oil	$C_{15}H_{21}BrN_2O$	324.0837 (^{79}Br)	324.0820 (^{79}Br)
11c	35	230	Yellowish oil	$C_{15}H_{22}N_2O$	246.1732	246.1729
11d	30	70	Yellowish oil	$C_{16}H_{24}N_2O$	260.1889	260.1878
11e	50	280	Yellowish oil	$C_{16}H_{24}N_2O_2$	276.1838	276.1840

Table 4. The ^{1}H NMR data ($CDCl_3$, chemical shifts in ppm and coupling constants in Hz) of the major chain tautomers **C** of *p*-substituted 4-(3-aryl-3-oxoprop-1-enyl)amino-2-amino-2-methylpentanes **11a–e**

R	CH_3, s	CH_3, s	CH_3–CH, d	J_{CH-CH_3}	H-a, dd (CH_2)	J_{gem}	J_{CH-CH_a}	H-b, dd (CH_2)	J_{CH-CH_b}	CH–CH_3, m
NO_2	1.17	1.19	1.34	6.6	1.61	14.4	3.3	1.72	9.0	3.66
Br	1.14	1.15	1.29	7.0	1.58	14.8	3.2	1.69	8.8	3.57
H	1.15	1.16	1.31	6.4	1.58	14.5	3.4	1.70	8.8	3.57
CH_3	1.15	1.16	1.30	6.6	1.57	14.4	3.0	1.70	8.7	3.55
OCH_3	1.14	1.15	1.30	6.6	1.57	14.4	3.0	1.69	8.7	3.55

R	=CH–CO, d	J_{CHCH}	=CHNH, dd	J_{CHNH}	H-2′, H-6′, d	H-3′, H-5′, d	J_{arom}	NH, br t	H_R
NO_2	5.69	7.2	7.13	13.2	7.99	8.24	9.0	10.72	—
Br	5.63	7.5	7.03	13.0	7.73	7.52	8.5	10.47	—
H	5.70	7.4	7.01	12.9	7.87	7.40	n.d.	10.45	7.44
CH_3	5.68	7.2	6.99	12.9	7.77	7.20	7.8	10.40	2.38
OCH_3	5.66	7.2	6.97	13.4	7.85	6.90	9.0	10.34	3.83

$J_{CH_3-CH_2}$=7.5, CH_3CH_2), 1.00 (3H, d, J_{CH_3-CH}=6.5, CH_3–CH), 1.41 (1H, m, H-a from CH_2–CH), 1.50 (1H, m, H-b from CH_2–CH), 1.53 (3H, s, CH_3–C=), 2.41 (2H, q, $J_{CH_3-CH_2}$=7.5, CH_2CH_3), 2.81 (1H, m, CH–CH_3), 3.24 (2H, m, CH_2NH), 6.55 (1H, m, NH), 7.42 (1H, d, J_{CH-NH}=13.5, =CH). δ_C (DMSO-d_6): 8.9 (CH_3C=), 10.4 (CH_3CH_2), 24.3 (CH_3CH), 28.2 (CH_2CH_3), 40.7 (CH_2–CH), 44.0 (CH–CH_3), 45.2 (CH_2NH), 103.4 (=$C(CH_3)$–CO), 149.6 (=CH–NH), 195.4 (CO). Compound *E*-**10A** (trans-minor chain): δ_H (DMSO-d_6): 0.95 (3H, t, $J_{CH_3-CH_2}$=7.5, CH_3CH_2), 1.15 (CH_3–CH), 1.41 (1H, m, H-a from CH_2–CH), 1.50 (1H, m, H-b from CH_2–CH), 1.54 (3H, s, CH_3–C=), 2.41 (2H, q, $J_{CH_3-CH_2}$=7.5, CH_2CH_3), 2.57 (2H, m, CH_2–NH_2), 3.47 (1H, m, CH–CH_3), 6.42 (1H, m, NH), 7.44 (1H, d, J_{CH-NH}=13.5, =CH). δ_C (DMSO-d_6): 9.1 (CH_3C=), 10.3 (CH_3CH_2), 22.0 (CH_3CH), 28.2 (CH_2CH_3), 38.3 (CH_2NH_2), 40.0 (CH_2–CH), 51.6 (CH–CH_3), 103.2 (=C–CH_3), 148.3 (=CH), 195.5 (CO).

4.3.1.4. 4-(4,4-Dimethyl-3-oxopent-1-enyl)amino-2-amino-2-methylpentane (12). Yield 58% (260 mg), colorless oil. HRMS: $C_{13}H_{26}N_2O$ $M^{+\bullet}$ calcd 226.2045; obsd 226.2038. Compound *Z*-**12C** (major chain): δ_H ($CDCl_3$): 1.12 (3H, s, CH_3 from $C(CH_3)_2$), 1.13 (3H, s, CH_3 from $C(CH_3)_2$), 1.14 (9H, s, $C(CH_3)_3$), 1.25 (3H, d, J_{CH_3CH}=6.5, CH_3–CH), 1.53 (1H, dd, J_{CH_a-CH}=4.0, J_{gem}=14.5, H-a from CH_2), 1.63 (1H, dd, J_{CH_b-CH}=8.3, J_{gem}=14.7, H-b

Table 5. The ^{13}C NMR chemical shifts (in ppm, $CDCl_3$) of the major chain tautomers **C** of *p*-substituted 4-(3-aryl-3-oxoprop-1-enyl)amino-2-amino-2-methylpentanes **11a–e**

R	CH_3CH	CH_3	CH_3	Cq	CH_2	CH–CH_3	=CH–CO
NO_2	24.4	31.3	31.8	49.5	51.2	52.3	90.2
Br	24.6	31.2	31.3	49.4	51.2	52.1	89.7
H	24.7	31.4	31.5	49.4	51.4	52.1	90.0
CH_3	24.7	31.4	31.5	49.4	51.5	52.1	89.9
OMe	24.8	31.4	31.4	49.4	51.5	52.0	89.6

R	C-2′,6′	C-3′,5′	C-4′	C-1′	=CH–NH	CO	C_R
NO_2	127.9	123.5	145.3	149.0	153.5	186.5	—
Br	128.6	131.3	125.3	138.6	152.8	188.0	—
H	127.0	128.2	130.8	139.8	152.4	189.6	—
CH_3	127.1	128.9	137.1	141.1	152.1	189.5	21.5
OMe	130.3	113.8	163.7	132.5	151.9	188.8	55.3

Table 7. The ^{13}C NMR chemical shifts (in ppm, $CDCl_3$) of the minor chain tautomers **A** of *p*-substituted 2-(3-aryl-3-oxoprop-1-enyl)amino-4-amino-2-methylpentanes **11a–e**

R	CH_3–CH	CH_3	CH_3	CH–CH_3	CH_2	$(CH_3)_2C$	=CH–CO
NO_2	27.0	28.2	28.9	43.9	51.8	55.0	90.3
Br	26.5	28.1	28.8	43.7	51.9	54.5	89.8
H	26.6	28.2	28.9	43.8	52.2	54.4	90.2
CH_3	26.6	28.3	29.0	43.7	52.2	54.3	90.0
OCH_3	26.6	28.3	29.0	43.7	52.2	54.3	89.7

R	C-2′,6′	C-3′,5′	C-4′	C-1′	=CH–NH	CO	C_R
NO_2	129.3	123.5	145.5	148.8	150.9	186.3	—
Br	129.5	131.8	125.3	138.7	150.2	187.8	—
H	127.0	128.3	130.7	n.d.	149.8	189.5	—
CH_3	128.4	129.2	134.7	143.9	149.6	189.4	21.6
OMe	130.9	113.7	163.5	132.6	149.3	188.6	55.2

Table 6. The ^{1}H NMR data ($CDCl_3$, chemical shifts in ppm and coupling constants in Hz) of the minor chain tautomers **A** of *p*-substituted 2-(3-aryl-3-oxoprop-1-enyl)amino-4-amino-2-methylpentanes **11a–e**

R	CH_3CH, d	J_{CH_3-CH}	$(CH_3)_2C$, s	CH_2, m	CH–CH_3, m	=CH–CO, d	$J_{CH=CH}$
NO_2	1.14	6.6	1.40	1.64	3.17	5.71	7.2
Br	1.11	6.0	1.35	1.61	3.13	5.65	7.5
H	1.11	6.4	1.37	1.62	3.15	5.73	7.6
CH_3	1.11	6.0	1.36	1.62	3.15	5.72	7.2
OCH_3	1.11	6.0	1.36	1.60	3.15	5.69	7.8

R	=CH–NH, dd	J_{CH-NH}	H-3′,5′	H-2′,6′	J_{arom}	NH, d	H_R
NO_2	7.21	13.8	8.12	8.32	9.0	11.17	—
Br	7.12	13.5	7.59	7.80	8.5	10.90	—
H	7.11	12.8	7.45	7.94	n.d.	10.86	7.46
CH_3	7.09	13.2	7.26	7.86	7.8	10.81	2.41
OCH_3	7.07	13.2	Overlap.	7.94	n.d.	10.75	3.86

Table 8. The ^{1}H NMR data ($CDCl_3$, chemical shifts in ppm and coupling constants in Hz) of the cyclic tautomer **B** of 4,4,6-trimethyl-2-(2-aryl-2-oxoethyl)-hexahydropyrimidines **11a–e**

R	H-5ax, dd	$J_{gem}=J_{5ax6ax}$	CH_3CH, d	J_{CH_3-CH}	CH_3-eq, s	CH_3-ax, s	H-5eq, dd	J_{5eq6ax}	CHCH_3, m
NO_2	0.94	12.3	1.07	6.0	1.13	1.21	1.54	2.7	3.03
Br	0.95	12.2	1.06	6.0	1.12	1.18	1.51	3.0	3.01
H	0.96	12.4	1.07	6.4	1.13	1.19	1.52	2.8	3.03
CH_3	0.95	12.0	1.07	6.0	1.12	1.19	1.51	2.4	3.03
OCH_3	0.95	12.3	1.06	6.0	1.12	1.19	1.51	2.4	3.02

R	H_a, dd, CH_2CO	J_{CH-H_a}	H_b, dd, CH_2CO	J_{gem}	J_{CH-H_b}	H-2, dd	H-3′,5′	H-2′,6′	J_{arom}	H_R
NO_2	3.20	6.0	3.27	18.0	4.8	4.26	8.09	8.31	8.4	—
Br	3.13	6.5	3.21	17.5	4.8	4.22	7.59	7.80	8.5	—
H	3.17	6.4	3.26	17.6	4.8	4.24	7.93	7.4–7.5	7.6	7.56
CH_3	3.16	6.6	3.23	17.4	4.2	4.23	7.25	7.83	7.8	2.40
OCH_3	3.12	6.3	3.21	17.7	4.5	4.22	6.92	7.91	9.0	3.86

Table 9. The ^{13}C NMR chemical shifts (in ppm, $CDCl_3$) of cyclic tautomer **B** of 4,4,6-trimethyl-2-(2-aryl-2-oxoethyl)hexahydropyrimidines **11a–e**

R	CH_3CH	CH_3 ax	CH_3 eq	CH_2–CO	CH_2	CH–CH_3	$(CH_3)_2C$
NO_2	23.0	24.1	33.2	46.2	46.4	47.1	50.0
Br	22.9	24.0	33.0	45.1	46.2	47.0	49.9
H	23.0	24.1	33.2	45.4	46.5	47.1	49.9
CH_3	23.0	24.1	33.2	45.3	46.5	47.1	49.9
OCH_3	23.0	24.1	33.2	45.0	46.5	47.0	49.9

R	C-2	C-2′,6′	C-3′,5′	C-4′	C-1′	CO	C_R
NO_2	62.7	123.9	129.9	144.7	n.d.	197.4	
Br	62.7	129.8	131.9	128.6	135.4	197.9	
H	62.8	128.0	128.6	133.4	136.8	199.0	—
CH_3	62.8	128.1	129.3	134.4	144.3	198.7	21.6
OMe	62.9	128.9	113.2	161.8	129.5	197.5	55.3

from CH_2), 3.46 (1H, m, CH–CH_3), 5.15 (1H, d, $J_{CH=CH}$=7.5, =CHCO), 6.80 (1H, dd, J_{CHNH}=12.8, $J_{CH=CH}$=8.0, =CHNH), 9.92 (1H, br s, NH). δ_C ($CDCl_3$): 24.8 (CH_3CH), 27.8 (C(CH_3)$_3$), 31.3 (2C, (CH_3)$_2$C), 44.2 (C(CH$_3$)$_3$), 49.4 (C(CH$_3$)$_2$), 51.7 (CH_2), 51.9 (CH–CH_3), 88.8 (=CHCO), 151.4 (=CHNH), 205.9 (CO). Compound *Z*-**12A** (minor chain), detected signals: δ_H ($CDCl_3$): 1.08 (3H, d, J_{CH_3CH}=6.5, CH_3–CH), 1.14 (9H, s, C(CH_3)$_3$), 1.31 (6H, s, C(CH_3)$_2$), 1.57 (2H, m, CH_2), 3.11 (1H, m, CH–CH_3), 5.19 (1H, d, $J_{CH=CH}$=8.0, =CHCO), 6.91 (1H, dd, J_{CHNH}=13.0, $J_{CH=CH}$=7.5, =CHNH), 10.27 (1H, d, J_{NHCH}=12.5, NH). δ_C ($CDCl_3$): 52.3 (CH_2), 53.9 (C(CH$_3$)$_2$), 89.0 (=CHCO), 205.8 (CO). Compound **12B** (cyclic): δ_H ($CDCl_3$): 0.92 (1H, t, $J_{5ax6ax}=J_{gem}$=12.5, H-5ax), 1.05 (3H, d, J_{CH_3CH}=6.0, CH_3–CH), 1.10 (3H, s, CH_3-eq), 1.14 (9H, s, C(CH_3)$_3$), 1.16 (3H, s, CH_3-ax), 1.49 (1H, dd, J_{5eq6ax}=3.0, J_{gem}=13.0, H-5eq), 2.71 (1H, dd, J_{H_aCH}=6.5, J_{gem}=18.0, H-a from CH_2–CO), 2.80 (1H, dd, J_{H_bCH}=4.5, J_{gem}=18.0, H-b from CH_2–CO), 2.97 (1H, m, CHCH$_3$), 4.02 (1H, dd, J_{CH-H_b}=4.7, J_{CH-H_a}=6.3, H-2). δ_C ($CDCl_3$): 23.0 (CH_3CH), 24.1 (CH_3-ax), 26.4 (C(CH_3)$_3$), 33.2 (CH_3-eq), 43.7 (CH_2CO), 44.2 (C(CH$_3$)$_3$), 46.5 (C-5), 47.0 (CH), 49.8 (C-4), 62.6 (C-2), 215.8 (CO).

4.3.1.5. 4-(2-Methyl-3-oxopent-1-enyl)amino-2-amino-2-methylpentane (13). Yield 34% (80 mg), colorless oil. HRMS: $C_{12}H_{24}N_2O$ $M^{+\bullet}$ calcd 212.1889; obsd 212.1898. Compound *E*-**13C** (major chain): δ_H (DMSO-d_6): 0.96 (3H, t, $J_{CH_3-CH_2}$=7.5, CH_3CH$_2$), 1.03 (1H, s, CH_3 from (CH$_3$)$_2$C), 1.05 (1H, s, CH_3 from (CH$_3$)$_2$C), 1.17 (3H, d, J_{CH_3-CH}=6.5, CH_3–CH), 1.40 (1H, dd, J_{gem}=14.0, J_{H_a-CH}=3.5, H-a from CH_2), 1.53 (3H, s, CH_3C=), 1.59 (1H, dd, J_{gem}=14.0, J_{H_b-CH}=9.5, H-b from CH_2), 2.44 (2H, q, $J_{CH_3-CH_2}$=7.5, CH_2CH$_3$), 3.57 (1H, m, CH–CH_3), 7.20 (1H, dd, $J_{NH-CH=}$=13.1, J_{NHCH}=5.1, NH), 7.48 (1H, d, J_{CH-NH}=13.0, =CH). δ_C (DMSO-d_6): 9.1 (CH_3C=), 10.5 (CH_3CH$_2$), 23.8 (CH_3CH), 28.2 (CH_2CH$_3$), 29.5 (CH_3 from (CH$_3$)$_2$C), 32.2 (CH_3 from (CH$_3$)$_2$C), 49.2 (C(CH$_3$)$_2$), 49.3 (CH_2), 50.2 (CH–CH_3), 103.7 (=CCH_3), 147.5 (=CH), 195.3 (CO). Compound *E*-**13A** (minor chain), detected signals: δ_H (DMSO-d_6): 0.96 (3H, t, $J_{CH_3-CH_2}$=7.5, CH_3CH$_2$), 1.06 (3H, overlap. d, CH_3CH), 1.24 (3H, s, from (CH$_3$)$_2$C), 1.27 (3H, s, from (CH$_3$)$_2$C), 1.45–1.55 (2H, m, CH_2), 1.54 (3H, s, CH_3–C=), 2.41 (2H, q, $J_{CH_3-CH_2}$=7.5, CH_2CH$_3$), 3.00 (1H, m, CH–CH_3), 7.52 (1H, d, J_{CH-NH}=13.5, =CH), 8.48 (1H, d, $J_{NH-CH=}$=14.0, NH). δ_C (DMSO-d_6): 9.2 (CH_3C=), 10.5 (CH_3CH$_2$), 27.6, 28.0 and 29.2 ((CH_3)$_2$C and CH_3CH), 28.3 (CH_2CH$_3$), 43.8 (CH–CH$_3$), 49.4 (CH_2), 53.9 (C(CH$_3$)$_2$), 103.9 (=C–CH_3), 144.5 (=CH), 195.2 (CO). Cyclic diastereomers **13B**: δ_H (DMSO-d_6): 0.70 (1H, t, $J_{5ax6ax}=J_{5ax5eq}$=12.0, H-5ax), 0.88–0.92 (6H, m, CH_3CH$_2$, CH_3–CH), 0.94–0.98 (3H, m, CH_3-4eq), 0.97–1.05 (6H, m, CH_3CH (side chain), CH_3-4ax), 1.35 (1H, m, H-5eq), 2.40–2.57 (3H, m, CH_2CH$_3$, CHCH$_3$, side chain), 2.70–2.80 (1H, m, H-6), 3.57 and 3.60 (1H, d, J_{H-2-CH}=8.0, H-2). δ_C (DMSO-d_6): 7.6 (2C, CH_3CH$_2$), 12.5 and 13.2 (CH_3CH, side chain), 22.8 and 22.9 (CH_3-6), 23.9 and 24.0 (CH_3-4ax), 32.8 and 32.9 (CH_3-4eq), 33.6 and 34.4 (CH_2–CH$_3$), 46.0 (C-5), 46.6 and 46.7 (C-6), 49.1 (2C, C-4), 51.0 and 51.6 (CO–CH–CH$_3$), 67.9 and 68.0 (C-2), 213.0 (2C, CO).

4.3.1.6. 4-(2-Oxocyclohexylidenyl)methylamino-2-amino-2-methylpentane (14). Yield 31% (170 mg), yellowish oil. HRMS: $C_{13}H_{24}N_2O$ $M^{+\bullet}$ calcd 224.1889; obsd 224.1882. Cyclohexane ring carbon signals are not assigned. Compound *E*-**14C** (major chain): δ_H ($CDCl_3$): 1.11–1.15 (3H, m, CH_3), 1.19 (3H, s, CH_3), 1.25 (3H, d, J_{CH_3-CH}=6.5, CH_3–CH), 1.45–1.50 (2H, m, CH_2), 1.60–1.75 (4H, m, 2H-4′, 2H-5′), 2.12–2.20 (2H, m, 2H-6′), 2.25–2.35 (2H, m, 2H-3′), 3.62 (1H, m, CHCH$_3$), 7.68 (1H, br m, NH), 7.78 (1H, d, $J_{=CH-NH}$=13.5, =CH). δ_C ($CDCl_3$): 22.9 (CH_3CH), 27.6 (CH_3), 33.3 (CH_3), 48.5 (CH_2), 49.6 ((CH$_3$)$_2$C), 49.8 (CH–CH_3), 104.5 (=C), 145.4 (=CH), 196.0 (CO). Compound *Z*-**14C** (major chain): δ_H ($CDCl_3$): 1.11–1.15 (6H, m, (CH$_3$)$_2$C), 1.25 (3H, d, J_{CH_3-CH}=6.5, CH_3–CH), 1.54 (1H, dd, J_{CH-CH_a}=3.5, J_{gem}=14.5, H-a from CH_2), 1.60–1.68 (1H, m, H-b from CH_2), 1.60–1.75 (4H, m, 2H-4′, 2H-5′), 2.25–2.35 (4H, m, 2H-3′,

2H-6), 3.46 (1H, m, CH_3–C*H*), 6.67 (1H, d, $J_{=CH-NH}$= 12.5, =CH), 10.28 (1H, br s, NH). δ_C ($CDCl_3$): 24.9 (*C*H_3–CH), 31.2 (CH_3), 31.5 (CH_3), 49.3 (*C*$(CH_3)_2$), 51.6 (CH_2), 51.7 (*C*H–CH_3), 101.2 (=C), 151.2 (=CH), 196.9 (CO). Compound *E*-**14A** (minor chain): δ_H ($CDCl_3$): 1.16 (3H, d, J_{CH_3-CH}=6.0, C*H*$_3$CH), 1.29 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.45–1.50 (2H, m, CH_2), 1.60–1.75 (4H, m, 2H-4′, 2H-5′), 2.12–2.20 (2H, m, 2H-6′), 2.25–2.35 (2H, m, 2H-3′), 3.10–3.19 (1H, m, C*H*–CH_3), 7.87 (1H, d, $J_{=CH-NH}$=14.5, =CH), 8.39 (1H, d, $J_{=CH-NH}$=14.5, NH). δ_C ($CDCl_3$): 28.3 (CH_3), 28.6 (CH_3), 29.8 (CH_3), 44.5 (*C*H–CH_3), 49.9 (CH_2), 54.6 (*C*$(CH_3)_2$), 104.2 (=C), 143.8 (=CH), 195.6 (CO). Compound *Z*-**14A** (minor chain): δ_H ($CDCl_3$): 1.11–1.15 (3H, m, C*H*$_3$–CH), 1.31 (6H, s, $(CH_3)_2$C), 1.57 (2H, m, CH_2), 1.60–1.75 (4H, m, 2H-4′, 2H-5′), 2.25–2.35 (4H, m, 2H-3′, 2H-6), 3.10–3.19 (1H, m, C*H*–CH_3), 6.77 (1H, d, $J_{=CH-NH}$=13.0, =CH), 10.74 (1H, d, $J_{=CH-NH}$=12.5, NH). δ_C ($CDCl_3$): 26.5 (*C*H_3–CH), 28.4 (CH_3), 29.1 (CH_3), 43.6 (*C*H–CH_3), 52.3 (CH_2), 53.8 (*C*$(CH_3)_2$), 101.2 (=C), 148.7 (=CH), 196.7 (CO). Cyclic diastereomers **14B**, detected signals: δ_H ($CDCl_3$): 0.84 (1H, t, J_{5ax6ax}=J_{5ax5eq}=12.5, H-5ax), 1.03 and 1.04 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$CH), 1.10 and 1.12 (3H, s, CH_3-eq), 1.45–1.50 (1H, m, H-5eq), 2.42–2.51 (1H, m, H-1′), 2.89 (1H, m, H-6), 3.72 and 3.81 (1H, d, $J_{H\text{-}2\text{–}H\text{-}1'}$=5.0, H-2). δ_C ($CDCl_3$): 23.1 (2C, *C*H_3CH), 23.9 and 24.0 (CH_3-4ax), 35.3 (CH_3-4eq), 47.0 (2C, C-5), 47.1 and 47.4 (C-6), 49.0 and 49.2 (C-4), 55.9 and 56.1 (C-1′), 66.1 and 66.7 (C-2), 213.4 and 213.8 (CO).

4.3.1.7. 4-(2-Oxocyclopentylidenyl)methylamino-2-amino-2-methylpentane (15). Yield 27% (150 mg), yellow oil. HRMS: $C_{12}H_{22}N_2O$ $M^{+\bullet}$ calcd 210.1732; obsd 210.1730. Compound *E*-**15C** (major chain): δ_H ($CDCl_3$): 1.11–1.15 (3H, m, CH_3), 1.19 (3H, s, CH_3), 1.24 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$–CH), 1.45–1.50 (2H, m, CH_2), 1.84–1.93 (2H, m, 2H-4′), 2.25–2.30 (2H, m, 2H-3′), 2.35–2.42 (2H, m, 2H-5′), 3.60 (1H, m, C*H*CH_3), 7.43 (1H, d, $J_{=CH-NH}$=14.0, =CH), 7.60 (1H, br m, NH). δ_C ($CDCl_3$): 19.9 (C-4′), 22.7 (*C*H_3CH), 25.9 (C-5′), 27.7 (CH_3), 35.3 (CH_3), 39.3 (C-3′), 48.5 (CH_2), 49.7 (*C*H–CH_3), 50.0 ($(CH_3)_2$*C*), 105.9 (=C), 141.1 (=CH), 203.5 (CO). Compound *Z*-**15C** (major chain): δ_H ($CDCl_3$): 1.11–1.15 (6H, m, $(CH_3)_2$C), 1.24 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$–CH), 1.54 (1H, dd, J_{CH-CH_a}=3.5, J_{gem}=14.5, H-a from CH_2), 1.63 (1H, dd, J_{CH-CH_b}=8.8, J_{gem}=14.7, H-b from CH_2), 1.84–1.93 (2H, m, 2H-4′), 2.25–2.30 (2H, m, 2H-3′), 2.48–2.54 (2H, m, 2H-5′), 3.46 (1H, m, CH_3–C*H*), 6.69 (1H, d, $J_{=CH-NH}$=12.5, =CH), 9.07 (1H, br s, NH). δ_C ($CDCl_3$): 22.0 (C-4′), 24.8 (*C*H_3–CH), 27.6 (C-5′), 31.2 (CH_3), 31.5 (CH_3), 38.8 (C-3′), 49.4 (*C*$(CH_3)_2$), 51.4 (CH_2), 51.6 (*C*H–CH_3), 103.1 (=C), 145.4 (=CH), 204.7 (CO). Compound *E*-**15A** (minor chain): δ_H ($CDCl_3$): 1.16 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$CH), 1.29 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.45–1.50 (2H, m, CH_2), 1.84–1.93 (2H, m, 2H-4′), 2.25–2.30 (2H, m, 2H-3′), 2.34–2.39 (2H, m, 2H-5′), 3.09–3.19 (1H, m, C*H*–CH_3), 7.52 (1H, d, $J_{=CH-NH}$=14.5, =CH), 8.34 (1H, d, $J_{=CH-NH}$=14.5, NH). δ_C ($CDCl_3$): 19.9 (C-4′), 26.0 (C-5′), 28.3 (CH_3), 28.6 (CH_3), 29.7 (CH_3), 38.9 (C-3′), 44.6 (*C*H–CH_3), 49.8 (CH_2), 54.6 (*C*$(CH_3)_2$), 105.6 (=C), 139.5 (=CH), 204.0 (CO). Compound *Z*-**15A** (minor chain): δ_H ($CDCl_3$): 1.11–1.15 (3H, m, C*H*$_3$–CH), 1.30 (6H, s, $(CH_3)_2$C), 1.56 (2H, m, CH_2), 1.84–1.93 (2H, m, 2H-4′), 2.25–2.30 (2H, m, 2H-3′), 2.48–2.54 (2H, m, 2H-5′), 3.09–3.19 (1H, m, C*H*–CH_3), 6.80 (1H, d, $J_{=CH-NH}$=13.0, =CH), 9.50 (1H, d, $J_{=CH-NH}$=13.0, NH). δ_C ($CDCl_3$): 22.0 (C-4′), 26.5 (*C*H_3–CH), 27.8 (C-5′), 28.2 (CH_3), 29.1 (CH_3), 39.8 (C-3′), 43.7 (*C*H–CH_3), 52.1 (CH_2), 53.9 (*C*$(CH_3)_2$), 103.1 (=C), 142.9 (=CH), 204.5 (CO). Cyclic diastereomers **15B**, detected signals: δ_H ($CDCl_3$): 0.80–0.90 (1H, m, H-5ax), 1.04 and 1.05 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$CH), 1.09 and 1.10 (3H, s, CH_3-eq), 1.45–1.50 and 1.52–1.56 (1H, m, H-5eq), 1.84–1.93 (2H, m, 2H-4′), 2.27 and 2.32 (1H, m, H-1′), 2.25–2.30 (2H, m, 2H-3′), 2.35–2.42 (2H, m, 2H-5′), 2.89 (1H, m, H-6), 3.78 and 3.91 (1H, d, $J_{H\text{-}2\text{–}H\text{-}1'}$= 5.3, H-2). δ_C ($CDCl_3$): 20.5 and 20.6 (C-4′), 23.0 (2C, *C*H_3CH), 24.0 and 24.1 (CH_3-4ax), 22.5 and 26.4 (C-5′), 33.1 and 33.2 (CH_3-4eq), 39.2 and 39.3 (C-3′), 46.6 and 46.7 (C-5), 47.0 and 47.3 (C-6), 49.7 (2C, C-4), 53.9 and 54.4 (C-1′), 65.9 and 66.5 (C-2), 220.8 and 220.9 (CO).

4.3.2. Preparation of the bis-condensation product 16 (procedure B). To a solution of β-keto aldehyde (2 mmol) in 10 mL of ether, a solution of diamine **1** in 10 mL of ether was added dropwise. The mixture was left standing overnight, dried over Na_2SO_4, filtered, and concentrated in vacuo.

4.3.2.1. 1,3-Bis[(4,4-dimethyl-3-oxopent-1-enyl)amino]-butane (16). Yield 85% (520 mg), yellow oil. HRMS: $C_{18}H_{32}N_2O_2$ $M^{+\bullet}$ calcd 308.2464; obsd 308.2467. δ_H ($CDCl_3$): 1.14 (18H, s+s, 2×(C*H*$_3$)$_3$C), 1.24 (6H, d, J_{CH_3CH}=6.80, CH_3), 1.73 (2H, m, C*H*$_2$–CH), 3.15–3.35 (3H, m, C*H*CH_3, CH_2NH), 5.18 (2H, d+d, $J_{CH=CH}$=8.0, 2× =CH–CO), 6.70 (1H, dd, $J_{CH=CH}$=7.5, J_{CH-NH}=12.5, =C*H*–NH), 6.75 (1H, dd, $J_{CH=CH}$=7.5, J_{CH-NH}=12.5, =C*H*–NH), 9.79 (2H, br s, NH). δ_C ($CDCl_3$): 22.5 (CH_3), 26.2 (CH_3), 27.7 ((*C*H_3)$_3$C), 38.7 (*C*H_2CH), 41.6 ((CH$_3$)$_3$*C*), 45.5 (CH_2–NH), 52.0 (*C*H–CH_3), 89.3 (*C*H–CO), 89.5 (*C*H–CO), 151.8 (CHNH), 153.2 (CHNH), 206.5 (CO), 206.6 (CO).

4.3.3. Reaction of 1,3-diamines with β-diketones, β-keto esters, and β-keto amides (procedure C, substances 24, 26–28). A dicarbonyl compound (2–3 mmol) was added to an equimolar amount of diamine without solvent. The mixture was stirred in the presence of HCl vapor (trace amounts) until the reaction was complete (monitoring by TLC), and the product precipitated from hexane solution by freezing to −65 °C.

4.3.3.1. 1-(1-Methyl-3-phenyl-3-oxoprop-1-enylamino)-3-aminobutane, 22 and 23 (unseparated mixture). Yield 30% (140 mg) (procedure A), colorless oil. HRMS: $C_{14}H_{20}N_2O$ $M^{+\bullet}$ calcd 232.1576; obsd 232.1576. Major chain (**22**, 83%): δ_H ($CDCl_3$): 1.14 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$–CH), 1.60–1.75 (2H, m, C*H*$_2$–CH), 2.07 (3H, s, C*H*$_3$C=), 3.09 (1H, m, C*H*–CH_3), 3.41 (2H, m, CH_2–NH), 5.66 (1H, s, =CH), 7.35–7.41 (3H, m, H-3′, H-4′, H-5′), 7.84 (2H, dd, J_{23}=8.0, J_{24}=1.7, H-2′, H-6′), 11.45 (1H, br m, NH). δ_C ($CDCl_3$): 19.3 (*C*H_3C=), 24.3 (*C*H_3–CH), 39.3 (*C*H_2–CH), 40.4 (CH_2–NH), 44.5 (*C*H–CH_3), 91.9 (=CH), 126.7 (C-2′, C-6′), 128.0 (C-3′, C-5′), 130.2 (C-4′), 140.3 (C-1′), 164.9 (=*C*–CH_3), 187.4 (CO). Minor chain (**23**, 17%): δ_H ($CDCl_3$): 1.26 (3H, d, J_{CH_3-CH}=6.5,

C*H*$_3$CH), 1.60–1.75 (2H, m, C*H*$_2$–CH), 2.09 (3H, s, C*H*$_3$C=), 2.80 (2H, m, C*H*$_2$–NH$_2$), 3.80 (C*H*–CH$_3$), 5.62 (1H, s, =CH), 7.35–7.41 (3H, m, H-3′, H-4′, H-5′), 7.84 (2H, dd, J_{23}=8.0, J_{24}=1.7, H-2′, H-6′), 11.45 (1H, br m, NH). δ_C ($CDCl_3$): 19.3 (*C*H$_3$C=), 22.1 (*C*H$_3$–CH), 38.5 (CH$_2$–NH$_2$), 40.8 (*C*H$_2$–CH), 46.9 (*C*H–CH$_3$), 91.8 (=CH), 126.7 (C-2′, C-6′), 128.0 (C-3′, C-5′), 130.2 (C-4′), 140.3 (C-1′), 164.0 (=*C*–CH$_3$), 187.3 (CO).

4.3.3.2. 4-(1-Methyl-3-oxobut-1-enyl)amino-2-amino-2-methylpentane (24). Yield 85% (330 mg), colorless oil. HRMS: $C_{11}H_{22}N_2O$ $M^{+\bullet}$ calcd 198.1732; obsd 198.1740. δ_H ($CDCl_3$): 1.02 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.11 (3H, d, J_{CH-CH_3}=6.4, C*H*$_3$–CH), 1.46 (1H, dd, J_{CH-H_a}=3.4, J_{gem}=14.5, H-a from CH_2), 1.56 (1H, dd, J_{CH-H_b}=8.3, J_{gem}=14.5, H-b from CH_2), 1.87 (6H, s, C*H*$_3$C=CH, CH$_3$–CO), 3.60 (1H, m, C*H*–CH$_3$), 4.80 (1H, s, =CH), 10.81 (1H, br d, $J_{NH-CH(CH_3)}$=7.7). δ_C ($CDCl_3$): 18.6 (*C*H$_3$C=), 24.5 (C*H*$_3$–CH), 28.5 (*C*H$_3$–CO), 30.7 (CH_3), 31.7 (CH_3), 45.8 (*C*H–CH$_3$), 49.0 (*C*(CH$_3$)$_2$), 51.6 (CH_2), 94.8 (=CH), 161.3 (=*C*–CH$_3$), 194.1 (CO).

4.3.3.3. 4-(1-Methyl-3-phenyl-3-oxoprop-1-enyl)amino-2-amino-2-methylpentane (25). Yield 37% (190 mg) (procedure A), colorless oil. HRMS: $C_{16}H_{24}N_2O$ $M^{+\bullet}$ calcd 260.1889; obsd 260.1900. δ_H ($CDCl_3$): 1.28 (3H, d, J_{CH_3-CH}=6.0, C*H*$_3$–CH), 1.41 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.98 (1H, dd, J_{CH-CH_a}=9.3, J_{gem}=15.0, H-a from CH_2), 2.07 (1H, dd, J_{CH-H_b}=2.5, H-b from CH_2), 2.19 (3H, s, C*H*$_3$C=), 4.06 (1H, m, C*H*CH$_3$), 5.64 (1H, s, =CH), 7.35–7.42 (3H, m, H-3′, H-4′, H-5′), 7.81 (2H, dd, J_{23}=8.0, J_{24}=1.5, H-2′, H-6′), 11.49 (1H, d, $J_{NH-CH(CH_3)}$=9.0, NH). δ_C ($CDCl_3$): 19.6 (*C*H$_3$C=), 24.6 (*C*H$_3$–CH), 25.8 (CH_3), 28.0 (CH_3), 45.6 (*C*H–CH$_3$), 47.9 (CH_2), 54.3 (*C*(CH$_3$)$_2$), 92.6 (=CH), 126.9 (C-2′, C-6′), 128.2 (C-3′, C-5′), 130.6 (C-4′), 140.3 (C-1′), 163.9 (=*C*–CH$_3$), 187.8 (CO).

4.3.3.4. 3-((4-Methyl-4-aminopent-2-yl)amino)but-2-enoic acid, ethyl ester (26). Yield 68% (150 mg), transparent colorless oil. HRMS: $C_{12}H_{24}N_2O_2$ $M^{+\bullet}$ calcd 228.1838; obsd 228.1829. Compound *Z*-**26** (major chain, 83%): δ_H (DMSO-d_6): 0.97 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.09–1.14 (6H, m, C*H*$_3$–CH, C*H*$_3$CH$_2$), 1.47 (2H, d, *J*=5.8, CH_2), 1.93 (3H, s, CH$_3$C=), 3.75 (1H, m, CH$_3$–C*H*), 3.85–3.95 (2H, m, C*H*$_2$CH$_3$), 4.27 (1H, s, =CH), 8.43 (1H, d, $J_{NH-CH(CH_3)}$=9.5, NH). δ_C (DMSO-d_6): 14.5 (*C*H$_3$CH$_2$), 19.0 (*C*H$_3$C=), 24.7 (*C*H$_3$CH), 30.3 (CH_3), 32.1 (CH_3), 45.2 (CH$_3$*C*H), 48.7 (*C*(CH$_3$)$_2$), 51.8 (CH_2), 57.3 (*C*H$_2$CH$_3$), 80.9 (=CH), 160.7 (=*C*CH$_3$), 169.4 (CO). Compound *E*-**26** (minor chain, 17%): δ_H (DMSO-d_6): 0.98 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.04 (3H, m, C*H*$_3$–CH), 1.09–1.14 (3H, m, C*H*$_3$CH$_2$), 1.35 (1H, dd, J_{CH-H_a}=3.9, J_{gem}=14.2, H-a from CH_2), 1.58 (1H, m, H-b from CH_2), 2.14 (3H, s, CH$_3$C=), 3.46 (1H, m, C*H*CH$_3$), 3.85–3.95 (2H, m, C*H*$_2$CH$_3$), 4.43 (1H, s, =CH), 6.85 (1H, d, J_{NH-CH}=6.8, NH). δ_C (DMSO-d_6): 14.7 (*C*H$_3$CH$_2$), 21.7 (*C*H$_3$C=), 22.7 (*C*H$_3$CH), 29.6 (CH_3), 31.2 (CH_3), 45.0 (CH$_3$*C*H), 49.0 (*C*(CH$_3$)$_2$), 49.3 (CH_2), 57.0 (*C*H$_2$CH$_3$), 79.6 (=CH), 158.5 (=*C*CH$_3$), 168.1 (CO).

4.3.3.5. 2-((4-Methyl-4-aminopent-2-yl)amino)cyclohex-1-enic acid, ethyl ester (27). Yield 60% (220 mg), colorless oil. HRMS: $C_{15}H_{28}N_2O_2$ $M^{+\bullet}$ calcd 268.2151; obsd 268.2156. δ_H ($CDCl_3$): 1.13 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.15 (3H, d, J_{CH-CH_3}=6.0, C*H*$_3$CH), 1.27 (3H, t, $J_{CH_2-CH_3}$=7.2, C*H*$_3$CH$_2$), 1.55–1.59 (3H, m, 2H-4′, H-a from CH_2 amin), 1.63 (1H, dd, J_{CH-H_b}=9.0, J_{gem}=14.4, H-b from CH_2 amin), 1.65–1.69 (2H, m, 2H-5′), 2.27 (2H, t, *J*=6.3, 2H-6′), 2.35 (2H, m, H-6′), 3.74 (1H, m, C*H*–CH$_3$), 4.09 (2H, q, $J_{CH_2-CH_3}$=7.5, C*H*$_2$–CH$_3$), 8.89 (1H, d, J_{CH-NH}=9.6, NH). δ_C ($CDCl_3$): 14.6 (*C*H$_3$CH$_2$), 22.3 (C-5′), 22.7 (C-4′), 23.8 (C-3′), 25.1 (*C*H$_3$CH), 26.4 (C-6′), 30.9 (2C, 2×CH$_3$), 44.6 (*C*HCH$_3$), 49.6 (*C*(CH$_3$)$_2$), 51.9 (CH$_2$-amin), 58.6 (*C*H$_2$CH$_3$), 89.8 (C-2′), 158.2 (C-1′), 170.9 (CO).

4.3.3.6. 3-((4-Methyl-4-aminopent-2-yl)amino)but-2-enic acid, diethylamid (28). Yield 52% (100 mg), colorless oil. HRMS: $C_{14}H_{29}N_3O$ $M^{+\bullet}$ calcd 255.2311; obsd 255.2319. δ_H (DMSO-d_6): 0.95–1.05 (12H, m, (CH$_3$)$_2$C, 2C*H*$_3$CH$_2$), 1.08 (3H, d, J_{CH_3-CH}=6.6, C*H*$_3$–CH), 1.44 (2H, d, J_{CH-CH_2}=5.4, CH_2), 1.91 (3H, s, CH$_3$–C=), 3.20 (4H, m, C*H*$_2$CH$_3$), 3.68 (1H, m, C*H*CH$_3$), 4.47 (1H, s, =CH), 9.48 (1H, d, J_{NHCH}=9.6, NH). δ_C (DMSO-d_6): 14.0 (*C*H$_3$CH$_2$), 19.5 (CH$_3$C=), 25.1 (*C*H$_3$CH), 30.5 (CH_3), 31.9 (CH_3), 41.9 (*C*H$_2$CH$_3$), 44.7 (*C*H–CH$_3$), 48.8 (*C*(CH$_3$)$_2$), 52.1 (CH_2), 81.0 (=CH), 157.3 (=*C*–CH$_3$), 169.0 (CO).

4.3.3.7. 2,4,4,6-Tetramethyl-3,4,5,6-tetrahydropyrimidine (29). Yield 80% (220 mg), white powder, mp 135 °C. HRMS: $C_8H_{16}N_2$ $M^{+\bullet}$ calcd 140.1313; obsd 140.1314. δ_H (DMSO-d_6): 1.08 (1H, t, J_{5ax6ax}=J_{gem}=13.0, H-5ax), 1.11 (3H, s, CH_3), 1.14 (3H, d, J_{CH_3-CH}=6.5, C*H*$_3$–CH), 1.18 (3H, s, CH_3), 1.74 (1H, dd, J_{5eq6ax}=3.5, J_{gem}=13.0, H-5eq), 1.90 (3H, s, C*H*$_3$–C=), 3.38 (1H, m, CH$_3$–C*H*). δ_C (DMSO-d_6): 20.1 (*C*H$_3$C=), 21.4 (*C*H$_3$CH), 29.1 (CH_3), 29.9 (CH_3), 41.0 (CH_2), 43.4 (CH), 49.3 (*C*(CH$_3$)$_2$), 154.5 (=C).

Acknowledgements

We thank Dr. V. Ovcharenko from University of Turku, Finland, for help, fruitful discussions and HRMS spectra. We also thank Dr. S. I. Yakimovich from University of St. Petersburg, Russia, for fruitful discussions.

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Tetrahedron 62 (2006) 9467–9474

Highly regioselective [3,3] rearrangement of aliphatic allyl vinyl ethers catalyzed by a metalloporphyrin complex, Cr(TPP)Cl

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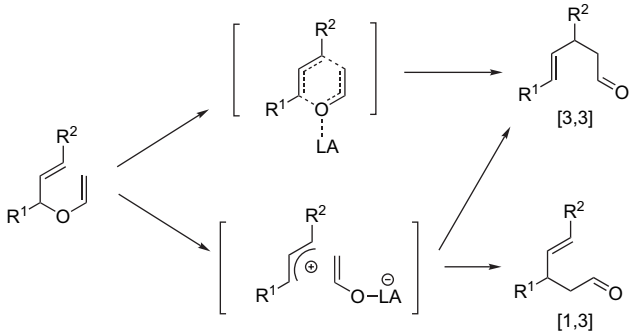
Received 2 June 2006; accepted 4 July 2006
Available online 14 August 2006

Abstract—The Claisen rearrangement of simple aliphatic allyl vinyl ethers catalyzed by a metalloporphyrin, Cr(TPP)Cl, is described. The porphyrin-based Lewis acid catalyst can effectively accelerate the rearrangement via a concerted [3,3] pathway with a minimal degree of bond ionization of the substrates, providing the corresponding Claisen products in moderate to high yields and almost perfect regioselectivity at low catalyst loading.

1. Introduction

The Claisen rearrangement, a [3,3] sigmatropic rearrangement of allyl vinyl ether, is a powerful carbon–carbon bond forming process[1,2] and its catalytic version employing a substoichiometric amount of metal catalysts is a topic of ongoing interest.[3] While the rearrangement using palladium- and related transition metal-based catalysts has been well developed,[3,4] only a few reports have appeared in the literature that utilize Lewis acids, especially in a catalytic fashion.[3,5–7] To date, several Lewis acids, including Al(III),[5] Sn(IV),[6] Cu(II),[7] and lanthanide(III)[7] Lewis acids, have been available for the Claisen rearrangement of aliphatic allyl vinyl ethers. These examples, however, require stoichiometric amounts of reagents or specific substrates such as 2-alkoxycarbonyl-substituted allyl vinyl ethers. In addition, most of these Lewis acid-mediated methods appear to suffer from a lack of regioselectivity, being troubled by the formation of the regioisomeric [1,3] rearrangement products. The reason might be that, under Lewis acid conditions, the rearrangement often proceeds through a process involving formation of an allyl cation and a metallo-enolate ion pair, which diverges from the generally accepted concerted mechanism, affording a regioisomeric mixture of [3,3]- and [1,3]-rearrangement products (Scheme 1).[8] Herein lies the difficulty with the Lewis acid-catalyzed Claisen rearrangement, as the ionic intermediates may be long-lived, to give rise to undesired regioisomeric [1,3] products. Actually, Rovis and Nasveschuk recently reported that an increase in the strength of the Lewis acid and/or in stability of the allyl cation results in increased [1,3] selectivity.[9,10] Although bulky organoaluminum Lewis acids, such as MABR, ATPH, and BINAL, developed by Yamamoto et al., are known as indeed potential reagents capable of circumventing these problems associated with the Lewis acid-mediated Claisen rearrangement. These aluminum Lewis acids are, unfortunately, a stoichiometric reagent rather than a catalyst: more than a stoichiometric amount of the reagent is usually necessary to promote the rearrangement.[5,11]



Scheme 1. Putative mechanistic scheme for the competitive formation of the [3,3] and [1,3] adducts in the Lewis acid-mediated Claisen rearrangement of aliphatic allyl vinyl ethers.

Recently, we have reported that a metalloporphyrin complex, Cr(TPP)Cl, can be used as a mild and efficient Lewis acid catalyst, and it enhances reversal *E*/*Z* selectivity in the thermal Claisen rearrangement of 4,5- and 4,6-disubstituted allyl vinyl ethers.[12–14] The purpose of this paper is to describe our results concerning the reactivity, regioselectivity, and scope of the Cr(TPP)Cl catalyst system in the Claisen rearrangement of simple aliphatic allyl vinyl ethers. This metalloporphyrin-based weak Lewis acid catalyst can

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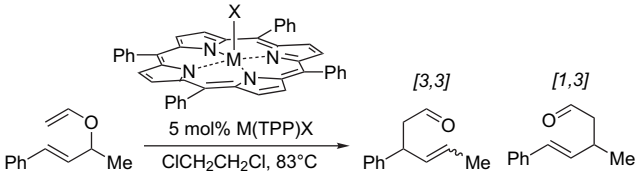
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.051

effectively depress the formation of ionic intermediates, yet enhances the concerted [3,3] process, exhibiting high regioselectivity over a broad range of substrates, exclusively providing the corresponding Claisen products in good to high yields, in a fully catalytic fashion.

2. Results and discussion

We initiated our studies by subjecting the vinyl ether of 4-phenyl-3-buten-2-ol **1a** to 5 mol % of Cr(TPP)Cl in dichloroethane at 83 °C for 7 h. While only moderate regioselectivity ([3,3]:[1,3]=1:1 to 1:2) has been reported for the rearrangement of **1a** with various Lewis acids, such as $Cu(OTf)_2$, $SnCl_4$, $TiCl_4$, and $B(C_6F_5)_3$,[9,10b] under the present catalytic conditions utilizing Cr(TPP)Cl catalyst, the substrate **1a** was cleanly converted to the [3,3] adduct **2a** in 94% yield; no other products including [1,3] adduct **4a** could be identified via ^1H NMR analysis of the crude reaction mixture (Table 1, entry 1). In the absence of the metalloporphyrin catalyst, the rearrangement was quite sluggish, and did not complete over 48 h, giving the [3,3] adduct **2a** as the sole product in only 40% yield (Table 1, entry 2). Regioselective transformation of **1a** to **2a** could also be accomplished with other metalloporphyrin catalysts, such as Fe(TPP)Cl and Mn(TPP)Cl (Table 1, entries 3 and 4). Likewise, metallosalen complexes, Cr(salen)Cl and Mn(salen)Cl, could serve as a highly regioselective catalyst for the rearrangement (Table 1, entries 5 and 6).[15] In both cases, however, the highest yield never exceeded 85%. On the other hand, stronger Lewis acid catalysts, Cr(TPP)OTf and Fe(TPP)OTf, which may enhance bond ionization of the substrate, proved less effective for the [3,3] selectivity, affording the undesired [1,3] adducts **4a** as the major products in 26 and 27% yields, respectively, along with the [3,3] adducts **2a** in less than 20% yield (Table 1, entries 7 and 8). Thus, the use of porphyrin catalysts possessing weaker Lewis acidity, especially the chromium complex Cr(TPP)Cl, was found to be effective to achieve high [3,3] selectivity in the Claisen rearrangement of aliphatic allyl vinyl ethers, and these observations are consistent with the hypothesis that a weaker Lewis acid is capable of accelerating the Claisen rearrangement via a concerted [3,3] pathway, while stronger Lewis acids result in bond ionization.[9]

Table 1. Porphyrin-based Lewis acid-catalyzed Claisen rearrangement of vinyl ether of 4-phenyl-3-buten-2-ol **1a**



1a **2a** **4a**

Entry	Catalyst	Time (h)	**2a** (%) (*E*/*Z*)[a,b]	**4a** (%)[a]
1	Cr(TPP)Cl	7	94 (15:85)	—
2	None	58	40 (94:6)	—
3	Mn(TPP)Cl	24	62 (94:6)	—
4	Fe(TPP)Cl	24	83 (95:5)	—
5	Cr(salen)Cl[c]	11	59 (85:15)	—
6	Mn(salen)Cl[d]	24	62 (94:6)	—
7	Cr(TPP)OTf	24	19 (77:23)	26[e]
8	Fe(TPP)OTf	2	16 (>99:1)	27[e]

[a] Isolated yield.
[b] *E*/*Z* ratios were determined by 300 MHz ^1H NMR.
[c] Cr(salen)Cl: (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino chromium(III) chloride.
[d] Mn(salen)Cl: (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride.
[e] An inseparable complex mixture of by-products was also produced in the catalytic rearrangement.

To assess the inherent regioselectivity of the chromium porphyrin catalyst, Cr(TPP)Cl, we then explored the reactivity of several cinnamyl vinyl ethers **1**. Although these substrates **1** are known to be less suited for the [3,3] selectivity,[9] the presence of 5 mol % of Cr(TPP)Cl[16] led to the formation of the corresponding [3,3] adducts **2** in moderate to high yields and excellent regioselectivity (Table 2). In the catalytic process, substituents on the vinyl moiety in the substrates did not affect the regioselectivity (Table 2, entries 2 and 3). Notably, even in the presence of an electron-donating substituent on the ring, the rearrangements occurred with high [3,3] selectivity, giving the Claisen adducts solely in good yields (Table 2, entries 6 and 7).

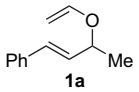
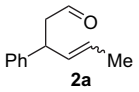
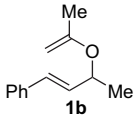
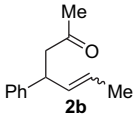
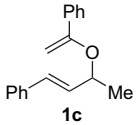
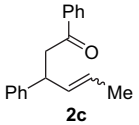
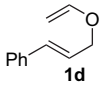
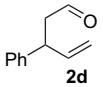
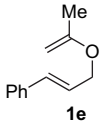
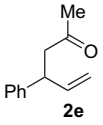
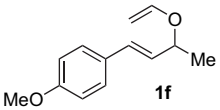
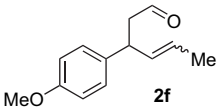
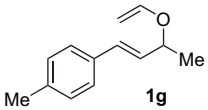
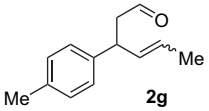
As illustrated in Table 3, allyl vinyl ethers beyond those derived from cinnamyl alcohol also underwent the catalytic [3,3] rearrangement. For example, the Cr(TPP)Cl-catalyzed rearrangement of the substrates **3a** and **3b**, which are the regio isomers of **1a** and **1d**, respectively, took place smoothly to give the corresponding [3,3] adducts, **4a** and **4b**, as the sole products in high yields (Table 3, entries 1 and 2). Replacing the Ph substituent of **1a**, **1b**, and **1c** with a Bu group (**3c**, **3d**, and **3e**) also produced the corresponding Claisen products, **4c**, **4d**, and **4e**, respectively, in high yields and excellent regioselectivity (Table 3, entries 3–5).

To further explore the scope of the [3,3] rearrangement of allyl vinyl ethers, the rearrangement of the substrates **5** bearing trisubstituted alkenes in the allyl systems was examined. It has been known that the rearrangement of trisubstituted allyl vinyl ethers **5** generally provides high [1,3] selectivity with a range of Lewis acids, such as $Cu(OTf)_2$, $SnCl_4$, $TiCl_4$, Me_2AlCl, and $EtAlCl_2$: under such ionizing conditions, recombination of the metallo-enolate and allyl cation at the less hindered secondary position to give [1,3] adducts should be fast compared with [3,3] recombination to form a quaternary carbon center at the tertiary cation (Fig. 1).[9] However, when the Cr(TPP)Cl catalyst was applied to the substrates **5**, moderate to high-yielding [3,3] rearrangement to create quaternary carbon centers occurred without any formation of the corresponding [1,3] products (Table 4). In addition, under the present catalytic conditions, all the substrates examined generally rearranged more rapidly and had higher yields of the [3,3] products than those rearrangements performed under non-catalytic thermal conditions (see footnotes in Tables 2–4). These findings, thus, should lend significant support to our view that the Cr(TPP)Cl catalyst can exert its influence on accelerating the rearrangement via a concerted [3,3] pathway with a minimal degree of bond ionization (Scheme 1).

3. Conclusion

In summary, we have shown a regioselective Claisen rearrangement of simple aliphatic allyl vinyl ethers utilizing

Table 2. Cr(TPP)Cl-catalyzed Claisen rearrangement of cinnamyl vinyl ethers[a]

Entry	Substrates	Products	Time (h)	Yield (%) (*E*/*Z*)[b,c,d]
1	 **1a**	 **2a**	7	94 (15:85)
2	 **1b**	 **2b**	5	93 (69:31)
3	 **1c**	 **2c**	0.5	82 (76:24)
4	 **1d**	 **2d**	52	41
5	 **1e**	 **2e**	6	72
6	 **1f**	 **2f**	7	62 (38:62)
7	 **1g**	 **2g**	8	57 (39:61)

[a] Conditions: 5 mol % Cr(TPP)Cl, $ClCH_2CH_2Cl$, 83 °C.
[b] Isolated yield.
[c] *E*/*Z* ratios were determined by 300 MHz ^1H NMR.
[d] The reaction time, yields, and *E*/*Z* ratios obtained in the non-catalytic thermal rearrangement ($ClCH_2CH_2Cl$, 83 °C) of **1a–g** were as follows: **2a** (58 h, 40%, *E*/*Z*=94:6); **2b** (48 h, 74%, *E*/*Z*>99:1); **2c** (4 h, 43%, *E*/*Z*>99:1); **2d** (93 h, 15%); **2e** (48 h, 10%); **2f** (50 h, 76%, *E*/*Z*=94:6); **2g** (25 h, 54%, *E*/*Z*=98:2).

a metalloporphyrin-based Lewis acid catalyst, Cr(TPP)Cl, at low catalyst loading. This weak Lewis acid catalyst, Cr(TPP)Cl, is believed to accelerate the rearrangement via a concerted [3,3] pathway, and can provide the corresponding Claisen adducts in good to high yields, with almost perfect regioselectivity. The sense of regioselectivity observed in the catalytic process is hardly attainable with any other Lewis acid reagents or catalysts thus far reported for the Claisen rearrangement, where bond ionization of the substrates usually takes place to give a regioisomeric mixture of [3,3] and [1,3] adducts. Moreover, the present catalytic reaction provides a complementary method to the [1,3] selectivity obtained by Rovis and Nasveschuk.[9] Current efforts are directed at second-generation designs for the porphyrin-based Lewis acid catalysts that will lead to catalytic asymmetric Claisen rearrangement of simple aliphatic allyl vinyl ethers.

4. Experimental

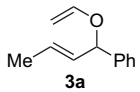
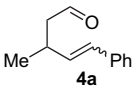
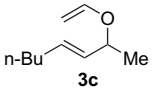
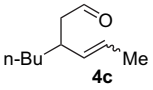
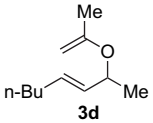
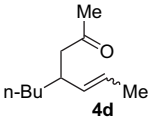
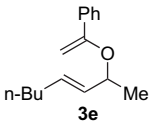
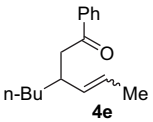
4.1. General

^1H and ^{13}C NMR spectra were recorded on JEOL JNM-EX270, JNM-AL300, and JNM-GSX400 spectrometers. The chemical shifts were reported in parts per million relative to $CHCl_3$ (δ=7.24) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. IR spectra were recorded on a JASCO FT/IR-7000 spectrophotometer. The mass spectroscopic data were obtained on a JEOL JNM-DX302 spectrometer. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). 1,2-Dichloroethane was distilled from CaH_2. Chromium(III) and iron(III) tetraphenylporphyrin complexes, Cr(TPP)Cl,[17] Cr(TPP)OTf,[13a] and Fe(TPP)OTf,[13a] were prepared by the literature methods. Fe(TPP)Cl was purchased from Aldrich Chemical Co. Other chemicals were commercial products and were used without further purifications.

4.2. General procedure for the preparation of vinyl and isopropenyl ethers of allylic alcohols[18]

A mixture of allylic alcohol (30 mmol), mercury(II) acetate (6.4 g, 20 mmol), and freshly distilled ethyl vinyl ether or 2-methoxypropene (150 mL) was heated under reflux for 30 h under an argon atmosphere. The reaction mixture was quenched with 5% KOH aqueous solution (30 mL) and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on alumina (Merck Aluminum

Table 3. Cr(TPP)Cl-catalyzed Claisen rearrangement of allyl vinyl ethers[a]

Entry	Substrates	Products	Time (h)	Yield (%) (*E*/*Z*)[b,c,d]
1	 **3a**	 **4a**	9	86 (>99:1)
2	 **3b**	 **4b**	2	93 (>99:1)
3	 **3c**	 **4c**	12	62 (28:72)
4	 **3d**	 **4d**	3	89 (77:23)
5	 **3e**	 **4e**	1	93 (80:20)

[a] Conditions: 5 mol % Cr(TPP)Cl, $ClCH_2CH_2Cl$, 83 °C.
[b] Isolated yield.
[c] *E*/*Z* ratios were determined by 300 MHz ^1H NMR.
[d] The reaction time, yields, and *E*/*Z* ratios obtained in the non-catalytic thermal rearrangement ($ClCH_2CH_2Cl$, 83 °C) of **3a–e** were as follows: **4a** (30 h, 83%, *E*/*Z*>99:1); **4b** (24 h, 70%, *E*/*Z*>99:1); **4c** (24 h, 22%, *E*/*Z*=97:3); **4d** (24 h, 59%, *E*/*Z*>99:1); **4e** (6 h, 90%, *E*/*Z*>99:1).

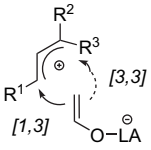
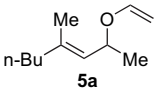
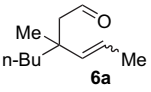
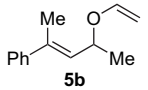
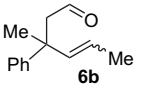
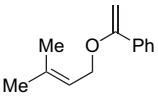
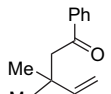


Figure 1. [1,3] Selective rearrangement of trisubstituted allyl vinyl ethers **6** under ionic conditions.

Oxide 90 active basic, activity III) using hexane as an eluent to give the corresponding allyl vinyl ethers in 95–60% yields. The following obtained allyl vinyl ethers are known compounds: (*E*)-1-phenyl-3-vinyloxybut-1-ene (**1a**),[9] (*E*)-1-phenyl-3-vinyloxyprop-1-ene (**1d**),[5i] (*E*)-1-phenyl-3-isopropenyloxyprop-1-ene (**1e**),[19] (*E*)-1-(4-methoxyphenyl)-3-vinyloxybut-1-ene (**1f**),[9] (*E*)-1-(4-methylphenyl)-3-vinyloxybut-1-ene (**1g**),[9] (*E*)-4-phenyl-4-vinyloxybut-2-ene (**3a**),[9] 3-phenyl-3-vinyloxyprop-1-ene (**3b**),[5d] (*E*)-4-methyl-2-vinyloxyoct-3-ene (**5a**),[9] and (*E*)-2-phenyl-4-vinyloxypent-2-ene (**5b**).[9]

4.2.1. (*E*)-1-Phenyl-3-isopropenyloxybut-1-ene (1b). Colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.12 (m, 5H), 6.45 (d, *J*=16.1 Hz, 1H), 6.12 (dd, *J*=16.1 and 6.2 Hz, 1H), 4.62 (dq, *J*=6.2 and 6.2 Hz, 1H), 3.84 (br d, *J*=3.3 Hz, 2H), 1.77 (s, 3H), 1.34 (d, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$,

Table 4. Cr(TPP)Cl-catalyzed Claisen rearrangement of trisubstituted allyl vinyl ethers[a]

Entry	Substrates	Products	Time (h)	Yield (%) (*E*/*Z*)[b,c,d]
1	 **5a**	 **6a**	20	57 (>99:1)
2	 **5b**	 **6b**	50	51 (>99:1)
3	 **5c**	 **6c**	3	78

[a] Conditions: 5 mol % Cr(TPP)Cl, $ClCH_2CH_2Cl$, 83 °C.
[b] Isolated yield.
[c] *E*/*Z* ratios were determined by 300 MHz ^1H NMR.
[d] The reaction time, yields, and *E*/*Z* ratios obtained in the non-catalytic thermal rearrangement ($ClCH_2CH_2Cl$, 83 °C) of **5a–c** were as follows: **6a** (70 h, 38%, *E*/*Z*>99:1); **6b** (98 h, 30%, *E*/*Z*>99:1); **6c** (48 h, 27%).

100 MHz) δ 157.9, 136.7, 130.8, 129.8, 128.4, 127.4, 126.3, 83.0, 73.0, 21.7, 21.3. Exact EIMS calcd for $C_{13}H_{16}O$: 188.1201. Found: 188.1198.

4.2.2. (*E*)-2-Vinyloxyoct-3-ene (3c). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.30 (dd, *J*=6.4 and 14.1 Hz, 1H), 5.58–5.67 (m, 1H), 5.44–5.35 (m, 1H), 4.28 (dd, *J*=14.1 and 1.5 Hz, 1H), 4.26 (dq, *J*=6.4 and 6.4 Hz, 1H), 3.97 (dd, *J*=6.4 and 1.5 Hz, 1H), 2.05–1.99 (m, 2H), 1.27 (d, *J*=6.4 Hz, 3H), 1.40–1.26 (m, 4H), 0.88 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 132.9, 130.7, 88.5, 76.6, 31.9, 31.3, 22.5, 21.3, 14.0. Exact EIMS calcd for $C_{10}H_{18}O$: 154.1358. Found: 154.1356.

4.2.3. (*E*)-2-Isopropenyloxyoct-3-ene (3d). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (dt, *J*=15.5 and 6.6 Hz, 1H), 5.41 (dd, *J*=15.5 and 6.2 Hz, 1H), 4.46 (dq, *J*=6.3 and 6.3 Hz, 1H), 3.86 (br s, 1H), 3.82 (br s, 1H), 2.01 (q, *J*=6.8 Hz, 2H), 1.78 (s, 3H), 1.41–1.28 (m, 4H), 1.27 (d, *J*=6.4 Hz, 3H), 0.87 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 158.6, 132.2, 131.5, 83.1, 73.5, 32.4, 31.8, 22.6, 22.1, 21.6, 14.4. Exact EIMS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1514.

4.3. Preparation of α-styryl ether of allylic alcohols by methylenation of esters with a Zn–$TiCl_4$–TMEDA reagent system[20]

Under an argon atmosphere, 2.0 M solution of $TiCl_4$ (4 mmol) in dichloromethane was added to THF (10 mL) at 0 °C. After the resulting yellow suspension was warmed to 25 °C, TMEDA (1.2 mL, 8 mmol) was added. The brown solution was stirred for 10 min, and then acid washed zinc powder (1.6 g, 9 mmol) was added at 25 °C. After being stirred at 25 °C for 30 min, the color of the suspension changed from dark brown to dark greenish blue. Dibromomethane (0.15 mL, 2.1 mmol) and a solution of the ester (1.0 mmol) in THF (1 mL) were added to the mixture. The color of the resulting mixture gradually turned to dark brown while being stirred at 25 °C for 2 h. After hydrolysis with a saturated K_2CO_3 solution (1.3 mL) at 0 °C, the reaction mixture was diluted with ether (5 mL) and filtered through a short column of alumina (Merck Aluminum Oxide 90 active basic, activity III) using pentane as a solvent. The solvent was removed under a reduced pressure and the residue was purified by column chromatography on alumina (Merck Aluminum Oxide 90 active basic, activity III) using *n*-hexane/Et_3N (200:1) as an eluent to give the corresponding allyl vinyl ethers in 45–20% yields.

4.3.1. (*E*)-1-Phenyl-3-(α-styryl)oxybut-1-ene (1c). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65–7.59 (m, 2H), 7.39–7.18 (m, 8H), 6.58 (d, *J*=16.1 Hz, 1H), 6.27 (dd, *J*=16.1 and 6.2 Hz, 1H), 4.86 (dq, *J*=6.2 and 6.2 Hz, 1H), 4.70 (d, *J*=2.7 Hz, 1H), 4.29 (d, *J*=2.7 Hz, 1H), 1.52 (d, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 136.8, 136.5, 130.6, 130.1, 128.4, 128.2, 127.9, 127.5, 126.3, 125.4, 84.8, 73.9, 21.5. Exact EIMS calcd for $C_{18}H_{18}O$: 250.1358. Found: 250.1357.

4.3.2. 2-(α-Styryl)oxyoct-3-ene (3e). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58–7.53 (m, 2H), 7.29–7.22 (m, 3H), 5.61 (dt, *J*=15.6 and 6.5 Hz, 1H), 5.46 (dd, *J*=15.6 and 6.2 Hz, 1H), 4.62 (d, *J*=2.4 Hz, 1H), 4.60 (dq, *J*=6.2 and 6.2 Hz, 1H), 4.18 (d, *J*=2.4 Hz, 1H), 1.99 (q, *J*=6.8 Hz, 2H), 1.36 (d, *J*=6.2 Hz, 3H), 1.31–1.21 (m, 4H), 0.84 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 158.5, 137.2, 132.0, 130.9, 128.2, 128.0, 125.5, 84.4, 73.9, 31.9, 31.3, 22.2, 21.4, 13.9. Exact EIMS calcd for $C_{16}H_{22}O$: 230.1671. Found: 230.1675.

4.3.3. 2-Methyl-4-(α-styryl)oxybut-2-ene (5c). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63–7.57 (m, 2H), 7.34–7.27 (m, 3H), 5.50 (br t, *J*=6.6 Hz, 1H), 4.64 (d, *J*=2.6 Hz, 1H), 4.40 (br d, *J*=6.6 Hz, 2H), 4.21 (d, *J*=2.6 Hz, 1H), 1.79 (s, 3H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 159.9, 137.2, 136.7, 128.3, 128.0, 125.4, 119.9, 82.4, 64.8, 25.7, 18.2. Exact EIMS calcd for $C_{13}H_{16}O$: 188.1201. Found: 188.1200.

4.4. General procedure for the Cr(TPP)Cl-catalyzed Claisen rearrangements of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds

The catalyst Cr(TPP)Cl was dried over silica gel for 10 h under a reduced pressure (1 mmHg) at 100 °C just before its use. To a round bottle flask (5 mL) equipped with a three-way stopcock and a stirring bar were successively added an allyl vinyl ether (1 mmol), a freshly distilled 1,2-dichloroethane (3 mL), and Cr(TPP)Cl (35 mg, 0.05 mmol). The mixture was stirred at 83 °C under an argon atmosphere. After completion of the reaction (monitored by TLC analysis), the solution was directly passed through a silica gel column (AcOEt/*n*-hexane = 1:50) to give the corresponding Claisen rearrangement product. The configurations of the double bonds in the products were established by comparison of their ^{1}H and ^{13}C NMR data with those of γ,δ-unsaturated aldehydes or ketones with *E*-configuration, which were prepared from non-catalytic thermal Claisen rearrangement reactions of the corresponding allyl vinyl ethers in dichloroethane at 83 °C (the reaction time, yields, and *E*/*Z* ratios are listed in the footnotes of Tables 2–4).[21] The following obtained γ,δ-unsaturated aldehydes and ketones are known compounds: (*E*)-1,3-diphenylhex-4-en-1-one (*E*-**2c**),[22] 3-phenylpent-4-enal (**2d**),[5d] 4-phenylhex-5-en-2-one (**2e**),[23] (*E*)-5-phenylpent-4-enal (**4b**),[5d] (*E*)-4-propenyloctan-2-one (*E*-**4d**),[24] and 3,3-dimethyl-1-phenylpent-4-en-1-one (**6c**).[25]

4.4.1. 3-Phenylhex-4-enal (2a) (*E*/*Z*=15:85).[12] Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.71 (t, *J*=2.2 Hz, 1H×0.85, C*H*O in (*Z*)-**2a**), 9.70 (t, *J*=2.0 Hz, 1H×0.15, C*H*O in (*E*)-**2a**), 7.33–7.17 (m, 5H), 5.64–5.46 (m, 2H, C*H*=C*H*), 4.24 (q, *J*=8.2 Hz, 1H×0.85, PhC*H* in (*Z*)-**2a**), 3.89 (q, *J*=7.3 Hz, 1H×0.15, PhC*H* in (*E*)-**2a**), 2.87–2.69 (m, 2H), 1.67 (d, *J*=5.1 Hz, 3H×0.85, CH_3 in (*Z*)-**2a**), 1.67 (d, *J*=5.9 Hz, 3H×0.15, CH_3 in (*Z*)-**2a**); ^{13}C NMR ($CDCl_3$, 100 MHz) for (*E*)-**2a**: δ 201.3, 142.9, 132.9, 128.6, 127.3, 126.5, 125.9, 49.3, 42.9, 18.0; ^{13}C NMR ($CDCl_3$, 100 MHz) for (*Z*)-**2a**: δ 201.1, 143.2, 132.1, 128.6, 126.9, 126.4, 125.0, 50.1, 37.4, 14.3; IR (neat) 2866, 1725, 1603, 1493, 1454, 758, 719, 700 cm^{-1}. Exact EIMS calcd for $C_{12}H_{14}O$: 174.1045. Found: 174.1047.

4.4.2. 4-Phenylhept-5-en-2-one (2b) (*E*/*Z*=69:31). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.14 (m, 5H), 5.60–5.37 (m, 2H, C*H*=C*H*), 4.19 (q, *J*=7.5 Hz,

1H×0.31, PhC*H* in (*Z*)-**2b**), 3.82 (q, *J*=7.2 Hz, 1H×0.69, PhC*H* in (*E*)-**2b**), 2.81–2.78 (m, 2H), 2.07 (s, 3H×0.31, COCH_3 in (*Z*)-**2b**), 2.06 (s, 3H×0.69, COCH_3 in (*E*)-**2b**), 1.68 (d, *J*=5.1 Hz, 3H×0.31, CH=CHCH_3 in (*Z*)-**2b**), 1.63 (d, *J*=6.2 Hz, 3H×0.69, CH=CHCH_3 in (*E*)-**2b**); ^{13}C NMR ($CDCl_3$, 100 MHz) for (*E*)-**2b**: δ 207.0, 143.6, 133.3, 128.4, 127.3, 126.3, 125.3, 49.8, 44.0, 30.7, 18.0; ^{13}C NMR ($CDCl_3$, 100 MHz) for (*Z*)-**2b**: δ 206.5, 143.6, 132.6, 128.5, 127.0, 126.2, 124.7, 50.5, 44.1, 31.2, 14.3; IR (neat) 2920, 1717, 1603, 1493, 1454, 1359, 1162, 969, 754, 733, 540 cm^{-1}. Exact EIMS calcd for $C_{13}H_{16}O$: 188.1201. Found: 188.1199.

4.4.3. 1,3-Diphenylhex-4-en-1-one (2c) (*E*/*Z*=76:24). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93–7.89 (m, 2H), 7.56–7.40 (m, 3H), 7.30–7.14 (m, 5H), 5.68–5.38 (m, 2H, C*H*=C*H*), 4.40 (dt, *J*=8.3 and 6.3 Hz, 1H×0.24, PhC*H* in (*Z*)-**2c**), 4.05 (dt, *J*=7.0 and 7.0 Hz, 1H×0.76, PhC*H* in (*E*)-**2c**), 3.42–3.25 (m, 2H), 1.65 (dd, *J*=6.3 and 1.4 Hz, 3H×0.24, m, CH_3 in (*Z*)-**2c**), 1.62 (ddd, *J*=6.3, 1.5, and 1.1 Hz, 3H×0.76, CH_3 in (*E*)-**2c**); ^{13}C NMR ($CDCl_3$, 100 MHz) for (*E*)-**2c**: δ 198.2, 143.9, 137.1, 133.4, 132.8, 128.4, 128.0, 127.9, 127.4, 126.2, 125.4, 44.8, 43.9, 18.1; ^{13}C NMR ($CDCl_3$, 100 MHz) for (*Z*)-**2c**: δ 197.7, 144.3, 137.1, 133.4, 132.7, 128.5, 128.4, 127.9, 127.1, 126.1, 124.8, 45.7, 38.9, 13.3; IR (neat) 2920, 1688, 1601, 1582, 1493, 1452, 971 cm^{-1}. Exact EIMS calcd for $C_{18}H_{18}O$: 250.1358. Found: 250.1361. Anal. calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25; O, 6.39. Found: C, 86.47; H, 7.33.

4.4.4. 3-(4-Methoxyphenyl)hex-4-enal (2f) (*E*/*Z*=38:62). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (t, *J*=2.2 Hz, 1H×0.62, C*H*O in (*Z*)-**2f**), 9.67 (t, *J*=2.2 Hz, 1H×0.38, C*H*O in (*E*)-**2f**), 7.13 (d, *J*=8.7 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 5.58–5.46 (m, 2H, C*H*=C*H*), 4.18 (q, *J*=6.8 Hz, 1H×0.62, ArC*H* in (*Z*)-**2f**), 3.83 (q, *J*=7.1 Hz, 1H×0.38, ArC*H* in (*E*)-**2f**), 3.76 (s, 3H, OCH_3), 2.82–2.64 (m, 2H), 1.69 (d, *J*=5.1 Hz, 3H×0.62, CH=CHCH_3 in (*Z*)-**2f**), 1.64 (d, *J*=5.9 Hz, 3H×0.38, CH=CHCH_3 in (*E*)-**2f**); ^{13}C NMR ($CDCl_3$, 67.8 MHz) for (*E*)-**2f**: δ 201.9, 158.3, 135.1, 133.3, 128.3, 125.7, 114.1, 55.3, 49.3, 42.0, 17.9; ^{13}C NMR ($CDCl_3$, 67.8 MHz) for (*Z*)-**2f**: δ 201.7, 158.2, 135.5, 132.6, 128.0, 124.7, 114.0, 55.2, 50.2, 36.5, 13.1; IR (neat) 3828, 2840, 1725, 1611, 1584, 1514, 1251, 1180, 1036, 971, 830 cm^{-1}. Exact EIMS calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1149.

4.4.5. 3-(*p*-Tolyl)hex-4-enal (2g) (*E*/*Z*=39:61). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (t, *J*=2.2 Hz, 1H×0.61, C*H*O in (*Z*)-**2g**), 9.68 (t, *J*=2.2 Hz, 1H×0.39, C*H*O in (*E*)-**2g**), 7.16–7.04 (m, 4H), 5.58–5.47 (m, 2H, C*H*=C*H*), 4.19 (q, *J*=6.6 Hz, 1H×0.61, ArC*H* in (*Z*)-**2g**), 3.84 (q, *J*=7.3 Hz, 1H×0.39, ArC*H* in (*E*)-**2g**), 2.84–2.66 (m, 2H), 2.30 (s, 3H, ArCH_3), 1.69 (d, *J*=5.1 Hz, 3H×0.61, CH=CHCH_3 in (*Z*)-**2g**), 1.64 (d, *J*=5.9 Hz, 3H×0.39, CH=CHCH_3 in (*E*)-**2g**); ^{13}C NMR ($CDCl_3$, 67.8 MHz) for (*E*)-**2g**: δ 201.9, 140.0, 136.2, 133.2, 129.4, 127.2, 125.8, 49.2, 42.4, 21.0, 17.9; ^{13}C NMR ($CDCl_3$, 67.8 MHz) for (*Z*)-**2g**: δ 201.7, 158.6, 135.9, 128.3, 128.0, 124.7, 114.1, 55.2, 50.2, 36.5, 13.1; IR (neat) 2924, 2728, 1721, 1516, 1452, 1417, 1381, 1112, 1044, 1021, 969, 816 cm^{-1}. Exact EIMS calcd for $C_{13}H_{16}O$: 188.1201. Found: 188.1202.

4.4.6. (*E*)-3-Methyl-5-phenylpent-4-enal (4a). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.76 (t, *J*=2.2 Hz, 1H, C*H*O), 7.34–7.17 (m, 5H), 6.40 (d, *J*=15.9 Hz, 1H, CH=C*H*–Ph), 6.14 (dd, *J*=15.9 and 7.3 Hz, 1H, C*H*=CH–Ph), 2.99–2.89 (m, 1H, MeC*H*), 2.59–2.38 (m, 2H), 1.16 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 202.1, 137.1, 133.9, 129.1, 128.5, 127.3, 126.1, 50.4, 31.9, 20.4; IR (neat) 694, 750, 969, 1073, 1450, 1493, 1601, 1725, 2968 cm^{-1}. Exact EIMS calcd for $C_{12}H_{14}O$: 174.1045. Found: 174.1048.

4.4.7. 3-Propenylheptanal (4c) (*E*/*Z*=28:72).[5d,12] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, *J*=2.4 Hz, 1H×0.28, C*H*O in (*E*)-**4c**), 9.66 (t, *J*=2.4 Hz, 1H×0.72, C*H*O in (*Z*)-**4c**), 5.49 (ddq, *J*=10.4, 6.8, and 0.9 Hz, 1H×0.72, CH=C*H*–Me in (*Z*)-**4c**), 5.45 (ddq, *J*=15.2, 5.9, and 0.7 Hz, 1H×0.28, CH=C*H*–Me in (*E*)-**4c**), 5.24 (ddq, *J*=15.2, 8.3, and 1.5 Hz, 1H×0.28, C*H*=CH–Me in (*E*)-**4c**), 5.13 (ddq, *J*=10.4, 10.4, and 1.8 Hz, 1H×0.72, C*H*=CH–Me in (*Z*)-**4c**), 2.97–2.84 (m, 1H×0.72, BuC*H* in (*Z*)-**4c**), 2.58–2.48 (m, 1H×0.28, BuC*H* in (*E*)-**4c**), 2.44–2.23 (m, 2H), 1.63 (dd, *J*=5.9 and 1.7 Hz, 3H×0.32, CH=CH–CH_3 in (*E*)-**4c**), 1.62 (dd, *J*=6.8 and 1.6 Hz, 3H×0.72, CH=CH–CH_3 in (*Z*)-**4c**), 1.36–1.14 (m, 6H), 0.86 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) for (*E*)-**4c**: δ 202.7, 133.6, 125.7, 49.2, 37.6, 35.1, 29.3, 22.7, 18.0, 14.2; ^{13}C NMR ($CDCl_3$, 100 MHz) for (*Z*)-**4c**: δ 202.4, 133.2, 124.7, 49.7, 37.6, 35.4, 29.4, 22.8, 18.0, 14.2; IR (neat) 1729, 1460, 1408, 1379, 1263, 1067, 969, 932, 803, 729 cm^{-1}. Exact EIMS calcd for $C_{10}H_{18}O$: 154.1358. Found: 154.1353.

4.4.8. 4-Propenyloctan-2-one (4d) (*E*/*Z*=77:23). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.51–5.34 (m, 1H, CH=C*H*–Me), 5.19 (ddq, *J*=15.2, 8.3, and 1.6 Hz, 1H×0.77, C*H*=CH–Me in (*E*)-**4d**), 5.08 (ddq, *J*=9.9, 9.9, and 1.8 Hz, 1H×0.23, C*H*=CH–Me in (*Z*)-**4d**), 2.93–2.80 (m, 1H×0.23, BuC*H* in (*Z*)-**4d**), 2.50–2.43 (m, 1H×0.77, BuC*H* in (*E*)-**4d**), 2.42–2.26 (m, 2H), 2.09 (s, 3H×0.23, COCH_3 in (*Z*)-**4d**), 2.08 (s, 3H×0.77, COCH_3 in (*E*)-**4d**), 1.61 (dd, *J*=6.2 and 1.6 Hz, 3H×0.77, CH=CH–CH_3 in (*E*)-**4d**), 1.61 (dd, *J*=7.0 and 1.5 Hz, 3H×0.23, CH=CH–CH_3 in (*Z*)-**4d**), 1.31–1.18 (m, 6H), 0.86 (t, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) for (*E*)-**4d**: δ 208.3, 133.9, 125.2, 49.9, 38.8, 35.1, 30.6, 29.4, 22.8, 18.0, 14.2; ^{13}C NMR ($CDCl_3$, 100 MHz) for (*Z*)-**4d**: δ 208.2, 133.7, 124.4, 50.2, 38.8, 35.4, 30.7, 29.5, 22.9, 18.0, 13.3; IR (neat) 729, 969, 1166, 1359, 1458, 1717, 2930 cm^{-1}. Exact EIMS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1514.

4.4.9. 1-Phenyl-3-propenylheptan-1-one (4e) (*E*/*Z*=80:20). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92–7.89 (m, 2H), 7.55–7.40 (m, 3H), 5.48–5.34 (m, 1H, CH=C*H*–Me), 5.26 (ddq, *J*=15.1, 7.9, and 1.5 Hz, 1H×0.8, C*H*=CH–Me in (*E*)-**4e**), 5.14 (ddq, *J*=10.8, 10.8, and 1.8 Hz, 1H×0.2, C*H*=CH–Me in (*Z*)-**4e**), 3.11–3.00 (m, 1H×0.2, BuC*H* in (*Z*)-**4e**), 2.91 (d, *J*=7.4 Hz, 2H, PhCOCH_2), 2.70–2.59 (m, 1H×0.8, BuC*H* in (*E*)-**4e**), 1.59 (dd, *J*=6.2 and 1.3 Hz, 3H×0.8, CH=CH–CH_3 in (*E*)-**4e**), 1.54 (dd, *J*=6.8 and 1.8 Hz, 3H×0.2, CH=CH–CH_3 in (*E*)-**4e**), 1.45–1.17 (m, 6H), 0.86 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) for (*E*)-**4e**: δ 199.6, 137.4, 134.2, 132.6, 128.3, 128.0, 125.1, 44.7, 39.0, 35.0, 29.5,

22.8, 18.0, 14.2; ^{13}C NMR ($CDCl_3$, 100 MHz) for (*Z*)-**4e**: δ 199.5, 137.4, 134.1, 133.9, 132.5, 125.0, 124.3, 44.8, 38.9, 35.5, 29.5, 22.9, 18.0, 13.3; IR (neat) 3018, 2808, 1688, 1599, 1582, 1450, 967, 752, 690, 572 cm^{-1}. Exact EIMS calcd for $C_{16}H_{22}O$: 230.1671. Found: 230.1672.

4.4.10. (*E*)-3-Methyl-3-propenylheptanal (6a). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.69 (t, *J*=3.2 Hz, 1H, C*H*O), 5.46 (d, *J*=15.6 Hz, C*H*=CH–Me), 5.38 (dq, *J*=15.6 and 4.9 Hz, CH=C*H*–Me), 2.32 (dd, *J*=14.7 and 3.2 Hz, 1H), 2.22 (dd, *J*=14.7 and 3.2 Hz, 1H), 1.67 (d, *J*=4.9 Hz, 3H, CH=CH–CH_3), 1.36–1.08 (m, 6H), 1.08 (s, 3H), 0.87 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 204.1, 138.1, 123.2, 53.7, 41.8, 38.1, 26.1, 24.2, 23.3, 18.1, 14.1; IR (neat) 2934, 1723, 1458, 1381, 975 cm^{-1}. Exact EIMS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1510.

4.4.11. (*E*)-3-Methyl-3-phenylhex-4-enal (6b). Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.56 (t, *J*=3.0 Hz, 1H), 7.39–7.17 (m, 5H), 5.71 (dq, *J*=15.5 and 1.5 Hz, 1H, C*H*=CH–Me), 5.51 (dq, *J*=15.5 and 6.3 Hz, 1H, CH=C*H*–Me), 2.78 (dd, *J*=15.2 and 2.9 Hz, 1H), 2.71 (dd, *J*=15.2 and 2.9 Hz, 1H), 1.73 (dd, *J*=6.3 and 1.5 Hz, 3H, CH=CH–CH_3), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 203.3, 146.4, 138.0, 128.5, 126.4, 126.2, 123.7, 53.8, 42.1, 26.8, 18.1; IR (neat) 2972, 1721, 1448, 1495, 1379, 1035, 975, 762, 700 cm^{-1}. Exact EIMS calcd for $C_{13}H_{16}O$: 188.1201. Found: 188.1200.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (KAKENHI) from JSPS and a Special Grant (GAKUCHO-GRANT) from Meiji Pharmaceutical University.

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The use of (−)-8-phenylisoneomenthol and (−)-8-phenylmenthol in the enantioselective synthesis of 3-functionalized 2-azabicyclo[2.2.1]heptane derivatives via aza-Diels–Alder reaction

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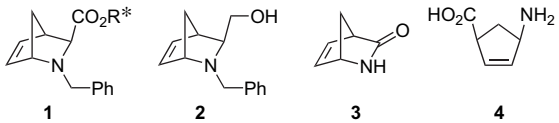
Received 1 June 2006; accepted 23 June 2006
Available online 14 August 2006

Abstract—The asymmetric aza-Diels–Alder reaction of the (1*R*)-8-phenylmenthyl or (1*R*)-8-phenylisoneomenthyl glyoxylate-derived *N*-benzylimine with cyclopentadiene resulted in the enantioselective synthesis of the corresponding pure [(1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylates (80 or 69% yield, respectively). Reduction of these cycloadducts with $LiAlH_4$ afforded pure (−)-[(1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol. Furthermore, a reaction sequence based on Barbier–Wieland degradation of both (1*S*,3-*exo*)-adducts afforded pure (+)-(1*R*)-2-benzoyl-2-azabicyclo[2.2.1]heptan-3-one. In the course of the two transformation sequences referred, the chiral auxiliaries were recovered in a virtually quantitative way.

1. Introduction

Chiral nitrogen containing heterocycles are versatile structures, which often occur in natural products and frequently show biological activity;[1] therefore, the development of efficient and stereoselective methods for their preparation is of great interest for organic chemists. The aza-Diels–Alder reaction is a well-known method for the preparation of such nitrogen containing monocyclic and bicyclic molecules,[2] like 2-azabicyclo[2.2.1]heptane and its derivatives, which can be transformed into a variety of compounds of great interest. For example, [2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylates (**1**) are used in the preparation of the corresponding bicyclic derivatives of [2-azabicyclo[2.2.1]-hept-5-en-3-yl]methanol (**2**), which have been successfully employed as chiral ligands in asymmetric synthesis or catalysis (carbon–carbon bond formation,[3] asymmetric transfer hydrogenation of ketones[4]). Carboxylates of type **1** have been used in the enantioselective synthesis of lactam **3** and its enantiomer and of their saturated analogues,[5] key intermediates in the synthesis of several compounds with biological interest; among them are the four stereoisomers of 4-aminocyclopent-2-ene carboxylic acid (**4**) and the corresponding saturated analogues,[6] which show specific inhibitory activity toward some processes of the action and metabolism of GABA (Fig. 1).[7] On the other hand, isomer (1*R*,3*S*)-3-aminocyclopentane carboxylic acid is the core structure of the antibiotic amidomycin.[8]

These bicyclic compounds containing the 2-azabicyclo-[2.2.1]hept-5-ene system are, through cleavage of the N–C_3 bond, the precursors of an important group of synthons useful in the preparation of chiral amino alcohols derived from cyclopentene or cyclopentane, necessary for the synthesis of carbocyclic nucleosides with antiviral and antineoplastic properties.[9] On the other side, oxidation of the double bond and reduction or hydrolysis of the ester functionality would lead to a great number of chiral nonnatural amino alcohols and α-aminoacids (pyrrolidine derivatives), which,



1 2 3 4

Figure 1.

Keywords: Asymmetric synthesis; Aza-Diels–Alder reaction; Induction; Chiral alcohols.
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doi:10.1016/j.tet.2006.06.118

in turn, are potential nonnucleosidic inhibitors of HIV replication.[10]

In what concerns the aza-Diels–Alder reaction, imines are the most commonly used aza-dienophiles and generally require activation by an electron-withdrawing group and a Lewis acid to participate in these [4+2] cycloaddition reactions.[2c–g] In order to perform the enantioselective synthesis of the referred adducts (**1**), chiral imines must be used. The use of glyoxylates as precursors of chiral electron deficient imines allows the introduction of chirality either through the use of chiral amines[2e,g] or chiral alcohols. Among the latter, (−)-8-phenylmenthol (**5a**) is one of the most widely employed, being used to achieve enantioselectivity in numerous syntheses.[11] Its popularity is due, both to the good enantiomeric excesses it affords (specially in face differentiation processes, in which its capacity for face selective π-stacking interactions is decisive) and to its ready availability (it can be prepared in good yields from the inexpensive (*R*)-(+)-pulegone).[12] Nevertheless, much less is known about the chiral induction behavior of its isomers; for example, its enantiomer, (+)-8-phenylmenthol,[13] which seems just as attractive as **5a** as a chiral auxiliary from a structural point of view, has rarely been used as such due to its high cost.

Whitesell[14] reported that the region C_1–C_2 in 8-phenylmenthol is the one responsible for chiral induction; this led us to the conclusion that we could have similar induction results using diastereomers of (−)-8-phenylmenthol without necessity to use (+)-8-phenylmenthol. Based on this hypothesis, our group has been optimizing various methods of synthesis of the isomers of (−)-8-phenylmenthol from inexpensive, readily available materials.[11a–d] In a recent work,[15] we reported the use of (+)-8-phenylneomenthol and (+)-8-phenylisomenthol in the synthesis of [2-azabicyclo[2.2.1]-hept-5-ene]-3-carboxylates by an aza-Diels–Alder reaction, where a high asymmetric (1*R*,3-*exo*) induction was observed.

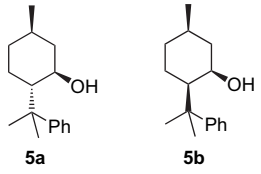
We now report the high asymmetric (1*S*,3-*exo*) induction observed in the same reaction using cyclopentadiene and the iminium ions of the *N*-benzylimines of the glyoxylates of the two diastereomeric alcohols (−)-8-phenylmenthol (**5a**) and (−)-8-phenylisoneomenthol (**5b**).

2. Results and discussion

The chiral auxiliaries (Fig. 2), (−)-8-phenylmenthol [(1*R*,3*R*,4*S*)-8-phenylmenthan-3-ol; **5a**] and (−)-8-phenylisoneomenthol [(1*R*,3*R*,4*R*)-8-phenylmenthan-3-ol; **5b**] were prepared by Bouveault–Blanc reduction of (1*R*,4*S*)-8-phenyl-*p*-menthan-3-one,[11a] which was easily obtained by conjugate addition of phenylmagnesium bromide to (+)-(*R*)-pulegone.[12] Alcohols **5a** and **5b** were straightforwardly separated by flash chromatography on silica gel.

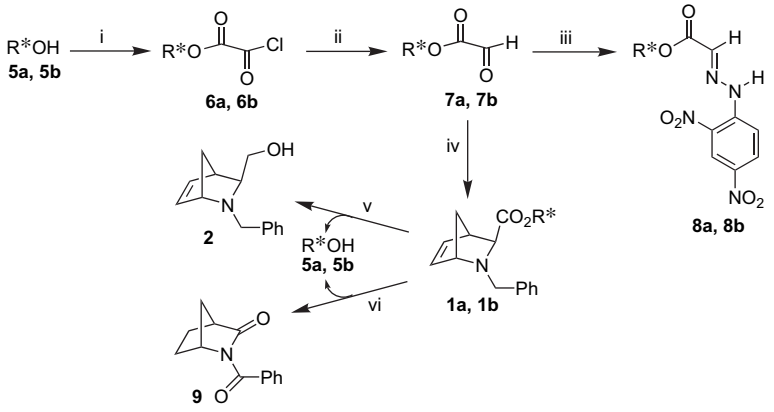
Conversion of the alcohols into their glyoxylates[16] was achieved by reaction with excess oxalyl chloride in chloroform, followed by treatment of the resulting alkyloxy oxalyl chlorides (**6a**, **6b**)[17] with excess tributyltin hydride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), at room temperature (Scheme 1). Once reaction was complete, the excess hydride was destroyed by heating in anhydrous chloroform, yielding tributyltin chloride as the only tin co-product. The glyoxylates (**7a**, **7b**) were separated from the reaction mixture by column chromatography on silica gel. Compounds **7a** and **7b** were characterized by the determination of their spectroscopic and physical properties and those of their 2,4-dinitrophenylhydrazone derivatives (**8a**, **8b**).[16] Although, **7a** and **7b** were each isolated initially as a mixture of the anhydrous glyoxylate and of its hydrate, this presented no problem since both forms react with primary amines to give the desired imines.

Treatment of **7a** or **7b** with equimolar amounts of benzylamine, trifluoroacetic acid, and boron trifluoride etherate in dichloromethane generated the corresponding iminium salt (protonated imine), which reacted in situ with excess cyclopentadiene at −78 °C to give mixtures of diastereomeric adducts. Chromatographic purification of each mixture of



5a **5b**

Figure 2.

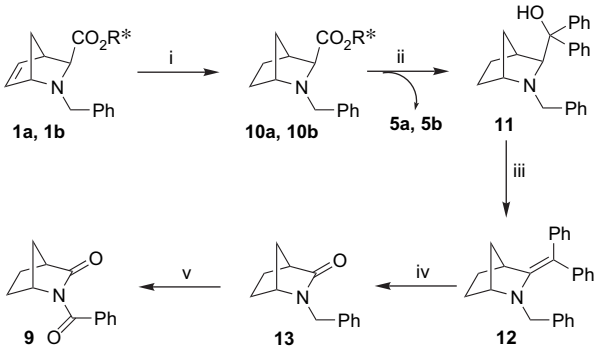


Scheme 1. Reagents and conditions: (i) oxalyl chloride, $CHCl_3$, 0 °C, 1 h; (ii) Bu_3SnH, $Pd(PPh_3)_4$, PhH, 85–89% (overall yield from **5a**, **5b**); (iii) 2,4-dinitrophenyl hydrazine, H_2SO_4, MeOH, 89–92%; (iv) $PhCH_2NH_2$, TFA, $F_3B{\cdot}OEt_2$, cyclopentadiene, CH_2Cl_2, −78 °C, 69–80%; (v) $LiAlH_4$, Et_2O, 5 h, rt, 96–97%; (vi) See Scheme 2 (74–76% overall yield from **1a**, **1b**).

adducts allowed isolation of the most abundant (1*S*,3-*exo*)-diastereoisomer, **1a** (80%yield) or **1b** (69% yield).

Both bicyclic adducts **1a** and **1b** were converted into the same amino alcohol, (−)-[(1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]-hept-5-en-3-yl]-methanol (**2**), by treatment with $LiAlH_4$, and into the same lactam, (+)-(1*R*)-2-benzoyl-2-azabicyclo[2.2.1]heptan-3-one (**9**), through a longer reaction sequence based on Barbier–Wieland degradation (Scheme 1). The transformations into these two target compounds were accomplished with a virtually quantitative recovery of the chiral auxiliaries **5a** (98%) and **5b** (97%). Since the absolute configuration of the bicyclic system of adduct **1a** had already been established by X-ray crystallography as being (1*S*,3-*exo*),[18] this outcome allowed to determine the absolute configuration of adduct **1b** (also 1*S*,3-*exo*).

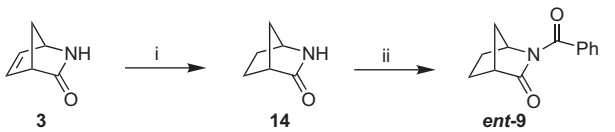
Transformations of **1a** and **1b** into (1*R*)-2-benzoyl-2-azabicyclo[2.2.1]heptan-3-one (**9**) began with their catalytic hydrogenation to **10a** and **10b**, respectively, in order to prevent rearrangements of the norbornene-type (Scheme 2). Treatment of **10a** or **10b** with an excess phenylmagnesium bromide,[19] followed by hydrolysis of the crude product, gave tertiary amino alcohol **11**, with high recovery of the chiral auxiliary (94–96%).



Scheme 2. Reagents and conditions: (i) H_2, 10% Pd/C, 99:1 EtOAc/AcOH, 40 psi, rt, 3 h, 95–97%; (ii) PhMgBr (10 equiv), THF, 12 h, 90–91%; (iii) HMPA (2 equiv), 210 °C, 2 h, 94–95%; (iv) O_2 (air stream), Cu_2Cl_2 (cat.), $CHCl_3$, 0 °C, 6 h, 92–93%; (v) $KMnO_4$ (4 equiv), 18-crown-6 (cat.), 85:15 Me_2CO/AcOH, 60 °C, 15 h, 95–96%.

Amino alcohol **11**[20] was easily dehydrated to enamine **12** by heating with HMPA;[21] Cu(I)-catalyzed oxidation of **12** with molecular oxygen[22] gave a mixture of products from which benzophenone and lactam **13** were easily separated by chromatography on silica gel. Finally, oxidation of **13** with potassium permanganate afforded imide **9** (76 and 74% overall yield from **1a** and **1b**, respectively). Imide **9** had identical melting point and spectroscopic properties, differing only in its $[\alpha]_D$, which was positive, as a sample of *ent*-**9**,[18] prepared from authentic (1*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (**3**)[18,23] by catalytic hydrogenation to **14**, followed by reaction with benzoyl chloride (Scheme 3).

In an attempt to explain the stereochemical outcome of the aza-Diels–Alder reaction, we present in Figure 3 a model for the approach of diene and dienophile. The high *exo*-selectivity observed in these cases may be explained considering that:



Scheme 3. Reagents and conditions: (i) H_2, 10% Pd/C, AcOEt, 40 psi, rt, 1.5 h, 98%; (ii) (a) NaH, Et_2O; (b) BzCl, Et_2O, 14 h, 85%.

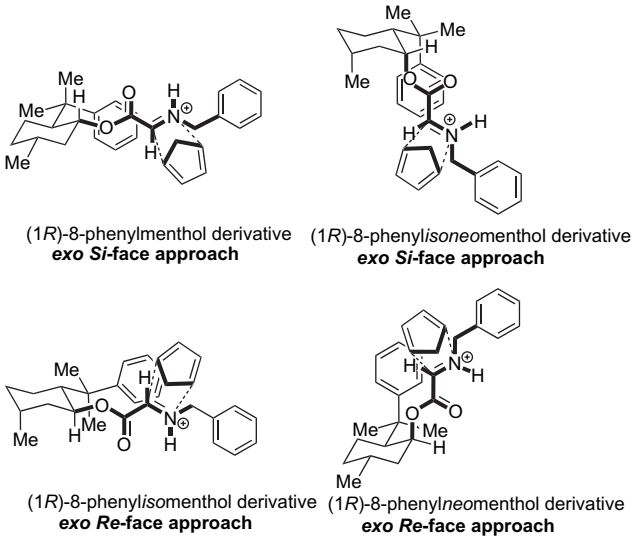


Figure 3.

* the iminium ion, which is the species that acts as dienophile in the reaction, should have an *E* configuration, more stable for both stereochemical (bulky groups far apart) and polar (hydrogen bonding N^+–H···O=C) reasons.
* in the close vicinity of the C=N bond, the (C_{sp^3}) benzyl group exerts a larger steric hindrance than the (C_{sp^2}) ester group.

Consequently, in order to minimize stereochemical interactions in the transition state between the (C_{sp^3}) methylene group of the diene and the bulkier substituents of the dienophile, the approach of diene/dienophile must occur in a manner that places the (C_{sp^3}) benzyl group in an *endo* position and therefore, given the *E* configuration of the dienophile, the ester group in an *exo* position. That is, to say that the stereochemical factors are more important than the secondary orbital interactions between the π systems of cyclopentadiene and the ester group in the dienophile. The configuration of the nitrogen atom in the final adduct is irrelevant, since it exists as a tertiary amine capable of undergoing inversion of the lone pair of electrons to achieve the most stable conformation.

In what concerns the preference observed in the approach of the diene to the diastereotopic faces (due to the presence of the chiral auxiliary) of the dienophile, it is more difficult to suggest a hypothesis, since the geometry of the fragment that connects the chiral auxiliary to the reacting dienophilic site (C=N) in the transition state (diene/dienophile) is not fully known. This fragment consists of three single bonds a, b, and c; for each one, two extreme conformations, *syn* and *anti*, are depicted in Figure 4.

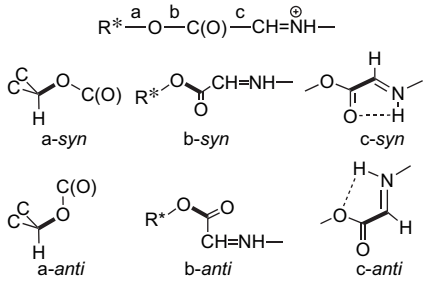


Figure 4.

Some plausible qualitative considerations may be taken into account to offer a rationale for the observed results:

* the $-C(Me)_2Ph$ group of the chiral auxiliary necessarily has to lie in an *equatorial* position with regard to the cyclohexane ring. Given the configurations of the different stereoisomers of the chiral auxiliary, this means that the $C_{(sp^3)}$–O bond will be in an *equatorial* position for 8-phenylmenthol and 8-phenylisomenthol derivatives, and in an *axial* position for 8-phenylneomenthol and 8-phenylisoneomenthol ones.
* π-stacking interactions are supposed to be established between the phenyl group and the aza-diene system, in order to account for the improved results obtained with 8-phenylmenthol derivatives compared to the simple menthol derivatives in achieving better facial diastereoselectivity, which is the base for their use as chiral auxiliaries. This means that the C–Ph bond should lie almost parallel to the $C_{(sp^3)}$–O bond, which determines the conformations of the C–C(Ph) and $C_{(sp^3)}$–O bonds, as is shown in Figures 3 and 4 (a-*syn* bond).
* On the other hand, eclipsing between C═O and $C_{(sp^3)}$–O bonds is the most favored conformation for esters (b-*syn* bond), while preference for c-*syn* conformation in the aza-diene system is justified by the establishment of a stronger hydrogen bond in N^+–H···O═C than in N^+–H···O<.

In consequence, taking into account simultaneously all polar, steric, and electronic prevailing interactions in the system, which includes the *syn*-*syn*-*syn*-alignment of the $C_{(sp^3)}$–O–$C_{(sp^2)}$–$C_{(sp^2)}$ fragment, the geometrical approaches depicted in Figure 3 are the ones, which best explain the stereochemical outcome of these reactions, i.e., formation of the major adducts (1*S*,3-*exo*) as a result of the predominant attack on the *si*-face of the dienophile when using (1*R*)-8-phenylmenthol and (1*R*)-8-phenylisoneomenthol derivatives as chiral auxiliaries, and of the major adducts (1*R*,3-*exo*) as a result of the predominant attack on the *re*-face of the dienophile when using (1*R*)-8-phenylneomenthol and (1*R*)-8-phenyl*iso*menthol derivatives.

3. Conclusion

The results obtained illustrate the utility of (1*R*)-8-phenylmenthol (**5a**) and (1*R*)-8-phenylisoneomenthol (**5b**) as two easily recoverable stereo controlling auxiliaries, affording optically pure 3-functionalized 2-azabicyclo[2.2.1]hept-5-enes with (1*S*,3-*exo*) configuration, by means of an asymmetric aza-Diels–Alder reaction between cyclopentadiene and the protonated imine formed from benzylamine and the glyoxylates of these alcohols. It is noteworthy that a common rationale may be advanced to explain this outcome as well as the opposite asymmetric induction that leads to the corresponding optically pure adducts with (1*R*,3-*exo*) configuration observed when using as chiral auxiliaries the diastereomeric alcohols (1*R*)-8-phenylneomenthol and (1*R*)-8-phenylisomenthol.[15]

From a practical point of view, it is of major importance that the chiral auxiliaries used (isomers of 8-phenylmenthol) to obtain the two enantiomeric families of these azabicyclic compounds (1*S*,3-*exo* and 1*R*,3-*exo*) can be obtained from the same inexpensive starting material, (*R*)-pulegone, with no need to use (+)-(1*S*)-8-phenylmenthol (derived from the prohibitively expensive (*S*)-pulegone).

4. Experimental

4.1. General

Silica gel was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Flash column chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical thin-layer chromatography (TLC) on pre-coated silica gel plates (Merck 60 GF_{254}) using iodine vapor and/or UV light for visualization. Melting points were determined on a Reichert Kofler Thermopan or in capillary tubes on a Büchi 510 apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1640-FT spectrophotometer and the main bands are given in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded on a Bruker WM AMX spectrometer using TMS as an internal standard (chemical shifts (δ) in parts per million, *J* in hertz). Elemental analyses were obtained on a Perkin–Elmer 240B microanalyser by the Microanalysis Service of the University of Santiago de Compostela. Mass spectra were performed on a Hewlett–Packard HP5988A mass spectrometer by electron impact (EI), or on a Finnigan Trace-MS mass spectrometer by chemical ionization (CI). Optical rotations at the sodium D-line were determined using a Perkin–Elmer 241 thermostated polarimeter. GLC analyses were carried out on a Hewlett–Packard 5890 II apparatus provided with a flame ionization detector, using a semi-capillary column (5 m× 0.53 mm i.d., film thickness 2.65 μm) and helium as carrier gas. The hydrogenations were carried out using a Parr 3915 hydrogenator.

4.1.1. (−)-(1*R*)-8-Phenylmenthyl (1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate, 1a. A solution of benzylamine (877 mg, 0.89 mL, 8.18 mmol) in dry CH_2Cl_2 (16 mL) was added under argon to a stirred suspension of **7a**[16] (2.36 g, 8.18 mmol) and 3 Å molecular sieves (6 g) in dry CH_2Cl_2 (48 mL) at 0 °C. When the addition was complete the reaction mixture was cooled to −78 °C and treated successively with TFA (933 mg, 0.63 mL, 8.18 mmol), $BF_3{\cdot}OEt_2$ (1.16 g, 1.04 mL, 8.18 mmol), and freshly distilled cyclopentadiene (ca. 2 equiv, 1.3 mL). After 6 h, a mixture of saturated aqueous $NaHCO_3$ solution (20 mL) and then solid $NaHCO_3$ (2 g) were added. The

reaction mixture was allowed to reach room temperature and filtered. The organic layer was separated from the filtrate and washed with H_2O (50 mL) and CH_2Cl_2 (50 mL) on a Celite pad; the organic layer of the resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The pooled organic layers were washed with saturated $NaHCO_3$ solution (128 mL) and brine (130 mL), and were dried over Na_2SO_4. Removal of the solvent on a rotary evaporator yielded an orange oil (ca. 3.7 g), which was purified by chromatography on silica gel (105 g), using hexane/EtOAc 7:1 as eluent affording a white solid identified as the pure major adduct (1*S*,3-*exo*)-**1a** (2.90 g, 6.54 mmol; yield 80%). Mp 125–126 °C. $[\alpha]_D^{25}$ −56.7 (*c* 1, $CHCl_3$). IR (neat): ν=2992, 2965, 2927, 2880, 2855, 2801, 1736, 1598, 1541, 1495, 1457, 1235, 1187, 1161, 1094, 1082, 1007, 736, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.73–1.06 (m, 3H), 0.86 (d, *J*=6.5 Hz, 3H, 1′-CH_3), 1.08 and 1.09 [2s, 6H, 8′-$(CH_3)_2$], 1.28 (d, *J*=8.3 Hz, 1H, 7_{anti}-H), 1.39–1.60 (m, 3H), 1.79 (d, *J*=8.3 Hz, 1H, 7_{syn}-H), 1.87 (s, 1H), 1.84–1.97 (m, 2H), 2.79 (s, 1H, 4-H), 3.38–3.56 (AB system, *J*=13.1 Hz, 2H, NCH_2Ph), 3.84 (br s, 1H, 1-H), 4.74 (td, J_t= 10.7 Hz, J_d=4.3 Hz, 1H, $3'_{ax}$-H), 6.20 (dd, *J*=5.6, 1.6 Hz, 1H, 5-H), 6.35 (dd, *J*=5.6, 2.3 Hz, 1H, 6-H), 7.09–7.38 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): 22.20 (1′-CH_3), 26.56 and 27.12 [8′-$(CH_3)_2$], 27.20 (C-5′), 31.63 (C-1′), 35.00 (C-6′), 40.20 (C-8′), 41.88 (C-2′), 46.68 (C-7), 49.18 (C-4), 50.78 (C-4′), 59.43 (NCH_2Ph), 64.91 (C-1), 65.53 (C-3), 75.02 (C-3′), 125.39 [aromatic C-4 (Ph)], 125.88 [aromatic C-2+C-6 (Ph)], 127.37 [aromatic C-4 (Bn)], 128.28 [aromatic C-3+C-5 (Ph)], 128.61 [aromatic C-2+ C-6 (Bn)], 129.40 [aromatic C-3+C-5 (Bn)], 134.09 (C-5), 136.76 (C-6), 139.52 [aromatic C-1 (Bn)], 151.98 [aromatic C-1 (Ph)], 173.11 [C(O)O]. MS (EI, *m*/*z*): 443 (M^+). Anal. Calcd for $C_{30}H_{37}NO_2$: C 81.22, H 8.41, N 3.16; found: C 81.47, H 8.61, N 3.09.

4.1.2. (−)-(1*R*)-8-Phenylisoneomenthyl (1*S*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate, 1b. Prepared from **7b**[16] by the same procedure used to prepare **1a** from **7a**. Yield: 69%. Mp 94–96 °C. $[\alpha]_D^{22}$ −60.4 (*c* 0.23, $CHCl_3$). IR (KBr): ν=2974, 2935, 2897, 2843, 1735, 1601, 1495, 1456, 1150, 1116, 1003, 738, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.06 (d, *J*=7.4 Hz, 3H, 1′-CH_3), 1.18 and 1.19 [2s, 6H, 8′-$(CH_3)_2$], 1.23–1.28 (m, 1H), 1.39 (d, *J*=8.2 Hz, 1H, 7_{anti}-H), 1.46 (dt, J_d=12.9 Hz, J_t=4.3 Hz, 1H), 1.52–1.62 (m, 3H), 1.67–1.80 (m, 2H), 1.87–1.92 (m, 1H), 1.94 (d, *J*=8.2 Hz, 1H, 7_{syn}-H), 2.28 (s, 1H, 3_{endo}-H), 3.20 (s, 1H, 4-H), 3.50 and 3.65 (AB system, *J*=13.0 Hz, 2H, NCH_2Ph), 3.88 (d, *J*=1.2 Hz, 1H, 1-H), 5.04 (br s, $w_{1/2}$= 7.4 Hz, 1H, $3'_{eq}$-H), 6.23 (dd, *J*=5.6, 1.8 Hz, 1H, 5-H), 6.48 (ddd, *J*=5.6, 3.3, 1.0 Hz, 1H, 6-H), 7.15–7.42 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): 17.75 (1′-CH_3), 21.49 (C-5′), 25.90 (C-1′), 26.61 and 26.84 [8′-$(CH_3)_2$], 32.62 (C-6′), 36.89 (C-8′), 40.49 (C-2′), 46.90 (C-7), 48.41 (C-4), 51.80 (C-4′), 59.60 (NCH_2Ph), 64.26 (C-1), 66.13 (C-3), 72.36 (C-3′), 125.97 [aromatic C-4 (Ph)], 126.45 [aromatic C-2+C-6 (Ph)], 127.48 [aromatic C-4 (Bn)], 128.35 [aromatic C-3+C-5 (Ph)], 128.71 [aromatic C-2+C-6 (Bn)], 129.37 [aromatic C-3+C-5 (Bn)], 134.31 (C-5), 136.58 (C-6), 139.42 [aromatic C-1 (Bn)], 150.37 [aromatic C-1 (Ph)], 173.23 [C(O)O]. MS (EI, *m*/*z*): 443 (M^+). Anal. Calcd for $C_{30}H_{37}NO_2$: C 81.22, H 8.41, N 3.16; found: C 81.44, H 8.64, N 3.07.

4.1.3. (−)-[(1*S*,3-*exo*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanol, 2. A solution of adduct **1a** (or **1b**) (1.20 g, 2.70 mmol) in dry Et_2O (20 mL) was added dropwise under argon to a suspension of $LiAlH_4$ (607 mg, 16 mmol) in dry Et_2O (20 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and a mixture of MeOH (30 mL) and H_2O (100 mL) was added dropwise at 0 °C; the resulting mixture was extracted with AcOEt (4×100 mL) and the pooled organic layers were washed with H_2O (2×100 mL) and brine (100 mL), and dried with Na_2SO_4. Removal of solvent in a rotary evaporator left a residue that when chromatographed on silica gel with hexane/EtOAc 3:1 as eluent afforded the chiral auxiliary **5a**[25] (615 mg, 98%) [or **5b**[24] (609 mg, 97%)] in the early fractions and compound **2** (563 mg, 97% yield from **1a** and 557 mg, 96% yield from **1b**), as a colorless oil, in the later fractions. $[\alpha]_D^{25}$ −71.3 (*c* 1, $CHCl_3$). IR (neat): ν=3364, 3060, 2985, 2870, 1495, 1452, 1367, 1324, 1208, 1134, 1028, 910, 717 cm^{-1}. ^1H NMR ($CDCl_3$): 1.25–1.28 (d, 1H, *J*=8.40 Hz, 7_{anti}-H), 1.68–1.71 (d, 1H, *J*=8.40 Hz, 7_{syn}-H), 1.82–1.86 (t, 1H, *J*=5.55 Hz, 3-H), 2.32 (br s, 1H, OH), 2.69 (s, 1H, 4-H), 3.32–3.44 (m, 4H, CH_2OH+CH_2Ph), 3.69 (s, 1H, 1-H), 6.10–6.13 (dd, 1H, *J*=5.65, 1.80 Hz, 5-H), 6.41–6.45 (dd, 1H, *J*=5.65, 3.24 Hz, 6-H), 7.16–7.28 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): 46.13 (C-7), 47.16 (C-4), 59.34 (NCH_2Ph), 64.43 (C-1), 64.98 (C-3), 65.66 (CH_2OH), 127.55 (C-4′), 128.80 (C-2′+C-6′), 129.43 (C-3′+C-5′), 132.71 (C-5), 138.27 (C-6), 140.11 (C-1′). MS (EI, *m*/*z*): 215 (M^+). Anal. Calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 77.99, H 8.11, N 6.38.

4.1.4. (−)-(1*R*)-8-Phenylmenthyl [(1*R*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]heptane]-3-carboxylate, 10a. To a solution of **1a** (1.00 g, 2.25 mmol) and 99.5% AcOH (0.13 mL, 2.30 mmol) in AcOEt (15 mL) was added 10% Pd–C (ca. 34 mg). The reaction mixture was hydrogenated at room temperature for 3 h under a hydrogen pressure of 40 psi. Then a saturated aqueous $NaHCO_3$ solution (10 mL) was added, the reaction mixture was filtered, and the organic solvents were removed in a rotary evaporator. The resulting mixture (aqueous layer/oil) was extracted with CH_2Cl_2 (3×20 mL), the pooled organic layers were washed with 3% $NaHCO_3$ solution (20 mL) and brine (30 mL), and were then dried with Na_2SO_4. The solvent was removed in a rotary evaporator yielding **10a** as white solid, which was crystallized from hexane (0.95 g; Yield 95%). Mp 121–122 °C. $[\alpha]_D^{22}$ −21.1 (*c* 1, $CHCl_3$). IR (KBr): ν=2971, 1734, 1600, 1540, 1496, 1304, 1195, 1154, 1046, 993, 750, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.85 (d, *J*=6.5 Hz, 3H, 1′-CH_3), 1.10 and 1.13 [2s, 6H, 8′-$(CH_3)_2$], 0.75–1.69 (m, 8H), 1.19–1.33 (m, 2H), 1.76 (dt, J_d=9.5 Hz, J_t=1.80 Hz, 1H), 1.82–1.99 (m, 3H), 2.14 (s, 1H, 3_{endo}-H), 2.21 (d, *J*=3.7 Hz, 1H, 4-H), 3.28 (s, 1H, 1-H), 3.67 and 3.70 (AB system, *J*=13.0 Hz, 2H, NCH_2Ph), 4.71 (td, J_t=10.7 Hz, J_d=4.3 Hz, 1H, $3'_{ax}$-H), 7.12–7.42 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): δ=22.23 (1′-CH_3), 22.79 (C-5′), 26.67 and 27.02 [(8′-$(CH_3)_2$], 27.14 (C-1′), 29.56 (C-5), 31.62 (C-6′), 35.02 (C-6), 36.62 (C-7), 40.14 (C-8′), 41.88 (C-2′), 42.95 (C-4), 50.67 (C-4′), 55.94 (NCH_2Ph), 60.11 (C-1), 70.01 (C-3), 74.62 (C-3′), 125.38 [aromatic C-4 (Ph)], 125.87 [aromatic C-2+C-6 (Ph)], 127.29 [aromatic C-4 (Bn)], 128.31 [aromatic C-3+C-5 (Ph)], 128.58 [aromatic C-2+C-6 (Bn)], 129.45 [aromatic

C-3+C-5 (Bn)], 139.78 [aromatic C-1 (Bn)], 152.17 [aromatic C-1 (Ph)], 172.91 [C(O)O]. MS (EI, *m/z*): 445 (M^+). Anal. Calcd for $C_{30}H_{39}NO_2$ C 80.85, H 8.82, N 3.14, found C 80.69, H 8.96, N 3.08.

4.1.5. (−)-(1*R*)-8-Phenylisoneomenthyl [(1*R*,3-*exo*)-2-benzyl-2-azabicyclo[2.2.1]heptane]-3-carboxylate, 10b. Prepared from **1b** by the same procedure used to prepare **10a** from **1a**. Yield: 96%. Mp 60–61 °C. $[\alpha]_D^{22}$ −25.0 (*c* 0.5, $CHCl_3$). IR (KBr): ν=2971, 1734, 1654, 1636, 1559, 1496, 1457, 1172, 1115, 758, 694 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.03 (d, *J*=7.4 Hz, 3H, 1′-CH_3), 1.18 and 1.21 [2s, 6H, 8′-$(CH_3)_2$], 1.24–2.05 (m, 14H), 2.62 (br s, 2H, 3_{endo}-H+4-H), 3.31 (s, 1H, 1-H), 3.71 and 3.99 (AB system, *J*=13.2 Hz, 2H, NCH_2Ph), 4.97 (br s, $w_{1/2}$=8.6 Hz, 1H, $3'_{eq}$-H), 7.14–7.45 (m, 10H, 2×C_6H_5). ^{13}C NMR ($CDCl_3$): δ=17.80 (1′-CH_3), 21.44 (C-5′), 22.80 (C-1′), 26.04 (C-6′), 26.59 and 26.85 [8′-$(CH_3)_2$], 29.61 (C-5), 32.62 (C-6), 36.79 (C-7), 36.85 (C-8′), 40.48 (C-2′), 42.26 (C-4), 51.73 (C-4′), 56.12 (NCH_2Ph), 59.45 (C-1), 71.16 (C-3), 72.14 (C-3′), 125.94 [aromatic C-4 (Ph)], 126.42 [aromatic C-2+C-6 (Ph)], 127.31 [aromatic C-4 (Bn)], 128.33 [aromatic C-3+C-5 (Ph)], 128.61 [aromatic C-2+C-6 (Bn)], 129.37 [aromatic C-3+C-5 (Bn)], 129.68 [aromatic C-1 (Bn)], 150.32 [aromatic C-1 (Ph)], 172.83 [C(O)O]. MS (EI, *m/z*): 445 (M^+). Anal. Calcd for $C_{30}H_{39}NO_2$: C 80.85, H 8.82, N 3.14; found: C 80.64, H 8.94, N 3.04.

4.1.6. (+)-(1*R*,3-*exo*)-2-Benzyl-3-[(hydroxy)diphenylmethyl]-2-azabicyclo[2.2.1]heptane, 11. A solution of **10a** (or **10b**) (800 mg, 1.80 mmol) in dry THF (5 mL) was added dropwise under argon to a solution of PhMgBr [prepared, under argon, from Mg (470 mg, 19.4 mmol) and PhBr (1.9 mL, 18 mmol) in dry THF (25 mL)] at room temperature. The reaction mixture was refluxed overnight. Then the mixture was cooled to 0 °C and saturated aqueous NH_4Cl solution (16 mL) was added dropwise, the resulting mixture was filtered and the organic solvents were removed in a rotary evaporator. The remaining mixture was then extracted with CH_2Cl_2 (3×20 mL). The pooled organic layers were washed with saturated aqueous NH_4Cl solution (16 mL) and brine (20 mL), and dried with Na_2SO_4. The solvent was removed in a rotary evaporator and the resulting residue was treated with MeOH (12 mL) yielding **11** as a white solid (591 mg, 89% from **10a** and 578 mg, 87% from **10b**).[20] Removal of the solvent from the mother liquor left an oil, which when flash chromatographed on silica gel (75 g) using hexane/EtOAc 3:1 as eluent afforded the chiral auxiliary (393 mg of **5b**,[24] 94% and 402 mg of **5a**,[25] 96%). Mp 179–180 °C. $[\alpha]_D^{23}$ +51 (*c* 1, $CHCl_3$). IR (KBr): ν=2992, 2910, 1426, 1332, 1255, 1094, 966, 788 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.97 (d, *J*=9.8 Hz, 1H, 7-H), 1.22–1.33 (m, 1H), 1.38–1.61 (m, 2H), 1.94 (d, *J*=9.8 Hz, 1H, 7-H), 1.98–2.07 (m, 1H), 2.22 (s, 1H), 2.98 (d, *J*=13.0 Hz, 1H, NC*H*HPh), 3.11 (s, 1H), 3.25 (s, 1H), 3.32 (d, *J*=13.0 Hz, 1H, NCH*H*Ph), 5.17 (br s, 1H, D_2O exch.), 7.08–7.36 (m, 11H, arom.), 7.60 [dd, *J*=7.3, 1.2 Hz, 2H, H_{ortho}-2 (Ph′)], 7.74 [dd, *J*=7.5, 1.2 Hz, 2H, H_{ortho}-2 (Ph″)]. ^{13}C NMR ($CDCl_3$): δ= 22.14 (C-5), 30.73 (C-6), 36.06 (C-7), 41.21 (C-4), 53.86 (C-1), 58.00 (NCH_2Ph), 75.49 (C-3), 77.34 [C(OH)Ph_2], 126.12 [aromatic, C_{para} (Ph′ and Ph″)], 126.67 and 126.84 [aromatic, 2×C_{ortho} (Ph′ and Ph″)], 127.30 [aromatic C_{para} (Bn)], 128.52 [aromatic C_{meta} (Bn)], 128.56 [aromatic C_{ortho} (Bn)], 128.66 and 129.22 [aromatic, 2×C_{meta} (Ph′ and Ph″)], 139.78 [aromatic C-1 (Bn)], 146.63 and 148.89 [aromatic, 2×C-1 (Ph′ and Ph″)]. MS (CI, *m/z*): 370 (MH^+). Anal. Calcd for $C_{26}H_{27}NO$: C 84.51, H 7.36, N 3.79; found: C 84.28, H 7.51, N 3.84.

4.1.7. (+)-(1*R*)-2-Benzyl-3-(diphenylmethylidene)-2-azabicyclo[2.2.1]heptane, 12. A solution of **11** (500 mg, 1.35 mmol) in HMPA (4.9 mL, 27.9 mmol) was heated at 215–220 °C with stirring for 2 h. Then the mixture was cooled to room temperature and chromatographed on silica gel (170 g) using hexane/EtOAc 4:1 as eluent affording in the early fractions compound **12** as a white solid, which was crystallized from hexane. Yield 452 mg (95%). Mp 139–140 °C. $[\alpha]_D^{23}$ +938 (*c* 1, $CHCl_3$). IR (KBr): ν=3021, 2961, 1609, 1593, 1492, 1350, 1219, 1148, 938, 731 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.26 (d, *J*=9.0 Hz, 1H, 7-H), 1.48 (tdd, J_t=11.7 Hz, J_d=4.5 Hz, J_d=2.4 Hz, 1H), 1.74–2.03 (m, 4H), 3.11 (d, *J*=1.9 Hz, 1H), 3.35 (s, 1H), 3.50 (d, *J*=15.2 Hz, 1H, NC*H*HPh), 4.03 (d, *J*=15.2 Hz, 1H, NCH*H*Ph), 6.98 (tt, *J*=7.3, 1.3 Hz, 1H), 7.07–7.27 (m, 14H, arom.). ^{13}C NMR ($CDCl_3$): δ=24.86 (C-5), 28.75 (C-6), 39.54 (C-7), 44.57 (C-4), 49.74 (C-1), 59.91 (NCH_2Ph), 108.69 (CPh$_2$), 124.98 and 125.53 [aromatic, 2×C_{ortho} (Ph′ and Ph″)], 126.82 [aromatic C_{para} (Bn)], 127.96 [aromatic, 2×C_{para} (Ph′ and Ph″)], 128.00 [aromatic C_{ortho} (Bn)], 128.20 [aromatic C_{meta} (Bn)], 130.34 and 131.02 [aromatic, 2×C_{meta} (Ph′ and Ph″)], 139.45 [aromatic C-1 (Bn)], 143.04 and 145.20 [aromatic, 2×C-1 (Ph′ and Ph″)], 154.02 (C-3). MS (CI, *m/z*): 352 (MH^+). Anal. Calcd for $C_{26}H_{25}N$: C 88.85, H 7.17, N 3.98; found: C 88.73, H 7.28, N 4.14.

4.1.8. (+)-(1*R*)-2-Benzyl-2-azabicyclo[2.2.1]heptan-3-one, 13. To a vigorously stirred solution of **12** (400 mg, 1.14 mmol) in $CHCl_3$ (18 mL) was added Cu_2Cl_2 (ca. 14 mg) at 0 °C and the resulting cooled suspension was bubbled for 6 h with O_2 (air stream). The reaction mixture was filtered. Removal of the solvent from the filtrate in a rotary evaporator left an oil (438 mg) that upon chromatography on silica gel (15 g) with hexane/AcOEt 2:1 as eluent afforded benzophenone (206 mg) in the early fractions and **13**, as an oil, in the later fractions. Yield 208 mg (91%). $[\alpha]_D^{22}$ +41 (*c* 0.56, $CHCl_3$). IR (neat): ν=2954, 2930, 1693, 1409, 1227, 993, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.33 (d, *J*=9.4 Hz, 1H, 7_{anti}-H), 1.47–1.72 (m, 3H), 1.82 (dd, *J*= 9.4, 1.5 Hz, 1H, 7_{syn}-H), 1.82–1.90 (m, 1H), 2.85 (dd, *J*=3.8, 1.5 Hz, 1H, 4-H), 3.68 (s, 1H), 3.93 (d, *J*=15.1 Hz, 1H, NC*H*HPh), 4.68 (d, *J*=15.1 Hz, 1H, NCH*H*Ph), 7.24–7.35 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ=24.94 (C-5), 27.30 (C-6), 40.30 (C-7), 44.35 (C-4), 45.90 (C-1), 59.00 (NCH_2Ph), 127.66 [aromatic C-4 (Bn)], 128.17 [aromatic C-2+C-6 (Bn)], 128.85 [aromatic C-3+C-5 (Bn)], 137.56 [aromatic C-1 (Bn)], 178.21 (C-3). MS (EI, *m/z*): 201 (M^+). Anal. Calcd for $C_{13}H_{15}NO$: C 77.58, H 7.51, N 6.96; found: C 77.33, H 7.72, N 6.84.

4.1.9. (+)-(1*R*)-2-Benzoyl-2-azabicyclo[2.2.1]heptan-3-one, 9. To a solution of **13** (150 mg, 0.75 mmol) and 18-crown-6 (ca. 1 mg) in 10 mL of Me_2CO/AcOH (85:15, v/v) was added water (0.5 mL). The mixture was heated to 60 °C, finely powdered $KMnO_4$ (476 mg, 3 mmol) was added in portions during 5 h, and heating was continued for 10 h more. The reaction mixture was then cooled to

room temperature, 1 M $Na_2S_2O_5$ (8 mL) was added, and the mixture was extracted with CH_2Cl_2 (4×20 mL). The pooled organic layers were washed with 1 M $Na_2S_2O_5$ solution (8 mL) and brine (20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated, affording a solid residue. Purification of the resulting solid through a short column of silica gel (6 g) using $CHCl_3$ as eluent afforded **9** as a white solid. Yield 154 mg (96%). The purity of the compound obtained was verified by GLC [99.9%; semi-capillary column (5 m×0.53 mm i.d., film thickness 2.65 μm); oven temperature 150 °C isothermal, helium as carrier gas]. Mp 180–181 °C (hexane/CCl_4). $[\alpha]_D^{22}$ +286 (*c* 1, $CHCl_3$). IR (KBr): ν=2979, 2954, 2876, 1746, 1660, 1600, 1452, 1337, 1310, 1216, 1178, 1159, 1099, 1056, 1027, 952, 907, 804, 781, 732, 698, 675, 611 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.59 (dt, J_d=10.0 Hz, J_t=1.1 Hz, 1H, 7_{anti}-H), 1.73–1.80 (m, 1H), 1.95–2.03 (m, 3H), 2.06 (dt, J_d=10.0 Hz, J_t=1.8 Hz, 1H, 7_{syn}-H), 2.94 (t, *J*=1.6 Hz, 1H, 4-H), 4.81 (s, 1H, 1-H), 7.37–7.42 [m, 2H, (3′-H, 5′-H)], 7.49–7.54 (m, 1H, 4′-H), 7.61–7.65 [m, 2H, (2′-H, 6′-H)]. ^{13}C NMR ($CDCl_3$): δ=24.99 (C-5), 28.24 (C-6), 37.64 (C-7), 47.36 (C-4), 59.24 (C-1), 127.90 [aromatic C-3+C-5 (Bz)], 129.57 [aromatic C-2+C-6 (Bz)], 132.38 [aromatic C-4 (Bz)], 134.22 [aromatic C-1 (Bz)], 169.56 [N*C*(O)Ph], 175.73 (C-3). MS (EI, *m*/z): 215 (M^+). Anal. Calcd for $C_{13}H_{13}NO_2$: C 72.54, H 6.09, N 6.51; found: C 72.48, H 6.12, N 6.47.

4.1.10. (−)-(1*S*)-2-Azabicyclo[2.2.1]heptan-3-one, 14. To a solution of **3**[23] [(160 mg, 1.47 mmol), $[\alpha]_D$ −563.4 (*c* 1, $CHCl_3$)] in AcOEt (50 mL) was added 10% Pd/C (300 mg). The vigorously stirred black suspension was hydrogenated under a hydrogen pressure of 40 psi at room temperature. After the reaction was complete (1.5 h), the reaction mixture was filtered and the filtrate was concentrated to give a white solid (161 mg, 98%). The purity of the compound obtained was verified by GLC [99.5%, semi-capillary column (5 m×0.53 mm i.d., film thickness 2.65 μm), oven temperature 85 °C isothermal, helium as carrier gas]. An analytical sample was obtained through crystallization from cyclohexane and subsequent sublimation at 90–95 °C (0.05–0.1 mmHg). Mp 96–98 °C. $[\alpha]_D^{22}$ −160 (*c* 1, $CHCl_3$).[26] IR (KBr): ν=3219, 2946, 1684, 1507, 1398, 1239, 1109, 954, 814, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.31 (dq, *J*=9.3, 1.3 Hz, 1H), 1.47–1.57 (m, 2H), 1.72–1.80 (m, 2H), 1.83 (dquint, *J*=9.3, 2.0 Hz, 1H), 2.73 (d, *J*=1.0 Hz, 1H), 3.88 (d, *J*=0.8 Hz, 1H), 6.74 (br s, D_2O exch., 1H). ^{13}C NMR ($CDCl_3$): δ=23.93, 30.43, 41.73, 45.37, 55.70, 181.97. MS (EI, *m*/z): 111 (M^+). Anal. Calcd for C_6H_9NO: C 64.84, H 8.16, N 12.60; found: C 64.63, H 8.33, N 12.54.

4.1.11. (−)-(1*S*)-2-Benzoyl-2-azabicyclo[2.2.1]heptan-3-one, *ent*-9. A solution of **14** (85 mg, 0.765 mmol) in dry Et_2O (3 mL) was added under argon to a stirred suspension of 60% NaH (46 mg, 1.15 mmol) in dry Et_2O (5 mL) at 0 °C. The mixture was stirred for 20 min and then a solution of benzoyl chloride (163 mg, 1.16 mmol) in dry Et_2O (3 mL) was added under argon. The reaction mixture was stirred at room temperature overnight and then filtered through a short column of silica gel using Et_2O as eluent. The solvent was removed in a rotary evaporator affording (−)-**9** as a white solid. Yield 140 mg (85%). The purity of the compound obtained was verified by GLC [99.9%, semi-capillary column (5 m×0.53 mm i.d., film thickness 2.65 μm), oven temperature 150 °C isothermal, helium as carrier gas]. Mp 179–181 °C (CCl_4). $[\alpha]_D^{22}$ −287 (*c* 1, $CHCl_3$). Spectroscopic data (IR, ^1H NMR, ^{13}C NMR) were identical to those of compound (+)-**9**.

Acknowledgements

The authors thank the Xunta de Galicia for financial support of this work under project PGIDIT05PXIB20301PR.

References and notes

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24. The recovered alcohol [$[\alpha]_D^{25}$ −4.3 (*c* 0.5, $CHCl_3$)] was identified as (−)-8-phenylisoneomenthol by comparison of its spectroscopic and specific rotation data with those reported in literature.[11a]
25. The recovered alcohol [$[\alpha]_D^{25}$ −25.2 (*c* 0.5, $CHCl_3$)] was identified as (−)-8-phenylmenthol by comparison of its spectroscopic and specific rotation data with those reported in literature.[11a]
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Tetrahedron 62 (2006) 9483–9496

Total synthesis, elucidation of absolute stereochemistry, and adjuvant activity of trihydroxy fatty acids

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Received 10 April 2006; accepted 16 June 2006

Abstract—Pinellic acid from the tuber of *Pinellia ternate*, an active herbal component of the traditional Japanese herbal (Kampo) medicine Sho-seiryu-to, is a C18 trihydroxy fatty acid whose absolute stereochemistry has now been determined. All stereoisomers of pinellic acid were synthesized via regioselective asymmetric dihydroxylation, regioselective inversion, and stereoselective reduction in order to determine their absolute stereochemistries and adjuvant activities. Among this series of isomers, the (9*S*,12*S*,13*S*)-compound, which is a natural product, exhibited the most potent adjuvant activity. Spectral data for all of the stereoisomers of the 1,2-allylic diols were compared and related to their stereochemistries.

1. Introduction

Infection with the influenza virus is epidemic and can be lethal for patients with respiratory diseases and those who are elderly.[1] The primary method for the treatment of influenza is to use the influenza vaccine as a prophylaxis. Subcutaneous injection of this vaccine is known to induce production of serum antiviral IgG antibodies (Abs) that give a protective effect against proliferation of the virus in lung tissue. Because the influenza virus infects the nasal cavity first, intranasal inoculation of the influenza vaccine has been attempted in order to increase its safety and prevent antigenic variation. However, it has been shown that vaccinations in the nasal cavity are less effective than subcutaneous ones and may not provide sufficient immunostimulation. In order to overcome these problems, using adjuvants for enhancement of the local mucosal immune response has been reported.

Several traditional Japanese herbal (Kampo) medicines have been used for the treatment of cold-like symptoms in which the influenza virus is known to be the causative agent. Oral administration of the Kampo medicine, Sho-seiryu-to (SST), has been used clinically for the treatment of cold symptoms. In preliminary studies SST exhibited potent antiviral activity against influenza due to an immunostimulating activity against nasally inoculated influenza antigen. Our research indicated that SST had oral adjuvant activity for nasally administered influenza vaccine.[2–4] It was clear that the activity of SST was due to ingredients from *Pinellia ternate*, one of the component herbs of SST. Further investigation determined that pinellic acid **1** isolated from *P. ternate* was the compound responsible for the adjuvant activity (Fig. 1). Pinellic acid **1** is an effective oral adjuvant candidate for nasal influenza vaccine; however, *P. ternate* contains only a small amount of **1** and their stereochemistry was unknown.[5] Although information about the stereochemistry of these types of fatty acids has been reported,[6] there were not absolute to overcome our problems. Herein, not only the enantioselective total synthesis and assignment of the stereochemistry of **1**, but also the synthesis of stereoisomers and their adjuvant activities, are reported.

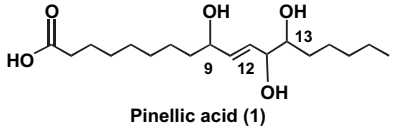

Figure 1. Structure of pinellic acid **1**.

Keywords: Total synthesis; Adjuvant; Determination of stereochemistry.
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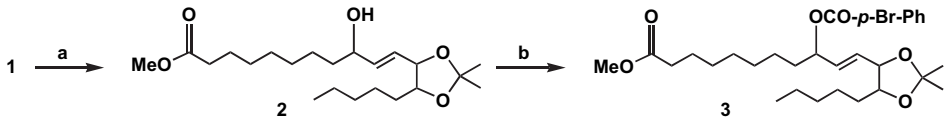
0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.06.088



Scheme 1. Derivatization of **1**. Reagents and conditions: (a) (1) $TMSCHN_2$, benzene/MeOH (10:1), rt, 2.5 h; (2) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 60 °C, 48 h (100% from **1**); (b) *p*-Br-BzCl, DMAP, pyridine, rt, 10 h (68%).

2. Estimation of absolute stereochemistry of 1

To determine the absolute stereochemistry of pinellic acid, spectral analysis of its derivatives provided insightful information. The CD exciton method[7] was used for the estimation of C9 stereochemistry at the allylic alcohol. The esterification of **1** followed by dimethylacetalization gave acetonide **2** with free alcohol at C9 (Scheme 1). Both coupling constant ($J_{12,13}$=8.0 Hz) in the ^{1}H NMR spectrum of **2** and NOE analysis indicate a *syn* configuration at the C12–C13 diol (Fig. 2).

The corresponding *p*-bromobenzoate **3** was prepared with *p*-bromobenzoyl chloride from **2**. The coupling constant between H9 and H10 in the ^{1}H NMR spectrum of **3** was 7.0 Hz, indicating an antiperiplanar conformation of these two protons. Moreover, a positive Cotton effect [λ_{max} ($\Delta\varepsilon$): 244.8 (+6.97), 220.8 (+2.13), 209.1 (+5.97) (MeOH)] of **3** in the CD spectrum suggested a 9*S* configuration[8] (Fig. 3).

Based on these results, the absolute configuration of **1** was determined to be either **4** (9*S*,12*S*,13*S*) or **5** (9*S*,12*R*,13*R*) (Fig. 4). We then attempted to establish a convergent synthetic route to **4** and **5** in order to synthesize all of the possible stereoisomers.

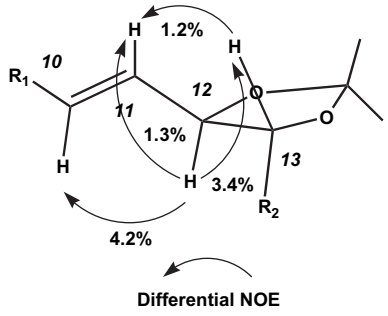


Figure 2. NOE analysis of **2**.

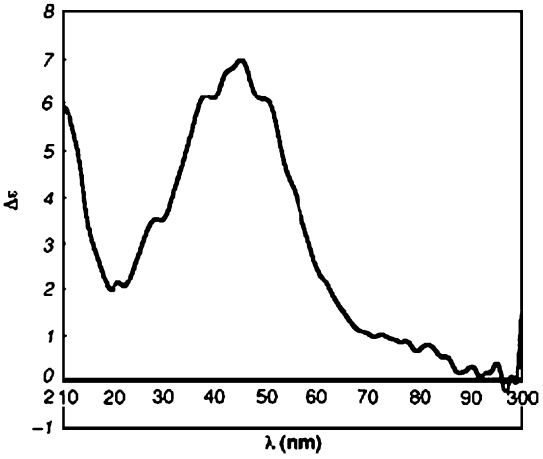


Figure 3. CD spectrum of **3**.

3. Total synthesis

3.1. Synthetic strategy

The strategic disconnection is outlined in Figure 5. The most important challenge in this synthesis is to construct the stereochemistry of the three hydroxy groups. The *syn*-diol at C12–C13 would be prepared from a diene by regioselective asymmetric dihydroxylation,[9] and the C12–C13 *anti*-diol would be constructed via regioselective protection of the C12 hydroxy group followed by inversion of the C13 hydroxy group. Stereoselective reduction from the corresponding enone would give the allylic alcohol at C9.

3.2. Synthesis of the C18 skeleton

The synthesis of C18 skeleton **11** utilizing dithiane coupling[10] is shown in Scheme 2. *tert*-Butyl ester **7** was converted from the carboxylic acid moiety in suberic acid monomethyl ester **6** with $(Boc)_2O$ and DMAP in *t*-BuOH. The diester **7** was transformed to iodide **8** in good yield by hydrolysis of the methyl ester, followed by reduction of the carboxylic acid,[11] and iodination of the resultant primary alcohol. The C9–C18 skeleton **10** was derived from commercially available 2,4-decadienal **9**. Lithiation of **10** with *n*-BuLi and subsequent addition of **8** gave diene **11** in high yield (Scheme 2).

3.3. Synthesis of 4

The regioselective asymmetric dihydroxylation of **11** using AD-mix containing $(DHQ)_2PHAL$ gave C12–C13 *syn*-diol (−)-**12**[12] in disappointing yield and enantiomeric excess (55%, 80% ee). However, the use of modified Sharpless ligand [(DHQ)PHAL(DHQ)$Me^+\cdot I^-$][9] for the hydroxylation resulted in 64% yield with 95% ee. The protection of the diol (−)-**12** with excess TBSOTf followed by the deprotection of dithioacetal (−)-**13** provided enone (−)-**14**.

The stereoselective reduction of enone (−)-**14** to provide the (9*S*)-alcohol was attempted. Diastereoselectivity was not achieved with $NaBH_4$ or (*R*)-CBS[13] (diastereoselectivity 5:1). (*S*)-BINAL-H[12,14] noticeably improved the diastereoselectivity due to the π-electron at C10–C11 and the bulky *O*-TBS group (diastereoselectivity >20:1). The desilylation with TBAF gave triol (−)-**15** as a single isomer. Since deprotection of *tert*-butyl ester with TFA caused elimination of the hydroxy groups at the C9 and C12 allylic positions, the hydrolysis of the *tert*-butyl ester was achieved by a highly concentrated alkaline solution to afford (−)-**4**, which has the 9*S*,12*S*,13*S* configuration (Scheme 3). Compound (−)-**4** was

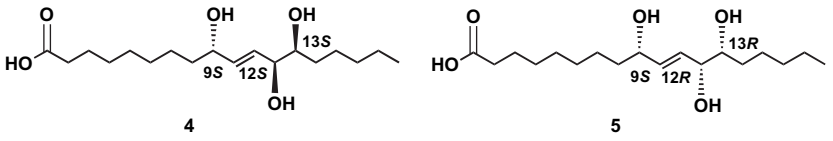


Figure 4. Possible structures for **1**.

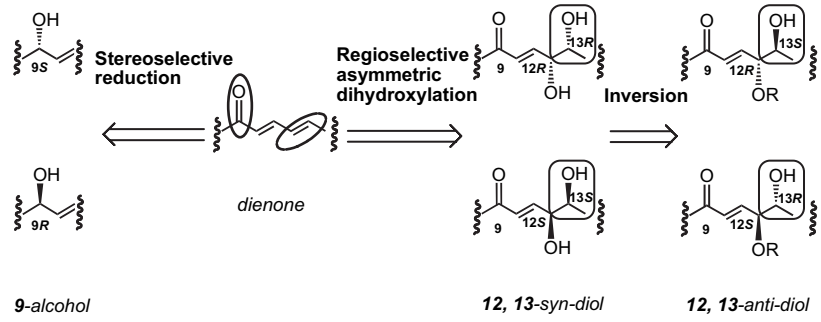
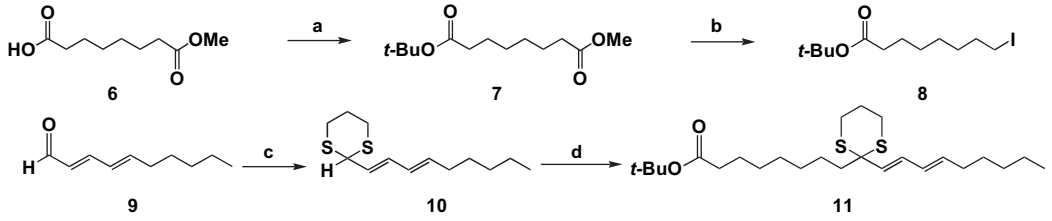
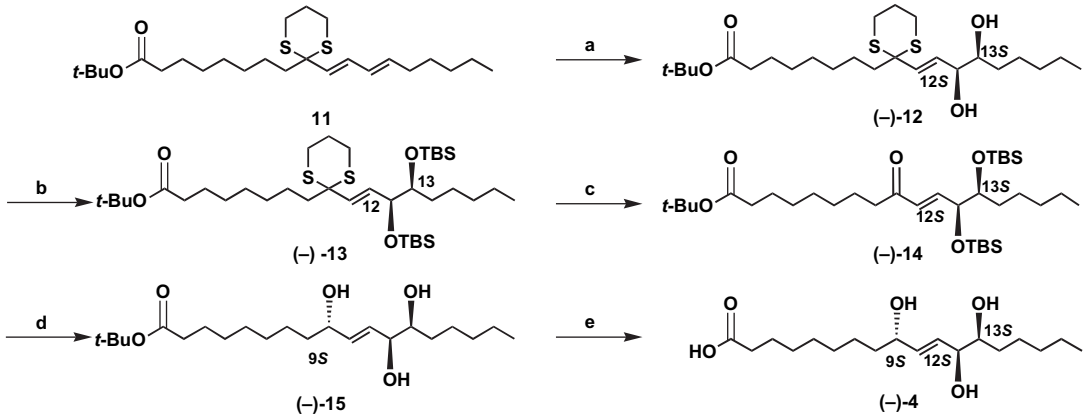


Figure 5. Synthetic strategy for all stereoisomers of **1**.



Scheme 2. Synthesis of the C18 skeleton **11**. Reagents and conditions: (a) $(Boc)_2O$, DMAP, *t*-BuOH, rt, 1 h (82%); (b) (1) 0.1 N NaOH in THF/MeOH/H_2O (3:1:1), rt, 28 h; (2) $BH_3\cdot$THF, THF, 0 °C to rt, 24 h; (3) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 2 h (77% from **7**); (c) 1,3-propanedithiol, $BF_3\cdot OEt_2$, CH_2Cl_2, 0 °C to rt, 10 h (96%); (d) *n*-BuLi, THF, −78 °C, 1 h, then **8**, −78 °C, 1 h (85%).



Scheme 3. Synthesis of **4**. Reagents and conditions: (a) (DHQ)PHAL(DHQ)$Me^+\cdot I^-$, $K_3[Fe(CN)_6]$, K_2CO_3, $K_2OsO_4\cdot 2H_2O$, methanesulfonamide, *t*-BuOH/H_2O (1:1), 0 °C, 41 h (64%, 95% ee); (b) TBSOTf, 2,6-lutidine, −78 °C, 30 min (89%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 30 min (83%); (d) (1) (*S*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1); (2) TBAF, THF, 70 °C, 3 h [76% from (−)-**14**]; (e) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (82%).

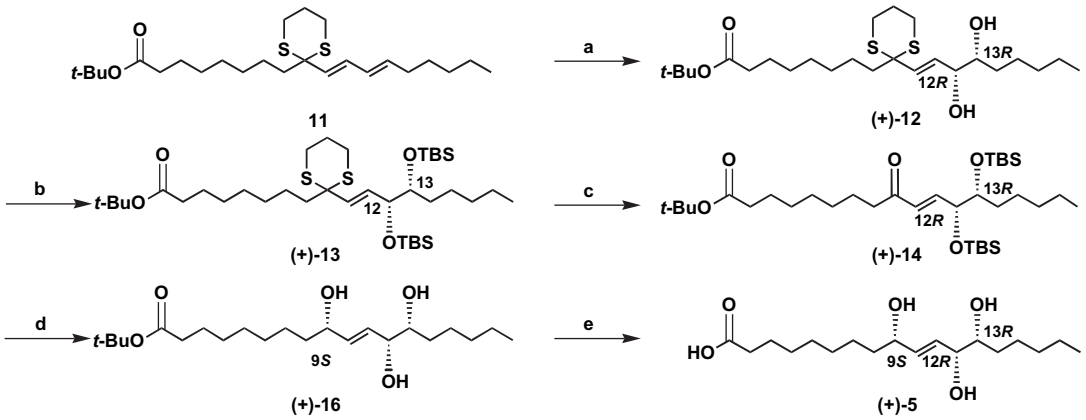
identical in all respects with natural product **1** [400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, IR, HRMS, optical rotation {$[\alpha]_D^{25}$ −8.0 (*c* 0.30, MeOH); natural:[4] $[\alpha]_D^{28}$ −8.1 (*c* 0.32, MeOH)}, and oral adjuvant activity] (Scheme 4).[15]

3.4. Synthesis of 5

For the synthesis of (+)-**5**, (+)-**12** with absolute configuration 12*R*,13*R* was required. Following the synthetic route for (−)-**4**, asymmetric dihydroxylation using AD-mix-β containing $(DHQD)_2PHAL$ of **11** gave diol (+)-**12** in 75% yield with 92% ee (Scheme 4). After the installation of the diol, the sequence of five reactions was the same, yielding (+)-**5**. The trihydroxy fatty acid (+)-**5** was not identical to natural product **1** [400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, and optical rotation {$[\alpha]_D^{23}$ +29.8 (*c* 0.45, MeOH)}].

3.5. Synthesis of (+)-4 and (−)-5

In order to investigate the oral administration of pinellic acid analogs as adjuvants for the intranasal inoculation of influenza HA vaccine, the synthesis of enantiomers of (−)-**4**

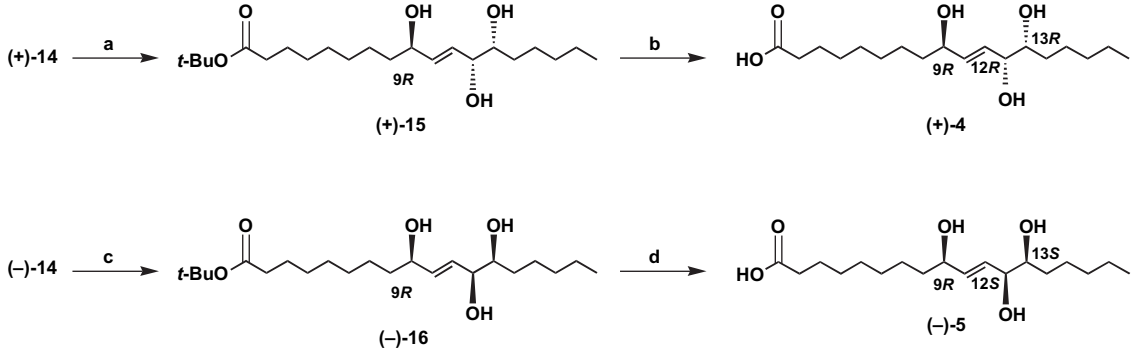


Scheme 4. Synthesis of **5**. Reagents and conditions: (a) $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, K_2CO_3, $K_2OsO_4 \cdot 2H_2O$, methanesulfonamide, *t*-BuOH/H_2O (1:1), 0 °C, 73 h (75%, 92% ee); (b) TBSOTf, 2,6-lutidine, −78 °C, 30 min (87%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 30 min (83%); (d) (1) (*S*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1); (2) TBAF, THF, 70 °C, 3 h [76% from (−)-**14**]; (e) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (76%).

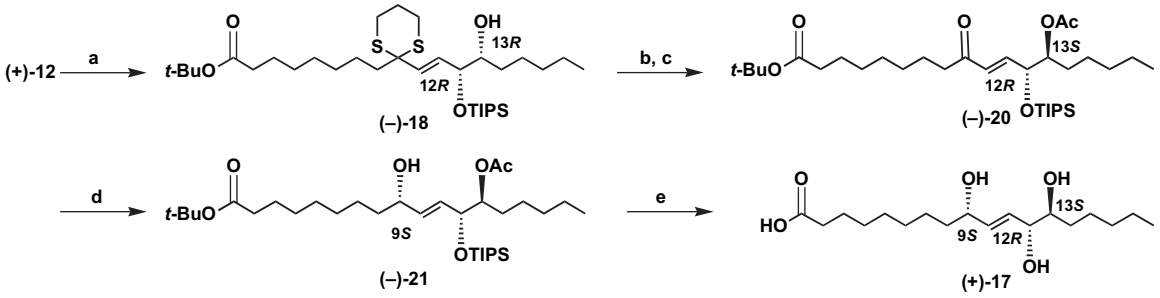
and (+)-**5** containing the *syn* configuration at C12–C13 is required. To construct the C9 hydroxy group, (*R*)-BINAL-H would be applied to the corresponding intermediates (+)-**14** and (−)-**14**.[12] As expected, stereoselective reduction (diastereoselectivity >20:1) followed by deprotection of the TBS group gave the (9*R*)-alcohol. Finally, hydrolysis according to the above procedure furnished (+)-**4** and (−)-**5** successfully (Scheme 5).

3.6. Synthesis of 17

The C12–C13 *anti*-isomers were also constructed in order to investigate structure–activity relationships. The key step is regioselective protection of the C12 hydroxy group in the C12–C13 *syn*-diol followed by inversion of the C13 hydroxy group. The preparation of **17** (9*S*,12*R*,13*S*) is shown in Scheme 6. The protecting groups were selected carefully because only one hydroxy group (C12 or C13) should be protected. The C12 hydroxy group is more reactive than C13 due to its allylic position, therefore, the chemoselective protection of the C12 hydroxy group in (+)-**12** was attempted. Installation of a TBS group only on the C12 hydroxy group was problematic even at low temperature with slow addition of reagent (C12 *O*-TBS: 75%, C13 *O*-TBS: 18%). The use of the more bulky TIPS group successfully provided C12 *O*-TIPS (−)-**18**[12] in good yield (90%), with no formation of the C13 *O*-TIPS compound.



Scheme 5. Synthesis of (+)-**4** and (−)-**5**. Reagents and conditions: (a) (1) (*R*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1); (2) TBAF, THF, 70 °C, 3 h [63% from (+)-**14**]; (b) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (67%); (c) (1) (*R*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1), (2) TBAF, THF, 70 °C, 3 h [57% from (−)-**14**]; (d) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (51%).



Scheme 6. Synthesis of (+)-**17**. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 8 h (90%); (b) (1) $ClCH_2SO_2Cl$, pyridine, 0 °C, 2 h; (2) CsOAc, 18-crown-6, benzene, 80 °C, 20 h (83%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 5 min (97%); (d) (*S*)-BINAL-H, THF, −78 °C, 90 min (99%, dr >20:1); (e) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, rt, 45 h (94%).

Next, we attempted inversion of the hydroxy group at C13. Failure of the normal conditions for Mitsunobu inversion[16] (DEAD, benzoic acid, PPh_3) necessitated the use of the new Mitsunobu conditions[17] (TMAD, *p*-nitrobenzoic acid, PBu_3), which gave the (13*S*)-compound in 55% yield. Unfortunately, this method presents difficulties for large-scale synthesis. We next attempted a stepwise reaction to construct a leaving group before inversion by nucleophilic attack. While a methanesulfonyl group would be ideal as a leaving group, Corey's conditions[18] using K_2O are too strong to get an inversion product. Fortunately, a small conversion with CsOAc provided an insight in the search for another leaving group. On the basis of this information, Nakata's method,[19] using a monochloromethanesulfonyl group ($ClSO_2CH_2Cl$, pyridine) followed by treatment with CsOAc, gave the protected C12–C13 *anti*-diol (−)-**19** in good yield.

In order to derive the alcohol group from the ketone, deprotection of the dithioacetal furnished enone (−)-**20**. The stereoselective reduction of the ketone at C9 in (−)-**20** required the reoptimization of reaction conditions due to the presence of the bulky *O*-TIPS group. While (*R*)-CBS reduction furnished (−)-**21**[12] in good selectivity (diastereoselectivity 16:1), (*S*)-BINAL-H was found to be more efficient[12] (diastereoselectivity >20:1). Finally deprotection of the acetyl and *tert*-butyl groups by hydrolysis and desilylation with TBAF gave (+)-**17** (Scheme 6).

3.7. Synthesis of the remaining stereoisomers

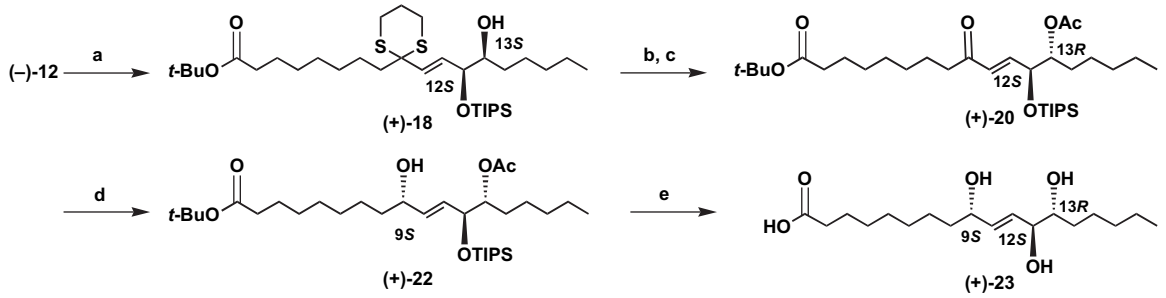
Synthesis of (+)-**23** with 9*S*,12*S*,13*R* stereocenters was accomplished according to the following synthetic route, utilizing (−)-**12** as the starting material (Scheme 7). It should be noted that the stereoselectivity of the (*S*)-BINAL reduction of (+)-**20** was lower than that of (−)-**20** (diastereoselectivity 13:1). The reason for this phenomenon is explained by the steric hindrance of the C12 *O*-TIPS group. With the completion of the syntheses for the C12–C13 *anti*-diols as shown in Schemes 7 and 8, all the stereoisomers of pinellic acid have now been prepared from their corresponding intermediates.[12]

4. Stereochemistry of the allylic 1,2-diol

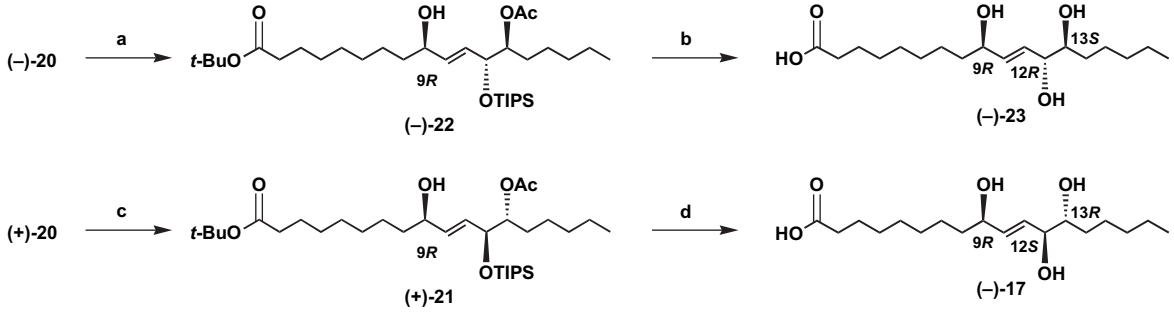
The syntheses of both allylic *syn*- and *anti*-1,2-diols of pinellic acid have been established and it is critical for the stereochemistries of the C12–C13 diols to be confirmed. The protection of the C12–C13 diol of (+)-**12** with 2-methoxypropene and CSA afforded (+)-**24**. In the ^1H NMR spectrum, an NOE between H11 and H13 resonances is observed, suggesting that H12 and H13 of (+)-**24** are antiperiplanar (Scheme 9, Fig. 6).

Deprotection of the OAc and *O*-TIPS groups in (−)-**19** afforded (+)-**26**. This was followed by acetalization of the C12–C13 diol to give (+)-**27**. In the ^1H NMR spectrum, while there is an NOE between protons H11 and H12, there is no NOE between protons H11 and H13, indicating that H12 and H13 of (+)-**27** are synperiplanar (Scheme 10, Fig. 7).

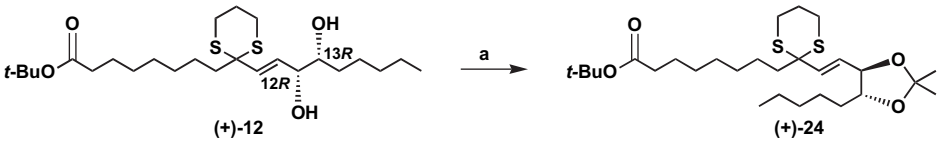
These studies have established a new method to determine the configuration of allylic 1,2-diols.



Scheme 7. Synthesis of (+)-**23**. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 8 h (79%); (b) (1) $ClCH_2SO_2Cl$, pyridine, 0 °C, 1 h; (2) CsOAc, 18-crown-6, benzene, 80 °C, 20 h (75%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 5 min (89%); (d) (*S*)-BINAL-H, THF, −78 °C, 1 h (99%, dr 13:1); (e) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, 45 h (98%).



Scheme 8. Synthesis of (−)-**23** and (−)-**17**. Reagents and conditions: (a) (*R*)-BINAL-H, THF, −78 °C, 1 h (82%, dr 13:1); (b) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, 45 h (94%); (c) (*R*)-BINAL-H, THF, −78 °C, 1 h (98%, dr >20:1); (d) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, 45 h (18%).



Scheme 9. Synthesis of (+)-**24**. Reagents and conditions: (a) 2-methoxypropene, CSA, CH_2Cl_2, 0 °C, 5 min (96%).

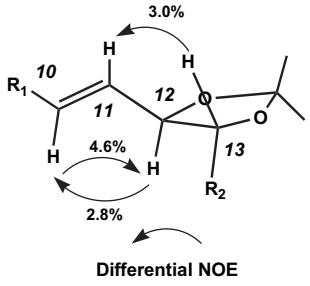


Figure 6. NOE analysis of (+)-**24**.

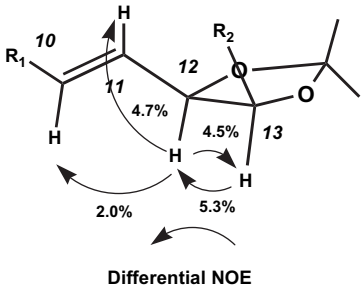


Figure 7. NOE analysis of (+)-**27**.

5. Comparison of spectral data of all the stereoisomers of pinellic acid

Comparison of the ^{1}H NMR spectra of all synthetic stereoisomers of pinellic acid (Fig. 8) shows a relationship between the stereochemistry and the pattern of the ^{1}H NMR resonances. Focusing on the peaks of C12–C13 diol, the H13 proton in the *syn*-diol is at higher field than in the *anti*-diol. Moreover, the peak patterns of H10 and H11 are opposite in the *anti*- and *syn*-diols. The relationship between the stereochemistry of C9 and C12 and the coupling pattern of H10 and H11 is also interesting. When the configuration of C9 and C12 is the same (*S*,*S* or *R*,*R*), the chemical shifts of H10 and H11 (two doublet of doublets) are very close. When the configuration is different, the chemical shifts of H10 and H11 are further apart.

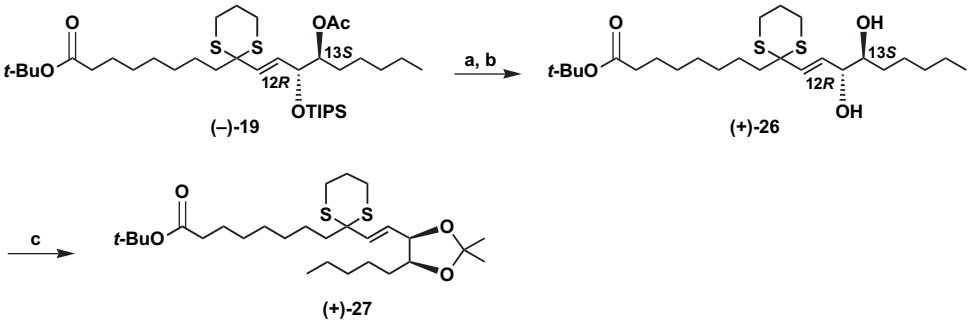
This type of information could never have been discovered until all the stereoisomers had been synthesized. Syntheses of fatty acids like pinellic acid could contribute to the determination of stereochemistry of molecules of the same type as **1**.[6]

6. Adjuvant activity of all the stereoisomers of pinellic acid

The oral administration of pinellic acid analogs as an adjuvant for the intranasal inoculation of influenza HA vaccine was investigated. Mice were orally administered with pinellic acid analogs (1 g/mouse) using intragastric gavage followed by the intranasal inoculation of HA vaccine (1 g/mouse). Three weeks later, the same procedure was repeated. The IgA and IgG antibody responses against anti-influenza virus in the nasal cavity and serum in the vaccinated mice were examined one week after vaccination. The results of the adjuvant activity of all stereoisomers are shown in Figure 9.[20]

The antiviral IgA and IgG antibody responses, induced in the nasal cavities of mice given pinellic acid (−)-**1** with vaccine, were enhanced 5.2- and 2-folds, respectively, compared with control mice given the vaccine and solvent alone. Among the C9 isomers of pinellic acid, the (9*S*)-compounds showed much stronger activity compared with the (9*R*)-compounds. Thus, stereochemistry at the C9 hydroxyl group is critical for adjuvant activity. Among the (9*S*)-derivatives, the adjuvant activities of the C13 (*S*)-compounds were stronger than that of the C13 (*R*)-compounds, while the stereochemistry of the C12 hydroxyl group was not important for adjuvant activity. It is interesting that the adjuvant activity of the enantiomer of natural pinellic acid is weaker than that of the natural one.

Also, in the data shown in Figure 9, the adjuvant activity of pinellic acid (−)-**1** from a natural source was lower than that of the synthetic one. This result is presumably due to the chemical purity of the available sample.



Scheme 10. Synthesis of (+)-**27**. Reagents and conditions: (a) KO*t*-Bu, *t*-BuOH, rt, 16 h (47%); (b) TBAF, THF, rt, 16 h (97%); (c) 2-methoxypropene, CSA, CH_2Cl_2, 0 °C, 20 min (98%).

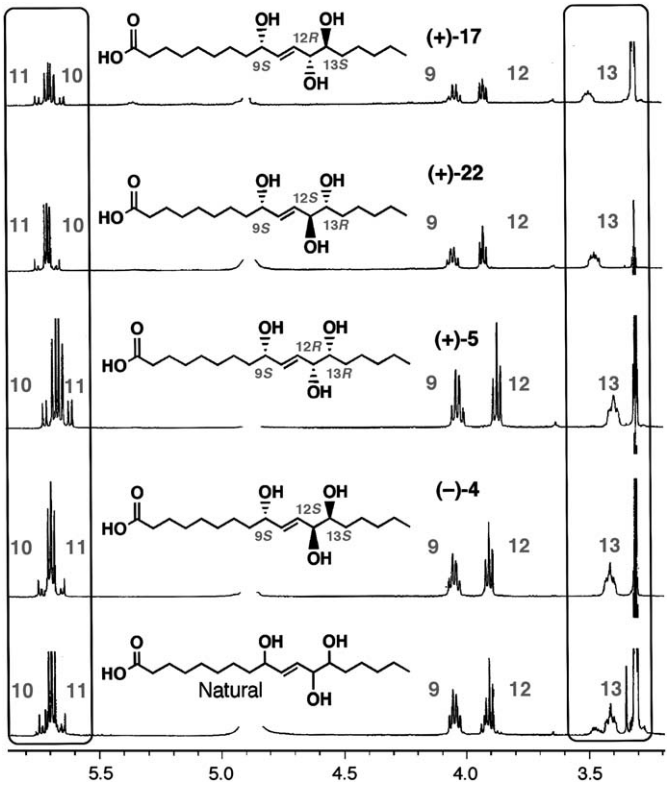


Figure 8. ^{1}H NMR spectra of all stereoisomers of pinellic acid.

In conclusion, we have established synthetic routes to prepare all the stereoisomers of **1** via regioselective asymmetric dihydroxylation, stereoselective inversion, and stereoselective reduction. In this series, the (9*S*,12*S*,13*S*)-compound has the most potent adjuvant activity. Studies on the mechanism of adjuvant and protective effects of

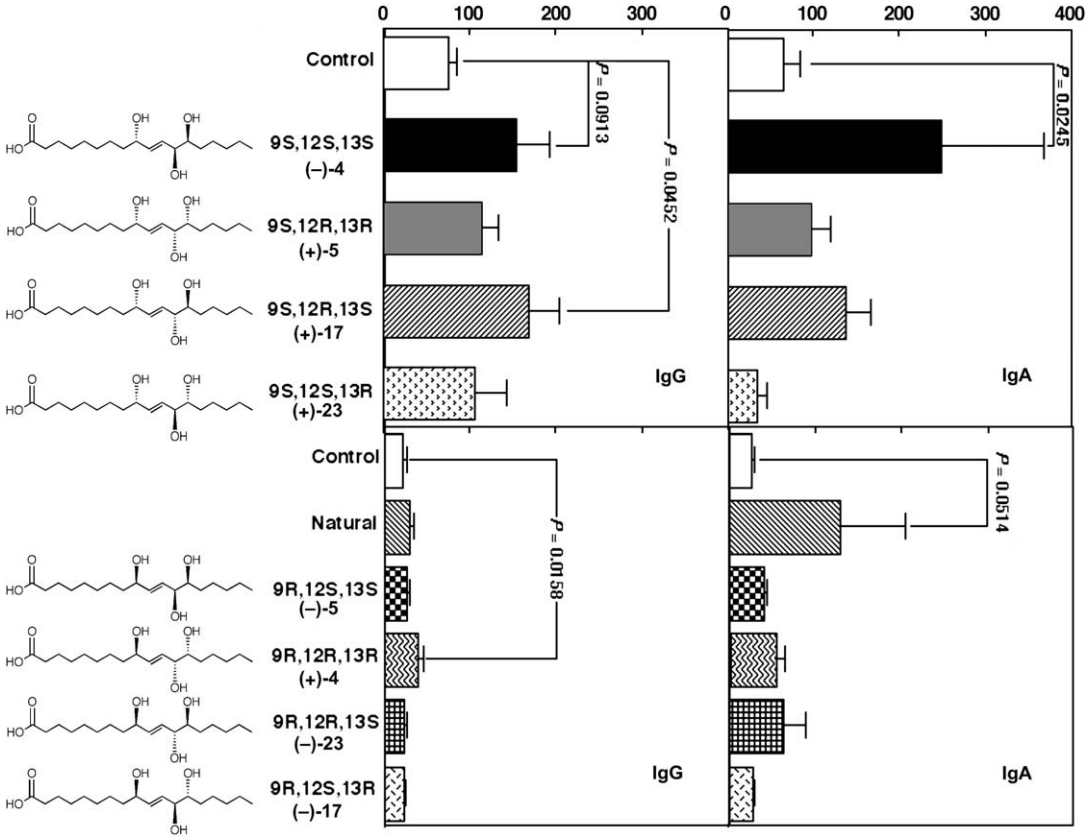


Figure 9. Anti-influenza virus antibody titer (fluorescence intensity).

pinellic acid with nasal influenza HA vaccine against influenza virus infection are currently under way.

7. Experimental

7.1. General

Dry THF, toluene, ethyl ether, and CH_2Cl_2 were purchased from Kanto Chemical Co. Precoated silica gel plates with a fluorescent indicator (Merck 60 F_{254}) were used for analytical and preparative thin-layer chromatography. Flash column chromatography was carried out with Merck silica gel 60 (Art. 1.09385). ^1H and ^{13}C NMR spectra were measured on JEOL JNM-EX270 (270 MHz) or Varian VXR-300 (300 MHz) or Varian XL-400 (400 MHz) or Varian UNITY-400 (400 MHz). All infrared spectra were measured on a Horiba FT-210 spectrometer. Melting points were measured on a Yanagimoto Micro Melting Apparatus. High- and low-resolution mass spectra were measured on a JEOL JMS-DX300 and JEOL JMS-AX505 HA spectrometer. Elemental analysis data were measured on a Yanaco CHN CORDER MT-5.

7.2. Estimation of absolute stereochemistry of 1

7.2.1. 12,13-*O*-Isopropylidene-9,12,13-trihydroxyoctadecaenoic acid methyl ester (2). To a solution of pinellic acid (**1**, 9.6 mg, 29 μmol) in benzene/MeOH (10:1) (2.2 mL) was added $TMSCHN_2$ (2.0 M solution in hexane, 29 μL, 58 μmol) and stirred at rt for 2.5 h, after that time the solution was concentrated. To the solution of residue in CH_2Cl_2 (0.6 mL) were added 2,2-dimethoxypropane (14 μL, 0.12 mmol) and PPTS (7.3 mg, 29 μmol), and then stirred at 60 °C for 48 h. The solution was cooled to rt and treated with H_2O (500 μL) followed by extraction with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (3 mL), dried, and evaporated, and the residue was purified by column chromatography (hexane/AcOEt=7:1) to give **2** (11 mg, 100%) as a colorless oil. R_f=0.48 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{28}$ 0.00 (*c* 0.15, MeOH); IR (KBr) ν cm^{-1}: 3452, 1741; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.84 (dd, *J*=15.5, 5.6 Hz, 1H), 5.65 (dd, *J*=15.5, 7.1 Hz, 1H), 4.16 (m, 1H), 4.00 (dd, *J*=8.0, 7.1 Hz, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 2.30 (t, *J*=7.6 Hz, 2H), 1.63–1.24 (m, 20H), 1.412, 1.405 (s, 3H each), 0.89 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 137.9, 127.4, 108.4, 81.8, 80.9, 71.8, 51.4, 37.1, 34.1, 31.9, 31.9, 29.3, 29.14, 29.05, 27.3, 27.0, 25.8, 25.2, 24.9, 22.5, 14.0; HRMS (FAB, NBA matrix) *m/z*: 407.2742 $[M+Na]^+$, Calcd for $C_{22}H_{40}O_5Na$: 407.2773 [M+Na].

7.2.2. 9-(4-Bromobenzoyloxy)-12,13-*o*-isopropylidene-12,13-dihydroxyoctadecaenoic acid methyl ester (3). To a solution of **2** (1.0 mg, 2.6 μmol) in pyridine were added *p*-bromobenzoyl chloride (5.5 mg, 26 μmol) and DMAP (0.3 mg, 26 μmol), and then stirred at rt for 10 h. The resulting mixture was treated with H_2O (0.5 mL) and extracted with $CHCl_3$ (3 mL×3). The organic layer was washed with satd aq NaCl (2 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=5:1) to give **3** (1.0 mg, 68%) as a colorless oil. R_f=0.60 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{22}$ −10.0 (*c* 0.06, $CHCl_3$); CD (*c* 5.3×10^{-5}, MeOH) λ_{max} ($\Delta\varepsilon$): 244.8 (+6.97), 220.8 (+2.13), 209.1 (+5.97); IR (KBr) ν cm^{-1}: 1724, 1633; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J*=8.9 Hz, 2H), 7.58 (d, *J*=8.9 Hz, 2H), 5.84 (dd, *J*=15.2 Hz, 1H), 5.76 (dd, *J*=15.2, 6.8 Hz, 1H), 5.50 (dt, *J*=7.0, 6.0 Hz, 1H), 3.99 (dd, *J*=8.5, 6.8 Hz, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 2.29 (t, *J*=7.9 Hz, 2H), 1.21–1.79 (m, 20H), 1.41, 1.40 (s, 3H each), 0.88 (t, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9, 131.7 (2C), 131.1 (2C), 130.7, 81.6, 80.8, 74.7, 51.4, 34.3, 34.0, 31.9, 31.9, 29.3, 29.2 (2C), 27.3, 27.0, 25.6, 25.0, 24.9, 22.5, 14.0; HRMS (FAB, NBA matrix), *m/z*: 589.2149 $[M+Na]^+$, Calcd for $C_{29}H_{43}O_6BrNa$: 589.2141 [M+Na].

7.3. Total synthesis

7.3.1. Synthesis of C18 skeleton.

7.3.1.1. *tert*-Butyl-7-methoxycarbonylheptanoate (7). To a solution of suberic acid monomethyl ester (**6**, 5.00 mL, 5.24 g, 27.8 mmol) in *t*-BuOH (56 mL) were added $(Boc)_2O$ (9.58 mL, 41.7 mmol) and DMAP (1.02 g, 0.34 mmol). The mixture was stirred at rt for 1 h. The resulting mixture was treated with 0.2 N HCl (20 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=10:1) to give **7** (5.58 g, 82%) as a colorless oil. R_f=0.41(silica gel, hexane/AcOEt=5:1); IR (KBr) ν cm^{-1}: 1734; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.62 (s, 3H), 2.26 (t, *J*=7.3 Hz, 2H), 2.16 (t, *J*=7.3 Hz, 2H), 1.51–1.61 (complex m, 4H), 1.40 (s, 9H), 1.31–1.21 (complex m, 4H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 174.1, 173.0, 79.8, 51.3, 35.4, 33.9, 28.7, 28.6, 28.0 (3C), 24.8, 24.7; HRMS (FAB NBA matrix) *m/z*: 245.1750 $[M+H]^+$, Calcd for $C_{13}H_{25}O_4$: 245.1753 [M+H].

7.3.1.2. *tert*-Butyl-8-iodooctanoate (8). To a solution of 1.5 N NaOH in MeOH/H_2O/THF (3:1:1) (113 mL) was added **7** (5.51 g, 22.6 mmol) and stirred at rt for 28 h. The mixture was treated with 1.0 N HCl (50 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated.

The residue was dissolved in THF (41.6 mL) at 0 °C. To the mixture was added BH_3·THF (1.0 M solution in THF, 20.8 mL), after that time, the solution was warmed up to rt and stirred at rt for 12 h. The resulting mixture was treated with satd aq $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated.

The residue was dissolved in CH_2Cl_2 (100 mL) at 0 °C. To the mixture were added imidazole (2.10 g, 30.9 mmol), PPh_3 (8.10 g, 30.9 mmol), and I_2 (6.27 g, 24.7 mmol), after that time, the solution was warmed up to rt and stirred at rt for 2 h. The resulting mixture was treated with satd aq $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with H_2O (50 mL), 0.1 N Na_2SO_3 soln (50 mL), 30% aq H_2O_2 (50 mL), satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give **8** (5.53 g, 77% from **7**) as

a colorless oil. R_f=0.47 (silica gel, hexane/AcOEt=4:1); IR (KBr) ν cm^{-1}: 1730; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.18 (t, J=7.3 Hz, 2H), 2.20 (t, J=7.6 Hz, 2H), 1.76–1.87 (complex m, 2H), 1.53–1.60 (complex m, 2H), 1.44 (s, 9H), 1.26–1.41 (complex m, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.0, 79.8, 35.4, 33.3, 30.2, 29.0, 28.7, 28.1, 28.0 (3C), 24.9; HRMS (EI) m/z: 326.0763 $[M]^+$, Calcd for $C_{12}H_{23}O_2I$: 326.0743 [M].

7.3.1.3. (*E*,*E*)-1-(1,3-Dithian)-2,4-decadiene (10). To a solution of (*E*,*E*)-2,4-decadienal (**9**, 21.4 g, 25.0 mL, 141 mmol) in CH_2Cl_2 (140 mL) at 0 °C were added 1,3-propanedithiol (18.3 g, 17.0 mL, 169 mmol) and $BF_3\cdot Et_2O$ (3.92 g, 3.40 mL, 27.6 mmol), and then the reaction mixture was warmed up to rt, stirred for 12 h. The resulting mixture was treated with satd aq $NaHCO_3$ (200 mL) and extracted with $CHCl_3$ (100 mL×3). The organic layer was washed with satd aq NaCl (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=100:1) to give **10** (32.7 g, 96%) as a colorless oil. R_f=0.52 (silica gel, hexane/AcOEt=5:1); IR (KBr) ν cm^{-1}: 1653; ^1H NMR (270 MHz, $CDCl_3$) δ: 6.34 (dd, J=15.2, 10.6 Hz, 1H), 5.99 (dd, J=15.2, 10.6 Hz, 1H), 5.73 (dt, J=15.2, 7.2 Hz, 1H), 5.59 (dd, J=15.2, 7.9 Hz, 1H), 4.66 (d, J=7.9 Hz, 1H), 2.96–2.79 (complex m, 4H), 2.23–2.02 (complex m, 3H), 1.91–1.77 (m, 1H), 1.39–1.19 (complex m, 6H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 137.3, 133.9, 128.8, 126.8, 47.6, 32.8, 31.3, 30.2 (2C), 29.0, 25.1, 22.5, 14.0; HRMS (EI) m/z: 242.1169 $[M]^+$, Calcd for $C_{13}H_{22}O_2$: 242.1163 [M].

7.3.1.4. (*E*,*E*)-9-(1,3-Dithian)-10,12-octadecadienoic acid-*tert*-butyl ester (11). To a solution of **10** (200 μL, 206 mg, 0.851 mmol) in THF (8.5 mL) was added *n*-BuLi (1.53 M solution in hexane, 612 μL, 0.936 mmol) at −78 °C dropwise (ca. 15 min). The resulting mixture was stirred at −78 °C for 1 h followed by the addition of **8** (327 μL, 416 mg, 1.28 mmol) in one portion. The reaction mixture was stirred at −78 °C for 1 h, after that time, the solution was treated with satd aq NH_4Cl (10 mL) and extracted with AcOEt (10 mL×3). The organic layer was washed with satd aq NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=100:1) to give **11** (318 mg, 85%) as a colorless oil. R_f=0.36 (silica gel, hexane/AcOEt=20:1, twice); IR (KBr) ν cm^{-1}: 1730, 1695; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.39 (dd, J=15.2, 10.4 Hz, 1H), 6.12 (dd, J=14.9, 10.4 Hz, 1H), 5.76 (dt, J=14.9, 7.2 Hz, 1H), 5.54 (d, J=15.2 Hz, 1H), 2.88 (ddd, J=14.0, 11.2, 2.5 Hz, 2H), 2.64 (ddd, J=14.0, 5.2, 3.0 Hz, 2H), 2.18 (t, J=7.2 Hz, 2H), 2.12–2.06 (m, 2H), 2.05–1.98, 1.93–1.91 (m, 1H each), 1.82–1.78 (m, 2H), 1.59–1.52 (m, 2H), 1.47–1.36 (complex m, 4H), 1.44 (s, 9H), 1.34–1.19 (complex m, 10H), 0.89 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 173.2, 135.5, 133.8, 133.6, 129.0, 79.8, 54.9, 42.3, 35.5, 32.6, 31.4, 29.5, 29.0 (2C), 28.9, 28.1 (3C), 27.2 (2C), 25.5, 25.0, 23.7, 22.5, 14.0; HRMS (EI) m/z: 440.2779 $[M]^+$, Calcd for $C_{25}H_{44}O_2S_2$: 440.2783 [M].

7.3.2. Synthesis of (9*S*,12*S*,13*S*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((−)-4).

7.3.2.1. (12*S*,13*S*)-(*E*)-12,13-Dihydroxy-9-(1,3-dithian)-10-octadecaenoic acid-*tert*-butyl ester ((−)-12). A well-stirred solution of (DHQ)PHAL(DHQ)$Me^+\cdot I^-$ (10.0 mg, 11.0 μmol), $K_3[Fe(CN)_6]$ (264.4 mg, 0.803 mmol), K_2CO_3 (110.8 mg, 0.803 mmol), and $K_2OsO_4\cdot 2H_2O$ (4.0 mg, 0.011 mmol) in *t*-BuOH/H_2O (1:1) (2.6 mL) was treated with methanesulfonamide (25.5 mg, 0.268 mmol) at ambient temperature. The clear yellow solution was cooled to 0 °C and **11** (117.8 mg, 0.268 mmol) was added. The solution was stirred vigorously at 0 °C for 40 h 50 min and then quenched with solid Na_2SO_3 (50 mg), warmed to ambient temperature, and stirred for further 30 min. The resultant mixture was extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=1:1) to give (−)-**12** (81.2 mg, 64%, 95% ee) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{24}$ −4.5 (*c* 1.08, $CHCl_3$); IR (KBr) ν cm^{-1}: 3421, 1730, 1628; ^1H NMR (270 MHz, $CDCl_3$) δ: 5.91 (dd, J=15.5, 6.6 Hz, 1H), 5.75 (d, J=15.5 Hz, 1H), 4.04 (dd, J=6.6, 5.3 Hz, 1H), 4.01–3.00 (m, 1H), 2.87 (ddd, J=14.2, 11.5, 2.6 Hz, 2H), 2.68–2.63 (m, 2H), 2.35 (br s, 1H), 2.26 (br s, 1H), 2.19 (t, J=7.3 Hz, 2H), 2.06–2.01 (m, 2H), 1.93–1.88 (m, 2H), 1.67–1.28 (complex m, 18H), 1.44 (s, 9H), 0.89 (t, J=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.8, 136.5, 133.6, 80.4, 75.9, 75.1, 54.7, 42.4, 35.9, 33.5, 32.3, 29.8, 29.4, 29.3, 28.5 (3C), 27.5 (2C), 25.8, 25.6, 25.4, 24.0, 22.9, 14.4; HRMS (FAB, NaI matrix), m/z: 497.2743 $[M+Na]^+$, Calcd for $C_{25}H_{46}O_4S_2Na$: 497.2735 [M+Na].

7.3.2.2. (12*S*,13*S*)-(*E*)-9-(1,3-Dithian)-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-13). To a solution of (−)-**12** (372 mg, 0.787 mmol) in CH_2Cl_2 (7.9 mL) were added 2,6-lutidine (916 μL, 7.87 mmol) and TBSOTf (900 μL, 3.93 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. The resultant mixture was treated with H_2O (1 mL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=100:1) to give (−)-**13** (489 mg, 89%) as a colorless oil. R_f=0.60 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{24}$ −24.1 (*c* 1.01, $CHCl_3$); IR (KBr) ν cm^{-1}: 3442, 1731, 1630; ^1H NMR (270 MHz, $CDCl_3$) δ: 5.98 (dd, J=15.2, 6.6 Hz, 1H), 5.59 (d, J=15.8 Hz, 1H), 4.24 (m, 1H), 3.59 (m, 1H), 2.98–2.87 (complex m, 1H), 2.86–2.64 (complex m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.00–1.87 (complex m, 2H), 1.80 (m, 2H), 1.44 (s, 9H), 1.67–1.14 (complex m, 18H), 0.91–0.86 (complex m, 21H), 0.11–0.03 (m, 12H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 133.4, 133.0, 79.9, 75.5, 75.0, 55.0, 42.3, 35.6, 31.9, 31.1, 29.6, 29.1 (2C), 28.1 (3C), 27.1, 27.0, 26.0, 25.8 (3C), 25.7, 25.1, 23.7, 22.5, 18.2, 18.0, 14.0, −4.1, −4.6 (2C), −4.8; HRMS (FAB, NBA matrix), m/z: 701.4539 $[M]^+$, Calcd for $C_{37}H_{74}O_4Si_2S_2$: 702.4534 [M].

7.3.2.3. (12*S*,13*S*)-(*E*)-9-Oxo-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-14). To a mixture of (−)-**13** (494 mg, 0.704 mmol) and $CaCO_3$ (141 mg, 1.41 mmol) in THF (14 mL) was added a solution of $Hg(ClO_4)_3$ (638 mg, 1.41 mmol) in H_2O (2.8 mL) dropwise. The resultant mixture was stirred at rt for 30 min, and then diluted with ether (5 mL). This mixture was filtered through Celite. The residue was concentrated and dissolved in $CHCl_3$ (5 mL). This solution was washed with satd aq

NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give (−)-**14** (357 mg, 83%) as a colorless oil. R_f=0.55 (silica gel, hexane/AcOEt=6:1); $[\alpha]_D^{27}$ −49.7 (*c* 0.99, $CHCl_3$); IR (KBr) ν cm^{-1}: 1733, 1677, 1633; ^1H NMR (270 MHz, $CDCl_3$) δ: 6.97 (dd, *J*=16.2, 3.6 Hz, 1H), 6.29 (d, *J*=16.2 Hz, 1H), 4.31 (m, 1H), 3.61 (m, 1H), 2.55 (t, *J*=7.3 Hz, 2H), 2.19 (t, *J*=7.6 Hz, 2H), 1.44 (s, 9H), 1.67–1.18 (complex m, 18H), 0.92–0.89 (complex m, 18-H_3), 0.09–0.03 (m, 12H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 201.2, 173.7, 146.4, 129.8, 80.3, 76.2, 75.0, 40.7, 36.0, 32.2, 31.6, 29.6 (2C), 29.4, 28.6 (3C), 26.4, 26.3 (3C), 26.2 (3C), 25.5, 24.9, 23.0, 18.6, 18.4, 14.4, −3.8, −4.0, −4.3 (2C), −4.4.

7.3.2.4. (9*S*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-15). To a solution of (−)-**14** (349.0 mg, 0.570 mmol) in THF (11 mL) was added (*S*)-BINAL-H (0.5 M solution in THF, 7.52 mL, 3.76 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h 30 min. The resultant mixture was treated with 1.0 N HCl (10 mL) and extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with 1.0 N NaOH (20 mL), satd aq NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in THF (5.8 mL) at rt. To the mixture was added TBAF (1.0 M solution in THF, 1.25 mL, 1.25 mmol) and stirred at 70 °C for 3 h. This resultant mixture was treated with H_2O (1.0 mL) and extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with satd aq NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (toluene/AcOEt=2:1) to give (−)-**15** (168.1 mg, 76%) as a colorless oil. R_f=0.29 (silica gel, toluene/AcOEt=1:2); $[\alpha]_D^{27}$ −8.8 (*c* 0.16, $CHCl_3$); IR (KBr) ν cm^{-1}: 3305, 1727; ^1H NMR (270 MHz, $CDCl_3$) δ: 5.83 (dd, *J*=15.5, 5.6 Hz, 1H), 5.67 (dd, *J*=15.5, 5.9 Hz, 1H), 4.15 (dd, *J*=12.2, 5.9 Hz, 1H), 3.94 (t, *J*=5.93 Hz, 1H), 3.47 (m, 1H), 2.34 (br s, 1H), 2.26 (br s, 1H), 2.19 (t, *J*=7.6 Hz, 2H), 1.63 (m, 2H), 1.44 (s, 9H), 1.52–1.30 (complex m, 18H), 0.98 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 136.2, 129.7, 79.9, 75.3, 74.6, 72.0, 37.1, 35.6, 32.9, 31.8, 29.2, 29.1, 28.9, 28.1, 25.3, 25.2, 25.0, 22.6, 14.0; HRMS (FAB, NBA matrix), *m/z*: 409.2913 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.2.5. (9*S*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-4). To a solution of 2.0 N KOH in EtOH/H_2O (4:1) (500 μL) was added (−)-**15** (6.5 mg, 16.8 μmol) and stirred at rt for 46 h. The mixture was cooled to 0 °C, treated with 1.0 N HCl (500 μL), and extracted with $CHCl_3$ (2 mL×3). The organic layer was washed with satd aq $NaHCO_3$ (5 mL), satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography ($CHCl_3$/MeOH=10:1) to give (−)-**4** (4.5 mg, 82%) as a white solid. R_f=0.24 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 104–106 °C (MeOH); $[\alpha]_D^{25}$ −8.0 (*c* 0.30, MeOH), {natural; $[\alpha]_D^{28}$ −8.1 (*c* 0.32, MeOH)}; IR (KBr) ν cm^{-1}: 3372 (s), 1695 (m), 1637 (m); ^1H NMR (400 MHz, CD_3OD) δ: 5.72 (dd, *J*=15.5, 5.0 Hz, 1H), 5.67 (dd, *J*=15.5, 5.0 Hz, 1H), 4.05 (ddd, *J*=6.5, 6.0, 5.0 Hz, 1H), 3.91 (dd, *J*=5.5, 5.0 Hz, 1H), 3.41 (ddd, *J*=8.5, 5.5, 2.5 Hz, 1H), 2.27 (t, *J*=7.5 Hz, 2H), 1.60 (dt, *J*=7.5, 7.0 Hz, 2H), 1.55–1.50 (m, 4H), 1.45–1.25 (m, 14H), 0.91 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 177.8, 136.6, 131.1, 76.5, 75.8, 73.0, 38.3, 35.0, 33.6, 33.1, 30.5, 30.4, 30.2, 26.6, 26.5, 26.1, 23.7, 14.4; HR-FABMS *m/z*: 353.2305 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na]; Anal. Calcd for $C_{18}H_{34}O_5 \cdot 1/2H_2O$: C, 63.69; H, 10.39. Found: C, 63.77; H, 10.03.

7.3.3. Synthesis of (9*S*,12*R*,13*R*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((+)-5).

7.3.3.1. (12*R*,13*R*)-(*E*)-12,13-Dihydroxy-9-(1,3-dithian)-10-octadecaenoic acid-*tert*-butyl ester ((+)-12). A well-stirred solution of AD-mix-β (1.68 g) in *t*-BuOH/H_2O (1:1) (1.2 mL) was treated with methanesulfonamide (25.5 mg, 0.268 mmol) at ambient temperature. The clear yellow solution was cooled to 0 °C and **11** (528 mg, 1.20 mmol) was added. The solution was stirred vigorously at 0 °C for 73 h and then quenched with solid Na_2SO_3 (500 mg), warmed to ambient temperature, and stirred for further 30 min. The resultant mixture was extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with satd aq NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=1:1) to give (+)-**12** (424 mg, 75%) as a colorless oil. $[\alpha]_D^{24}$ +5.2 (*c* 1.08, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 497.2740 $[M+Na]^+$, Calcd for $C_{25}H_{46}O_4S_2Na$: 497.2735 [M+Na].

7.3.3.2. (12*R*,13*R*)-(*E*)-9-(1,3-Dithian)-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-13). According to the synthesis of (−)-**13**, (+)-**12** (77.9 mg) gave (+)-**13** (115 mg, 87%) as a colorless oil. $[\alpha]_D^{27}$ +22.4 (*c* 0.41, $CHCl_3$); HRMS (FAB, NBA matrix), *m/z*: 701.4534 $[M]^+$, Calcd for $C_{37}H_{74}O_4Si_2S_2$: 704.4534 [M].

7.3.3.3. (12*R*,13*R*)-(*E*)-9-Oxo-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-14). According to the synthesis of (−)-**14**, (+)-**13** (93.8 mg) gave (+)-**14** (67.4 mg, 83%) as a colorless oil. $[\alpha]_D^{27}$ +22.4 (*c* 0.41, $CHCl_3$).

7.3.3.4. (9*S*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-16). According to the synthesis of (−)-**15**, (+)-**14** (26.1 mg) gave (+)-**16** (12.4 mg, 76%) as a colorless oil. R_f=0.20 (silica gel, toluene/AcOEt=1:2), $[\alpha]_D^{28}$ +7.4 (*c* 0.19, $CHCl_3$); IR (KBr) ν cm^{-1}: 3392 (s), 1732 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 5.83 (dd, *J*=15.5, 5.6 Hz, 1H), 5.67 (dd, *J*=15.5, 5.9 Hz, 1H), 4.15 (dd, *J*=12.2, 5.9 Hz, 1H), 3.94 (1H, t, *J*=5.93 Hz, 1H), 3.47 (m, 1H), 2.34 (br s, 1H), 2.26 (br s, 1H), 2.19 (t, *J*=7.6 Hz, 2H), 1.63 (m, 2H), 1.44 (s, 9H), 1.52–1.30 (complex m, 18H), 0.98 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 136.2, 129.7, 79.9, 75.3, 74.6, 72.0, 37.1, 35.6, 32.9, 31.8, 29.2, 29.1, 28.9 (2C), 28.1 (3C), 25.3, 25.2, 25.0, 22.6, 14.0; HRMS (FAB, NBA matrix), *m/z*: 409.2913 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.3.5. (9*S*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-5). According to the synthesis of (−)-**4**, (+)-**16** (12.4 mg) gave (+)-**5** (8.1 mg, 76%) as a white solid. R_f=0.23 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 68–71 °C (MeOH); $[\alpha]_D^{23}$ +29.8 (*c* 0.45, MeOH); IR (KBr) ν cm^{-1}: 3430 (s), 1697 (m), 1632 (m); ^1H NMR (400 MHz, CD_3OD) δ: 5.70 (dd, *J*=15.5, 5.5 Hz, 1H), 5.64 (dd,

J=15.5, 6.0 Hz, 1H), 4.03 (ddd, J=6.5, 6.0, 5.5 Hz, 1H), 3.87 (dd, J=6.0, 5.5 Hz, 1H), 3.40 (ddd, J=7.0, 5.5, 2.0 Hz, 1H), 2.27 (t, J=7.5 Hz, 2H), 1.60 (dt, J=7.5, 7.0 Hz, 2H), 1.55–1.50 (m, 4H), 1.44–1.25 (m, 14H), 0.91 (t, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 178.2, 136.7, 131.3, 76.7, 75.7, 73.2, 38.3, 36.0, 33.8, 33.1, 30.5, 30.4, 30.2, 26.5, 26.5, 26.2, 23.7, 14.4; HR-FABMS m/z: 353.2309 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.4. Syntheses of (9*R*,12*R*,13*R*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((+)-4) and (9*R*,12*S*,13*S*)-trihydroxy-10-octadienoic acid ((−)-5).

7.3.4.1. (9*R*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-15). According to the synthesis of (−)-**15**, the reduction of (+)-**14** (26.1 mg) using (*R*)-BINAL-H gave (+)-**15** (10.8 mg, 63%) as a colorless oil. $[\alpha]_D^{27}$ +6.6 (c 0.21, $CHCl_3$); HRMS (FAB, NBA matrix), m/z: 409.2908 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.4.2. (9*R*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-4). According to the synthesis of (−)-**4**, the deprotection of (+)-**15** (10.8 mg) gave (+)-**4** (4.8 mg, 67%) as a white solid. Mp 98–104 °C (MeOH); $[\alpha]_D^{28}$ +12.9 (c 0.48, MeOH); HR-FABMS m/z: 353.2307 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.4.3. (9*R*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-16). According to the synthesis of (−)-**15**, the reduction of (−)-**14** (10.8 mg) using (*R*)-BINAL-H gave (−)-**16** (8.9 mg, 57%) as a colorless oil. $[\alpha]_D^{27}$ −9.9 (c 0.99, $CHCl_3$); HRMS (FAB, NBA matrix), m/z: 409.2910 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.4.4. (9*R*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-5). According to the synthesis of (+)-**5**, the deprotection of (−)-**16** (8.9 mg) gave (−)-**5** (3.7 mg, 51%) as a white solid. Mp 69–74 °C (MeOH); $[\alpha]_D^{22}$ −24.0 (c 0.30, MeOH); HR-FABMS m/z: 353.2307 [M+Na], Calcd for $C_{18}H_{34}O_5Na$: 353.2304.

7.3.5. Synthesis of (9*S*,12*R*,13*S*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((+)-17).

7.3.5.1. (12*R*,13*R*)-(*E*)-9-(1,3-Dithian)-13-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid *tert*-butyl ester ((−)-18). To a mixture of (+)-**12** (326 mg, 0.689 mmol) and 2,6-lutidine (160 μL, 7.87 mmol) in CH_2Cl_2 (14 mL) was added TIPSOTf (194 μL, 0.723 mmol) dropwise over 20 min at −78 °C. The reaction mixture was stirred at −78 °C for 8 h. The resultant mixture was treated with H_2O (1 mL) and extracted with $CHCl_3$ (10 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give (−)-**18** (391 mg, 90%) as a colorless oil. R_f=0.44 (silica gel, hexane/AcOEt=5:1); $[\alpha]_D^{24}$ −4.8 (c 1.01, $CHCl_3$); IR (KBr) ν cm^{-1}: 3442 (s), 1731 (m), 1630 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.91 (dd, J=15.5, 7.6 Hz, 1H), 5.68 (d, J=15.5 Hz, 1H), 4.16 (dd, J=7.6, 6.9 Hz, 1H), 4.01–3.00 (m, 1H), 2.92–2.77 (m, 2H), 2.69–2.63 (m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.11–1.87 (m, 2H), 1.83–1.67 (m, 2H), 1.67–1.58 (complex m, 18H), 1.42 (s, 9H), 1.15–1.02 (m, 21H), 0.89 (t, J=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 135.7, 133.7, 79.9, 77.3, 75.5, 54.2, 42.2, 35.5, 32.6, 31.9, 29.7, 29.6, 29.1, 29.0, 28.0 (3C), 27.0, 26.9, 25.7, 25.5, 23.9, 22.6, 18.1 (6C), 14.0, 12.5 (3C); HRMS (FAB, NaI matrix) m/z: 653.4061 $[M+Na]^+$, Calcd for $C_{34}H_{66}O_4SiS_2Na$: 653.4070 [M+Na].

7.3.5.2. (12*R*,13*S*)-(*E*)-13-Acetoxy-9-(1,3-dithian)-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-19). To a solution of (−)-**18** (13.0 mg, 0.021 mmol) in pyridine (0.5 mL) was added $ClCH_2SO_2Cl$ (3.9 μL, 0.030 mmol) at 0 °C. The resultant mixture was stirred at 0 °C for 2 h, treated with H_2O (0.5 mL), and successfully extracted with $CHCl_3$ (5 mL×3). The combined organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, and concentrated.

To a solution of the residue of previous reaction in benzene was added CsOAc (19.8 mg, 0.10 mmol) and 18-crown-6 (4.1 mg, 0.021 mmol) at rt. The resultant mixture was warmed, refluxed for 20 h, and then cooled to rt again to treat with H_2O (500 μL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give (−)-**19** (11.5 mg, 83% from (−)-**18**) as a colorless oil. R_f=0.50 (silica gel, hexane/AcOEt=8:1); $[\alpha]_D^{24}$ −21.8 (c 0.87, $CHCl_3$); IR (KBr) ν cm^{-1}: 1734 (s), 1635 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.89 (dd, J=15.5, 6.3 Hz, 1H), 5.69 (d, J=15.5 Hz, 1H), 4.95–4.89 (m, 1H), 4.47 (dd, J=6.3, 2.6 Hz, 1H), 2.93–2.79 (m, 2H), 2.69–2.61 (m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.05 (s, 3H), 2.02–1.87 (m, 2H), 1.83–1.66 (m, 2H), 1.47–1.15 (complex m, 18H), 1.43 (s, 9H), 1.10–0.95 (m, 21H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 170.8, 135.0, 133.1, 79.9, 77.4, 77.2, 54.3, 42.2, 35.5, 31.7, 29.6, 29.1, 29.0 (2C), 28.1 (3C), 27.0, 26.9, 25.5, 25.3, 25.0, 23.8, 22.4, 21.2, 18.0 (6C), 14.0, 12.5 (3C); HRMS (FAB, NaI matrix), m/z: 695.4162 $[M+Na]^+$, Calcd for $C_{36}H_{68}O_5SiS_2Na$: 695.4175 [M+Na].

7.3.5.3. (12*R*,13*S*)-(*E*)-13-Acetoxy-9-oxo-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-20). To a mixture of (−)-**19** (304 mg, 0.452 mmol) and $CaCO_3$ (90.4 mg, 0.904 mmol) in THF (4.5 mL) was added a solution of $Hg(ClO_4)_3$ (410 mg, 0.904 mmol) in H_2O (900 μL) dropwise. The resultant mixture was stirred at rt for 5 min, and then diluted with ether (2 mL). This mixture was filtered through Celite. The residue was concentrated and dissolved in $CHCl_3$ (15 mL). This solution was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=10:1) to give (−)-**20** (250 mg, 97%) as a colorless oil. R_f=0.55 (silica gel, hexane/AcOEt=6:1); $[\alpha]_D^{24}$ −22.0 (c 0.98, $CHCl_3$); IR (KBr) ν cm^{-1}: 1735 (m), 1680 (m), 1633 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.71 (dd, J=15.8, 5.9 Hz, 1H), 6.24 (d, J=15.8 Hz, 1H), 4.93 (m, 1H), 4.48 (dd, J=5.9, 3.6 Hz, 1H), 2.55 (t, J=7.6 Hz, 2H), 2.19 (t, J=7.3 Hz, 2H), 2.04 (s, 3H), 1.73–1.17 (complex m, 18H), 1.44 (s, 9H), 1.12–0.98 (m, 21H), 0.87 (t, J=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 200.3, 173.2, 170.6, 144.6, 130.5, 79.8, 76.4, 74.2, 40.2, 35.5, 31.5, 31.4, 29.0 (2C), 28.9, 28.9, 28.0 (3C), 25.2, 24.9, 24.1, 22.4, 21.0, 17.9 (6C), 13.9, 12.3 (3C); HRMS

(FAB, NaI matrix); *m/z*: 605.4202 [M+Na]$^+$, Calcd for $C_{33}H_{62}O_6SiS_2Na$: 605.4213 [M+Na].

7.3.5.4. (9*S*,12*R*,13*S*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-21). To a solution of (−)-**20** (18.7 mg, 0.033 mmol) in THF (300 μL) was added (*S*)-BINAL-H (0.5 M solution in THF, 215 μL, 0.107 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h 30 min. The resultant mixture was treated with 1.0 N HCl (1 mL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with 1.0 N NaOH (5 mL), satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=10:1) to give (−)-**21** (18.6 mg, 99%) as a colorless oil. R_f=0.44 (silica gel, hexane/AcOEt=4:1); $[\alpha]_D^{25}$ −18.9 (*c* 1.40, $CHCl_3$); IR (KBr) ν cm^{-1}: 1733 (m), 1630 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.69 (dd, *J*=15.8, 5.6 Hz, 1H), 5.62 (dd, *J*=15.8, 5.9 Hz, 1H), 4.93 (m, 1H), 4.29 (dd, *J*=5.9, 3.0 Hz, 1H), 4.11–4.07 (m, 1H), 2.19 (t, *J*=7.3 Hz, 2H), 2.03 (s, 3H), 1.79–1.20 (complex m, 20H), 1.44 (s, 9H), 1.10–0.98 (m, 21H), 0.87 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 170.8, 135.2, 130.2, 79.9, 77.1, 74.8, 72.2, 37.1, 35.5, 31.5, 29.3, 29.2, 29.0, 28.9, 28.1 (3C), 25.3, 25.2, 25.0, 22.5, 21.2, 18.0 (6C), 14.0, 12.4 (3C); HRMS (FAB, NaI matrix), *m/z*: 607.4372 [M+Na]$^+$, Calcd for $C_{33}H_{64}O_6SiNa$: 607.4370 [M+Na].

7.3.5.5. (9*S*,12*R*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-17). To a solution of 1.0 N KOH in EtOH/H_2O (4:1) (500 μL) was added (−)-**20** (17.2 mg, 29.8 μmol) and stirred at rt for 120 h. The mixture was cooled to 0 °C and treated with 1.0 N HCl (500 μL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq $NaHCO_3$ (5 mL), satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated.

To a solution of the residue of previous reaction in THF (10 mL) at 0 °C was added TBAF (1.0 M solution in THF, 30 μL, 29.8 μmol). The resultant mixture was warmed to rt and stirred for 45 h before being treated with satd aq NH_4Cl (500 μL) and extracted with AcOEt (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (AcOEt) to give (+)-**17** (9.3 mg, 94%) as a white solid. R_f=0.23 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 67–70 °C (MeOH); $[\alpha]_D^{25}$ +7.8 (*c* 0.18, MeOH); IR (KBr) ν cm^{-1}: 3421 (s), 1699 (m), 1637 (m); ^{1}H NMR (400 MHz, CD_3OD) δ: 5.72 (dd, *J*=15.8, 5.5 Hz, 1H), 5.66 (dd, *J*=15.8, 6.0 Hz, 1H), 4.04 (ddd, *J*=6.5, 6.0, 5.0 Hz, 1H), 3.91 (dd, *J*=5.5, 4.5 Hz, 1H), 3.49 (ddd, *J*=7.5, 4.5, 2.0 Hz, 1H), 2.27 (t, *J*=7.5 Hz, 2H), 1.60 (dt, *J*=7.6, 6.9 Hz, 2H), 1.55–1.50 (m, 4H), 1.45–1.25 (m, 14H), 0.91 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 177.8, 136.7, 130.9, 76.6, 75.7, 73.3, 38.4, 35.1, 33.7, 33.1, 30.6, 30.4, 30.2, 26.7, 26.5, 26.1, 23.7, 14.4; HR-FABMS *m/z*: 353.2307 [M+Na], Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.6. Syntheses of all the stereoisomers of pinellic acid.

7.3.6.1. (12*S*,13*S*)-(*E*)-9-(1,3-Dithian)-13-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-18). According to the synthesis of (−)-**18**, (−)-**12** (166 mg) gave (+)-**18** (154 mg, 79% based on recovered (−)-**12**) as a colorless oil. $[\alpha]_D^{29}$ +5.9 (*c* 0.37, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 653.4053 [M+Na]$^+$, Calcd for $C_{34}H_{66}O_4SiS_2Na$: 653.4070 [M+Na].

7.3.6.2. (12*S*,13*R*)-(*E*)-13-Acetoxy-9-(1′,3-dithian)-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-19). According to the synthesis of (−)-**19**, (+)-**18** (154 mg) gave (+)-**19** (124 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ +23.6 (*c* 1.10, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 695.4148 [M+Na]$^+$, Calcd for $C_{36}H_{68}O_5SiS_2Na$: 695.4175 [M+Na].

7.3.6.3. (12*S*,13*R*)-(*E*)-13-Acetoxy-9-oxo-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-20). According to the synthesis of (−)-**20**, (+)-**19** (114 mg) gave (+)-**20** (89 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ +22.6 (*c* 0.83, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 605.4201 [M+Na]$^+$, Calcd for $C_{33}H_{62}O_6SiS_2Na$: 605.4213 [M+Na].

7.3.6.4. (9*S*,12*S*,13*R*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-22). According to the synthesis of (−)-**21**, the reduction of (+)-**20** (78.0 mg) using (*S*)-BINAL-H gave (+)-**22** (70.3 mg, 99% based on recovered (+)-**20**) as a colorless oil. R_f=0.43 (silica gel, hexane/AcOEt=4:1); $[\alpha]_D^{25}$ +25.8 (*c*, $CHCl_3$); IR (KBr) ν cm^{-1}: 3439 (s), 1734 (m), 1640 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.71 (m, 2H), 4.86 (m, 1H), 4.28 (dd, *J*=5.3, 4.0 Hz, 1H), 4.13–4.07 (m, 1H), 2.19 (t, *J*=7.3 Hz, 2H), 2.04 (s, 3H), 1.79–1.20 (complex m, 18H), 1.44 (s, 9H), 1.10–0.98 (m, 21H), 0.87 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 170.9, 135.2, 130.5, 79.9, 77.2, 74.8, 72.2, 37.1, 35.5, 31.7, 29.4, 29.3, 29.0 (2C), 28.0 (3C), 25.3, 25.0, 21.2, 21.2, 18.0 (6C), 14.0, 12.4 (3C); HRMS (FAB, NBA matrix), *m/z*: 607.4364 [M+Na]$^+$, Calcd for $C_{33}H_{64}O_6SiNa$: 607.4370 [M+Na].

7.3.6.5. (9*S*,12*S*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-23). According to the synthesis of (+)-**17**, the deprotection of (+)-**22** (45.9 mg) gave (+)-**23** (25.7 mg, 98%) as a white solid. R_f=0.24 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 91–94 °C (MeOH); $[\alpha]_D^{25}$ +6.7 (*c* 0.14, MeOH); IR (KBr) ν cm^{-1}: 3420 (s), 1701 (m), 1637 (m); ^{1}H NMR (400 MHz, CD_3OD) δ: 5.73 (dd, *J*=15.9, 5.0 Hz, 1H), 5.68 (dd, *J*=15.9, 5.5 Hz, 1H), 4.05 (ddd, *J*=6.0, 5.5, 5.0 Hz, 1H), 3.93 (dd, *J*=5.0, 4.5 Hz, 1H), 3.47 (ddd, *J*=8.5, 4.5, 2.1 Hz, 1H), 2.27 (t, *J*=7.5 Hz, 2H), 1.60 (dt, *J*=7.5, 7.0 Hz, 2H), 1.55–1.50 (m, 2H), 1.45–1.25 (m, 16H), 0.91 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 177.7, 136.5, 130.9, 76.5, 75.7, 73.0, 38.3, 34.9, 33.5, 33.1, 30.5, 30.3, 30.2, 26.7, 26.4, 26.1, 23.7, 14.4; HR-FABMS *m/z*: 353.2336 [M+Na]$^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.6.6. (9*R*,12*R*,13*S*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-22). According to the synthesis of (+)-**22**, the reduction of (−)-**20** (67.8 mg) using (*R*)-BINAL-H gave (−)-**22** (55.4 mg, 82%) as a colorless oil.

7.3.6.7. (9*R*,12*R*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-23). According to the synthesis of (+)-**17**, the deprotection of (−)-**22** (26.5 mg) gave (−)-**23**

(14.0 mg, 94%) as a white solid. Mp 88–93 °C (MeOH); $[\alpha]_D^{30}$ −5.3 (*c* 0.15, MeOH); HR-FABMS *m/z*: 353.2307 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.6.8. (9*R*,12*S*,13*R*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-21). According to the synthesis of (−)-**21**, the reduction of (+)-**20** (32.9 mg) using (*R*)-BINAL-H gave (+)-**21** (79.4 mg, 98%) as a colorless oil.

7.3.6.9. (9*R*,12*S*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-17). According to the synthesis of (+)-**17**, the deprotection of (+)-**21** (32.9 mg) gave (−)-**17** (7.5 mg, 18%) as a white solid. Mp 65–74 °C (MeOH); $[\alpha]_D^{30}$ −7.1 (*c* 0.14, MeOH); HR-FABMS *m/z*: 353.2307 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.4. Stereochemistry on allylic 1,2-diol

7.4.1. (12*R*,13*R*)-(*E*)-9-(1,3-Dithian)-12,13-isopropylidenedioxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-24). To a solution of (+)-**12** (47.3 mg, 99.7 μmol) in CH_2Cl_2 (1.0 mL) were added CSA (2.3 mg, 9.97 μmol) and 2-methoxypropene (147 μL, 150 μmol) at 0 °C. The resultant mixture was stirred at 0 °C for 5 min, treated with H_2O (1 mL), and then extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=20:1) to give (+)-**24** (49.0 mg, 96%) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{22}$ +27.2 (*c* 1.50, $CHCl_3$); IR (KBr) ν cm^{-1}: 3461 (s), 1730 (m), 1630 (m); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.86 (dd, *J*=15.0, 7.2 Hz, 1H), 5.74 (d, *J*=15.0 Hz, 1H), 4.11 (dd, *J*=8.0, 7.2 Hz, 1H), 3.69 (ddd, *J*=8.0, 6.5, 5.0 Hz, 1H), 2.91–2.84 (m, 2H), 2.67–2.61 (m, 2H), 2.18 (t, *J*=7.2 Hz, 2H), 2.06–2.00 (m, 1H), 1.88–1.82 (m, 1H), 1.79 (ddd, *J*=11.0, 6.0, 3.5 Hz, 2H), 1.59–1.21 (complex m, 18H), 1.44 (s, 9H), 1.41 (s, 6H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 137.2, 131.3, 108.6, 81.8, 80.9, 79.9, 54.7, 42.4, 35.6, 32.0, 31.9, 29.6, 29.1, 29.0, 28.1 (3C), 27.3, 27.2 (2C), 27.0, 25.8, 25.5, 25.0, 23.6, 22.5, 14.0; HRMS (FAB, NAI matrix), *m/z*: 514.3145 $[M]^+$, Calcd for $C_{28}H_{50}O_2$: 514.3151 [M].

7.4.2. (12*R*,13*S*)-(*E*)-9-(1,3-Dithian)-13-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-25). To a solution of (−)-**19** (26.3 mg, 39.1 μmol) in *t*-BuOH (800 μL) was added KO*t*-Bu (17.5 mg, 157 μmol) at rt. The resultant mixture was stirred at rt for 16 h, treated with 1.0 N HCl (1 mL), and then extracted with $CHCl_3$ (3 mL×5). The combined organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=40:1) to give (−)-**25** (11.5 mg, 47%) as a colorless oil. R_f=0.44 (silica gel, hexane/AcOEt=5:1); $[\alpha]_D^{23}$ −12.5 (*c* 0.72, $CHCl_3$); IR (KBr) ν cm^{-1}: 3434 (s), 1724 (m), 1625 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 5.93 (dd, *J*=15.5, 7.3 Hz, 1H), 5.64 (d, *J*=15.5 Hz, 1H), 4.29 (dd, *J*=7.3, 3.3 Hz, 1H), 3.77–3.67 (m, 1H), 2.97–2.84 (m, 2H), 2.66–2.57 (m, 2H), 2.18 (t, *J*=7.6 Hz, 2H), 2.01 (br s, 1H), 1.82–1.76 (m, 2H), 1.67–1.58 (complex m, 20H), 1.44 (s, 9H), 1.14–1.07 (m, 21H), 0.87 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 135.7, 133.6, 79.9, 76.2, 75.2, 54.6, 42.4, 35.6, 32.6, 32.0, 29.7, 29.1, 29.0, 28.1 (3C), 27.1, 27.0, 25.6, 25.5, 25.1, 23.7, 22.5, 18.1 (6C), 14.1, 12.4 (3C); HRMS (FAB, NBA matrix), *m/z*: 630.4178 $[M]^+$, Calcd for $C_{34}H_{66}O_4S_2Si$: 630.4172 [M].

7.4.3. (12*R*,13*S*)-(*E*)-9-(1,3-Dithian)-12,13-dihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-26). To a solution of (−)-**25** (4.3 mg, 6.8 μmol) in THF (500 μL) was added TBAF (1.0 M solution in THF, 6.8 μL, 6.8 μmol) at rt. The resultant mixture was stirred at rt for 16 h, treated with H_2O (500 μL), and then extracted with $CHCl_3$ (3 mL×3). The combined organic layer was washed with satd aq NaCl (3 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=1:1) to give (+)-**26** (3.1 mg, 97%) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{24}$ +0.4 (*c* 0.52, $CHCl_3$); IR (KBr) ν cm^{-1}: 3428 (s), 1731 (m), 1630 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 5.98 (dd, *J*=15.2, 6.9 Hz, 1H), 5.72 (d, *J*=15.2 Hz, 1H), 4.23 (d, *J*=6.9, 3.6 Hz, 1H), 3.77–3.71 (m, 1H), 2.94–2.81 (m, 2H), 2.68–2.32 (m, 2H), 2.19 (t, *J*=7.3 Hz, 2H), 1.84–1.78 (m, 2H), 1.67–1.28 (complex m, 20H), 1.44 (s, 9H), 0.89 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 136.4, 131.3, 80.0, 75.1, 74.2, 54.7, 42.0, 35.5, 32.4, 31.8, 29.4, 29.0, 28.9, 28.1 (3C), 27.2 (2C), 25.5 (2C), 24.9, 23.7, 22.5, 14.0; HRMS (FAB, NBA matrix), *m/z*: 497.2744 $[M+Na]^+$, Calcd for $C_{25}H_{46}O_4S_2Na$: 497.2735 [M+Na].

7.4.4. (12*R*,13*S*)-(*E*)-9-(1,3-Dithian)-12,13-isopropylenedioxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-27). To a solution of (+)-**26** (17.1 mg, 37.3 μmol) in CH_2Cl_2 (0.7 mL) were added CSA (0.9 mg, 3.73 μmol) and 2-methoxypropene (5.3 μL, 56.0 μmol) at 0 °C. The resultant mixture was stirred at 0 °C for 20 min, treated with H_2O (1 mL), and then extracted with $CHCl_3$ (2 mL×3). The organic layer was washed with satd aq NaCl (2 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=20:1) to give (+)-**27** (18.2 mg, 98%) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{25}$ 0.0 (*c* 0.87, $CHCl_3$); IR (KBr) ν cm^{-1}: 3446 (s), 1730 (m), 1628 (m); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.88 (dd, *J*=15.0, 8.0 Hz, 1H), 5.67 (d, *J*=15.0 Hz, 1H), 4.60 (dd, *J*=8.0, 6.0 Hz, 1H), 4.15 (ddd, *J*=8.0, 6.0, 5.0 Hz, 1H), 2.94–2.84 (m, 2H), 2.67–2.60 (m, 2H), 2.18 (t, *J*=7.2 Hz, 2H), 2.06–2.00, 1.88–1.82 (m, 1H each), 1.80–1.75 (m, 2H), 1.58–1.23 (m, 18H), 1.49 (s, 3H), 1.43 (s, 9H), 1.37 (s, 3H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 136.7, 130.5, 108.1, 79.9, 78.9, 78.4, 54.5, 42.3, 35.6, 31.9, 30.7, 29.6, 29.1, 29.0, 28.4, 28.1 (3C), 27.1, 27.1, 25.9, 25.7, 25.5, 25.0, 23.7, 22.6, 14.0.

Acknowledgements

This work was supported by the Ministry of Education, Science, Sports, and Culture, Japan and the Japan Keirin Association, a Grant of the 21st Century COE Program. We acknowledge and thank Ms. Noriko Sato for NMR measurements and Ms. Chikako Sakabe and Ms. Akiko Nakagawa for mass spectrometric analysis.

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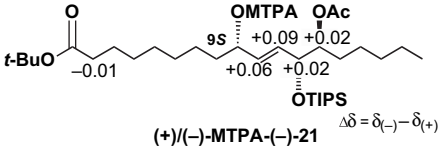
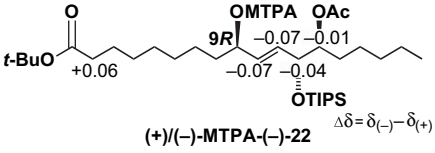


(+)/(–)-MTPA-(–)-21



(+)/(–)-MTPA-(–)-22

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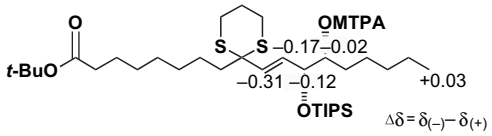

(+)/(–)-MTPA-(–)-18

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