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Tetrahedron

Tetrahedron Vol. 60, No. 37, 2004

Contents

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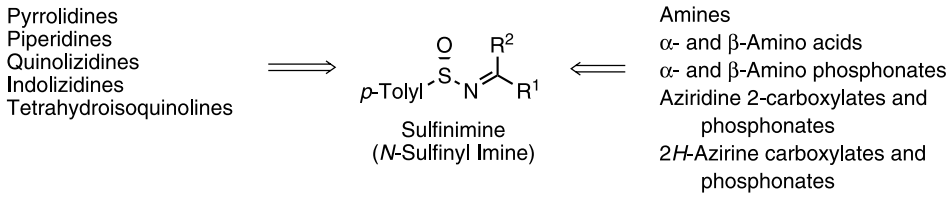

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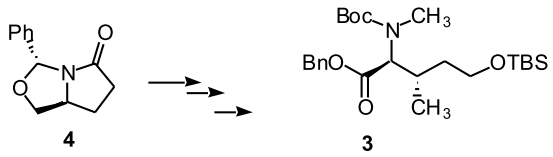
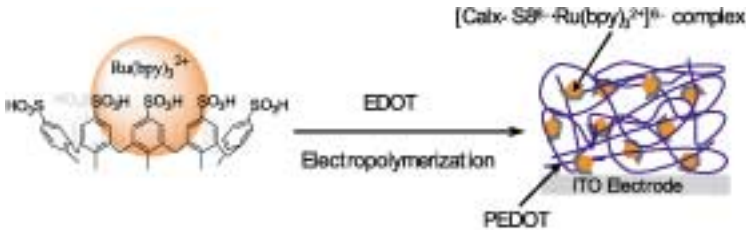
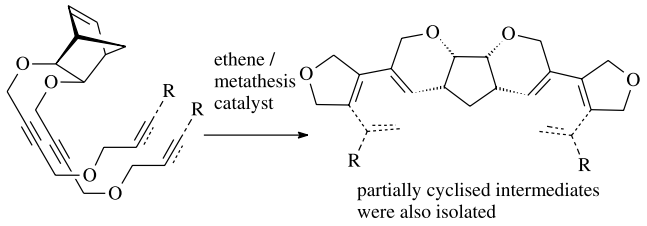
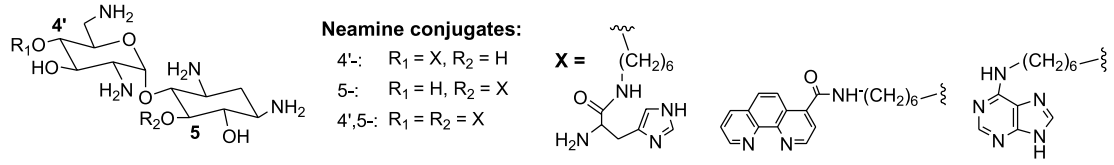
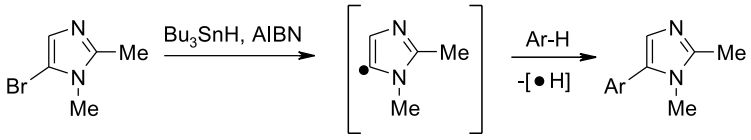


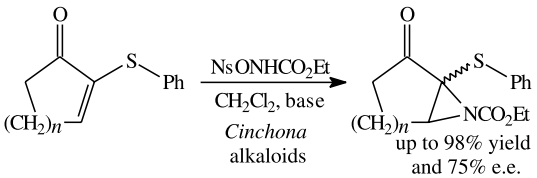


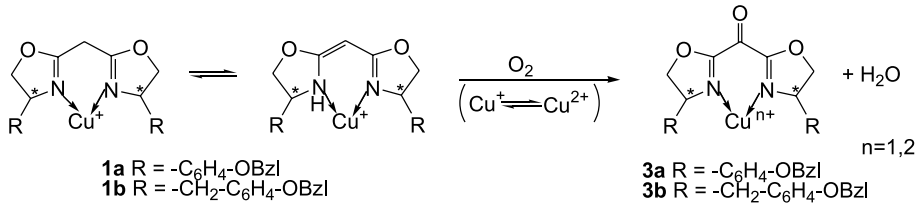


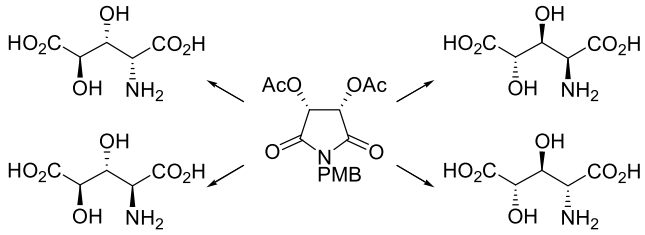


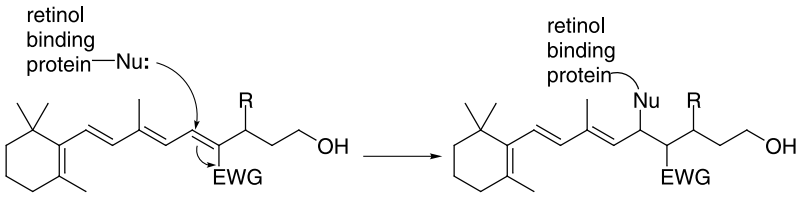
In the search for molecules possessing antibiotic or antiviral properties, a route for preparing 4′-neamine derivatives is reported for the first time. Most of the 4′-derivatives showed affinity and selectivity for TAR RNA close to those of the corresponding 5-derivatives and the most potent compound is the 4′-histidine conjugate.

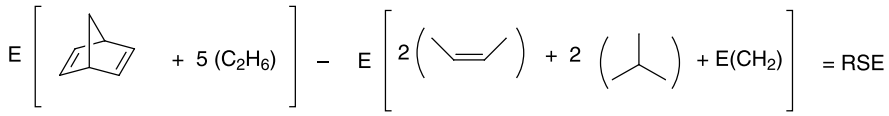


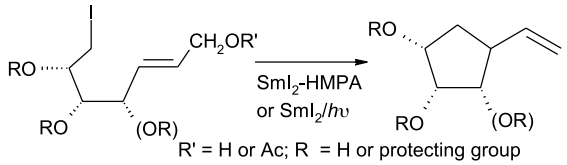




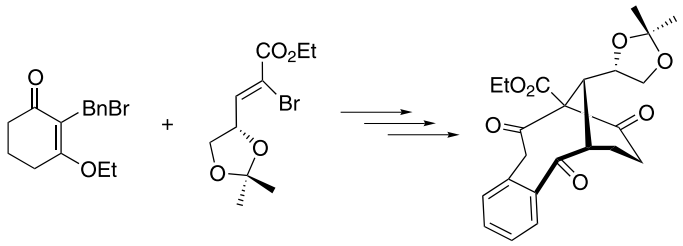




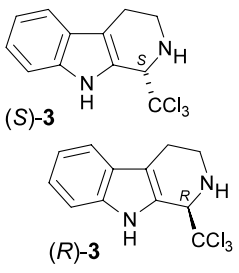


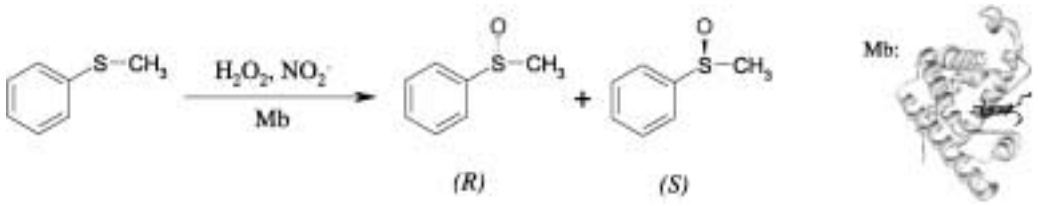


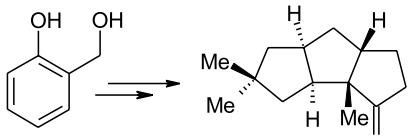
SmI_2 mediated reduction of ω-iodoallylic alcohols is facilitated by irradiation with a Xe lamp or addition of HMPA.

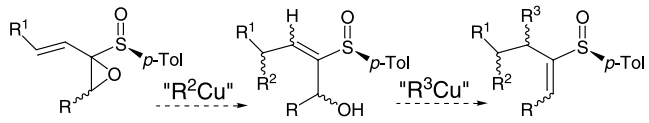


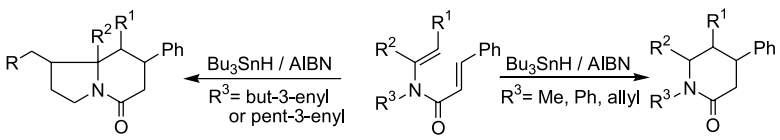
Assignment of the absolute configuration of the two TaClo enantiomers, (S)-TaClo [(S)-3] and (R)-TaClo [(R)-3] was achieved by CD spectroscopy and confirmed by X-ray crystallography.

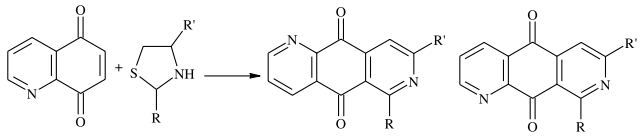


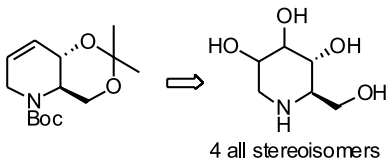


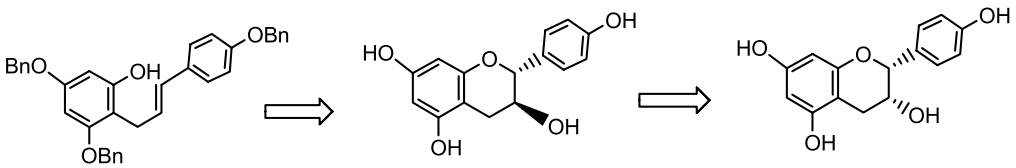


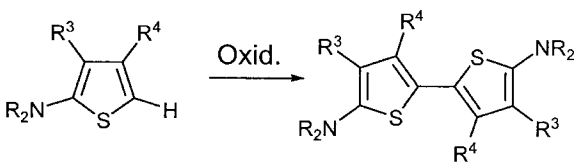




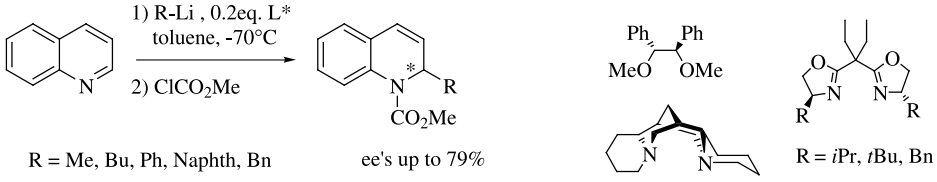


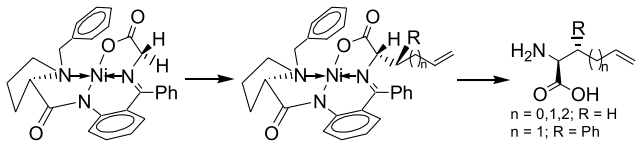


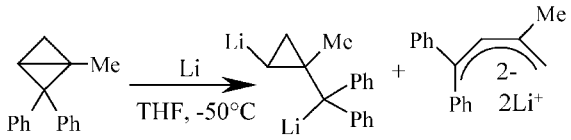


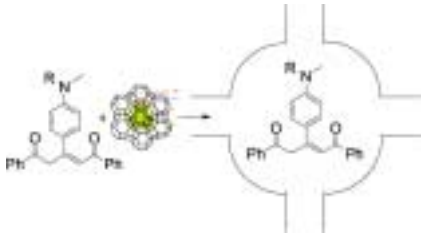


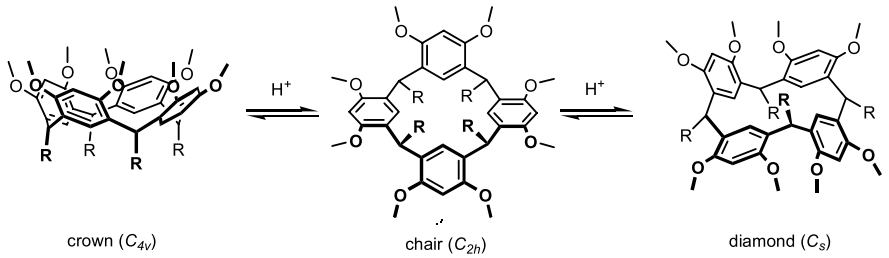
By the oxidative coupling of N,N-disubstituted 2-amino-5H-thiophenes performed by several heavy-metal free oxidating agents N,N′-persubstituted 5,5′-diamino-2,2′-bithiophenes, which are of interest as hole-transport materials for optoelectronic applications, have been prepared.



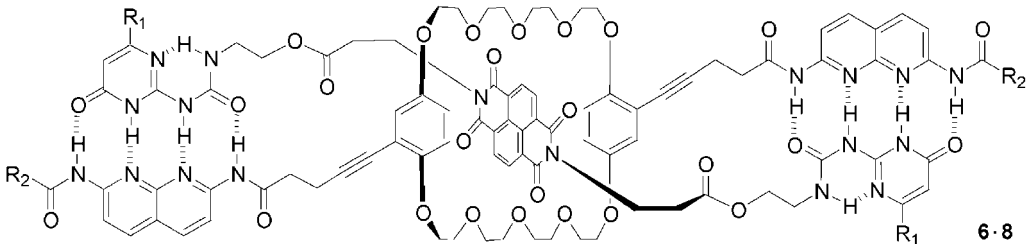








The interaction of the crown conformer of octamethoxy-resorcinarene with organic acids in carbon tetrachloride and benzene is described. The quantitative description of the observed conformational transformations was attempted, based on the proposed triconformational allosterical model.



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ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 8003–8030

Tetrahedron report number 688

Recent advances in asymmetric reactions using sulfinimines (*N*-sulfinyl imines)

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Received 26 April 2004

Contents

Keywords: Sulfinimines; *N*-Sulfinyl imines; Imine; Chiral amine derivatives.
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doi:10.1016/j.tet.2004.06.071

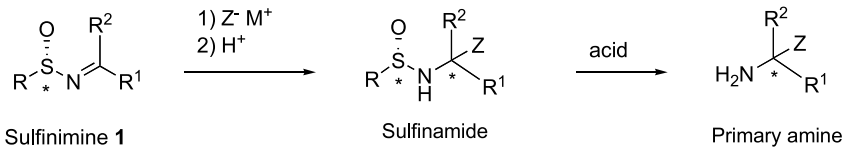
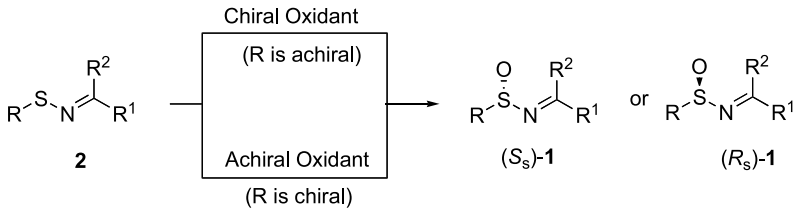


Figure 1.



Scheme 1.

1. Introduction

Sulfinimines (*N*-sulfinyl imines **1**) are a special class of imines that display unique reactivity and stereoselectivity due to the presence of the chiral and electron withdrawing *N*-sulfinyl group (Fig. 1).[1] Since their introduction almost three decades ago,[2] sulfinimines have played an important role in the asymmetric synthesis of a variety of structurally diverse nitrogen-containing molecules because they provide a general solution to the problem of addition of organometallic reagents to chiral imines.[1] In **1** the electron-withdrawing sulfinyl group activates the C=N bond for nucleophilic addition, which permits reactions to proceed at lower temperatures. The *N*-sulfinyl auxiliary also exerts powerful stereodirecting effects, which results in the addition of enolates and organometallic reagents to both enolizable and nonenolizable sulfinimines with high and predictable, asymmetric induction. Epimerization of the newly created carbon stereocenter in the sulfinamide product is inhibited because the sulfinyl group stabilizes anions at nitrogen (i.e., the sulfinyl moiety is a versatile amine protecting group). In contrast to aliphatic imines, aliphatic sulfinimines are stable and not particularly susceptible to deprotonation or self-condensation. Moreover, unlike other imine *N*-auxiliaries, the sulfinyl group in the product sulfinamide is easily removed under comparatively mild conditions.

The preparations and reactions of sulfinimines, including their applications in asymmetric synthesis, have been the subject of several reviews that cover the literature from their first preparation through 1999.[1] This report is intended to update the most recent advances in asymmetric transformations using enantiopure sulfinimines, focusing on the chemistry of the *p*-toluenesulfinyl imine derivatives. The literature on asymmetric syntheses using the complementary *tert*-butanesulfinimines is not, however, cataloged in detail in this report, as it has recently been covered in excellent reviews by Ellman.[3] Some overlap with earlier reviews is necessary for the sake of continuity.

2. Preparation of enantiopure *N*-sulfinimines

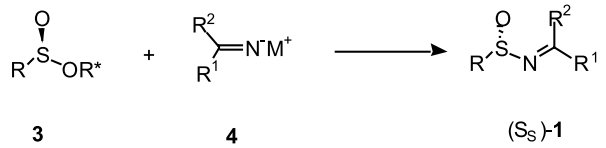
Three strategically different methods have been developed for the synthesis of enantiomerically pure sulfinimines:[1,3–5] (i) asymmetric oxidation of sulfenimines; (ii) asymmetric iminolysis of sulfinates and derivatives; and (iii) the condensation of enantiopure primary sulfinamides with aldehydes and ketones.

2.1. Asymmetric oxidation of *N*-sulfenimines

Chemo- and enantioselective oxidation of prochiral sulfenimines **2** was introduced by Davis and co-workers for the preparation of optically active sulfinimines, including those derived from aldehydes.[4] This method calls for a chiral, nonracemic *N*-sulfonyloxaziridine for use as the oxidizing reagent. Alternatively, optically active sulfinimines were obtained by the chemo- and diastereoselective oxidation of chiral, nonracemic sulfenimines with an achiral oxidizing reagent such as *m*-CPBA (Scheme 1).[1a] While this method played an important role in initiating the new area of chiral sulfinimine chemistry, it became less attractive from a practical synthetic point of view due to the inconvenience in the preparation of the nonracemic *N*-sulfonyloxaziridine reagents or the chiral nonracemic sulfenimine starting materials.

2.2. Asymmetric iminolysis of sulfinates and derivatives

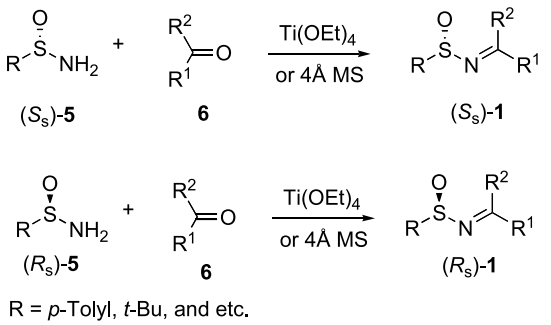
The second method, first introduced by Cinquini and co-workers, for the preparation of enantiomerically pure ketone-derived sulfinimines involved the reaction of imino-metallo reagents **4** with a chiral nonracemic sulfinate **3**, such as Andersen's reagent.[1a,b,5] The reaction is highly stereoselective, taking place at the chiral sulfur center in an S_N2 fashion (Scheme 2). However, this method cannot be employed in the synthesis of aldehyde-derived sulfinimines **1** (R^2=H).



Scheme 2.

2.3. Condensation of enantiopure primary sulfinamides with aldehydes and ketones

The third and now the most widely used method for the asymmetric synthesis of sulfinimines entails the



Scheme 3.

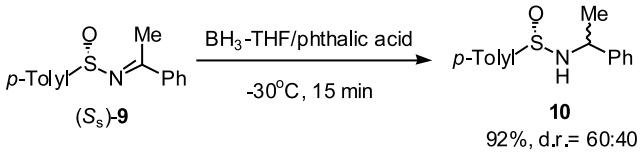
condensation of enantiopure primary sulfinamides **5** with aldehydes or ketones **6** (Scheme 3).[1,3] The condensation calls for a mild Lewis acid dehydrating reagent such as $Ti(OEt)_4$ or molecular sieves. A procedure has been recently published in *Organic Synthesis* on the synthesis of (*R*)- and (*S*)-*p*-toluenesulfinamide.[6]

p-Toluenesulfinamide **5** (R=*p*-tolyl), introduced by Davis and co-workers, was obtained in both the (*R*) and (*S*)- forms by treating the (*R*) and (*S*) Andersen reagent (menthyl *p*-toluenesulfinate) with LiHMDS followed by aqueous workup.[1c,6] *tert*-Butanesulfinamide **5** (R=*t*-Bu), developed by Ellman et al. is prepared by reaction of enantiomerically pure *tert*-butanethiosulfinate with lithium amide.[3] More recently, Senanayake and co-workers introduced *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxides **7** and **8** as versatile precursors for the enantioselective synthesis of diverse array of primary sulfinamides **5** (Scheme 4).[7,8] However, in the preparation of (*S*)-(+)-2,4,6-trimethylphenylsulfinamide **5** (R=Mes) by this procedure it was found important to use LiHMDS rather than NaHMDS or the enantiomeric purity of the product suffered significantly.[9] By far the most convenient sulfinamides to use for the preparation of chiral sulfinimines are the *p*-toluenesulfinamide **5** (R=*p*-tolyl) and *tert*-butanesulfinamide **5** (R=*t*-Bu) because they are commercially available in both the *R* and *S* forms.

3. Asymmetric reactions using sulfinimines

3.1. Hydride reductions

The stereoselective reduction of sulfinimines derived from ketones is a useful method for the preparation of optically active amines.[1] A number of reducing agents such as DIBAL, $NaBH_4$, $LiAlH_4$, $Li(RO)AlH_3$, and 9-BBN have been exploited for this purpose. DIBAL and 9-BBN were reported to be more advantageous in terms of diastereoselectivity.[1] Recently, BH_3–THF in combination with 1 equiv. of phthalic acid was found to reduce the imine double bond in (*S*)-**9** (Scheme 5).[10] The sulfinamide product **10** was obtained in 92% yield with a dr of 60:40. The selectivity is increased to 90:10 with addition of $Ti(OPr\text{-}i)_4$.



Scheme 5.

Ketone-derived sulfinimines containing groups attached to the imino carbon similar in size generally exist as mixture of inseparable *E*/*Z* isomers because the barrier to *syn*/*anti* inversion at nitrogen is low, ca. 12–13 kcal/mol.[11] This may account for the low dr's observed for reductions of these types of sulfimines.

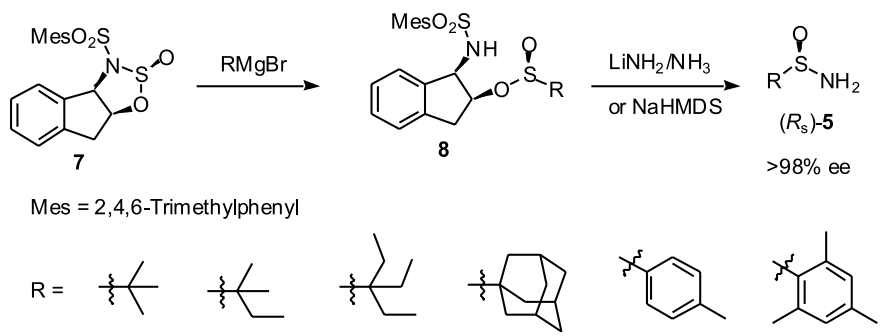
3.2. Additions to sulfinimines

Sulfinimines **1** are excellent Michael acceptors due to the presence of the strong electron withdrawing *N*-sulfinyl group. Sulfinimines **1** react with a variety of nucleophiles in a 1,2-addition fashion, including oxygen, nitrogen, sulfur, carbon, and phosphorous nucleophiles.[1,3] Carbon and phosphorous nucleophiles are reviewed below in greater detail.

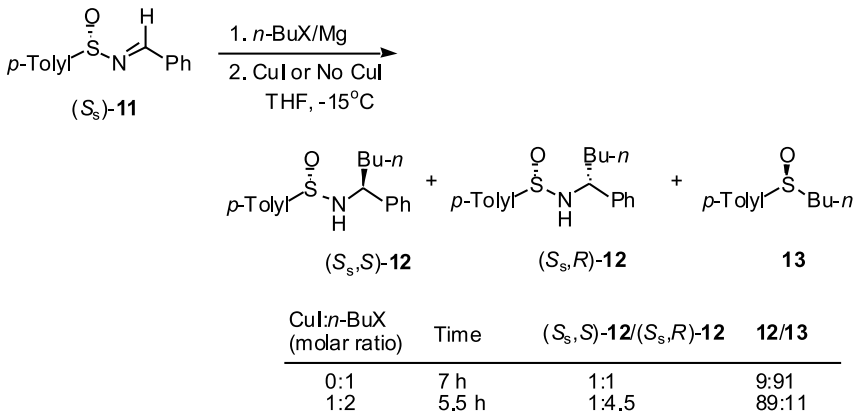
3.2.1. Carbon nucleophiles

3.2.1.1. Organometallic reagents. Organometallic reagents such as organolithium and Grignard reagents add to sulfinimines **1** to give sulfinamides in high diastereoselectivities and yields.[1,3] Generally, the *N*-*tert*-butanesulfinyl imines (**1**, R=*t*-Bu) are preferred for this purpose because organometallic reagents tend to attack at sulfur in the *N*-*p*-toluenesulfinyl imines (**1**, R=*p*-tolyl) to give sulfoxides.[1,3] There are, however, exceptions.

Chan and co-workers recently observed that addition of *n*-butylmagnesium bromide to (S_S)-**11** gave the desired product **12** in only 7% yield as a 1:1 diastereomeric mixture (Scheme 6).[12] The major product was *n*-butyl sulfoxide **13** resulting from the attack at the sulfur atom. Addition of CuI, however, improved the yield of the desired product **12** to 70% with an increase in diastereoselectivity (1:4.5).[12]

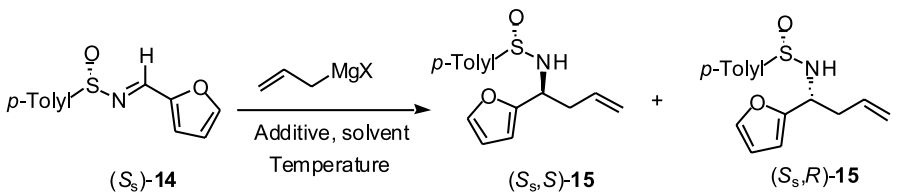


Scheme 4.



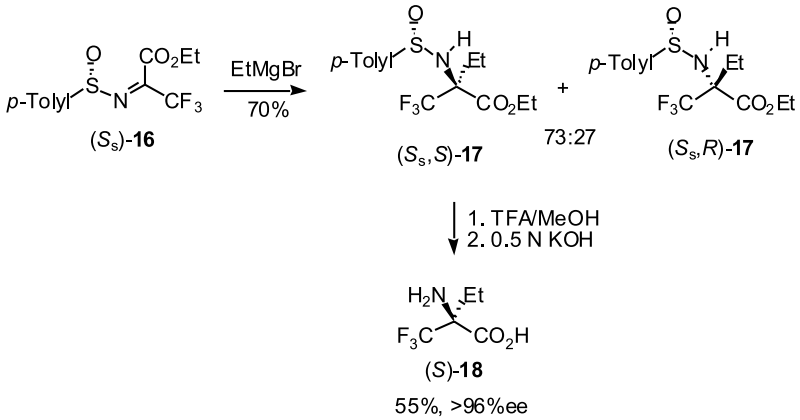
CuI:*n*-BuX (molar ratio)	Time	(S_s,S)-**12**/(S_s,R)-**12**	**12**/**13**
0:1	7 h	1:1	9:91
1:2	5.5 h	1:4.5	89:11

Scheme 6.



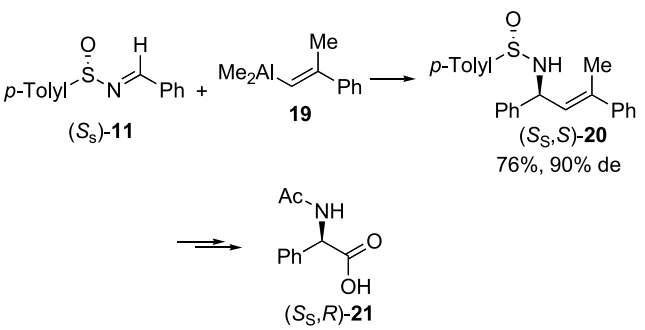
X	Additive	Solvent	Temp. (°C)	Time	Yield (%)	(S_s,S):(S_s,R)
Br	–	CH_2Cl_2	-78	4 h	98	9:91
Cl	BF_3-Et_2O	Et_2O	-78 to -40	2 h	83	>99:1

Scheme 7.



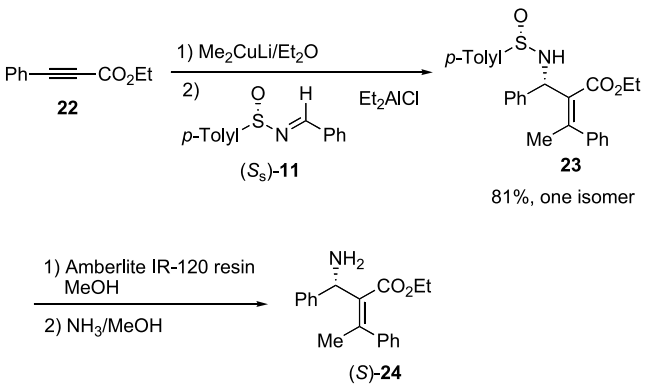
Scheme 8.

As previously observed,[1] addition of allyl Grignard reagents to sulfinimines was much more stereoselective and gave the desired products in higher yield.[1] Shimizu and co-workers found that by choosing an appropriate Grignard reagent and reaction conditions, high diastereoselectivity could be achieved with reversal of configuration at the newly formed chiral center.[13] For example, addition of the allylmagnesium bromide to (S_S)-**14** in CH_2Cl_2 afforded **15** in 98% yield with (S_S,*R*)-**15** being isolated as the major diastereoisomer. With allylmagnesium chloride in ether in the presence of BF_3–Et_2O, (S_S,*S*)-**15** was the major product (Scheme 7).[13]

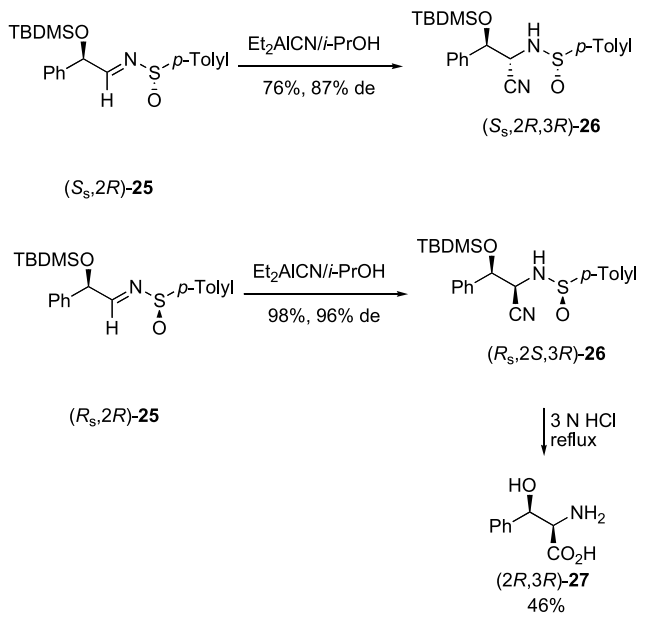


Scheme 9.

Addition of ethyl magnesium bromide to sulfinimine (S_S)-**16** gave (S_s,*S*)-**17** and (S_s,*R*)-**17** in 70% yield in a ratio of 73:27.[14] Treatment of (S_s,*S*)-**17** with TFA/MeOH followed by basic hydrolysis afforded α-trifluoro-α-amino acid (*S*)-**18** in 55% overall yield and >96% ee (Scheme 8).[14]



Scheme 10.



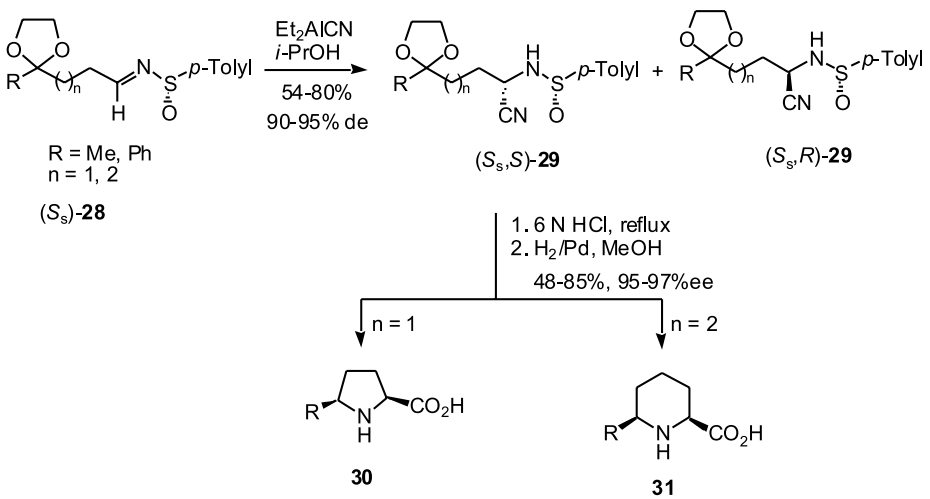
Scheme 11.

More recently, Wipf and co-workers found that the vinyl aluminum reagent generated from an alkyne and Me_3Al readily adds to *p*-toluenesulfinimines to give allylic amines in high yield and diastereoselectivities.[15] For example, addition of vinyl aluminum reagent **19** to benzaldehyde-derived sulfinimine (S_S)-**11** gave a 76% yield of allyllic amine **20**, which after protection and ozonolysis afforded *N*-acetyl phenylglycine **21** in 46% overall yield and 87% ee (Scheme 9).

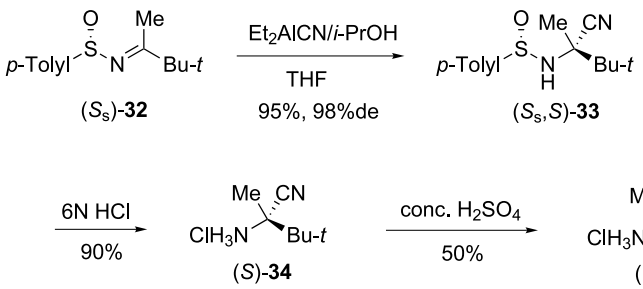
Li and co-workers, in a series of papers, described the addition of lithium (α-carbalkoxyvinyl)cuprates, prepared from **22**, to (S_S)-**11** afforded β,β-disubstituted α-(amino-alkyl)acrylates **23** in good yield (Scheme 10).[1,16] This reaction was originally carried out by using an excess of Et_2AlCl in diethyl ether solution as the Lewis acid promoter. It was found later that by using CH_2Cl_2 as a co-solvent and ytterbium (III) triflate as the catalyst, the scope of the reaction could be extended, as the method also allowed those *p*-toluenesulfinimines with low solubility in Et_2O to react with anionic (α-carbalkoxyvinyl)cuprates.[1,16] Deprotection of the sulfinyl group using Amberlite IR-120 resin in methanol afforded free α-alkylidene β-amino acid esters **24**, useful intermediates for the synthesis of β-lactam antibiotics, peptidomimetics, β-peptide oligomers, and many other biologically important molecules.[16]

3.2.1.2. Cyanides. Diastereoselective addition of cyanide to sulfinimines is an important extension of the Strecker α-amino acid synthesis.[1] The highest diastereoselectivity was observed by Davis and co-workers when a combination of Et_2AlCN/*i*-PrOH was used for the nucleophilic addition.[1] The α-amino nitrile intermediate, upon treatment with acids such as HCl, undergoes deprotection of the *N*-sulfinyl group and hydrolysis of the nitrile to give rise to α-amino acids.

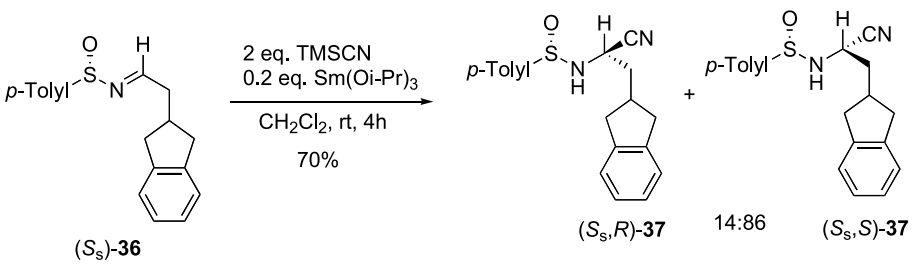
More recently, sulfinimine (S_S,2*R*)-**25**, derived from an α-hydroxy aldehyde, was reported to react with Et_2AlCN/*i*-PrOH to give (S_S,2*R*,3*R*)-**26** in 76% yield and 87% de (Scheme 11).[17] The corresponding enantiomer (R_S,2*R*)-**25** reacts similarly with Et_2AlCN/*i*-PrOH to give (R_S,2*S*,3*R*)-**26** in 98% yield and 96% de, indicating that the diastereoselectivity is primarily controlled by the sulfinyl group.[17] Hydrolysis of (R_S,2*S*,3*R*)-**26** afforded β-hydroxy-α-amino acid **27**.



Scheme 12.



Scheme 13.



Scheme 14.

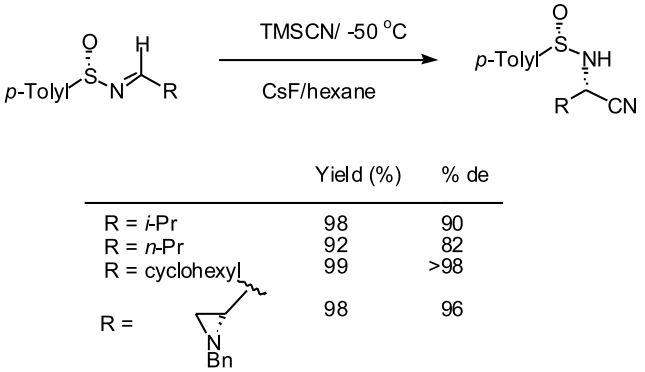
On addition of Et_2AlCN/i-PrOH, the masked oxo sulfinimines (S_S)-**28** give α-amino nitriles **29** that afford oxo α-amino acids on hydrolysis (Scheme 12).[18] These amino acids have been cyclized and reduced to *cis*-prolines **30** and *cis*-pipecolic acids **31** in high ee and good yield.

The sulfinimine-mediated asymmetric Strecker synthesis has also been applied to the preparation of α-alkyl-α-amino acids and their derivatives.[19] For example, reaction of (S_S)-**32** with Et_2AlCN/i-PrOH afforded compound (S_S,*S*)-**33** in 95% yield and 98% de, which could be converted to α-amino nitrile (*S*)-**34** and α-amino amide (*S*)-**35** (Scheme 13).

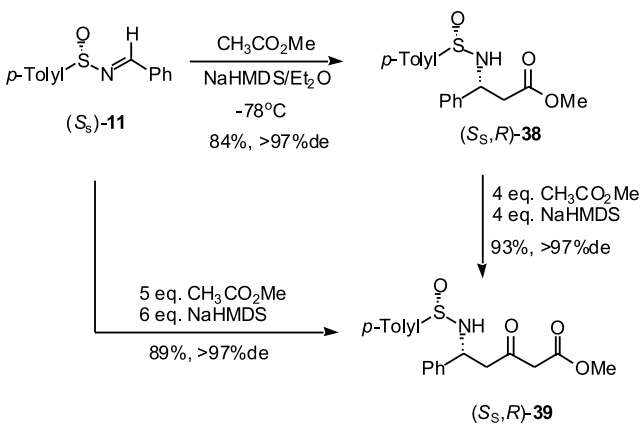
Mabic and Cordi studied the reaction of TMSCN with (S_s)-**36** in the presence of Lewis acids.[20] For example, reaction of (S_s)-**36** with 2 equiv. of TMSCN in the presence of 0.2 equiv. of Sm(Oi-Pr)$_3$ at room temperature for 4 h afforded products (S_S,*R*)-**37** and (S_S,*S*)-**37** in 70% yield and a ratio of 14:86 (Scheme 14).

The reaction of TMSCN in the presence of CsF with *N*-(benzylidine)-*p*-toluenesulfinimine (**11**) was earlier observed by Davis and co-workers to give *p*-toluenethiocyanate (*p*-MePhSCN).[21] However, Hou and co-worker recently reported that this reagent system gives excellent yields of the corresponding α-amino nitriles in good to excellent diastereoselectivities with enolizable sulfinimines (Scheme 15).[22] The formation of an intermediate *N*-sulfinyl enamine was suggested to play an important role in this transformation.

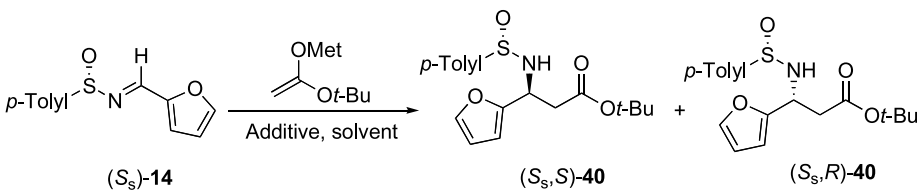
3.2.1.3. Enolates. Addition of metallo enolates to chiral, nonracemic sulfinimines affords β-amino esters in high yield and diasteroselectivity.[1] For example, addition of the sodium enolate of methyl acetate to benzaldehyde-derived sulfinimine (S_S)-**11** gave (S_S,*R*)-**38** in 84% yield and >97% de (Scheme 16).[23] Recently, it was found that the use of excess enolate resulted in the formation of the δ-amino-β-keto ester (S_S,*R*)-**39**.[24] The same compound could be directly obtained in 89% yield and >97% de by treating (S_s)-**11** with 5 equiv. of the sodium enolate. δ-Amino-β-keto esters are examples of sulfinimine-derived, polyfunctionalized, chiral building blocks and as such have



Scheme 15.



Scheme 16.



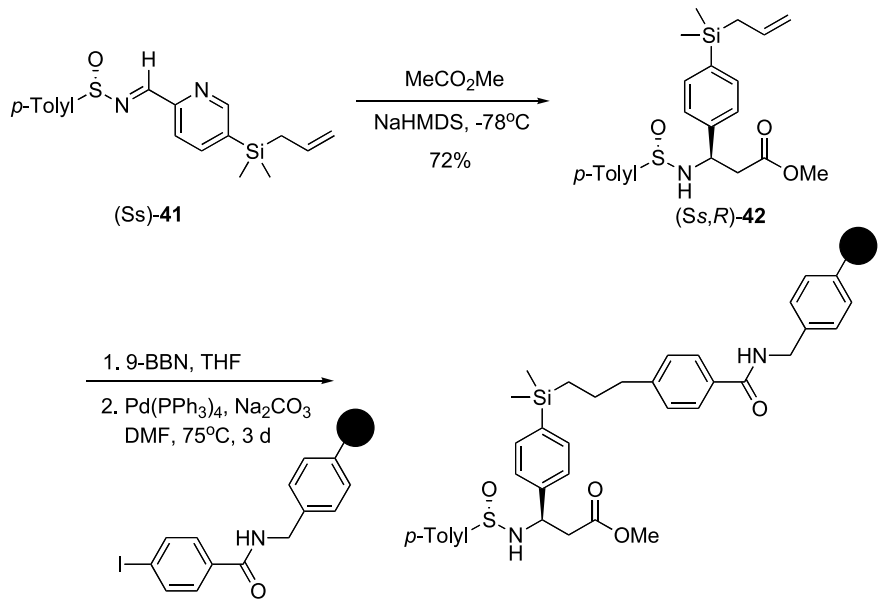
Met	Additive (eq.)	Solvent	Time	Yield (%)	(S_s,S):(S_s,R)
K	HMPA (30)	THF	5 min	88	86:14
$Ti(Oi\text{-}Pr)_3$	--	Et_2O	2 h	98	<1:99

Scheme 17.

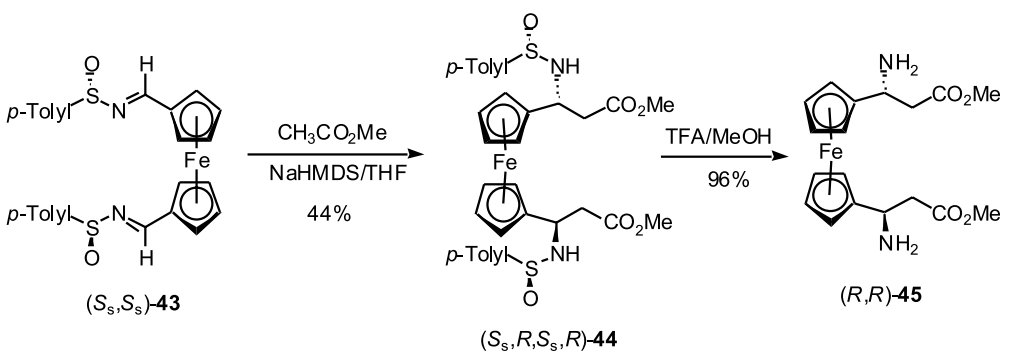
found many applications in the asymmetric synthesis of bioactive polysubstituted piperidine and pyrrolidine alkaloids.[25] Applications of this chiral building block to the asymmetric synthesis of natural products and related nitrogen heterocycles are presented in Section 5.

The diastereoselective addition of the enolate of *t*-butyl acetate to the furaldehyde-derived sulfinimine (S_S)-**14** was explored by Shimizu and co-workers (Scheme 17).[13] Reversal of diastereoselectivity was realized by using different metal species, solvents, and additives. For example, the use of the potassium enolate in THF in the presence of HMPA gave (S_S,S)-**40** and (S_S,R)-**40** in a ratio of 86:14 while the titanium enolate in ether afforded (S_S,R)-**40** as the major isomer. Nonchelation and chelation-control models, respectively, were given to explain the change in diastereoselectivity.

Reaction of sulfinimine (S_S)-**41** with the sodium enolate of methyl acetate gave (S_S,R)-**42** in 72% yield, a precursor useful for silicon-based aromatic transferring linkers for traceless solid-phase synthesis (Scheme 18).[26]



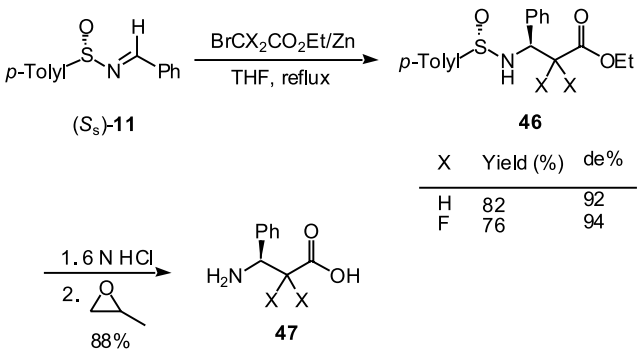
Scheme 18.



Scheme 19.

Reaction of bis-sulfinimine (S_S,S_S)-**43** with the sodium enolate of methyl acetate gave (S_S,*R*,S_S,*R*)-**44** in 44% isolated yield (Scheme 19).[27] Removal of the auxiliary with TFA/MeOH gave enantiopure ferrocenyl bis-β-amino acid (*R*,*R*)-**45** in 96% yield.

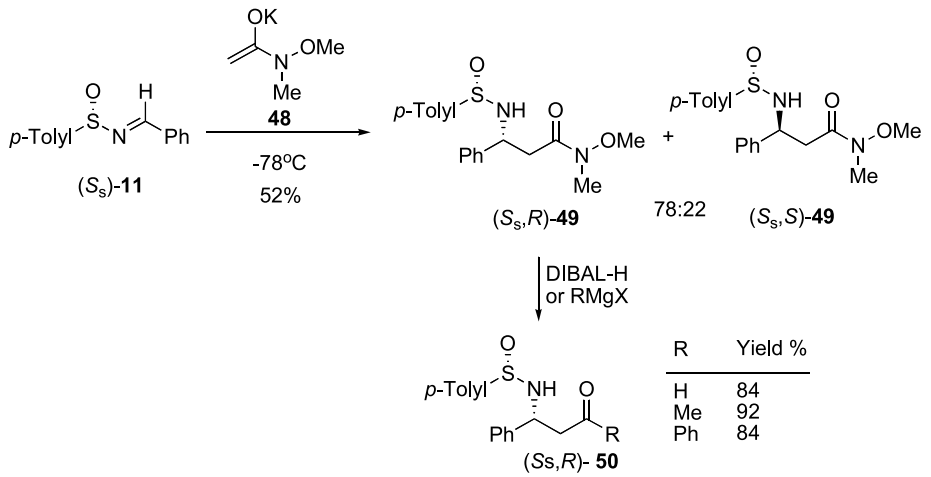
Enantiopure sulfinimines have also been found by Solosho-nok et al. to be efficient as chiral imine equivalents in Reformatsky-type additions.[28,29] High chemical and stereochemical yields have been observed with the usual Reformatsky reagent **46** (X=H) as well as the difluoro analog (X=F), making this method an efficient way to prepare β-substituted α,α-difluoro-β-amino acids **47** (Scheme 20).[28,29]



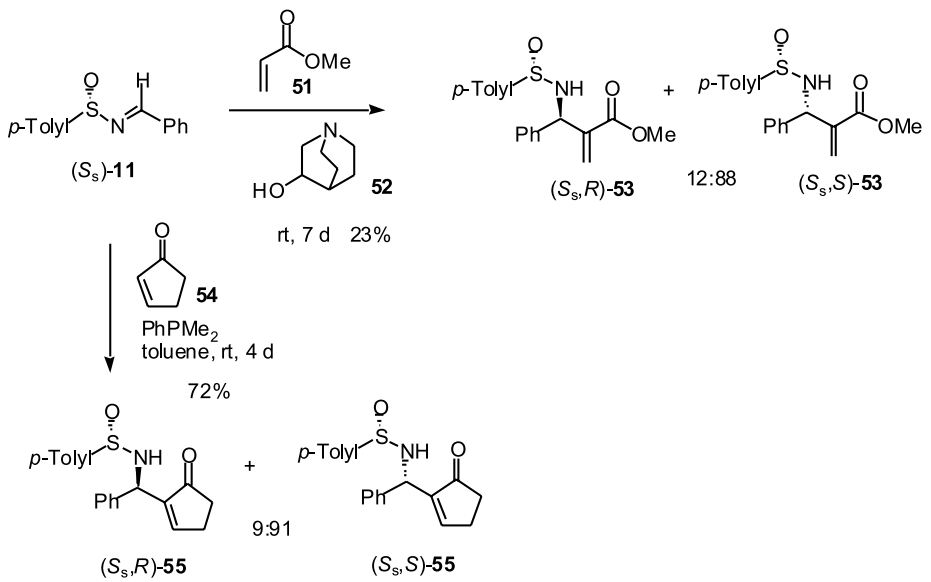
Scheme 20.

Condensation of (S_S)-**11** with the potassium enolate of *N*-methoxy-*N*-methylacetamide **48** afforded the *N*-sulfinyl β-amino Weinreb amide (S_S,*R*)-**49** in 56% de. The major diastereomer was separated in 52% yield (Scheme 21).[30] Compound (S_S,*R*)-**49** has been converted to β-amino aldehyde and ketones **50** in high yield. This sulfinimine-derived Weinreb amide was also prepared by treating the β-amino ester (S_S,*R*)-**38** with an excess of lithium dimethyl hydroxy amine.[30]

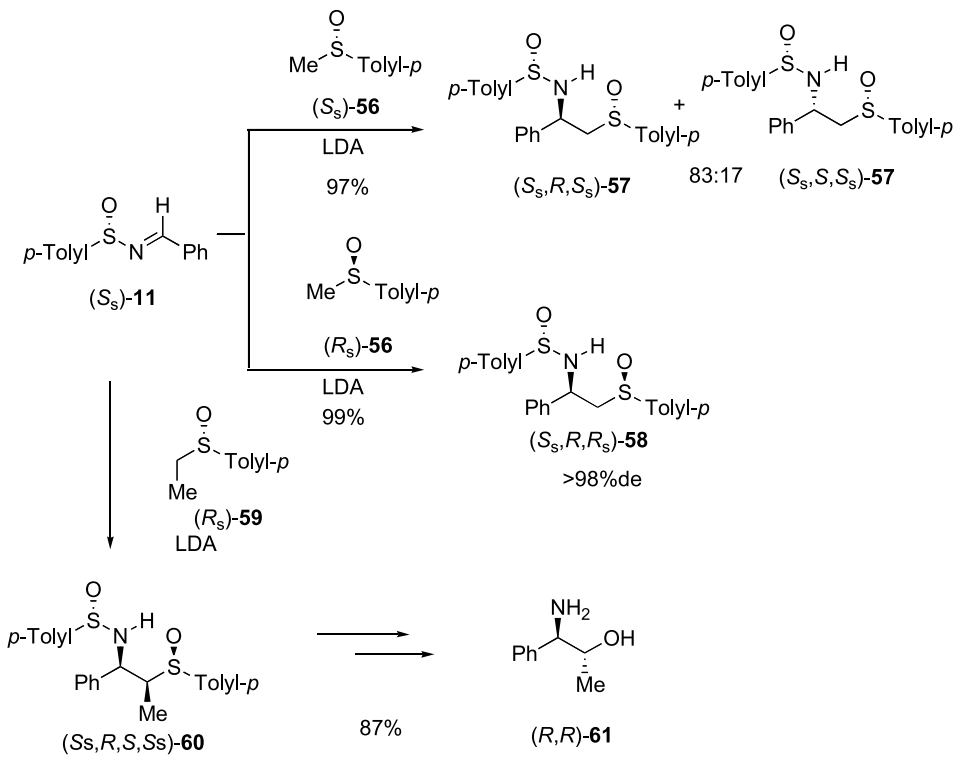
Recently, Aggarwal and co-workers developed an asymmetric Baylis–Hillman reaction using enantiopure sulfinimines.[31] Treatment of (S_S)-**11** with methyl acrylate (**51**) in the presence of 3-hydroxyquinuclidine **52** as the Lewis base



Scheme 21.



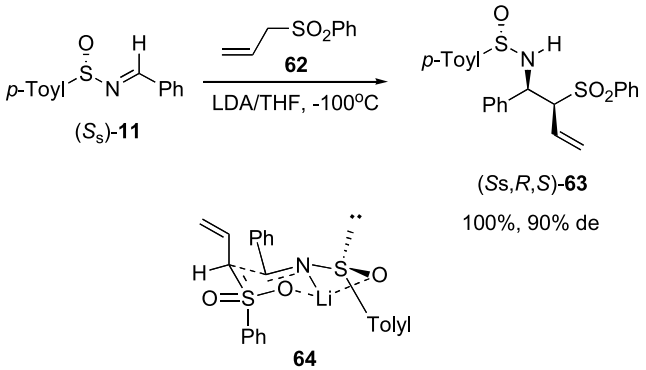
Scheme 22.



Scheme 23.

at room temperature for 7 days gave products (S_s,*R*)-**53** and (S_S,*S*)-**53** in 23% yield in a ratio of 12:88 (Scheme 22). The yield could be improved to 89% by using 0.05 equiv. of $In(OTf)_3$ as the Lewis acid. Shi and Xu reported a similar Baylis–Hillman type reaction of (S_S)-**11** and cyclopent-2-en-1-one (**54**) using a catalytic amount of $PhPMe_2$ as the Lewis base affording (S_S,*R*)-**55** and (S_S,*S*)-**55** as a 9:91 mixtures of isomers (Scheme 22).[32]

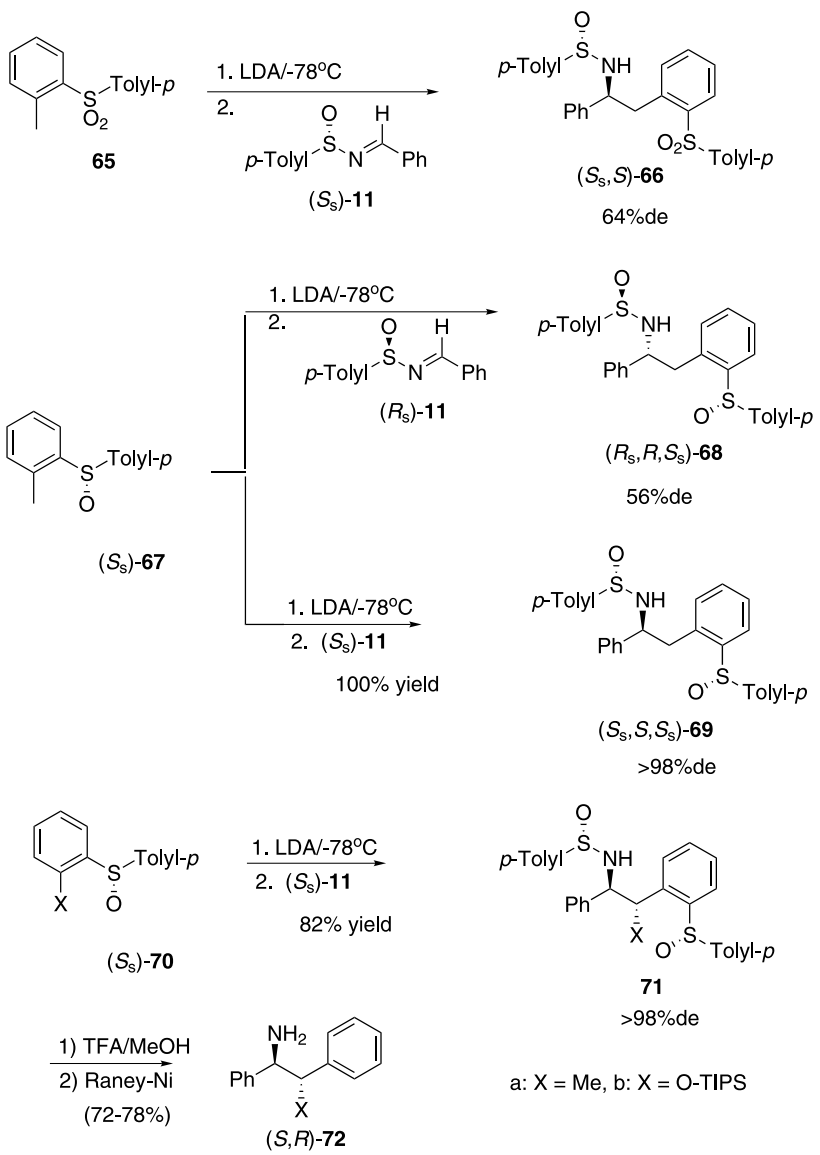
3.2.1.4. α-Sulfur stabilized carbanions. Reaction of the carbanion generated from (*S*)-methyl *p*-toluenesulfoxide (**56**) with (S_S)-**11** afforded a mixture of diastereomeric β-amino sulfoxides (S_S,*R*,S_S)-**57** and (S_S,*S*,S_S)-**57** in a ratio of 83:17 (Scheme 23).[33] Addition of the lithium carbanion derived from (*R*)-methyl *p*-toluenesulfoxide (**56**) to (S_S)-**11** gave (S_S,*R*,R_S)-**58** in 99% yield and >98% de. The lithium carbanion of (*R*)-ethyl *p*-toluenesulfoxide (**59**) gave **60** in 97% yield as a single diastereomer. In these reactions, it appears that the *N*-sulfinyl group primarily controls the configuration of the carbon bonded to the nitrogen, whereas the configuration of the α-sulfinyl carbanion is suggested to be responsible for the level of asymmetric induction. The resultant β-sulfinyl sulfinamide **60** could be converted to β-hydroxyamine **61** via a Pummerer rearrangement as one of the key transformations in the sequence (Scheme 23).[33]



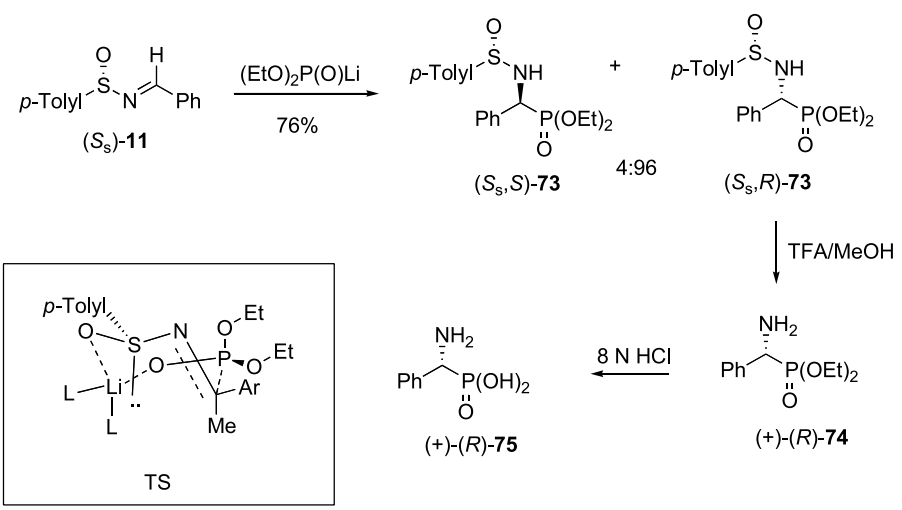
Scheme 24.

Addition of lithiated allylsulfone carbanion **62** to (S_S)-**11** afforded **63** in quantitative yield and 90% de (Scheme 24).[34] The observed diastereoselectivity was rationalized by invoking a six-membered cyclic transition state **64**, wherein Li^+ chelation between one of the sulfonyl oxygens and sulfinyl nitrogen forms a six-membered chair. Due to 1,3-diaxial Ar/Ph(SO_2) repulsion this chelation directs the aryl group to the equatorial position thus allowing the sulfonyl carbanion to attack exclusively from the *Si* face of the C=N bond.

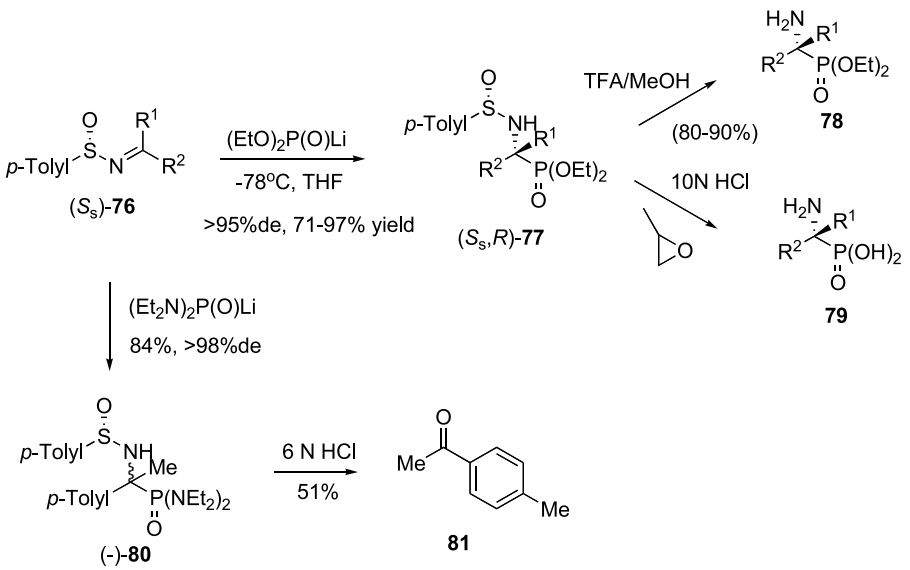
3.2.1.5. *o*-Stabilized benzylic carbanions. It is well documented that the presence of an *ortho* electron-withdrawing substituent in toluenes makes it possible to generate benzylic carbanions with strong bases such as LDA. Such benzylic carbanions, as expected, will react with a variety of electrophiles including sulfinimines.[1] Recently, Garcia Ruano and co-workers found that reaction of the benzylic carbanion generated from sulfone **65** with (S_S)-**11** gave adduct (S_S,S)-**66** in 64% de (Scheme 25).[35a] Reaction of the carbanion generated from (*S*)-sulfoxide **67** with (S_S)-**11** afforded (S_S,*S*,S_S)-**68** in >98% de. With (R_s)-**11** the de was lowered to 56%. Similarly, the carbanion of (*S*)-sulfoxides **70a** (X=CH_3) and **70b** (X=O-TIPS) react with (S_S)-**11** to give *anti* isomers **71a**[35a] and **71b**[35b] in 82 and 81% yield, respectively, and >98% de. These compounds were further transformed into enantiopure *anti*-1,3-diphenylpropylamine (**72a**)[35a] and *anti*-2-amino-1,2-diphenylethanol (**72b**)[35b] as shown in Scheme 25.



Scheme 25.

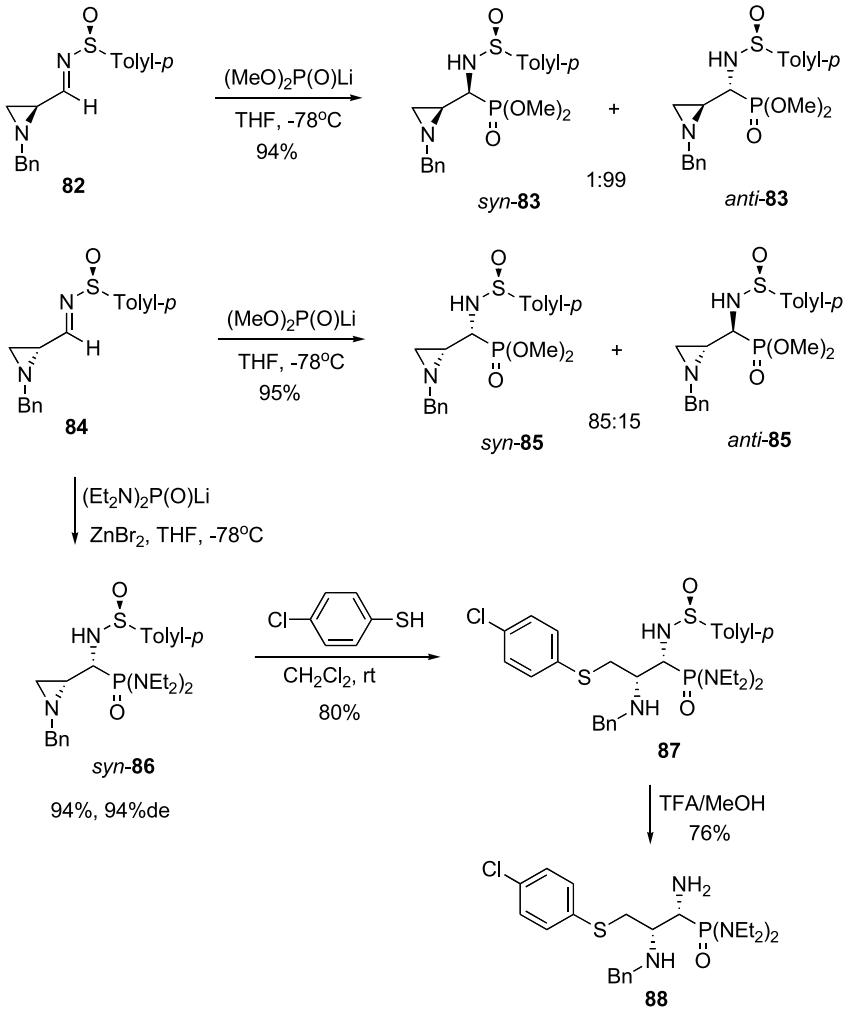


Scheme 26.

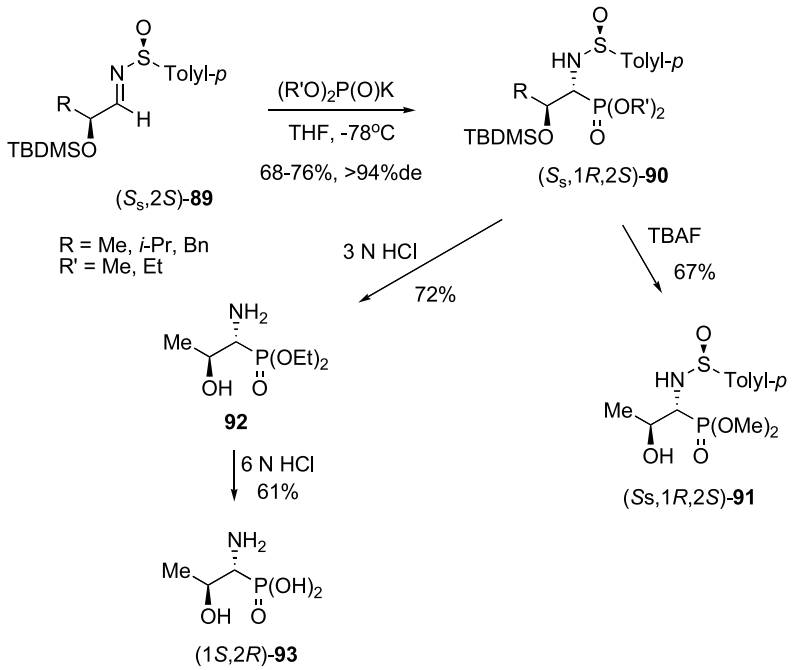


Scheme 27.

3.2.2. Phosphorus nucleophiles. Addition of lithium diethyl phosphite to sulfinimine (S_S)-**11** was previously reported to give α-amino phosphonate (S_S,*S*)-**73** as the major product (Scheme 26).[36] It was later found by Davis and co-workers that the reported configuration was in error.[37] It was shown that the major isomer has the (S_S,*R*)-configuration by hydrolyzing (+)-**74** to give (+)-α-amino (phenylmethyl)phosphonic acid **75**, the absolute configuration



Scheme 28.



Scheme 29.

of which had been previously determined to be *R* by X-ray crystallography. A seven-membered twisted chair-like transition state, wherein the lithium cation is chelated to the sulfinyl and phosphite oxygens, was proposed (Scheme 26).

Similarly, addition of lithium diethyl phosphite to keto-sulfinimines **76** afforded (S_S,*R*)-**77** in >95% de and 71–97% yield (Scheme 27).[37] Acidic hydrolysis of **77** gave quaternary α-amino phosphonates **78** and acids **79**. It should be pointed out that addition of lithium bis(*N*,*N*-diethylamino)phosphite afforded (−)-**80** in 84% yield and >98% de. Attempts to hydrolyze (−)-**80** to the acid in order to establish its absolute configuration was, however, unsuccessful under a variety of conditions. Decomposition to acetophenone (**81**) was observed to occur instead.

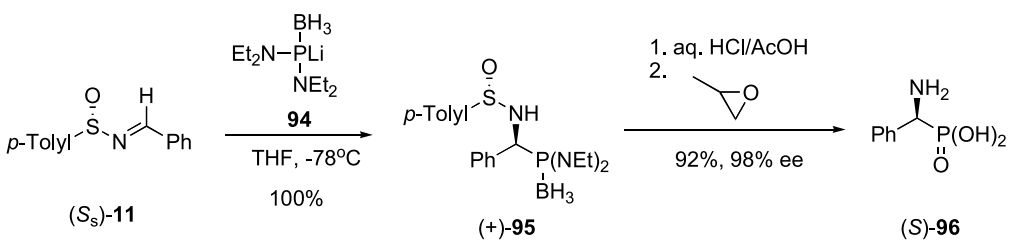
Aziridine sulfinimine **82**, on treatment with lithium dimethyl phosphite in THF at −78 °C, afforded a mixture of *syn*-**83** and *anti*-**83** products in 94% yield and a ratio of 1:99 (Scheme 28).[38] Under similar conditions aziridine **84** and lithium dimethyl phosphite, however, gave the *syn*- and *anti*-products **85** in a ratio of 85:15, suggesting that double stereo differentiation was taking place in the addition reaction. Addition of lithium bis(*N*,*N*-diethylamino)phosphite to **84** gave the *syn*-product **86**, which was converted to α,β-diamino phosphonate **88**, via the thiol addition product **87**, in good overall yield (Scheme 28).

Potassium dialkyl phosphonates react with enantiopure O-protected α-hydroxy sulfinimines (S_S,2*S*)-**89** to give β-hydroxy-α-amino phosphonates **90** in good yield and de (Scheme 29).[39] The protecting groups could be selectively removed to afford various β-hydroxy-α-amino phosphonate derivatives **91**, **92**, and **93** in moderate yields.

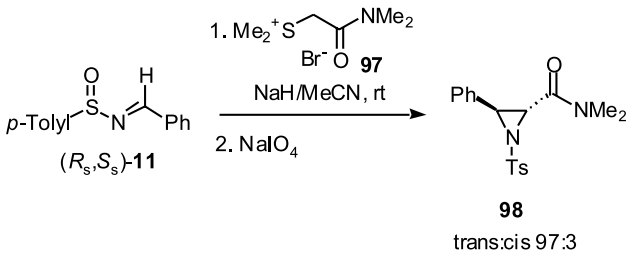
More recently, Mikolajczyk and co-workers described an alternative method for the preparation of α-amino phosphonic acids via addition of lithiated bis(diethylamino)phosphine borane complexes to enantiopure sulfinimines.[40] Addition of (S_S)-**11** to a freshly prepared solution of the borane complex **94** in THF at −78 °C afforded (+)-**95** in quantitative yield (Scheme 30). Subsequent treatment of (+)-**95** with aqueous HCl gave (*S*)-**96** in 92% yield and 98% ee.

3.3. Cycloadditions

3.3.1. [1+2]-Cycloadditions. Reaction of dimethyloxosulfonium methylide with racemic sulfinimines has been reported previously to give *N*-sulfinylaziridines as a mixture of diastereomers.[1] Hou and co-workers reported that on



Scheme 30.



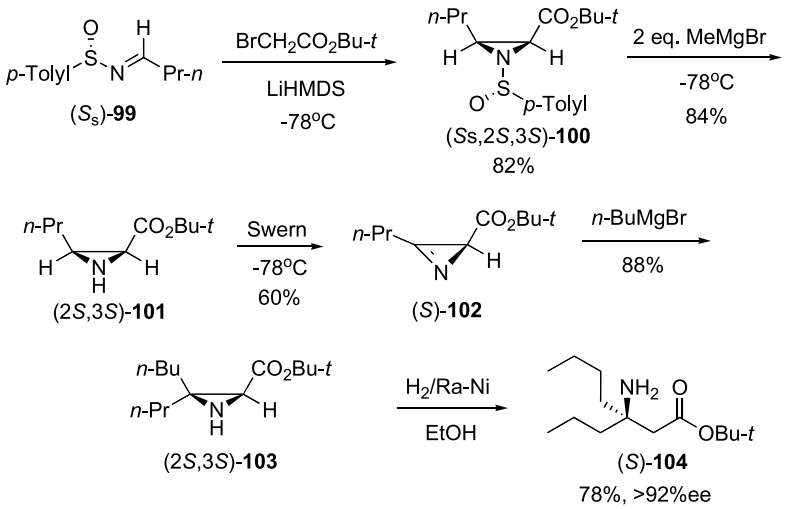
Scheme 31.

treatment with **11** the sulfonium ylide generated from **97** afforded *N*-tosylaziridine-2-carboxamide **98** as a mixture of *trans* and *cis*-isomers in a ratio of 97:3 (Scheme 31).[41]

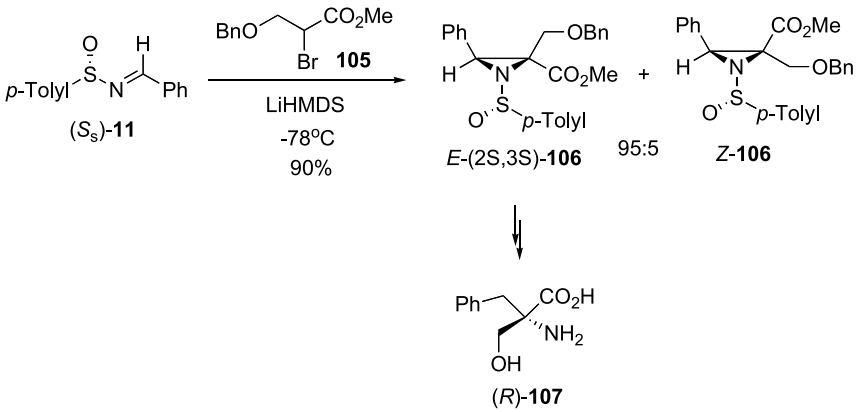
The Darzens-type reaction between sulfinimines and α-haloenolates affords *cis*-*N*-sulfinylaziridine-2-carboxylic esters in high yields and diastereoselectivities.[1] This method has been employed to prepare a variety of aziridines with diverse ring and nitrogen substituents and also in the asymmetric syntheses of natural products and biologically active compounds.[1] Davis and co-workers described the reaction of sulfinimine (S_S)-**99** with the lithium enolate of α-bromo *t*-butyl acetate to give aziridine (S_S,2*S*,3*S*)-**100** in 82% isolated yield (Scheme 32).[42] Removal of the *N*-sulfinyl auxiliary using MeMgBr followed by Swern oxidation of **101** afforded (*S*)-2*H*-azirine **102** in 60% overall yield. Azirine **102** has been converted to quaternary β-amino acid **104** via the Grignard addition product **103**.

The benzaldehyde sulfinimine (S_S)-**11** reacts with the lithium enolate of methyl 1-benzyloxy 2-bromopropanoate **105** in THF at −78 °C to give a 90% yield of the *E*- and *Z*-aziridines **106** in a ratio of 95:5 (Scheme 33).[43] The major isomer *E*-**106** was isolated in 70% yield and further transformed to (*S*)-α-benzylserine **107**.

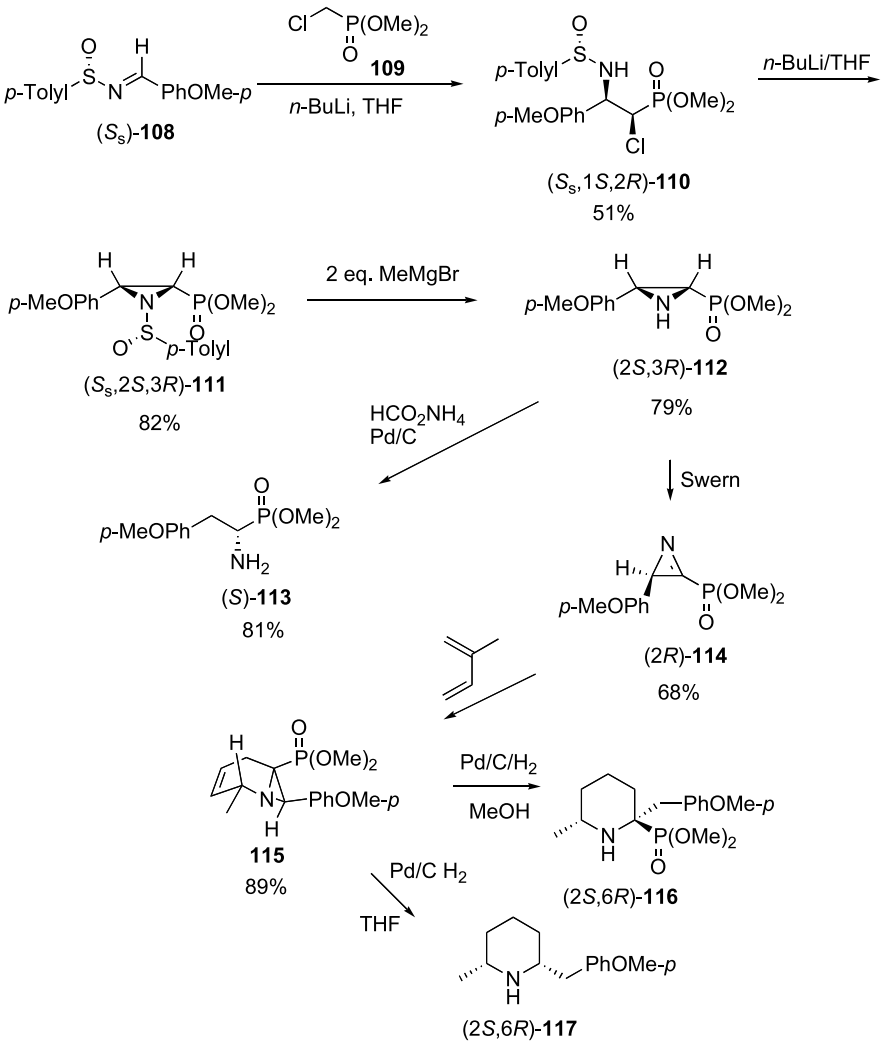
An aza-Darzens reaction, involving the addition of chloromethylphosphonate anions to enantiopure sulfinimines, also has been introduced by Davis and others for the asymmetric synthesis of aziridine-2-phosphonates.[44,45] For example, reaction of the lithium anion generated from dimethyl chloromethylphosphonate **109** with (S_S)-**108** gave α-chloro-β-amino phosphonate **110**, which could be isolated in 51% yield (Scheme 34).[44] Cyclization of **110** afforded *cis*-*N*-sulfinylaziridine-2-phosphonate **111** in 82% yield. Removal of the *N*-sulfinyl group with MeMgBr gave the corresponding NH aziridine **112**, a valuable chiral building block, that on hydrogenation gave α-aminophosphonate **113**.[44] Swern oxidation of **112** afforded 2*H*-azirine-3-phosphonate **114**, a new chiral iminodienophile.[46] For example, (2*R*)-**114** with *trans*-piperylene for 2–4 days at rt, gave the bicyclic



Scheme 32.



Scheme 33.



Scheme 34.

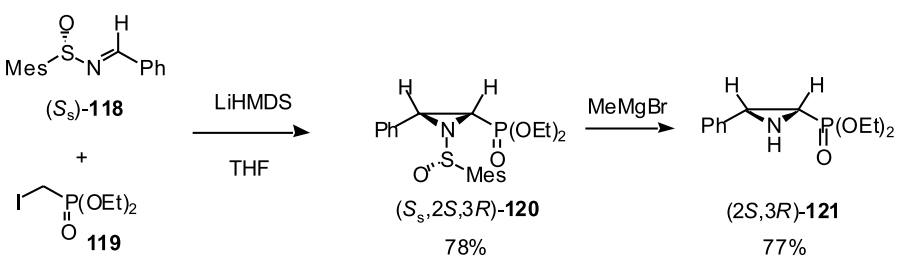
aziridine adduct **115** in 89% yield. Catalytic hydrogenation (H_2/Pd/C) of the bicyclic aziridine in MeOH and THF, respectively, afforded piperidines **116** and **117** (Scheme 34).[46]

More recently, an improved method for the asymmetric synthesis of aziridine-2-phosphonates has been introduced by Davis and co-workers using enantiopure *N*-(2,4,6-trimethylphenylsulfinyl) imines **118**.[9] Thus, treatment of the mixture of sulfinimine **118** and diethyl iodomethylphosphonate **119** with LiHMDS in THF at −78 °C gave compound **120** directly in 78% isolated yield as a single diastereoisomer (Scheme 35). The *N*-sulfinyl auxiliary could be removed, as before, by treating with MeMgBr.

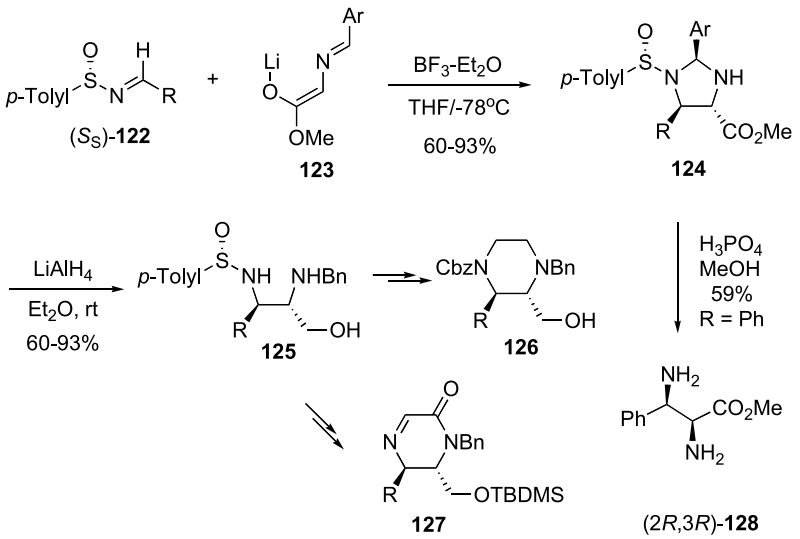
3.3.2. [3+2]-Cycloadditions. Viso and co-workers have explored the reaction between glycine iminoester enolates **123** and various sulfinimines.[47,48] In the presence of BF_3–Et_2O, **122** and **123** react to give *N*-sulfinyl-1,3-imidazolidines **124** with good stereoselectivity (Scheme 36). These adducts have been transformed to novel differentially protected vicinal diamine derivatives **125**-**127**.[47,48] Treatment of **124** (R=Ph) with H_3PO_4 in the presence of MeOH affords the *syn*-α,β-diamino ester **128**.[49]

4. Miscellaneous reactions

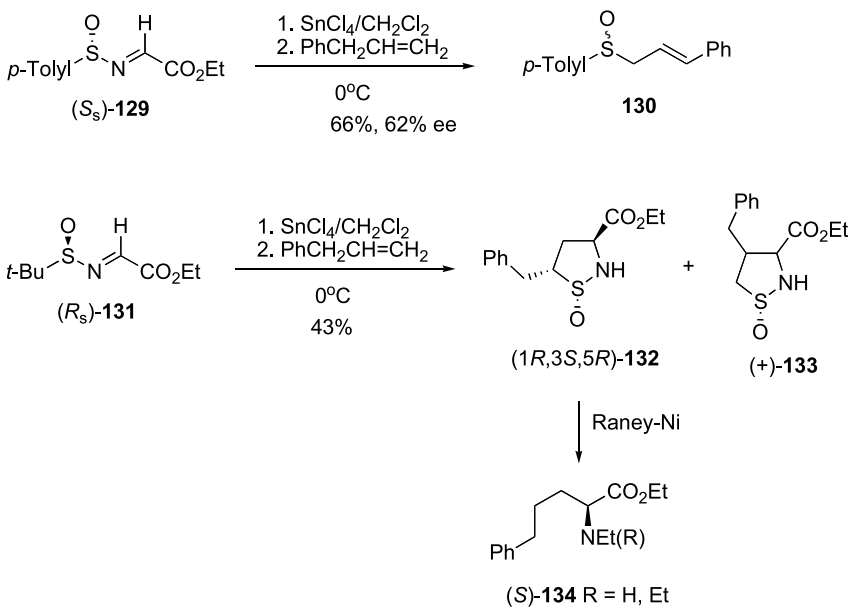
The *N*-*p*-toluenesulfinylimino ester (S_S)-**129** reacts with



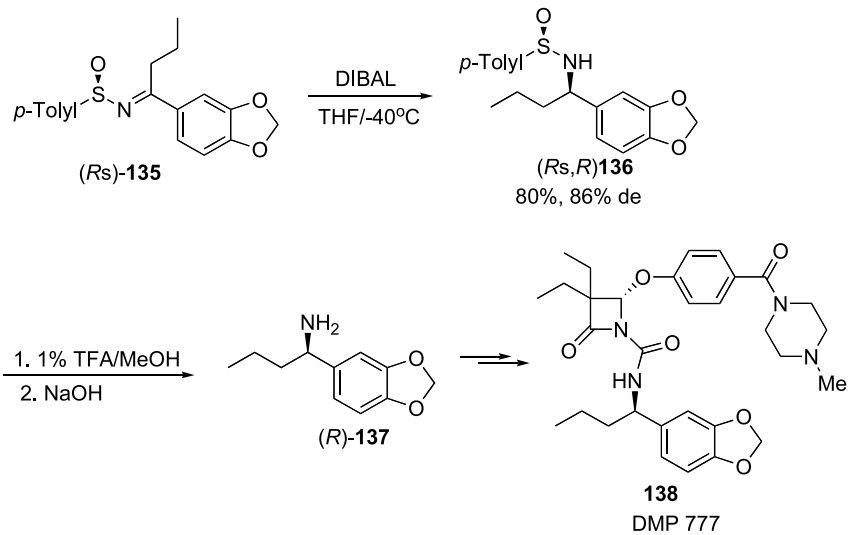
Scheme 35.



Scheme 36.



Scheme 37.



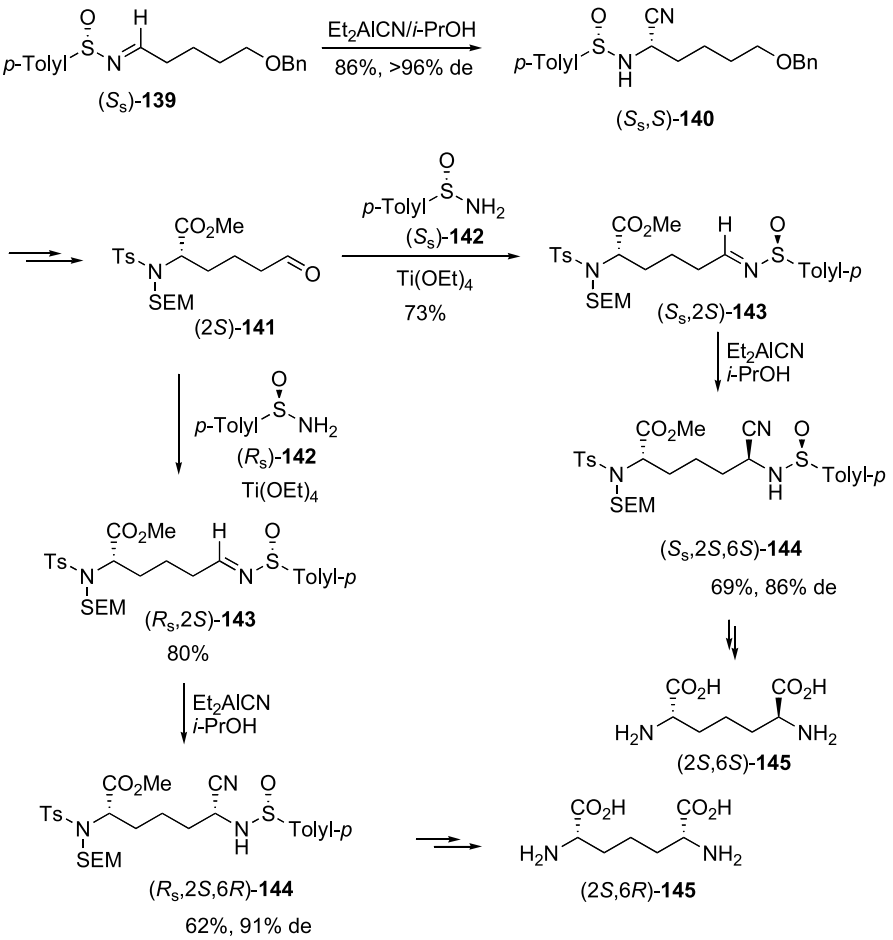
Scheme 38.

allyl benzene in the presence of $SnCl_4$ to give sulfoxide **130** in 66% yield and 62% ee of undetermined stereochemistry (Scheme 37).[50] Interestingly, under similar reaction conditions, the *N-tert*-butanesulfinyl derivative (R_S)-**131** undergoes an imino ene reaction with allyl benzene to afford (1*R*,3*S*,5*R*)-(+)-**132** and (+)-**133** in 43% yield. Compound **132** was transformed into α-amino acid derivatives **134** with Raney-Ni (Scheme 37).[50] Reductive amination, under the reaction conditions is believed responsible for the N-Et derivative **134**.

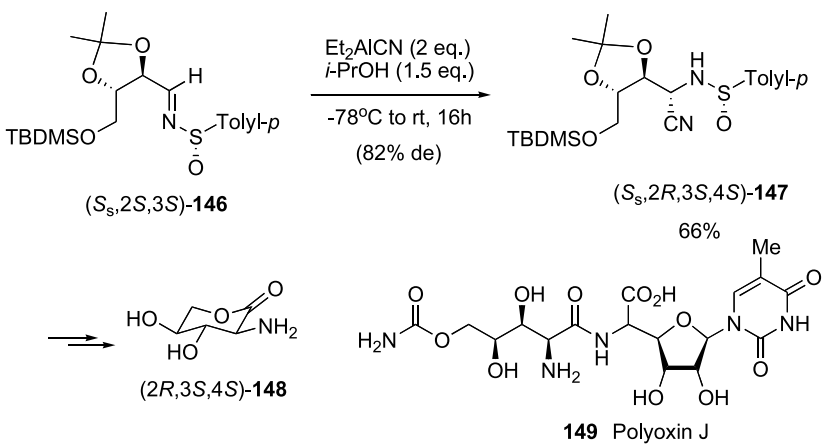
5. Applications of sulfinimines in the asymmetric synthesis of natural products and bioactive compounds

5.1. Amines

DIBAL−H reduction of the ketone-derived sulfinimine **135** afforded the corresponding sulfinamide **136** in 80% yield and 86% de (Scheme 38).[51] Removal of the sulfinyl group with TFA gave **137**, a chiral amino unit found in the human leukocyte elastase inhibitor, DMP 777, **138**.



Scheme 39.



Scheme 40.

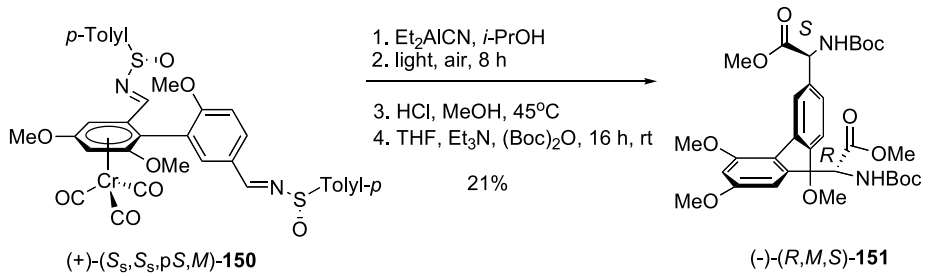
5.2. α- and β-Amino acids

(2*S*,6*S*)- and (2*S*,6*R*)-Diaminopimelic acids **145** are important bis(α-amino acids) that function as substrate-based inhibitors, that is, antibiotics. A new strategy, based on the sulfinimine-mediated asymmetric Strecker synthesis, was introduced by Davis and Srirajan for the preparation of these compounds (Scheme 39).[52] Reaction of (S_S)-**139** with Et_2AlCN/*i*-PrOH afforded α-amino nitrile (S_S,*S*)-**140** in 86% yield and >96% de. Further manipulation of **140** gave rise to aldehyde **141**, which could be condensed with (S_S)-(+)-*p*-toluenesulfinamide (**142**). The resulting (S_S,2*S*)-**143** upon treatment with Et_2AlCN/*i*-PrOH treatment gave **144** in 69% yield. Deprotection and hydrolysis afforded (2*S*,6*S*)-**145** (DAP) in >97% ee. Similarly, use of (R_S)-**142** for the condensation with **141** and subsequent transformations led to *meso*-DAP (2*S*,6*R*)-**145**.

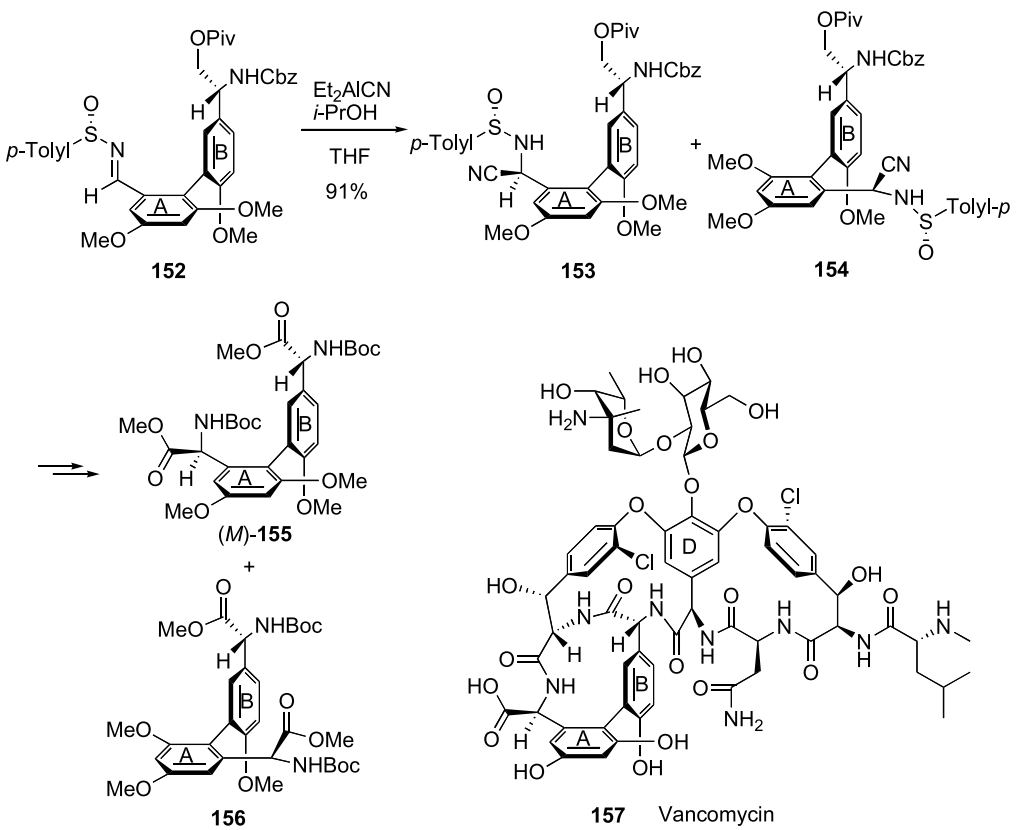
Treatment of sulfinimine (S_S,2*S*,3*S*)-**146** with 2 equiv. of Et_2AlCN in the presence of 1.5 equiv. of *i*-PrOH afforded a mixture of diastereomeric products in 82% de, from which the major isomer (S_S,2*R*,3*S*,4*S*)-**147** was isolated in 66% yield in diastereomerically pure form (Scheme 40).[53] Compound **147** was transformed into polyoxamic acid lactone **148**, a structural unit found in polyoxin J **149**.

Reaction of bis-sulfinimine **150** with Et_2AlCN/*i*-PrOH followed by decomplexation, hydrolysis, and amino group protection afforded compound **151** in 21% overall yield (Scheme 41).[54a] Similar reaction of sulfinimine **152** with Et_2AlCN/*i*-PrOH gave a mixture of amino nitriles **153** and **154** in 91% yield, from which (*M*)-**155**, the AB ring unit of the glycopeptide antibiotic Vancomycin (**157**), has been prepared (Scheme 42).[54b]

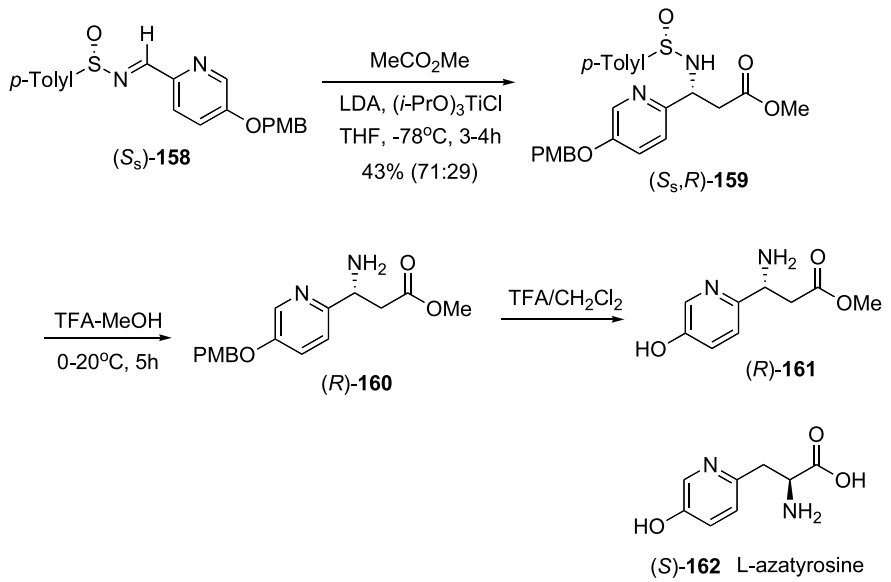
Asymmetric addition of enolates to sulfinimines is an important method for the synthesis of β-amino acid derivatives.[1] Adamczyk and Reddy used this method for



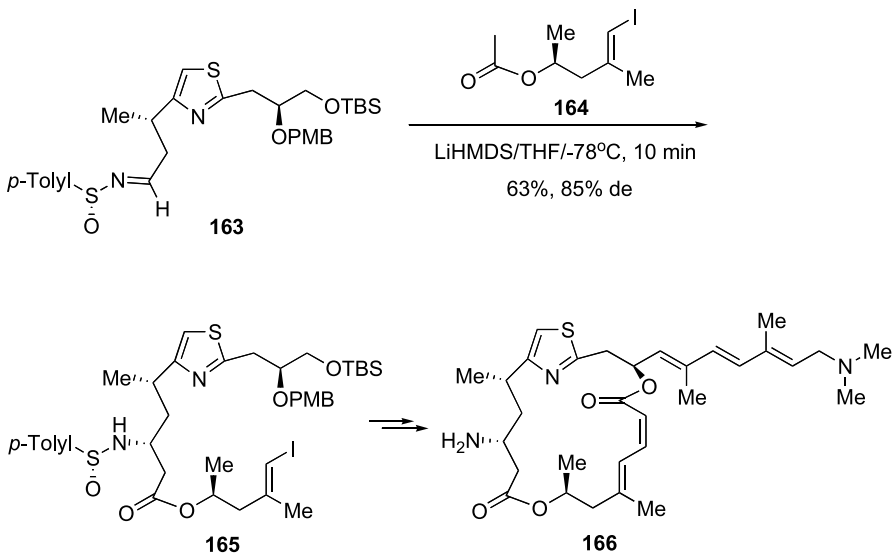
Scheme 41.



Scheme 42.



Scheme 43.



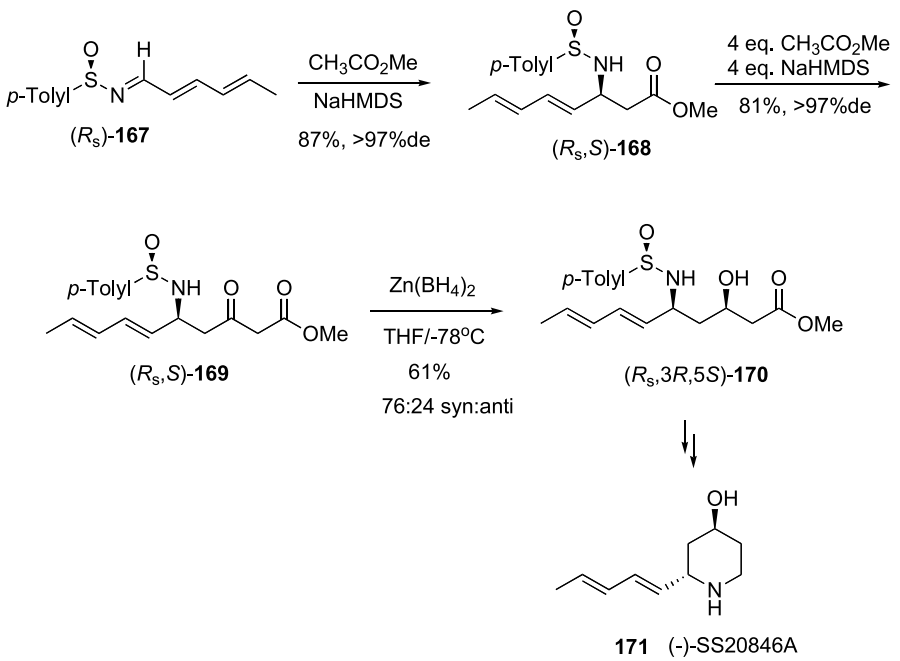
Scheme 44.

the preparation of (*R*)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate (**161**), an analog of L-azatyrosine (**162**), an antibiotic isolated from Streptomyces chibanesis.[55] Treatment of (S_S)-**158** with the lithium enolate of methyl acetate in the presence of $(i\text{-PrO})_3\text{TiCl}$ gave a mixture of diastereomeric products, from which the desired (S_S,*R*)-**159** was isolated in 43% yield. Removal of the protecting groups afforded (*R*)-**161** in >95% ee (Scheme 43).[55]

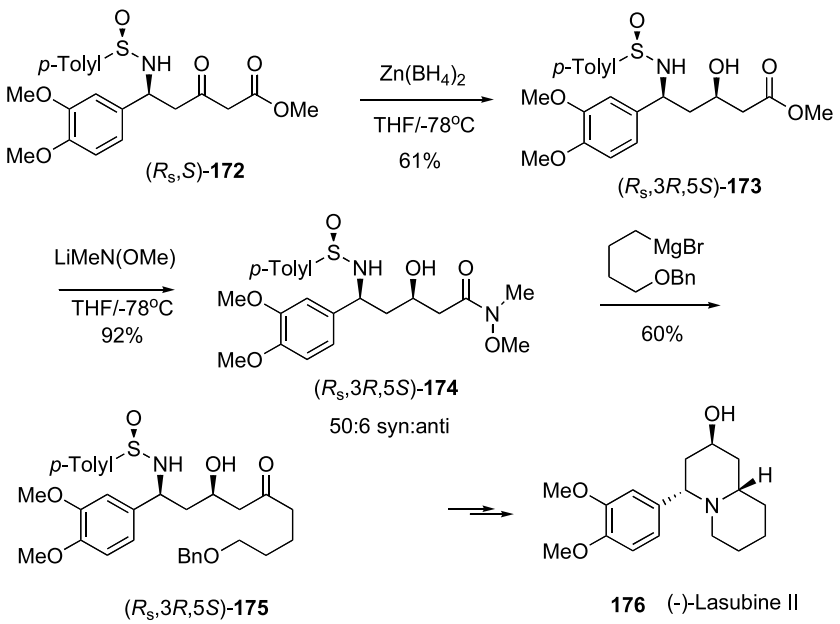
(−)-Pateamine **166** is a unique thiazole-containing 19-membered, bis lactone isolated from the marine sponge (*Mycale* sp.) that exhibits potent immunosuppressant activity with low cytotoxicity.[56] A concise and convergent synthesis of this compound has been described by Remuinan and Pattenden, involving sulfinimine-mediated β-amino ester formation as one of the key steps as shown in Scheme 44.[56] The addition of the lithium enolate of **164** to sulfinimine **163** resulted in the β-amino ester **165** in 63% yield and 85% diastereopurity.

5.3. Piperidines, quinolizidines, indolizidines

β-Amino ester (R_s,*S*)-**168** was prepared in 87% yield and >97% de by treating the sodium enolate of methyl acetate with sulfinimine (R_s)-**167** (Scheme 45).[24] Subsequent treatment of **168** with an excess of the enolate afforded δ-amino β-ketoester chiral building block (R_S,*S*)-**169** in 81% yield and >97% de. Reduction of **169** with $Zn(BH_4)_2$ gave a 76:24 *syn*/*anti* mixture of isomers resulting in isolation of (R_s,3*R*,5*S*)-**170** in 61% yield. Further elaboration of **170** afforded (−)-SS20846A **171**. (−)-SS20846A



Scheme 45.

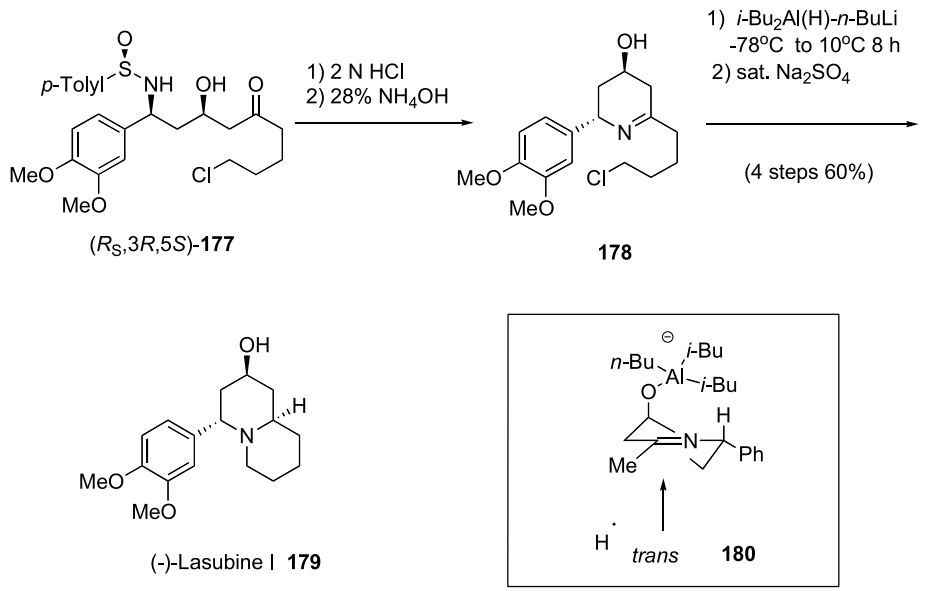


Scheme 46.

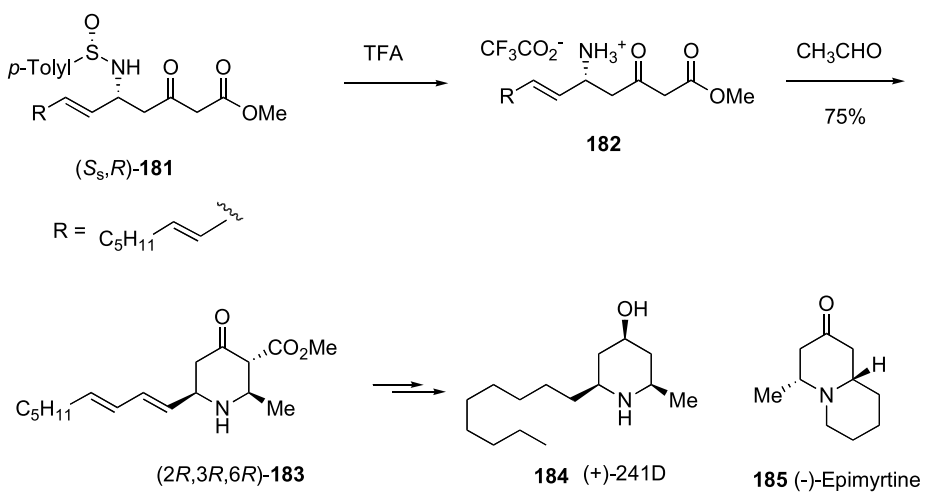
was isolated from *Steptomyces* sp. S20846 and is a proposed intermediate in the biosynthesis of the potent antimicrobial agent Streptazolin.

A similar strategy was employed in the synthesis of (−)-lasubine II (**176**), a member of a large family of naturally occurring alkaloids named lythraceaes (Scheme 46).[57] The keto group in sulfinimine derived δ-amino β-keto-ester (R_S,*S*)-**172** was selectively reduced to give **173** (50:6 *syn*/*anti*) followed by its conversion into Weinreb amide **174** as a key step. On reaction with 4-(benzyloxy)-1-butanemagnesium bromide **174** affords ketone **175** in 60% yield, which was used to install the quinolizidine ring.

The related (−)-lasubine I (**179**), that has the 2,6-substituents *trans*, was prepared similarly from hydroxy ketone **177** (Scheme 47).[58] The key step in this synthesis was the highly stereoselective reduction of an intermediate 1,2-dehydropiperidine **178** by the 'ate' complex prepared from DIBAL−H and *n*-BuLi. Here, it was suggested that alkoxy aluminum intermediate **180** shields the top face of the C−N double bond, which would favor the approach of the hydride from the bottom face.



Scheme 47.



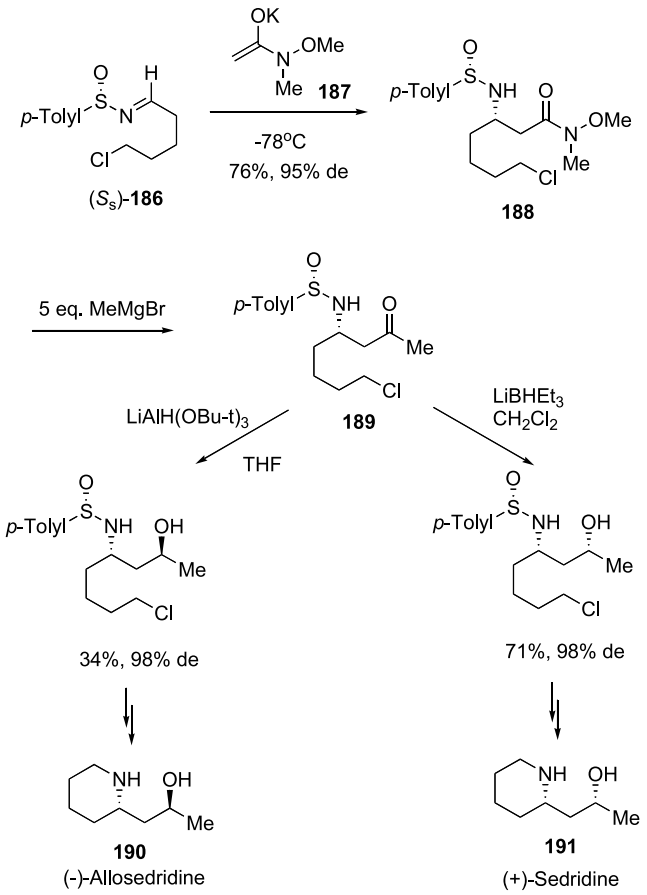
Scheme 48.

The *N*-sulfinyl group in δ-amino β-ketoester (S_s,*R*)-**181** is removed with TFA/MeOH to give the trifluoroacetate ammonium salt **182**, which on treatment with acetaldehyde affords piperidine (2*R*,3*R*,6*R*)-**183** in 75% yield for the two steps (Scheme 48).[59] This transformation, which involves an intramolecular Mannich reaction, permits the rapid assembly of 2,3,4,6-tetrasubstituted piperidines in a highly stereoselective fashion. Decarboxylation, hydrogenation of the double bonds, and stereoselective reduction of the 4-oxo group afforded the dendrobate alkaloid (+)-241D **184** (Scheme 48).[59] A similar strategy was employed in the preparation of the quinolizidine alkaloid (−)-epimyrtine (**185**).[60]

Reaction of sulfinimine (S_S)-**186** with the potassium enolate of *N*-methoxy-*N*-methylacetamide **187** gave Weinreb amide **188** in 76% yield and 95% de.[30] Treatment of **188** with methylmagnesium bromide afforded the methyl ketone **189**, which could be further elaborated to (−)-allosedridine (**190**) and (+)-sedridine (**191**) as illustrated in Scheme 49.[29] These are examples of sedrum alkaloids, members of a large family of 2-substituted and 2,6-disubstituted piperidines having various combinations of carbonyl and hydroxyl functionalities in the side chains.

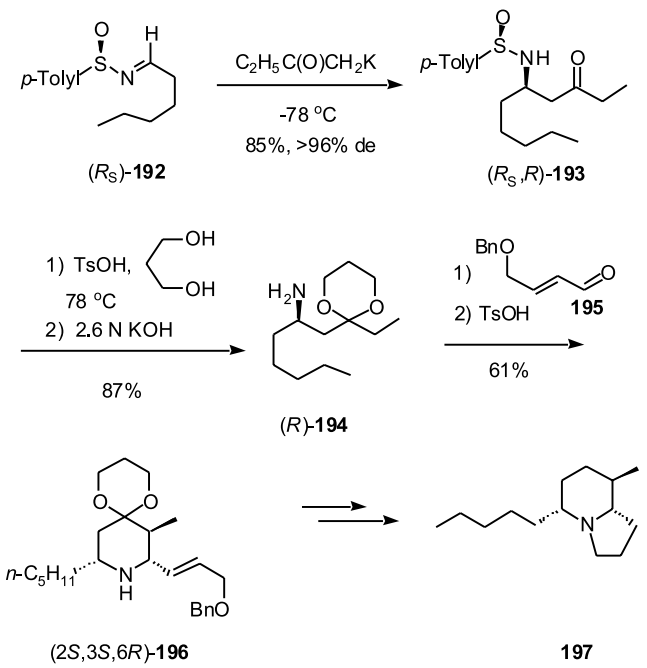
N-Sulfinyl β-amino ketone (R_S,*R*)-**193**, prepared by reaction of the potassium enolate of methyl ethyl ketone with sulfinimine (R_S)-**192**, undergoes deprotection/protection on treatment with TsOH and 1,3-propanediol to give β-amino ketal **194** (Scheme 50).[61] Amino ketals such as **194** are valuable building blocks for the asymmetric construction of polylsubstituted piperidines. For example, reaction of **194** with (*E*)-4-benzyloxy-but-2-enal (**195**) and TsOH afforded **196** in 61% yield. Further elaboration of **196** gave the indolizidine alkaloid **197** (Scheme 50).[61]

Deprotonation of allylphenylsulfone with LDA followed by reaction with sulfinimine (S_S)-**198** in THF at −100 °C

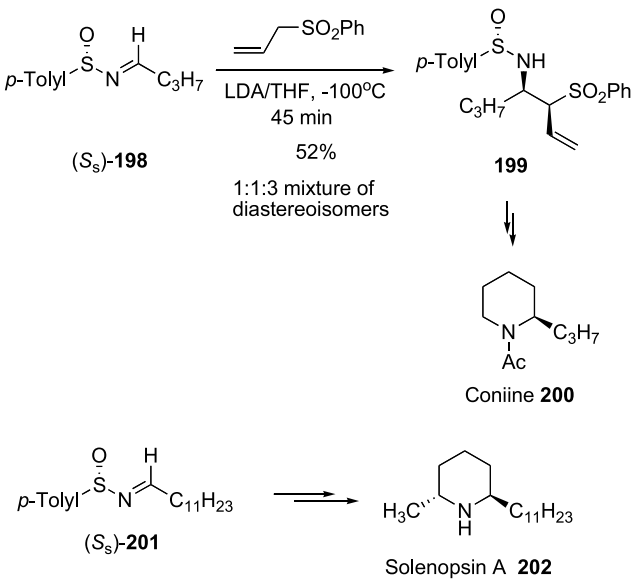


Scheme 49.

afforded **199** in 52% yield after separation of the 1:1:3 mixture of diastereoisomers (Scheme 51).[62] Desulfinylation of *N*-sulfinyl homoallylamine **199** followed by mono-allylation and subsequent transformations including Grubbs RCM gave rise to *N*-acetyl-(*R*)-coniine (**200**), the poisonous



Scheme 50.



Scheme 51.

hemlock alkaloid. (2*R*,6*R*)-*trans*-Solenopsin A (**202**), a constituent of fire-ant venom has been synthesized in a similar manner starting from sulfinimine **201** (Scheme 51).[62]

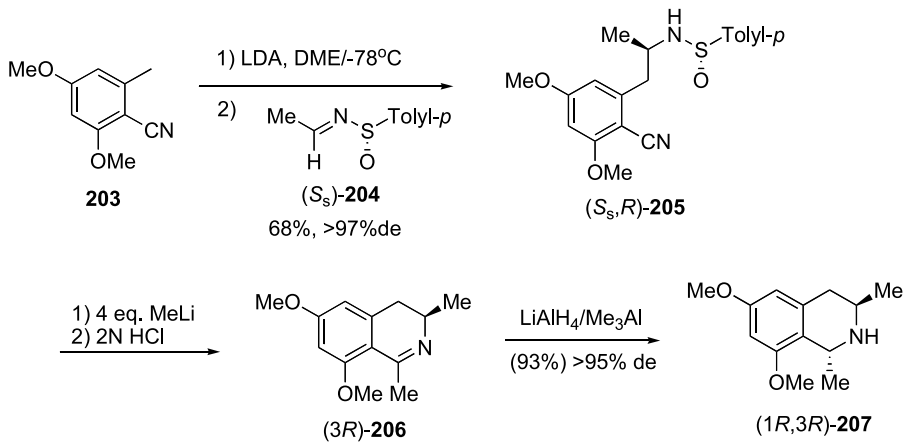
5.4. 1,2,3,4-Tetrahydroisoquinolines

Davis and Andermichael reported in 1999 that the benzylic carbanion generated from *O*-methylbenzoamide reacts stereoselectively with sulfinimines. The sulfinamide product was transformed to 3-substituted tetrahydroisoquinolines, important chiral building blocks for alkaloid synthesis.[1,63] More recently, this group described the reaction of the carbanion generated from benzonitrile **203** with (S_S)-**204** afforded sulfinamide (S_S,*R*)-**205** in 68% yield and >97% de (Scheme 52).[64] Treatment of (S_S,*R*)-**205** with 4 equiv. of methyllithium followed by acidification gave the isoquinoline (3*R*)-**206** directly in 65% yield. Reduction of **206** with $LiAlH_4/Me_3Al$ produced (1*R*,3*R*)-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**207**) in 93% yield and >95% de. This isoquinoline is a key segment of the anti-HIV michellamines.

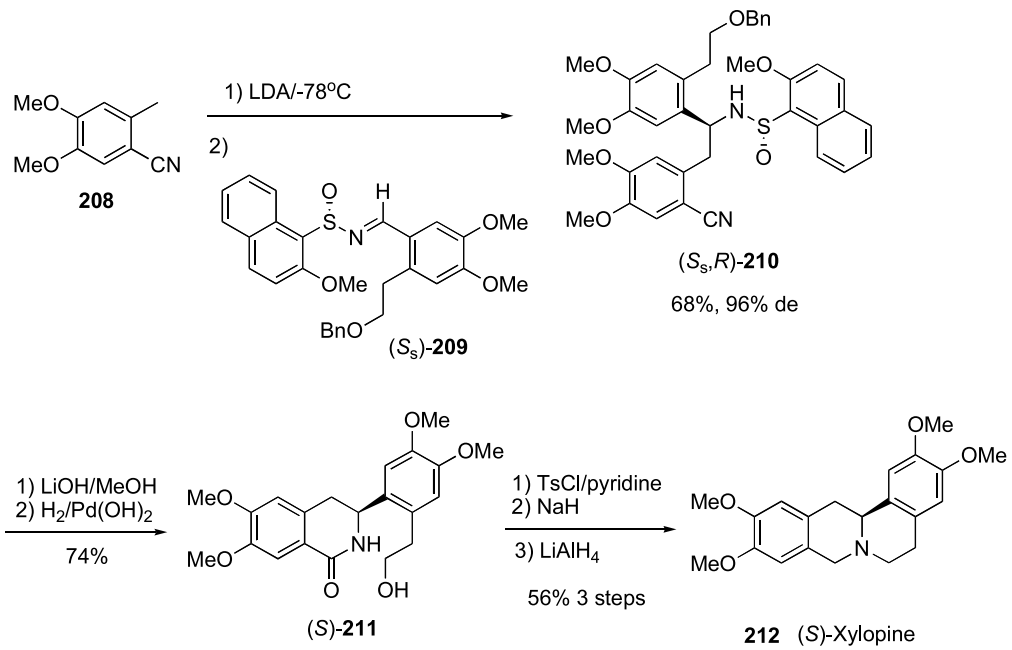
(*S*)-Xylopinine (**212**) is a prototypical member of the protoberberines, a large family of naturally occurring alkaloids characterized by a tetracyclic ring skeleton and an isoquinoline core. Davis and Mohanty described an asymmetric synthesis of this compound as illustrated in Scheme 53.[65] The key step in this synthesis is the diastereoselective addition of the benzylic carbanion generated from nitrile **208** to enantiopure sulfinimine (S_S)-**209** to give sulfinamide (S_S,*S*)-**210** in 68% yield and 96% de. Treatment of **210** with LiOH in methanol followed by debenzylation afforded (*S*)-**211** in 74% yield, which was then elaborated to (*S*)-xylopine (**212**) in three steps.

5.5. Pyrrolidines

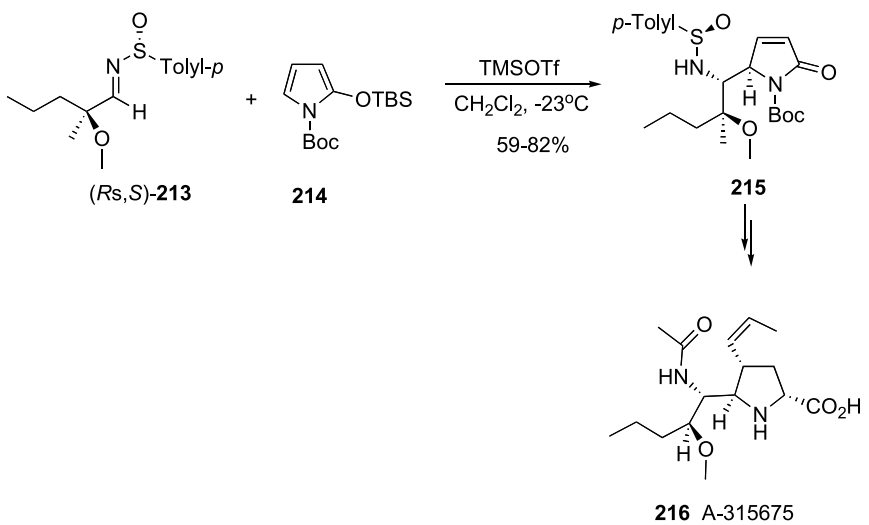
A-315675 (**216**) is a highly potent, broad-spectrum anti-influenza agent discovered at Abbott (Scheme 54). An



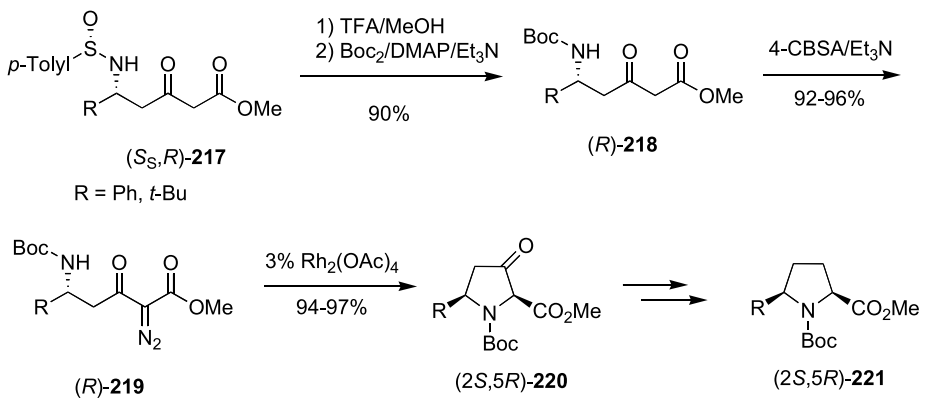
Scheme 52.



Scheme 53.



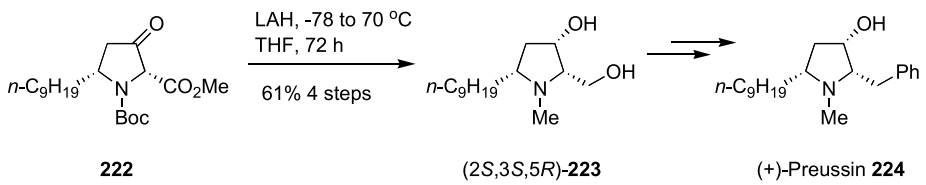
Scheme 54.



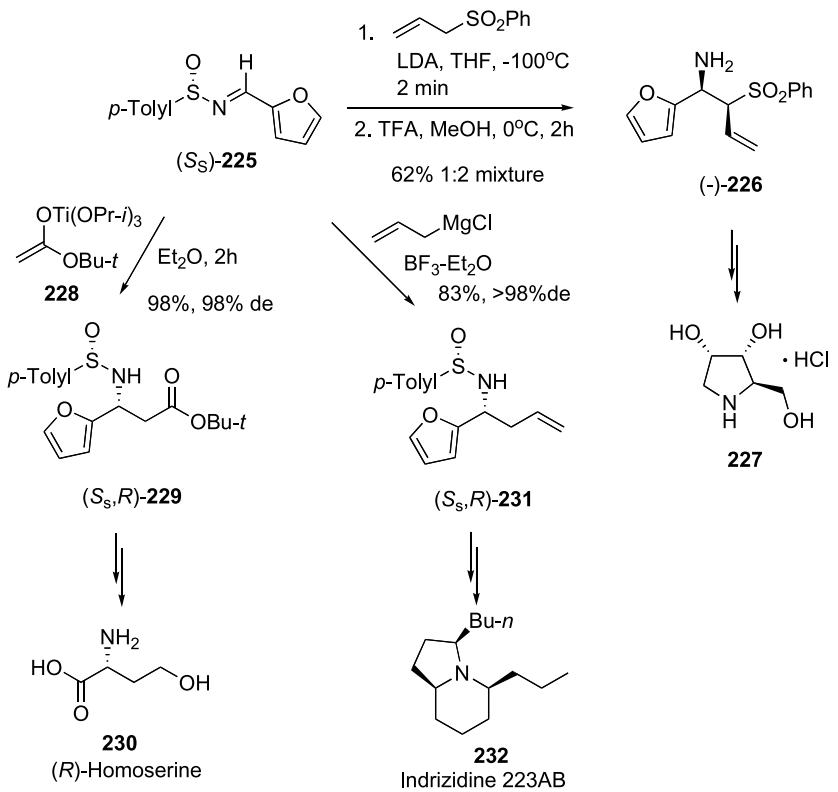
Scheme 55.

enantioselective synthesis of this compound was recently reported by DeGoey and co-workers.[66] One of the key steps in this procedure involved a diastereoselective addition of silyloxypyrrole **214** to sulfinimine **213** to give **215**. Further elaboration of **215** led to A-315675 (**216**).

The sulfinimine-derived δ-amino β-ketoester polyfunctionalized chiral building block not only provides efficient access to multi-substituted piperidine alkaloids (see Section 5.3), but to pyrrolidines as well. Thus, deprotection/protection of **217** gave the *N*-Boc-δ-amino β-ketoester (*R*)-**218** that on treatment with 4-carboxybenzenesulfonylazide (4-CBSA) and Et_3N afforded the δ-amino-β-ketone-α-diazoesters **219** in 92–96% yield (Scheme 55).[67,68] With 3 mol% of $Rh_2(OAc)_4$ in DCM **219** gave 3-oxo prolines (2*S*,5*R*)-**220** in excellent yield. The intramolecular metal carbenoid NH insertion reaction was highly stereospecific, affording the *cis*-isomers exclusively. Removal of the 3-oxo



Scheme 56.



Scheme 57.

group via hydrogenation of the vinyl triflate or enol phosphonate gave *cis*-5-phenylproline **221** (R=Ph)[67] and *cis*-5-*tert*-butylproline **221** (R=*t*-Bu),[68] respectively (Scheme 55). *cis*-5-Phenylproline is a component of (+)-RP 66803, a nonpeptide cholecystokinin antagonist, while *cis*-5-*tert*-butylproline has been used in probing peptide conformations.

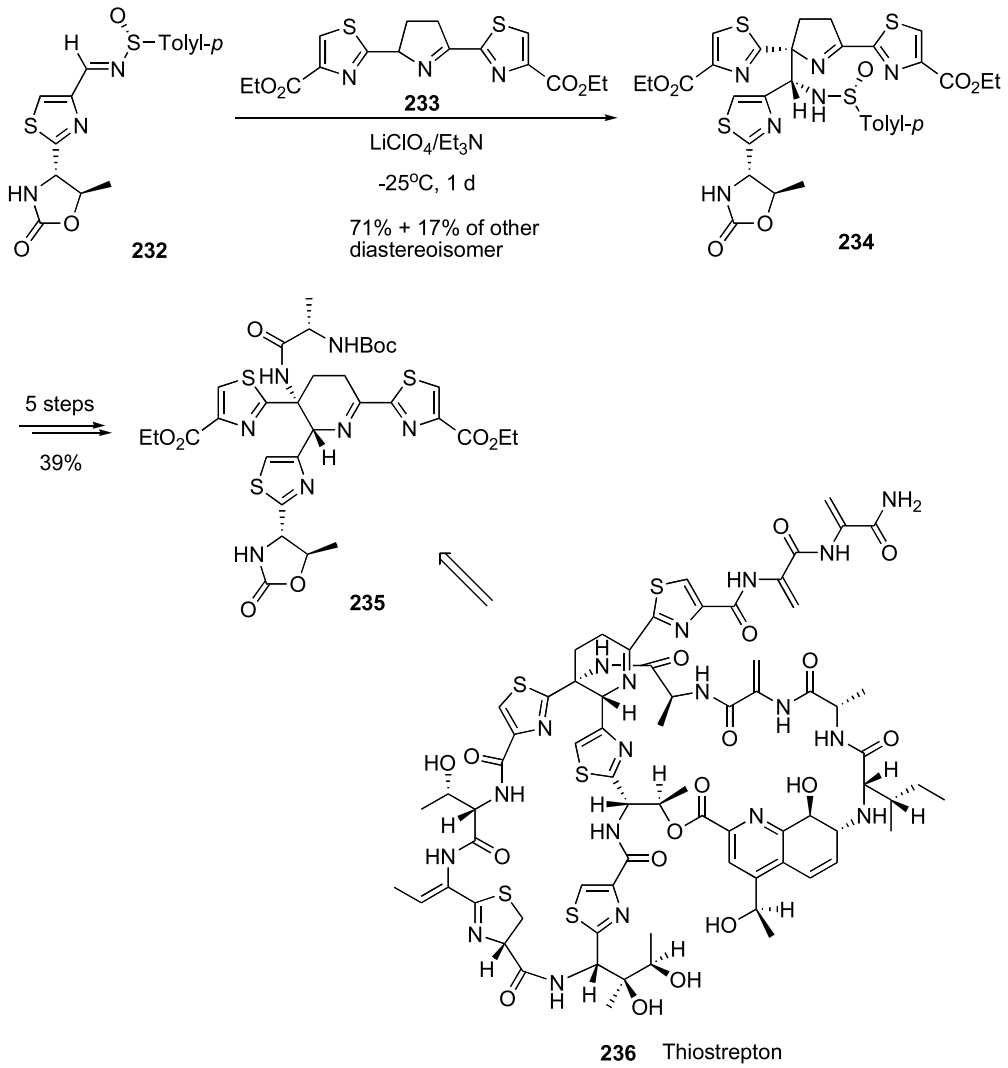
In a similar manner, 3-oxo proline **222** was prepared from the corresponding α-diazoester and was elaborated to the potent antifungal pyrrolidine alkaloid (+)-preussin **224** (Scheme 59).[69] A key step in the synthesis was the highly stereoselective one pot reduction of **222** to diol (2*S*,3*S*,5*R*)-**223** with LAH in 61% yield for the four step sequence.

Treatment of the 2-furaldehyde derived sulfinimine (S_S)-**225** with lithiated allylsulfone carbanion followed by removal of the sulfonyl group afforded amine (−)-**226** in 62% isolated yield as the major isomer (Scheme 57).[70] This amine was converted to 1,4-dideoxy-1,4-imino-D-ribitol **227** in a series of transformations. Reaction of **225** with titanium enolate **228** gave the β-amino ester (S_S,*R*)-**229** in 98% yield and >98% de which was transformed to (*R*)-homoserine **230** in three steps in 23% overall yield (Scheme 56).[13] Addition of allyl magnesium chloride to (S_S)-**225** in ether in the presence of BF_3 gave the homoallyl amine derivative (S_S,*S*)-**231**, which was converted in a number of steps to indrizidine 223AB (**232**) (Scheme 57).[13] This alkaloid was isolated from the skin extracts of the neotropical poison-dart frog (genus *Dendrobates*).

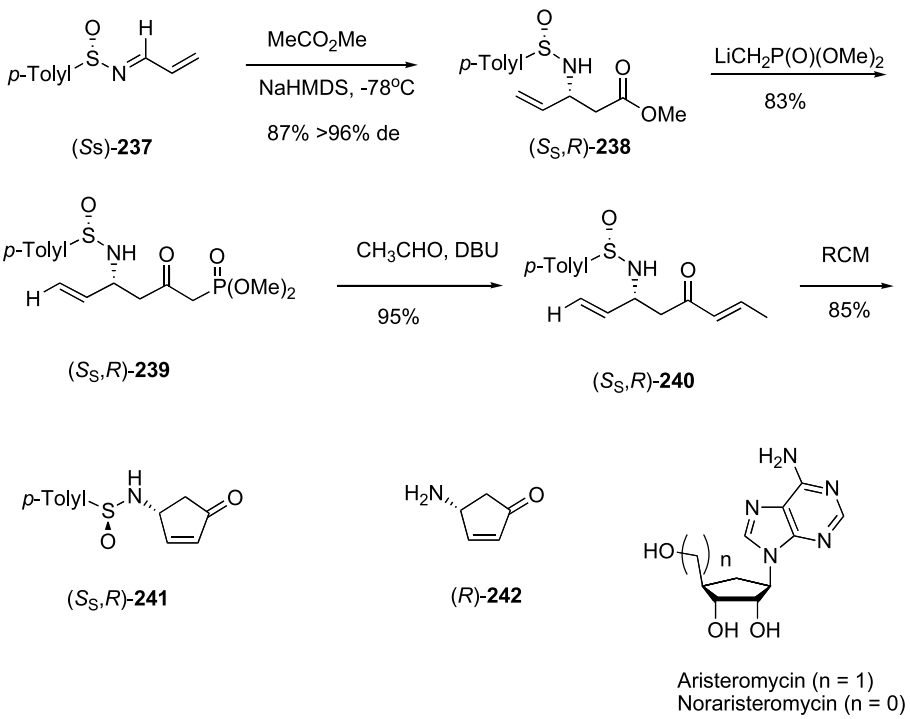
5.6. Miscellaneous

Dehydropiperidine **235** is the core of the peptide antibiotic thiostrepton **236** and its related family of compounds. Hashimoto and co-workers described recently the asymmetric synthesis of this material that is highlighted by the coupling between an azomethine ylide derived from **233** and enantiopure sulfinimine **232** (Scheme 58).[71] Sulfinamide **234** isolated in 71% yield along with 17% of the other diastereoisomer was further elaborated to **235** in five steps and 39% overall yield.

(*R*)-4-Aminocyclopentenone (**242**) is a valuable chiral building block for the asymmetric synthesis of structurally diverse antiviral and anticancer carbocyclic nucleosides



Scheme 58.



Scheme 59.

such as aristeromycin and noraristeromycin (Scheme 59).[72] Amino keto-2,7-diene **240** underwent ring closing metathesis with 5 mol % of Grubbs second generation catalyst to give the *N*-sulfinyl-4-aminocyclopentenone **241** in 85% yield. The amino ketodiene was readily prepared using Horner–Wadsworth–Emmons chemistry and *N*-sulfinyl-δ-amino β-ketophosphonate **239**. This new sulfinimine derived chiral building block was produced by treatment of the unsaturated β-amino ester **238**, prepared from crotonaldehyde derived sulfinimine (S_S)-**237**, with an excess of the lithium dimethyl methylphosphonate (Scheme 59).

6. Summary and conclusions

Sulfinimines (*N*-sulfinyl imines) have provided a general solution to the problem of the addition of organometallic reagents to the C–N double bond of chiral imines. The resulting amine derivatives, sulfinamides, produced in high de and with predictable stereochemistry, are readily converted to enantiopure amines; α- and β-amino acids; and α- and β-amino phosphonates. Moreover, sulfinimines are stable and easily prepared from diverse aldehydes and ketones by condensation of commercially available (*R*)- and (*S*)-*p*-toluenesulfinamide and *tert*-butanesulfinamide.

The availability of small, easily manipulated chiral building blocks and templates continues to have a significant impact on the asymmetric synthesis of biologically and pharmaceutically valuable molecules. The emergence of simple, easily prepared, sulfinimine-derived polyfunctionalized chiral building blocks, including *N*-*p*-toluenesulfinyl β-amino carbonyl compounds; *N*-sulfinyl aziridine 2-carboxylates and phosphonates; 2*H*-azirine 2-caboxylates and 3-phosphonates; *N*-*p*-toluenesulfinyl δ-amino β-ketoesters; and *N*-*p*-toluenesulfinyl δ-amino β-ketophosphonates, is expected to further facilitate the asymmetric syntheses of increasingly complex biologically active nitrogen containing molecules for both industrial and academic applications.

Acknowledgements

We are indebted to Professor Mukund P. Sibi, North Dakota State University, and Drs. Jeffrey S. Sabol and Philip M. Weintraub, Aventis Inc. for reviewing the manuscript and offering helpful suggestions on content and organization. It is a pleasure to acknowledge the important efforts of our co-workers whose names appear in the references. The National Institute of General Medicinal Sciences supported our own contributions to this chapter.

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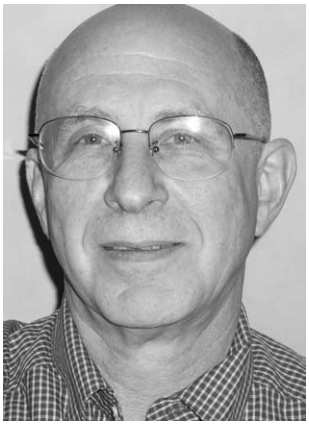
Biographical sketch

Ping Zhou was born in Shengxing, Zhejiang, China. She received her BS degree in 1984 from Hangzhou University. After working for 4 years in Zhejiang Agricultural University as an instructor she joined Professor Davis at Drexel University in 1988 and received her PhD degree in organic chemistry in 1994. After one and a half years of postdoctoral work with Professor Edward C. Taylor at Princeton University she joined Wyeth Ayerst Research in 1996 as a Research Scientist and now is a Principal Research Scientist in the Department of Medicinal Chemistry, Wyeth Research in Princeton, New Jersey. Her research has resulted in over 60 publications and patents.

Bang-Chi Chen was born in Ruian, Zhejiang, China. He received his BS degree in 1984 from Hangzhou University. He worked for 3 years in Hangzhou University as an instructor while conducting research with Professor Xian Huang. He joined Professor Davis at Drexel University in 1987 and received his PhD degree in organic chemistry 1991. In the same year he joined Bristol-Myers Squibb Company in Syracuse, New York as a Research Scientist and now is an Associate Director in the Department of Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb, in Princeton, New Jersey. His research efforts have resulted in over 120 publications and patents.



Franklin A. Davis received his BS degree from the University of Wisconsin in 1962 and his PhD degree from Syracuse University in 1966 working with Donald C. Dittmer. After 2 years with Michael J. S. Dewer as a Welch Postdoctoral Fellow at the University of Texas he joined the faculty of Drexel University where he was the George S. Sasin Professor of Chemistry until 1995. At this time he move across town to Temple University as Professor of Chemistry. His research interests are focused on the development of new synthetic methods for asymmetric synthesis related to chiral sulfur-nitrogen compounds; that is, *N*-sulfonyloxaziridines, *N*-fluorosulfinimides, and sulfinimines. The design and synthesis of sulfinimine derived polyfunctionalized chiral building blocks for the enantioselective synthesis of bioactive nitrogen heterocycles is a recent interest.

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Stereoselective synthesis of protected (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine, a component of halipeptins

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Received 28 May 2004; revised 16 June 2004; accepted 24 June 2004

Available online 29 July 2004

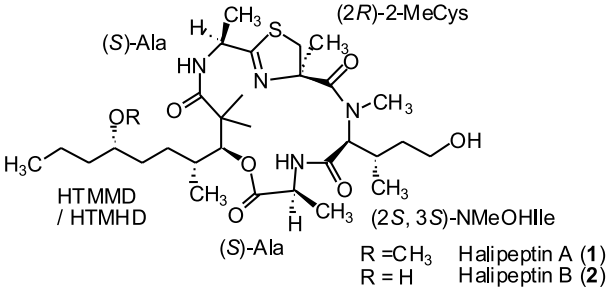
Abstract—The stereocontrolled synthesis of the protected (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine, a component of halipeptins A and B with potent anti-inflammatory activity, has been achieved. The key steps include (i) installation of a double bond to bicyclic lactam **4** using *N*-*tert*-butyl phenylsulfinimidoyl chloride, (ii) highly *exo*-selective Michael reaction with lithium dimethylcuprate in the presence of chlorotrimethylsilane, and (iii) Ru-catalyzed oxidative deprotection of *N*,*O*-benzylidene acetal to the acid anhydride.

1. Introduction

Halipeptins A (**1**) and B (**2**)[1] are novel 17-membered cyclic depsipeptides isolated from the marine sponge *Haliclona* sp. collected in waters off the Vanuatu Islands by Gomez-Paloma and co-workers in 2001. In 2002, Gomez-Paloma et al. corrected the original assignments for halipeptins and reported the structural revision of an oxazetidine ring to the thiazoline unit in halipeptins A and B (Fig. 1).[2] Halipeptin A is known to show strong anti-inflammatory activity in vivo, causing 60% reduction of edema in mice at the dose of 300 μg/kg. In addition to their potent biological activities, their intriguing structures containing (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine (*N*MeOHIle) and other unusual units prompted us and another group to initiate efforts directed towards the total synthesis. Very recently, Izzo and Riccardis reported the first synthesis of the *N*MeOHIle derivative in 10 steps and 1.1% overall yield, in which a diastereoselective silyl-assisted [3,3]-sigmatropic rearrangement was employed as a key step.[3] We required a practical synthesis of *N*MeOHIle for production of halipeptins and their analogues. Herein, we describe an enantioselective synthesis of protected (2*S*,3*S*)-*N*MeOHIle (**3**) based on the strategy of stereocontrolled transformation of chiral bicyclic lactam **4** and novel Ru-catalyzed oxidative deprotection of the benzylidene acetal originally developed by us.[4j]

2. Results and discussion

As the starting material for synthesis of (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine, we chose bicyclic lactam **4** derived from



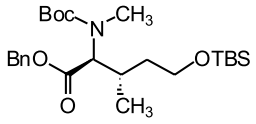


Figure 1. Structure of halipeptins.

Keywords: Halipeptin; Bicyclic lactam; *N*-*tert*-Butyl phenylsulfinimidoyl chloride; (2*S*,3*S*)-*N*-Methyl-5-hydroxyisoleucine.
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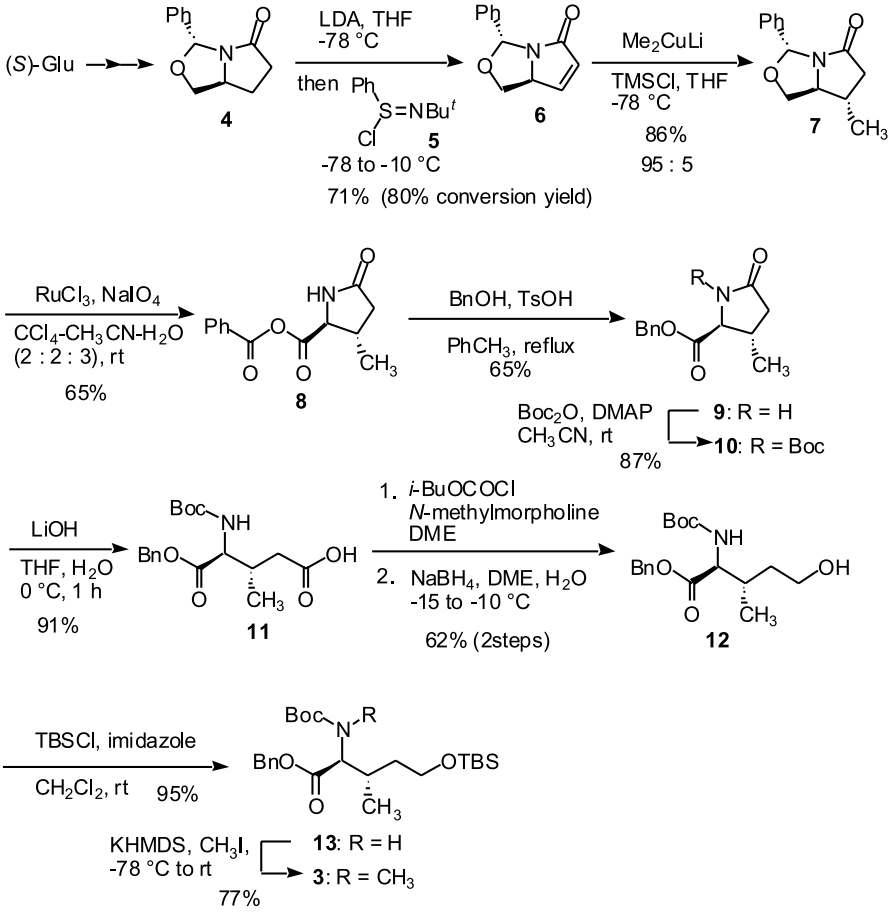
doi:10.1016/j.tet.2004.06.111

(*S*)-glutamic acid (Scheme 1). Bicyclic lactam **4** is a versatile synthon in the synthesis of a variety of natural products[4] and was prepared from (*S*)-pyroglutamic acid according to Thottathil's procedure.[5] First, introduction of a double bond to the lactam was performed by two-step conversion, phenylselenylation-phenylselenoxide elimination, developed by us.[4a,b] This method, however, requires highly toxic and expensive phenylselenium bromide or chloride, and in addition its reproducibility is sometimes problematic in large-scale production. In search of a solution for this problem we investigated the possibility of direct conversion using other less toxic reagents for the synthesis of the bicyclic unsaturated lactam. However, dehydrogenation of the lactam to give the unsaturated lactam proved difficult. For example, use of Saegusa method[6] and IBX oxidation[7] developed by Nicolaou for preparation of α,β-unsaturated ketones gave no desired product and/or recovery of the starting material. After several experiments, *N*-*tert*-butyl phenylsulfinimidoyl chloride (**5**) originally developed for ketonic compounds by Mukaiyama and Matsuo[8] was found to be effective and reliable for large-scale production of highly strained α,β-unsaturated lactam **6**. Thus, **4** was deprotonated with lithium diisopropylamide in tetrahydrofuran (−78 °C, 30 min) and treated with **5** (−78 to −10 °C, 8 h) to afford, in addition to a small amount of the starting material (11%), **6** in 71% isolated yield (80% conversion yield, 4.5 g scale). As expected, purification of **6** using silica gel column chromatography was difficult due to contamination of **4** with similar polarity. Fortunately, the latent methyl derivative **7** was found to be easily purified. Stereoselective introduction of the methyl group at the 6 position of the bicyclic lactam was carried out by using Hanessian's procedure.[9] Treatment of **6** with lithium dimethylcuprate (Me_2CuLi) in the presence of chlorotrimethylsilane[10] at −78 °C afforded methylated product **7** in 86% yield in a diastereomeric ratio of 95:5. The stereochemistry of the newly formed stereocenter was unambiguously assigned by NOE experiment using ^1H NMR.[4i] For removal of *N*,*O*-benzylidene acetal, we employed direct conversion to the acid anhydride using oxidative cleavage developed by us.[4j] Thus, acetal **7** was oxidized with a catalytic amount of ruthenium chloride (5 mol%) in the presence of sodium periodate in acetonitrile–carbon tetrachloride–water (2:2:3)[11] to give acid anhydride **8** in 65% yield, which was transformed to benzyl ester **9** by treatment with benzyl alcohol in the presence of *p*-toluenesulfonic acid in toluene under refluxing conditions. For selective cleavage of the lactam ring under coexistence of the benzyl ester, the nitrogen of the lactam was protected with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of *N*,*N*-dimethylaminopyridine (DMAP) to produce *tert*-butoxycarbonyl imide **10** in 87% yield. Functional group selective hydrolysis of the γ-lactam ring in **10** was carried out by using lithium hydroxide in aqueous THF to afford carboxylic acid **11** in excellent yield. Then **11** was converted to the mixed acid anhydride by treatment with isobutyl chloroformate in the presence of *N*-methylmorpholine and reduced to (2*S*,3*S*)-5-



Scheme 1. Stereoselective synthesis of (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine (*N*MeOHlle).

hydroxyisoleucine **12** with sodium borohydride in 62% yield. After protection of the hydroxy group as a *tert*-butyldimethylsilyl ether, *N*-methylation of **13** using iodomethane and potassium hexamethyldisilazide (KHMDS) in THF furnished protected (2*S*,3*S*)-*N*MeOHIle **3** in 77% yield.

3. Conclusion

In conclusion, we have achieved the stereoselective synthesis of protected (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine **3** in 9.9% overall yield by stereoselective transformation of chiral bicyclic lactam **4** based on (i) installation of a double bond using *N*-*tert*-butyl phenylsulfinimidoyl chloride, (ii) highly *exo*-selective Michael reaction in the presence of chlorotrimethylsilane, and (iii) Ru-catalyzed oxidative deprotection of *N*,*O*-benzylidene acetal **7** to acid anhydride **8** as the key steps. Further investigation toward the total synthesis of halipeptins is actively under way.

4. Experimental

4.1. General

Melting points were measured with a SHIBATA NEL-270 melting point apparatus. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM GSX400A and JNM ECP400 spectrometers. FAB mass spectra were obtained with a JEOL JMS-HX-110A spectrometer. Optical resolutions were determined on a JASCO DIP-140 and JASCO P-1020 polarimeter. Column chromatography was carried out with silica gel BW-820MH (Fuji silysia). Analytical thin layer chromatography was performed on Merck Kieselgel 60F254 0.25 mm thickness plates.

4.1.1. (2*R*,5*S*)-2-Phenyl-1-aza-3-oxabicyclo[3.3.0]oct-6-en-8-one (6). To a solution of diisopropylamine (3.4 mL, 24.3 mmol) in THF (82 mL) at 0 °C was added dropwise a solution of *n*-butyllithium in hexane (1.6 mol/L, 15.5 mL, 24.8 mmol) under argon atmosphere. After stirring at the same temperature for 30 min, the solution was cooled to −78 °C and a solution of **4** (4.49 g, 22.1 mmol) in THF (14 mL) was added dropwise via canula. After 30 min, a solution of *N*-*tert*-butyl benzenesulfinimidoyl chloride (9.63 g, 44.6 mmol) in THF (14 mL) was added in one portion. The reaction mixture was gradually warmed to −10 °C. After 8.5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL) and diluted with ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (1×100 mL). The organic extract was washed with saturated brine (100 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (200 g, *n*-hexane/ethyl acetate=1/1 to ethyl acetate only) to give **6** (3.33 g, 71%, conversion yield 80%) as a brown oil along with a small amount of the starting material **4** (0.506 g, 11.3%). The spectra of **6** were identical with those of the reference.[4b]

4.1.2. (2*R*,5*S*,6*S*)-6-Methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one (7). To a suspension of CuI (11.4 g, 59 mmol) in THF (344 mL) at −78 °C under argon atmosphere was added a solution of MeLi in ether (0.8 M, 105 mL, 84 mmol) and the mixture was stirred at 0 °C for 30 min. The resulting colorless solution was cooled to −78 °C and a solution of Me_3SiCl (7.57 mL, 59 mmol) and enone **6** (4.0 g, 19 mmol) in THF (30 mL) was added. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (250 mL). The aqueous phase was extracted with ether (3×120 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (3×100 mL), water (100 mL), and saturated brine (150 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (120 g, *n*-hexane/ethyl acetate=2/1) to give **7** (3.78 g, 86%) as a colorless oil: $[\alpha]_D^{22}=+228$ (*c* 0.64, $CHCl_3$) (lit.[9] (6*R*)-enantiomer: $[\alpha]_D=-2.3$ (*c* 1.47, $CHCl_3$)); IR (neat) 2962, 1710, 1453, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, $J=6.8$ Hz), 2.33–2.39 (1H, m), 2.46–2.69 (2H, m), 3.60 (1H, dd, $J=7.0$, 8.0 Hz), 3.62–6.77 (1H, m), 4.20 (1H, dd, $J=6.3$, 8.3 Hz), 6.35 (1H, s), 7.30–7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.16, 34.77, 42.31, 66.04, 70.77, 87.08, 125.95, 128.38, 128.49, 138.5, 177.5. HRMS (FAB, NBA) calcd for $C_{13}H_{16}NO_2$: 218.1181 ($M+H^+$). Found: 218.1185.

4.1.3. (2*S*,3*S*)-3-Methyl-5-oxo-pyrrolidine-2-carboxylic benzoic anhydride (8). To a solution of bicyclic lactam **7** (0.351 g, 1.62 mmol) and $NaIO_4$ (2.08 g, 9.72 mmol) in carbon tetrachloride (2 mL), and H_2O (3 mL) was added a solution of added $RuCl_3\cdot nH_2O$ (91% purity, 18.5 mg, 81.2 μmol) in acetonitrile (2 mL). After stirring at room temperature for 24 h, the reaction mixture was filtered through a pad of celite, and the filtrate was extracted with ethyl acetate, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by recrystallization (ethyl acetate/*n*-hexane) to give **8** (0.260 g, 1.05 mmol, 65%) as colorless solids: mp 172–174 °C; $[\alpha]_D^{23}=-18.9$ (*c* 1.06, $CHCl_3$); IR (KBr) 3854, 3821, 3745, 3676, 2966, 1741, 1680, 1291, 1247, 1212, 708, 633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, d, $J=7.1$ Hz), 2.29 (1H, dd, $J=5.4$, 17.8 Hz), 2.62–2.66 (1H, m), 2.92 (1H, dd, $J=8.5$, 17.8 Hz), 4.53 (1H, d, $J=4.9$ Hz), 7.41–7.45 (2H, m), 7.53–7.57 (1H, m), 7.66–7.68 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.0, 30.2, 39.9, 65.3, 127.9, 129.2, 132.5, 133.5, 170.7, 172.7, 175.2. Anal. calcd for $C_{13}H_{13}NO_4$: C, 63.15, H, 5.30, N, 5.67. Found: C, 63.29, H, 5.39, N, 5.69.

4.1.4. (2*S*,3*S*)-3-Methyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester (9). To a solution of **8** (0.197 g, 0.797 mmol) and benzyl alcohol (0.83 mL, 8.02 mmol) in toluene (4 mL) was added $TsOH\cdot H_2O$ (18.6 mg, 0.098 mmol). The reaction mixture was heated to reflux for 14.5 h. After cooling, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1 to $CHCl_3/CH_3OH$=4/1) to afford **9** (0.121 g, 65%) as a brown oil. The analytical sample was obtained by recrystallization (*n*-hexane/ether) as colorless needles: mp 79 °C; $[\alpha]_D^{19}=+21.1$ (*c* 0.66, $CHCl_3$); IR (KBr) 3218, 1701, 1669, 1457, 1264, 1090, 1005, 752, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, d, $J=$

6.6 Hz), 1.98–2.08 (1H, m), 2.53–2.65 (2H, m), 3.86 (1H, d, J=5.4 Hz), 5.18 (1H, d, J=12.2 Hz), 5.22 (1H, d, J=12.2 Hz), 5.94 (1H, s), 7.33–7.41 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.1, 34.1, 37.8, 62.4, 67.3, 128.3, 128.6, 128.7, 135.1, 171.4, 176.7. Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00. Found: C, 66.97, H, 6.51, N, 5.96.

4.1.5. (2*S*,3*S*)-3-Methyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester (10). A solution of **9** (0.200 g, 0.857 mmol), Boc_2O (0.565 g, 2.59 mmol), and DMAP (21.8 mg, 0.178 mmol) in CH_3CN (4.3 mL) was stirred at room temperature. After 9.5 h, the reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1) to give **10** (0.249 g, 87%) as a colorless oil: $[\alpha]_D^{22}=-14.7$ (c 1.03, $CHCl_3$); IR (neat) 2977, 1793, 1752, 1715, 1499, 1456, 1369, 1314, 1154, 1087, 1021, 911, 839, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, d, J=6.8 Hz), 1.42 (9H, s), 2.14 (1H, dd, J=4.2 Hz, 17.3 Hz), 2.31–2.40 (1H, m), 2.77 (1H, dd, J=8.5, 17.3 Hz), 4.22 (1H, d, J=3.4 Hz), 5.19 (1H, d, J=12.2 Hz), 7.33–7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.5, 27.8, 29.7, 39.4, 66.0, 67.3, 83.7, 128.5, 128.6, 128.7, 135.0, 149.3, 170.7, 172.7. HRMS (FAB, NBA) calcd for $C_{18}H_{24}NO_5$: 334.1654 ($M+H^+$). Found: 334.1628.

4.1.6. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-3-methyl-1,5-pentanedioic acid 1-benzyl ester (11). To a solution of **10** (0.249 g, 0.747 mmol) in THF (3.2 mL) and water (0.8 mL) at 0 °C was added $LiOH\cdot H_2O$ (36.3 mg, 0.865 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized by addition of acetic acid and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$=9/1) to give **11** (0.238 g, 91%) as a yellow oil: IR (neat) 3330, 2976, 1718, 1560, 1508, 1457, 1369, 1160, 1069, 1017, 753, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.982 (3 H, d, J=6.4 Hz), 1.43 (9H, s), 2.21–2.22 (1H, m), 2.42–2.46 (2H, m), 4.34 (1H, brs), 5.09–5.22 (3H, m), 7.30–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 16.5, 28.2, 33.5, 57.6, 67.2, 77.2, 80.2, 128.4, 128.5, 128.6, 135.1, 155.5, 171.6; $[\alpha]_D^{22}=+5.49$ (c 1.52, $CHCl_3$). HRMS (EI) calcd for $C_{18}H_{25}NO_6$: 351.1682. Found: 351.1693.

4.1.7. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-hydroxy-3-methylpentanoic acid benzyl ester (12). To a solution of **11** (0.126 g, 0.359 mmol) in 1,2-dimethoxyethane (DME, 0.5 mL) at −15 °C were successively added a solution of *N*-methyl morpholine (40.9 mg, 0.404 mmol) in DME (0.5 mL) and isobutyl chloroformate (53.9 mg, 0.395 mmol) in DME (0.5 mL), and the reaction mixture was stirred at −15 to −10 °C for 15 min. The precipitated *N*-methyl morpholine hydrochloride was removed by filtration and washed with DME, and the combined filtrates were chilled to −15 °C in an ice–salt bath. Then, a solution of $NaBH_4$ (41.0 mg, 1.08 mmol) in water (0.5 mL) was added in one portion at −15 °C. After stirring at −15 to −10 °C for 10 min, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1) to give **12** (75.5 mg, 62%) as a colorless oil: $[\alpha]_D^{22}=+5.49$ (c 1.52, $CHCl_3$); IR (neat) 3382, 2974, 1710, 1560, 1499, 1457, 1366, 1250, 1163, 1057, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.916 (3H, d, J=6.8 Hz), 1.43 (9H, s), 1.55–1.63 (1H, m), 2.16–2.17 (2H, m), 3.59 (1H, m), 3.70 (1H, m), 4.34–4.37 (1H, m), 5.13 (1H, d, J=12.2 Hz), 5.22 (1H, d, J=12.2 Hz), 5.36 (1H, d, J=7.8 Hz), 7.31–7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 16.0, 28.3, 33.2, 35.0, 57.3, 60.0, 67.0, 77.2, 79.9, 128.4, 128.5, 128.6, 135.3, 155.7, 171.9. HRMS (EI) calcd for $C_{18}H_{28}NO_5$: 338.1967 (MH^+). Found: 338.1935.

4.1.8. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsiloxy)-3-methylpentanoic acid benzyl ester (13). To a solution of TBSCl (0.230 g, 1.53 mmol) and imidazole (0.180 g, 2.64 mmol) in CH_2Cl_2 (1 mL) was added a solution of **12** (0.171 g, 0.507 mmol) in CH_2Cl_2 (1.5 mL) via cannula and the reaction mixture was stirred at room temperature for 10.5 h. The reaction was diluted with ethyl acetate, washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5/1) to give **13** (0.218 g, 95%) as a colorless oil: $[\alpha]_D^{24}=+1.72$ (c 0.99, $CHCl_3$); IR (neat) 3356, 2929, 1718, 1560, 1499, 1365, 1255, 1163, 1099, 836, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.030 (6H, s), 0.876 (9H, s), 0.940 (3H, d, J=7.0 Hz), 1.28–1.36 (1H, m), 1.43 (9H, s), 1.53–1.60 (2H, m), 2.17 (1H, m), 3.54–3.60 (1H, m), 3.62–3.67 (1H, m), 4.25–4.28 (1H, m), 5.13 (1H, d, J=12.5 Hz), 5.18 (1H, d, J=12.5 Hz), 5.32 (1H, d, J=8.8 Hz), 7.32–7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.40, 16.3, 18.3, 25.9, 28.3, 32.9, 35.0, 58.3, 60.5, 66.8, 79.6, 128.3, 128.5, 135.5, 155.7, 172.2. HRMS (FAB, NBA) calcd for $C_{24}H_{42}NO_5Si$: 452.2832 ($M+H^+$). Found: 452.2838.

4.1.9. (2*S*,3*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-5-(*tert*-butyldimethylsiloxy)-3-methyl pentanoic acid benzyl ester (3). To a solution of **13** (52.9 mg, 0.117 mmol) in THF (1 mL) under Ar atmosphere was added 0.5 M solution of KHMDS in toluene (0.26 mL, 0.130 mmol) at −78 °C and the mixture was stirred at the same temperature for 30 min. Then iodomethane (0.070 mL, 1.12 mmol) was added and the reaction temperature was gradually warmed to room temperature. After 18.5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5/1) to give **3** (42.0 mg, 77%) as a colorless oil: $[\alpha]_D^{19}=-42.2$ (c 0.52, $CHCl_3$); IR (neat) 2930, 1740, 1700, 1473, 1366, 1313, 1256, 1172, 1096, 1004, 836, 775, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.031 (6H, s), 0.880 (9H, s), 0.928 (3H, d, J=6.6 Hz), 1.20–1.26 (1H, m), 1.43 (9H, s), 1.65–1.67 (1H, m), 2.21 (1H, m), 2.80–2.84 (3H, m), 3.59–3.72 (3H, m), 5.12 (1H, d, J=12.7 Hz), 5.17 (1H, d, J=12.4 Hz), 7.28–7.33 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 45 °C, a mixture of conformational isomers) δ −5.40, −5.34, 16.3, 16.5, 18.3, 25.5, 25.7, 25.9, 28.4, 29.1, 30.3, 33.1, 35.2, 35.6, 51.5, 60.5, 60.7, 61.0, 62.4, 64.1, 66.2, 66.8, 80.1, 128.0, 128.1, 128.3, 128.5, 135.9, 155.7, 171.2.

HRMS (FAB, NBA) calcd for $C_{25}H_{44}NO_5Si$: 466.2989 ($M+H^+$). Found: 466.2945. Anal. calcd for $C_{25}H_{43}NO_5Si$: C, 64.48, H, 9.31, N, 3.01. Found: C, 64.21, H, 9.31, N, 3.04.

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Facile design of poly(3,4-ethylenedioxythiophene)-tris(2,2′-bipyridine)ruthenium (II) composite film suitable for a three-dimensional light-harvesting system

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Received 11 May 2004; revised 21 June 2004; accepted 24 June 2004

Available online 21 July 2004

Abstract—It has been confirmed that octasulfonatocalix[8]arene (Calx-S8) and tris(2,2′-bipyridine)ruthenium (II) ($Ru(bpy)_3^{2+}$) can form a stable host–guest complex in aqueous solution. The binding constant for 1:1 $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ complex formation was estimated to be $(2.4\pm0.8)\times10^4$ dm^3 mol^{-1} by fluorescence titration, which indicates that the $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ complex is the main species in 1:1 molar ratio aqueous solution of Calx-S8 and $Ru(bpy)_3^{2+}$. In situ UV–Vis spectroscopic measurements indicated that $Ru(bpy)_3^{2+}$ complexes can be readily deposited onto ITO electrode through electrochemical polymerization of 3,4-ethylenedioxythiophene (EDOT) using $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ host–guest complex as a dopant anion owing to the electrostatic interaction between the cationic conductive polymer and the anionic host–guest complex. The loading degree of the composite film with $Ru(bpy)_3^{2+}$ can be determined by Lambert-Beer law modified for the two-dimensional concentration. The obtained composite film showed good photoelectric conversion properties in response to visible light irradiation. This is a novel photocurrent generation system in which the photoexcited state energy is efficiently collected by the conductive polymeric layer.

1. Introduction

The tris(2,2′-bipyridine)ruthenium ($Ru(bpy)_3^{2+}$) complex is a well-known redox-active photosensitizer with a large molar absorption coefficient in visible light region and has been received much attention due to its light-induced electron and energy transfer properties.[1] The driving force of photoelectric conversion is electron transfer between photoexcited $Ru(bpy)_3^{2+}$ and various electron donors and acceptors, generating anodic and cathodic photocurrents. Recently, various $Ru(bpy)_3^{2+}$ derivatives have been synthesized and organized onto electrodes to construct artificial photoelectric conversion systems using Langmuir-Blodgett (LB) techniques,[2] self-assembled monolayers (SAMs)[3] and layer-by-layer alternate adsorption methods.[4] These approaches in surface chemistry are very significant toward the construction of artificial molecular devices, for the photoinduced electron transfer from or to $Ru(bpy)_3^{2+}$ in solution is not so efficient because of the difficulty to suppress the backward electron transfer between the redox couples.[5] Although a few successful studies have so far been reported for these surface chemistry systems, one must overcome the synthetic difficulty in covalently-linking all of the membrane-forming components in one molecular system.[2–4] Moreover, the number of molecules deposited on the electrode in SAMs is limited by the surface area as long as a planar electrode is used.[3] In addition, electron and energy transfer processes in LB films are known to depend on their layered structure, wherein the long alkyl chain, an essential structural unit in the LB film, often constitutes a disadvantage in acting as an insulator layer to electron transfer.[2]

To design a more effective photoelectric conversion system, it is important to find a suitable matrix to decrease the resistance of the obtained films and to increase the loading density of sensitizer molecules per unit area to improve the overall photocurrent generation efficiency. A new, alternate idea thus occurred to us that a conductive polymer, poly(3,4-ethylenedioxythiophene) (PEDOT), will be a promising matrix to load sensitizer molecules. It is

Keywords: Octasulfonatocalix[8]arene; Tris(2,2′-bipyridine)ruthenium (II); Host–guest complex; Poly(3,4-ethylenedioxythiophene); Photocurrent.
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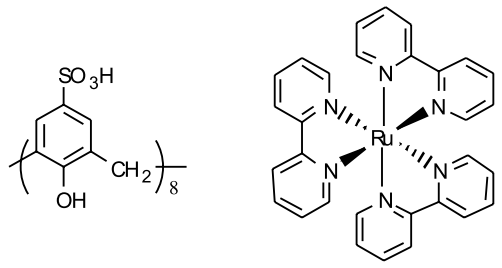
doi:10.1016/j.tet.2004.06.110



Calx-S8 $Ru(bpy)_3^{2+}$

Figure 1. Chemical structures of Calx-S8 and $Ru(bpy)_3^{2+}$.

well-known that PEDOT has a high charge transport property and shows satisfactory environment stability.[6] Thanks to these characteristics, the photoexcited state energy generated in the sensitizer can be efficiently transduced to the electrode through the electroconductive PEDOT matrix. Taking advantage of the conductive polymer into account, one can disperse sensitizer molecules into the three-dimensional matrix. On the basis of this viewpoint, we here report that $Ru(bpy)_3^{2+}$ can be readily deposited into the PEDOT film through electrochemical polymerization of 3,4-ethylenedioxythiophene (EDOT) in the presence of a water-soluble host–guest complex formed from octasulfonatocalix[8]arene (Calx-S8) and $Ru(bpy)_3^{2+}$ (Fig. 1), in which Calx-S8 plays roles of both a dopant anion and a host. This idea originated from our recent finding that polyanionic species are readily deposited into the PEDOT film formed through electrochemical polymerization.[7] In this paper, a novel three-dimensional light-harvesting system consisting of PEDOT and $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ host–guest complex has been prepared by electrochemical polymerization and its photoelectric conversion properties have been examined in detail.

2. Results and discussion

2.1. $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ host–guest complex

The preparation of host–guest complexes between water-soluble calixarene hosts and various guest molecules has become increasingly important due to their potential application in biological and chemical technology.[8] In this work, the 1:1 complexes between Calx-S8 and $Ru(bpy)_3^{2+}$ were prepared by mixing their equimolar stock solutions. To obtain evidence for the complex formation in aqueous solution, the absorption and emission spectra of 5×10^{-4} mol dm^{-3} solution of $Ru(bpy)_3^{2+}$ were measured in the absence and the presence of 1 equiv. Calx-S8 (Fig. 2). It is clear from Figure 2A that there is a small but significant difference ($\Delta\lambda=3$ nm) in the absorption maximum, which is attributed to the metal-to-ligand charge transfer (MLCT) band[1] of $Ru(bpy)_3^{2+}$. In the emission spectra (Fig. 2B), a distinct increase in the fluorescence intensity around 600 nm was observed upon addition of Calx-S8 to the aqueous solution of $Ru(bpy)_3^{2+}$. These changes imply complex formation between $Ru(bpy)_3^{2+}$ and Calx-S8, in which the $Ru(bpy)_3^{2+}$ species are insulated by inclusion in the cavity of Calx-S8.[9] To keep the solubility of the $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ host–guest complex in water, the 1:1 stoichiometric complex was used in this work, because the charge compensation complex which may be formed from one sulfonated calixarene and four guests should show the poor solubility in water.[10] The binding constant for formation of the 1:1 complex was determined to be $(2.4\pm0.8)\times10^4$ dm^3 mol^{-1} by fluorescence titration and the $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ complex is the main species (80%) in 1:1 molar ratio aqueous solution of Calx-S8 and $Ru(bpy)_3^{2+}$ (Fig. 3), and thereafter, $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ is used to denote the species in equimolar Calx-S8 and $Ru(bpy)_3^{2+}$ solution.

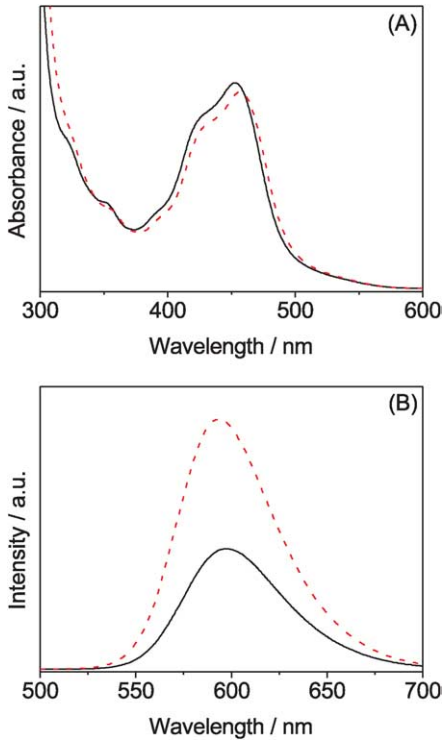


Figure 2. Absorption (A) and emission (B) spectra of 5×10^{-4} mol dm^{-3} $Ru(bpy)_3^{2+}$ in the absence (solid line) and the presence (dashed line) of an equimolar amount of Calx-S8 in water at 25 °C. Excitation wavelength: 450 nm.

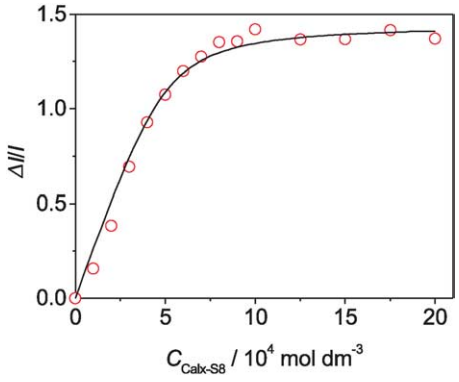


Figure 3. Fluorescence titration of 5×10^{-4} mol dm^{-3} $Ru(bpy)_3^{2+}$ with Calx-S8 in aqueous solution at 25 °C. Excitation wavelength: 450 nm.

2.2. Electrochemical polymerization of EDOT

In this work, the PEDOT films were prepared by a cyclic voltammetric method. Figure 4 shows the successive cyclic

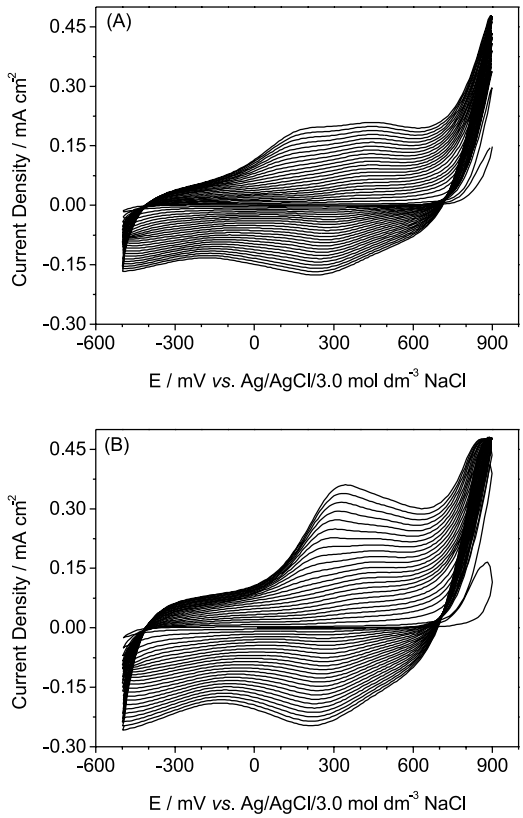


Figure 4. CVs (25 cycles) of electropolymerization of EDOT in the presence of 5×10^{-4} mol dm^{-3} [Calx-S8$^{8-}\cdot$Ru(bpy)$_3^{2+}$]$^{6-}$ complex (A) and 5×10^{-4} mol dm^{-3} Calx-S8 (B) in the range of -0.5–0.9 V with a potential scan rate of 0.05 V s^{-1}.

voltammograms (CVs) of electrochemical polymerization of EDOT in an aqueous 0.05 mol dm^{-3} $LiBF_4$ solution containing 5×10^{-4} mol dm^{-3} [Calx-S8$^{8-}\cdot$Ru(bpy)$_3^{2+}$]$^{6-}$ complex (Fig. 4A) or only 5×10^{-4} mol dm^{-3} Calx-S8 as reference (Fig. 4B). It is clear from these figures that a strong oxidation current is observable around 0.75 V, which is attributable to the oxidation of monomeric EDOT. Furthermore, in the 0.75–0.9 V region of the first CV scan, the current in the reverse scan is higher than that in the forward scan. The formation of this loop is characteristic of nucleation processes, as reported in the literature,[11] which only appears in the first voltammogram. During the successive potential scans the PEDOT film was deposited onto the ITO electrode surface. The regular increase in the anodic and cathodic peak current densities of the PEDOT film implies that the amount of the polymer deposited onto the electrode surface increases and the thickness increases regularly with the number of cycles. The CVs are very similar to those reported for an EDOT/SDS (anionic micelle) system, in which a bulky doping anion was used.[12] Moreover, electrochemical polymerization in a system without Ru(bpy)$_3^{2+}$ shows the bigger redox waves than that in the presence of 5×10^{-4} mol dm^{-3} Ru(bpy)$_3^{2+}$. We consider that the smaller waves in the presence of [Calx-S8$^{8-}\cdot$Ru(bpy)$_3^{2+}$]$^{6-}$ complex is due to partial neutralization of Calx-S8 anions by Ru(bpy)$_3^{2+}$ cations, which results in the lower electropolymerization faradic yield. To characterize the quality of the composite films, the obtained films were subjected to the SEM measurements (Fig. 5). The

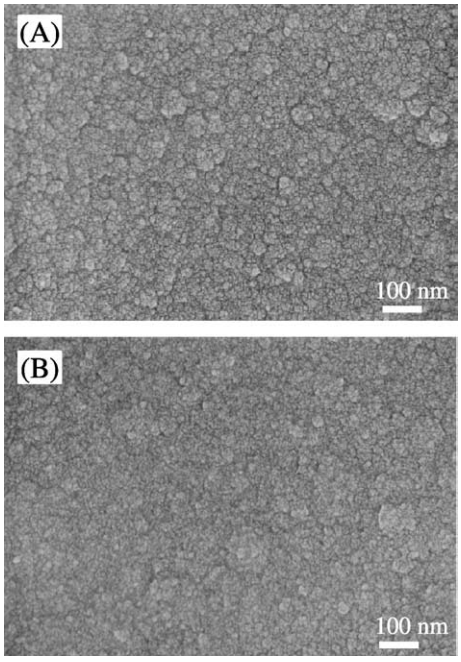


Figure 5. SEM images of the surface of PEDOT composite films electrochemically polymerized in the presence of [Calx-S8$^{8-}\cdot$Ru(bpy)$_3^{2+}$]$^{6-}$ complex (A) and Calx-S8 (B).

results indicated that electrochemical polymerization of EDOT in the presence of [Calx-S8$^{8-}\cdot$Ru(bpy)$_3^{2+}$]$^{6-}$ complex or Calx-S8 results in the films with the relatively smooth surface, suggesting that the uniform nucleation followed by the gradual growth of the polymer occurs on the ITO electrodes. This is consistent with the gradual increase in the redox waves in CVs.

2.3. In situ UV–Vis spectroscopy of composite films

Figure 6A shows in situ absorption spectra of the PEDOT composite films in 0.1 mol dm^{-3} aqueous $LiBF_4$ solution. The spectral patterns of both oxidized and reduced states of

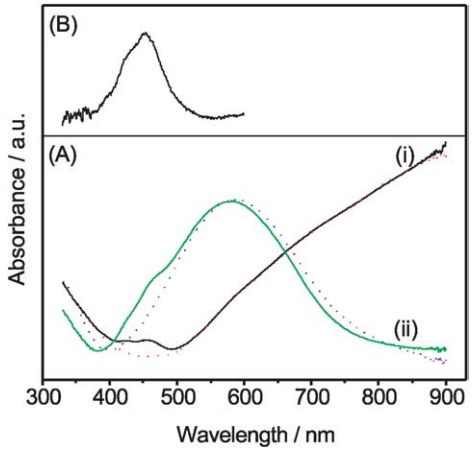


Figure 6. (A) In situ absorption spectra of PEDOT/[Calx-S8$^{8-}\cdot$Ru(bpy)$_3^{2+}$]$^{6-}$ composite film (solid line) and PEDOT film (dashed line; the absorbance was normalized to the composite film) at the oxidized and reduced states in 0.1 mol dm^{-3} aqueous $LiBF_4$ solution: (i) 0.8 V, (ii) -0.8 V vs. Ag/AgCl/3.0 mol dm^{-3} NaCl; (B) the difference absorption spectrum in the oxidized state.

the film deposited from the electrolyte solution containing $[Calix\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ complex are similar to those obtained in the absence of $Ru(bpy)_3^{2+}$, except a new shoulder peak appearing at around 450 nm. This peak clearly appearing in the difference spectrum (see Fig. 6B) is assigned to the MLCT band of $Ru(bpy)_3^{2+}$. Therefore, the absorption spectra give direct evidence that the $[Calix\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ complexes are entrapped into the PEDOT film during electrochemical polymerization. The peak intensity was scarcely decreased even after the electrode was rinsed with deionized water and the film was dedoped at -0.8 V vs. Ag/AgCl/3.0 mol dm^{-3} NaCl for 10 min. These results are consistent with those reported previously by Bay et al.[13]: that is, under the existence of the bulky dopant anions, the cation movement becomes dominating over the anion movement during the doping–dedoping processes since the larger dopant anions are more strongly bound to the polymer, and thus have less tendency to be replaced by smaller, mobile anions. From the Lambert-Beer law modified for the two-dimensional concentration, the surface concentration of $Ru(bpy)_3^{2+}$ in the composite film (25 CV scans) was calculated to be 1.8×10^{-9} mol cm^{-2}.

2.4. Photoelectric conversion ability of the composite film

When the PEDOT/$[Calix\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ composite film-modified ITO electrode was photoirradiated with 458 nm monochromatic light (2.00 mW cm^{-2}) at -0.2 V bias voltage, a cathodic photocurrent wave (ca. 100 nA cm^{-2}) was generated (Fig. 7). On the other hand, the $Ru(bpy)_3^{2+}$ free PEDOT film (which was prepared by 18 CV scans)-modified ITO electrode with the same thickness as PEDOT/$[Calix\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ composite film scarcely generated a cathodic photocurrent[14] (30–50 nA cm^{-2}). These results show that the photoexcited energy of $Ru(bpy)_3^{2+}$ is efficiently collected by electroconductive PEDOT and transferred to the ITO electrode. The quantum yield[15] for the photocurrent generation (η) of $Ru(bpy)_3^{2+}$ entrapped in the PEDOT matrix was calculated according to the following equations,

$$\eta = i/[eI(1-10^{-A})] \quad (1)$$

$$I = W\lambda/hc \quad (2)$$

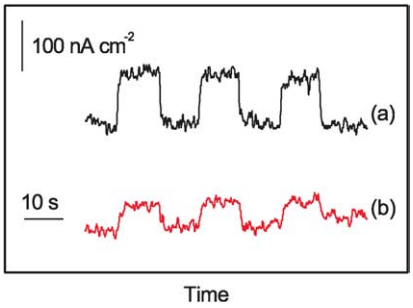


Figure 7. Photoelectric conversion response of PEDOT/$[Calix\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ composite film (a) and PEDOT film (b) on ITO electrodes: 0.1 mol dm^{-3} Na_2SO_4 and 5×10^{-3} mol dm^{-3} methylviologen; argon atmosphere; light irradiation at 458 nm with the intensity of 2.00 mW cm^{-2}; bias voltage -0.2 V vs. Ag/AgCl/3.0 mol dm^{-3} NaCl.

where i, e, I, A, λ, W, c and h denote the observed photocurrent, charge of electron, the number of photons per unit area and unit time, absorbance of the film, wavelength of light irradiation, light irradiation intensity at λ, light velocity and Planck constant, respectively. The quantum yield estimated at 458 nm and -0.2 V bias voltage was 0.15%. This value is comparable with those of the LB films obtained after complicated preparation procedures (10^{-4} to 10^{-2}).[2] Taking the convenience of the electrode preparation method into account, one may propose that the attained quantum yield is satisfactorily high and would be further improved by optimization of the preparation and measurement conditions.

3. Conclusion

The present study has addressed a novel approach to prepare the PEDOT/$Ru(bpy)_3^{2+}$ composite film by using $[Calix\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ host–guest complex as a dopant anion. We can emphasize that the present, non-covalent approach has many advantages: that is, (1) the preparation method is very simple, (2) sensitizer molecules (i.e., $Ru(bpy)_3^{2+}$) are insulated by hosts even when its concentration becomes high, (3) the light energy is efficiently harvested because of the three-dimensional conductivity of the PEDOT film matrix even when the film becomes somewhat thick, and (4) the composite is obtained as a stable polymer film, being different from unstable LB films. These advantages make the present system deserving further elaboration and eventually applicable to construct artificial light-to-photocurrent conversion devices. Furthermore, it is obvious from the present study that octaanionic Calx-S8 can act as a versatile vehicle to deposit various functional molecules into the conductive polymers yielded through electrochemical polymerization. From this viewpoint, we are currently applying this concept to deposition of photo- and redox-functional molecules such as fullerenes, porphyrin, ferrocenes, etc.

4. Experimental

4.1. Materials

3,4-Ethylenedioxythiophene (EDOT) was purchased from Aldrich Chemical Co. Lithium tetrafluoroborate ($LiBF_4$), tris(2,2′-bipyridine)ruthenium (II) ($Ru(bpy)_3^{2+}$) dichloride hexahydrate and methylviologen were products from Tokyo Kasei Kogyo Co., Ltd. Octasulfonatocalix[8]arene (Calx-S8) was obtained from Sugai Chemical Industry Co., Ltd. All chemicals were used as received. The electrolyte solutions were prepared with deionized water from a Millipore purification system.

4.2. Electrochemical polymerization

Voltammetric experiments were performed in a one-compartment, three-electrode electrochemical cell with the use of an electrochemical analyzer (BAS 100B). The cell consisted of an ITO electrode as the working electrode, a Pt wire as the counter electrode and an Ag/AgCl/3.0 mol dm^{-3} NaCl reference electrode. The electrolyte for

electrochemical polymerization was an aqueous 0.05 mol dm^{-3} $LiBF_4$ solution containing 0.014 mol dm^{-3} EDOT and 5×10^{-4} mol dm^{-3} $[Calx\text{-}S8^{8-}\cdot Ru(bpy)_3^{2+}]^{6-}$ complex or only 5×10^{-4} mol dm^{-3} Calx-S8 as reference. All solutions were deoxygenated by an argon stream before the electrochemical measurements. The PEDOT films were prepared by a cyclic voltammetric method, in which the potential scans were performed by 25 cycles in the range of −0.5–0.9 V with a scan rate of 0.05 V s^{-1} at 25 °C unless specially stated.

4.3. Ultraviolet–visible and fluoroscene spectroscopy

UV–Vis spectra were acquired on a Shimadzu UV-2500 PC spectrophotometer, and the fluroscene spectra were recorded on a Perkin Elmer LS 55 luminescence spectrometer. The in situ UV–Vis spectra were measured at room temperature with a simple quartz cuvette (10 mm pathlength) as the electrochemical cell.

4.4. SEM observations

Scanning electron microscopy (SEM) was used to observe morphology of the obtained films. The films were rinsed by copious water and then dried overnight at room temperature in vacuo before characterization. The films were shielded with platinum for 30 s and examined with a Hitachi S-5500. The accelerating voltage of SEM was 25.0 kV and the emission current was 10 μA.

4.5. Photoelectrochemical measurements

A 500 W Xe arc lamp (Ushio XB-50101AAA, XS-50102AAA) was used as a light source in the photoelectric conversion studies and a monochromater (Shimadzu SPG 120IR) was used to obtain desired wavelengths. The intensity of the light was measured with an energy and power meter (Adevantest TQ8210). Photocurrent measurements were carried out in aqueous 0.1 mol dm^{-3} Na_2SO_4 and 5×10^{-3} mol dm^{-3} methylviologen solution by using a three-electrode photoelectrochemical cell, consisting of the film-modified ITO electrode.

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Ene–yne metathesis of polyunsaturated norbornene derivatives

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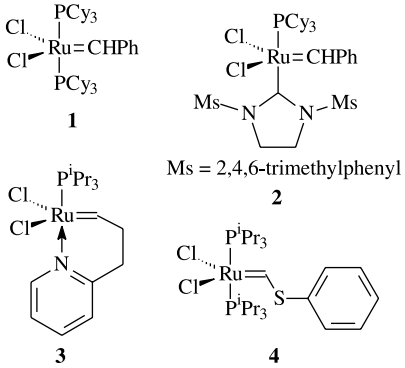
Received 4 May 2004; revised 28 May 2004; accepted 24 June 2004

Available online 29 July 2004

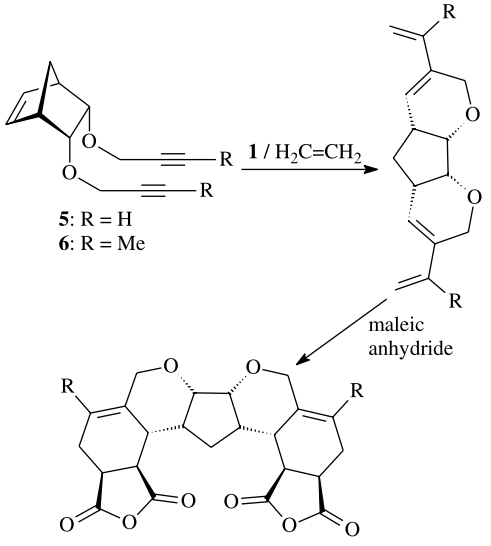
Abstract—Norbornene derivatives bearing *endo*-substituents in the 5- and 6-positions were studied as substrates for ene–yne metathesis cascades. Substrates which contained an internal alkyne and a terminal alkene or alkyne in each sidechain were found to undergo a metathesis cascade leading to pentacyclic bis-dienes and bis-trienes. Attempts to extend the chemistry further to sidechains containing two internal alkynes or two internal alkynes and a terminal alkene were not successful with the first generation Grubbs' catalyst. However, the substrate containing two internal alkynes did react with the second generation Grubbs' catalyst to give a tetra-diene containing product.

1. Introduction

The discovery by Grubbs of the air stable ruthenium complex **1** has sparked an enormous increase in interest in alkene metathesis.[1] The related reaction of ene–yne metathesis[1] is less well known, but is also catalysed by complex **1**. Ene–yne metathesis has the advantage of being a 100% atom economical reaction which converts an alkene and an alkyne into a diene. In recent years a number of other ruthenium based metathesis initiators have been developed including the 'second generation' catalyst **2**,[2] and complexes **3** and **4** developed by the Ciba group.[3]



Recently, we have shown that readily available substrates **5** and **6** undergo a cascade of alkene and ene–yne metathesis reactions when treated with catalyst **1**, leading to stereochemically controlled tricyclic products which undergo Diels–Alder reactions to give (up to) heptacyclic products (Scheme 1).[4–6] In this paper, we report the extension of this metathesis cascade to the more complex substrates **7** and **8** in which each sidechain attached to the norbornene ring contains an internal alkyne and either a terminal alkene or a terminal alkyne.[7] The attempted metathesis of substrate **25** containing two internal alkynes in each chain and compound **29** containing two internal alkynes and a terminal alkene in each chain will also be discussed.



Scheme 1.

Keywords: Norbornene; Metathesis; Alkene; Alkyne; Grubb's-catalyst; Ruthenium.

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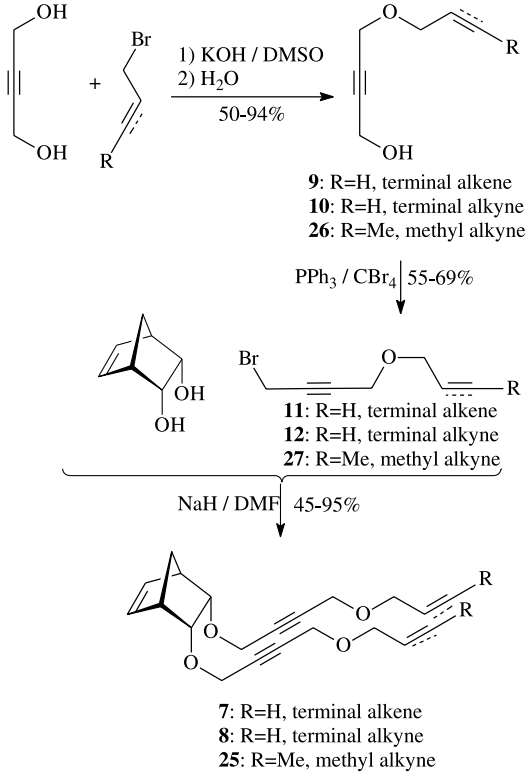
doi:10.1016/j.tet.2004.06.114

2. Results and discussion

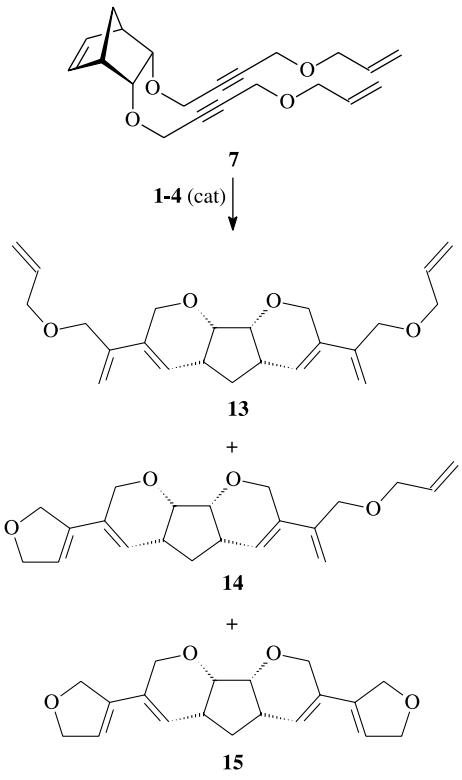
Bis-ene–yne **7** and tetrayne **8** were prepared from butyne-1,4-diol as shown in Scheme 2. Thus, treatment of allyl or propargyl bromide with an excess of the diol resulted in formation of the corresponding mono-ethers **9**[8] and **10**[9] in high yield. The ethers could be brominated by treatment with triphenylphosphine and tetrabromomethane to give the desired bromides **11**[9,10] and **12** in 69% yield. Reaction of compounds **11** or **12** with *endo-cis*-5,6-dihydroxynorborn-2-ene[11] gave the desired metathesis precursors **7** and **8**, respectively.

The metathesis of compound **7** was investigated using catalysts **1** and **2**. Initial reactions carried out under an inert atmosphere failed to give any identifiable products. However, when the atmosphere was changed to ethene,[12] a mixture of three products (**13**–**15**) was obtained as shown in Scheme 3. In each case, the starting material had undergone ring-opening metathesis of the norbornene ring and subsequent ring-closing ene–yne metathesis, but the products differed in the extent to which they had undergone a subsequent ring-closing metathesis with the terminal alkene. The results are summarised in Table 1.

At room temperature using 5 mol% of catalyst **1**, compounds **13**–**15** were obtained in 65% overall yield with the fully metathesised product **15** as the major product (entry 1). No improvement in the ratio of the products, or the total yield was observed if the reaction time was extended (entry 2), and increasing the reaction temperature was detrimental to both the yield and product ratio (entries 3 and 4). The second generation catalyst **2** was also tested as a catalyst for the ene–yne metathesis of compound **7**.



Scheme 2.



Scheme 3.

However, this catalyst failed to induce any metathesis of substrate **7** either at room temperature (entry 5) or in refluxing dichloromethane (entry 6), and the same result was obtained if the reaction was carried out under a nitrogen atmosphere. Catalyst **2** has previously been reported[13] to be a poor initiator for the ROMP of norbornene due to a poor initiation to propagation ratio. This observation may have some relevance to the failure of catalyst **2** to initiate the metathesis of compound **7**.

The use of catalysts **3** and **4** for the metathesis of compound **7** was also investigated. At room temperature, catalyst **3** (5 mol%) failed to react with substrate **7** (entry 7), whilst catalyst **4** gave a 40% conversion after 24 h (entry 8). When the reaction was carried out in refluxing dichloromethane, both catalysts were more reactive; catalyst **3** giving a 40% conversion (entry 9) and catalyst **4** an 80% conversion (entry 10).

The overall conversion of substrate **7** to pentacyclic product **15** involves the elimination of one molecule of ethene and so will be retarded by the presence of an ethene atmosphere. However, the fact that no reaction occurs under a nitrogen atmosphere; and the isolation of compounds **13** and **14** indicate that the reaction actually occurs through a series of steps, some of which require ethene and some of which generate ethene. The conversion of substrate **7** into compound **13** requires 1 equiv. of ethene, and the subsequent conversions of **13** into **14** and **14** into **15** each release 1 equiv. of ethene. Hence, the early stages of the cascade leading to compound **15** are favoured by an ethene atmosphere, whilst the latter stages are inhibited by the presence of excess ethene. Therefore, a series of reactions were carried out in which after initial reaction with catalyst

Table 1. Metathesis reactions on substrate **7**[a]

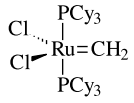
Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Conversion	**13** (%)	**14** (%)	**15** (%)
1	**1** (5)	rt	20	95	18	14	33
2	**1** (5)	rt	69	95	16	22	28
3	**1** (5)	35	4	100	8	13	12
4	**1** (5)	35	20	100	13	6	16
5	**2** (5)	rt	20	0			
6	**2** (5)	35	22	0			
7	**3** (5)	rt	24	0			
8	**4** (5)	rt	24	40[b]			
9	**3** (5)	35	38	40[b]			
10	**4** (5)	35	38	80[b]			
11	**1** (5)+**2** (5)	35	24	100	15	6	43

[a] All reactions were carried out in dichloromethane under an ethene atmosphere.
[b] The ratio of compounds **13**–**15** was only determined for reactions which proceeded to at least 95% conversion.

1 under an ethene atmosphere, additional catalyst was added and/or the atmosphere was changed. The results of these reactions are summarised in Table 2.

Simply adding a second batch of catalyst **1** did not improve the yield or ratio of products **13**–**15** (entry 1). Simultaneously changing the atmosphere to nitrogen did double the amount of product **14** produced, but disappointingly did not increase the amount of product **15** or the overall yield (entry 2). More encouraging results were obtained when the second batch of catalyst added was catalyst **2**, since under either an inert or ethene atmosphere, at room temperature or in refluxing dichloromethane, compound **15** was the only product isolated, though with no improvement in its yield (entries 3 and 4). These results suggested that the replacement of the ethene atmosphere by nitrogen made no difference to the outcome of the reaction, but also suggested that catalyst **2** was beneficial to the later stages of the metathesis cascade although as shown by entries 5 and 6 of Table 1, it was unable to initiate the cascade. Therefore, an experiment was conducted in which catalysts **1** and **2** were simultaneously added to substrate **7** under an ethene atmosphere (Table 1: entry 11) and gratifyingly, this resulted in the highest isolated yield for compound **15**.

An attempt was made to carry out a dissymmetric metathesis of substrate **7** using allyl trimethylsilane in place of the ethene atmosphere as previously reported for substrates **5** and **6**.[4] However, when substrate **7** was treated with catalyst **1** in the presence of allyl trimethylsilane, symmetrical bis-diene **15** was the only product isolated in 20% yield. Catalyst **1** can react with the terminal alkenes of substrate **7** to generate ruthenium complex **16**. The monophosphine species derived from compound **16** is known to be an extremely reactive metathesis initiator, and can react with substrate **7** to generate diene **15** without any external alkene (allyl trimethylsilane or ethene) being involved in the catalytic cycle. Thus, it is not possible to carry out dissymmetric metatheses of compounds such as **7** which contain a terminal alkene.



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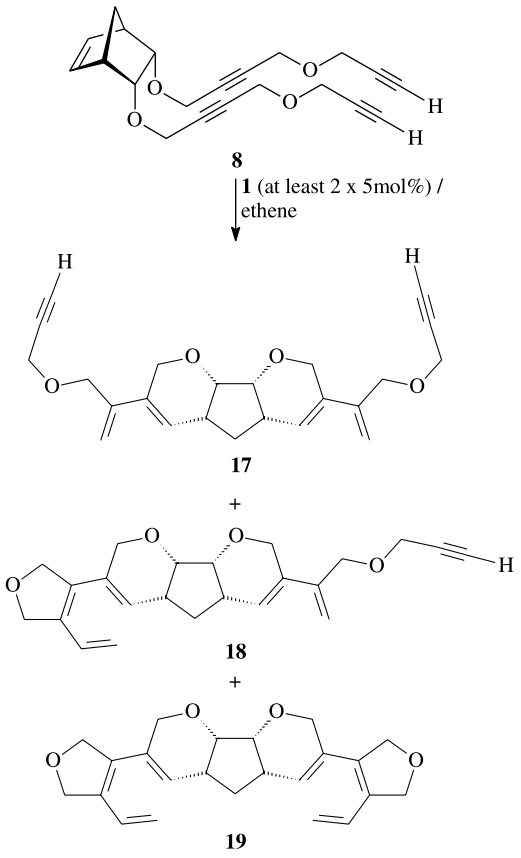
Having optimised the metathesis of substrate **7**, the metathesis of the analogous bis-diyne **8** was investigated. In this case however, all possible products resulting from metathesis of compound **8** involve the overall addition of one molecule of ethene to the substrate. Therefore, all reactions had to be carried out under an ethene atmosphere. The metathesis of substrate **8** by catalyst **1** was found to be relatively slow, and required two additions of 5 mol% of catalyst **1**, 48 h apart and a total reaction time of 96 h. Under these conditions, products **17**–**19** were obtained in 2:4:3 ratio and in 46% overall yield as shown in Scheme 4. By using six consecutive additions of 5 mol% of catalyst **1**, with a 24 h reaction time between each addition, it was possible to avoid the formation of compound **17**, and compounds **18** and **19** were obtained in 1:2 ratio and in 53% overall yield. Raising the reaction temperature to 35 °C did not improve the yield or ratio, and catalyst **2** was totally inactive with substrate **8**. Simultaneous or sequential addition of catalysts **1** and **2** was also not advantageous for this substrate.

Comparing substrates **7** and **8**, it is apparent that both substrates readily undergo ring-opening metathesis of the strained norbornene ring followed by ring-closing ene–yne metathesis and cross metathesis with ethene to give compounds **13** and **17**, respectively. However, subsequent

Table 2. Two stage metathesis of substrate **7**[a]

Entry	Second catalyst (mol%)	Atmosphere for second stage	Temperature (°C)	**13** (%)	**14** (%)	**15** (%)
1	**1** (5)	Ethene	rt	15	11	33
2	**1** (5)	Nitrogen	rt	16	22	28
3	**2** (5)	Nitrogen	r.t	0	0	36
4	**2** (5)	Ethene	35	0	0	37

[a] In all cases the reaction was first treated with catalyst **1** (5 mol%, except entry 2 where 10 mol% was used) under an ethene atmosphere at the same temperature specified in the table for the second stage. The first stage of the reaction was left for 4–43 h until all starting material had been consumed, and the second stage was left overnight.

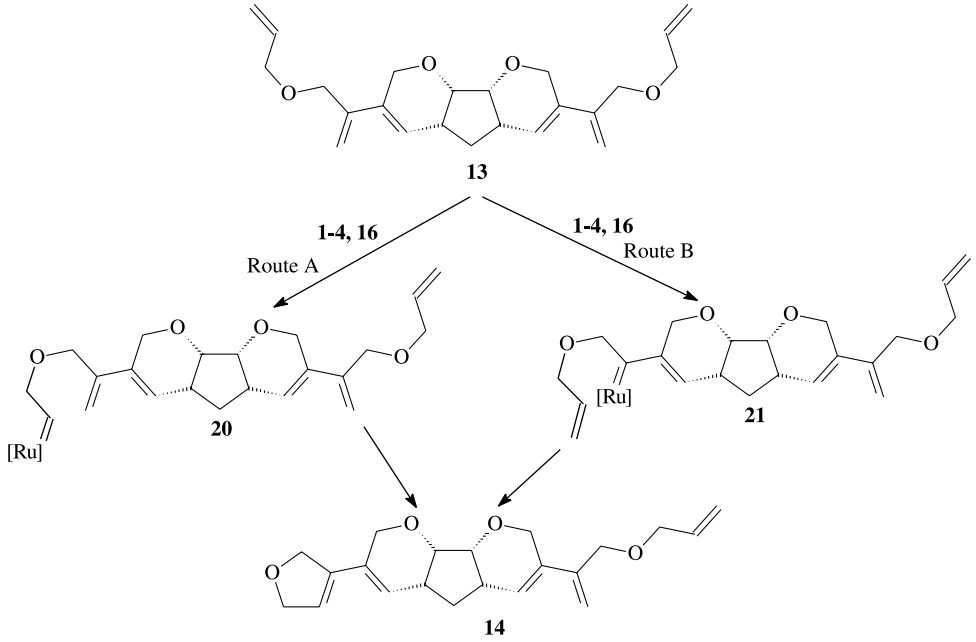


Scheme 4.

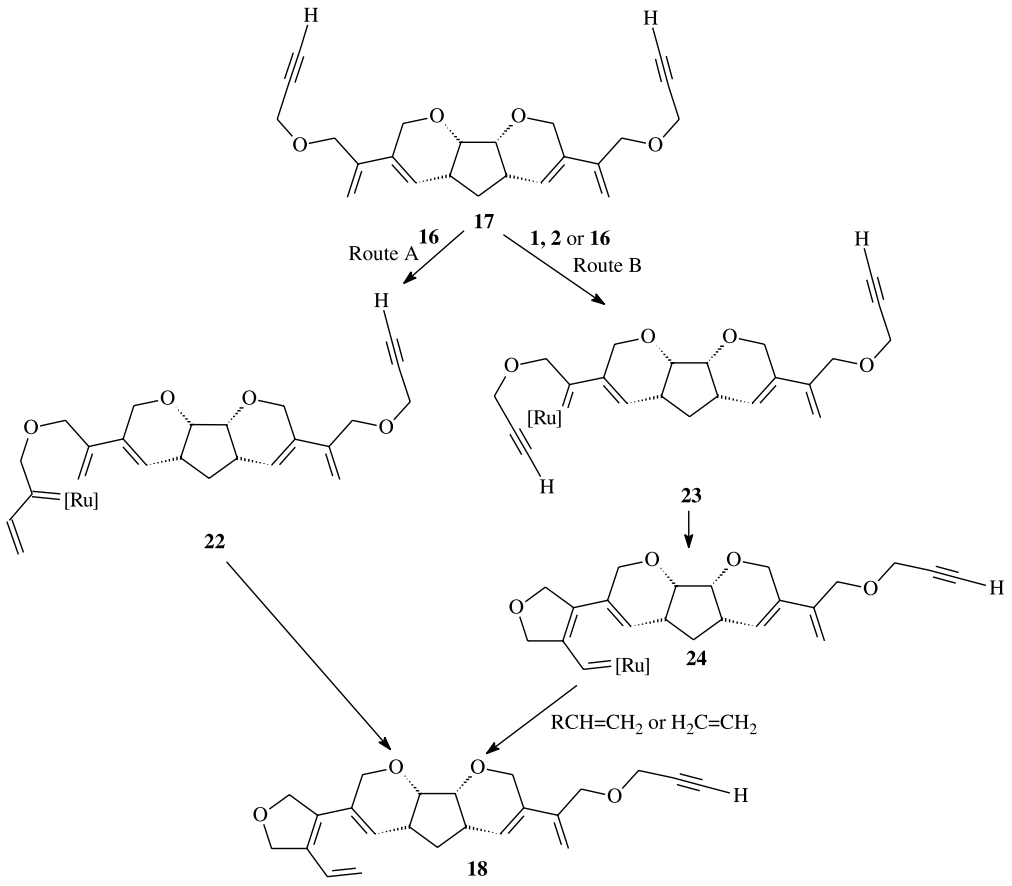
ring-closing diene-ene metathesis of compound **13** to give **14** and **15** is far more facile than the ring-closing diene–yne metathesis of compound **17** to give compounds **18** and **19**. These ring-closing metatheses can occur by two different mechanisms (Schemes 5 and 6). In the case of compound **13** (Scheme 5), any metathesis catalyst can react with the terminal alkene (Scheme 5: Route A) to generate a ruthenium alkylidene complex **20** which can cyclise onto the diene, forming product **14**. Alternatively, the metathesis catalyst could react with the diene (Scheme 5: Route B) to form conjugated ruthenium alkylidene complex **21** which could cyclise onto the terminal alkene to form product **14**. In both cases, the same metathesis cascade carried out on compound **14** would lead to compound **15**. Of these two processes, Route A seems more likely for both steric and electronic reasons. In particular, it is well known that dienes make poor substrates for metathesis reactions,[1] so it is unlikely that the metathesis catalyst would react with the diene in the presence of a terminal alkene.

The situation with substrate **17** is more complicated. Again, there are two possible routes (Scheme 6: Route A and B) for the conversion of compound **17** into compound **18** and the same two processes will convert **18** into **19**. If the initial reaction occurs on the terminal alkyne (Scheme 6: Route A), then this must involve complex **16** as the metathesis catalyst since the methylidene unit of catalyst **16** is also added to the alkyne. This would form conjugated alkylidene **22** which could cyclise onto the diene to form product **18**. The alternative process (Scheme 6: Route B) involves any of the metathesis catalysts (**1**, **2**, **16**) reacting with the diene unit to generate conjugated alkylidene **23** which can cyclise onto the alkyne to generate the more highly conjugated alkylidene **24**. Formation of product **18** from alkylidene **24** requires a cross metathesis reaction with a terminal alkene. This could be ethene (which would give catalyst **16** as the ruthenium containing product), or the diene of another molecule of compound **17**. In the case of compound **17**, it is not clear which of the two mechanisms is more likely. However, whichever route the reaction follows, the metathesis catalyst must react with a relatively unreactive alkyne or diene,[1] and this may explain the difference in reactivity between compounds **13** and **17**.

To further explore the scope of this metathesis cascade



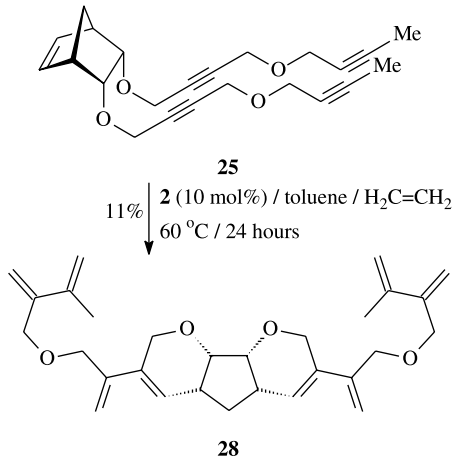
Scheme 5.



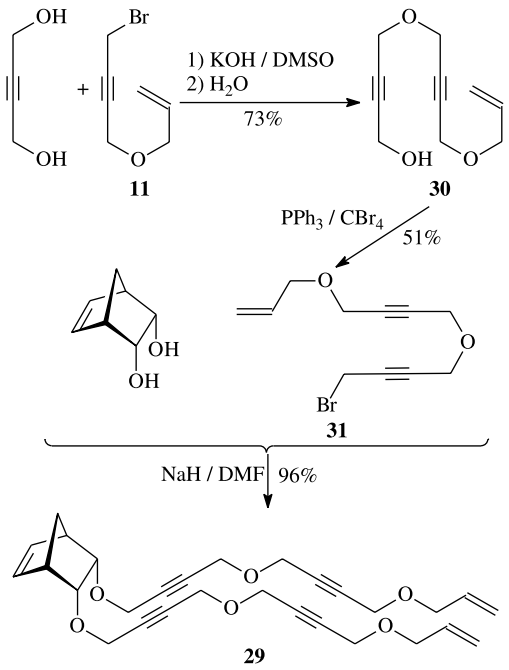
Scheme 6.

chemistry, two additional substrates were prepared. Compound **25** is analogous to substrate **8** except that the terminal alkyne has been replaced by an internal one. This substrate was prepared by the same chemistry developed for the synthesis of compounds **7** and **8** (Scheme 2) via alcohol **26** and alkyl bromide **27**. All attempts to metathesise compound **25** using catalyst **1** under a nitrogen or ethene atmosphere were unsuccessful and resulted only in recovery of unreacted starting material. Treatment of substrate **25** with the second generation catalyst **2** was however more successful. Use of 10 mol% of the second generation catalyst at 60 °C in toluene under an ethene atmosphere over a period of one day resulted in the complete reaction of compound **25**. Only one product (**28**) could be isolated from the reaction, albeit in low yield (Scheme 7). The formation of tetra-diene **28** can be explained by ring-opening metathesis of the norbornene and ring-closing ene–yne metathesis of the resulting terminal alkenes onto two of the internal alkynes to form the [5-6-5]-ring system and establish the two dienes which are fused to the six-membered rings. In a separate process, the remaining alkynes undergo cross-metathesis with ethene[14] to form the other two dienes and produce compound **28**. Either of these two processes could occur first, or they could occur at similar rates. Ring-closing bis-diene metathesis of compound **28** (or ring-closing ene–yne metathesis of the precursor which still has a methyl-alkyne) appear not to occur at significant rates, thus preventing the formation of a pentacyclic product analogous to compound **19**.

Finally, norbornene derivative **29** was prepared in which each sidechain contains two alkynes and a terminal alkene. Compound **29** was prepared as shown in Scheme 8. Thus, bromide **11** was reacted with but-2-yne-1,4-diol to form alcohol **30** which could be brominated to form propargylic bromide **31**. Reaction of compound **31** with *endo-cis*-5,6-dihydroxynorborn-2-ene gave the desired norbornene derivative **29**. However, all attempts to carry out metathesis reactions on substrate **29** using catalyst **1** in the presence of ethene were unsuccessful, and unreacted starting material was recovered. Thus, no reaction occurred at room



Scheme 7.



Scheme 8.

temperature or at 35 °C in dichloromethane. Reactions carried out using catalyst **2** in refluxing dichloromethane or at 60 °C in toluene did result in consumption of the starting material, but no products could be isolated.

3. Conclusions

The cascade metathesis of alkyne substituted norbornenes has been extended to substrates **7** and **8** leading to highly functionalised pentacyclic systems in a single step. The reactions illustrate that the metathesis catalysts **1** and **2** have very different reactivities, and that the usual generalisation that compound **2** is more reactive than catalyst **1** is not always valid. Thus, compound **2** will not start the metathesis cascades of compounds **7** and **8**, but in the case of substrate **7**, it was found that simultaneous addition of catalysts **1** and **2** gave better results than either catalyst used separately.

Attempts to extend the chemistry to more complex systems were less successful. Whilst compound **25** reacted with catalyst **2** to generate tetra-diene **28** as the only isolable product in low yield, no products could be isolated from the metathesis of compound **29**.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform on Bruker Avance 360 (^{1}H 360 MHz, ^{13}C 90 MHz) or Avance 500 (^{1}H 500 MHz, ^{13}C 125 MHz) spectrometers. Spectra were referenced to TMS and chemical-shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments. For metathesis products, ^{1}H and ^{13}C resonance assignments were made with the aid of ^{1}H–^{1}H and ^{1}H–^{13}C correlation experiments.

Infrared spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film of the pure compound between NaCl plates. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a Bruker Apex III FTMS or Jeol AX505W spectrometer within the chemistry department at King's College. The sample was ionised by electron ionisation (EI), chemical ionisation (CI), fast atom bombardment (FAB) or electrospray ionisation (ESI). The major fragment ions are reported and only the molecular ions are assigned.

Melting points were determined with a Buchi Melting Point apparatus No. 520092 and are uncorrected. Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin-layer chromatography was performed on polyester backed sheets coated with silica gel 60 F254, both supplied by Merck.

4.1.1. Compound 7. To a solution of 2,3-norbornen-5,6-diol[11] (1.56 g, 12.4 mmol), in dimethylformamide (15 ml) at 0 °C was added NaH (60% in mineral oil; 1.49 g, 37.1 mmol). The mixture was stirred for 1 h at 0 °C, then bromide **11**[9,10] (7.02 g, 37.1 mmol) was added. The mixture was then warmed to room temperature and stirred for 22 h. After hydrolysis at 0 °C with water (20 ml), the mixture was extracted with diethyl ether (4×50 ml) and evaporated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O 30/70) to give compound **7** (3.16 g, 75%) as an off-white oil. ν_{max} 3300 (w), 3074 (m), 2976 (s), 2940 (s), 2898 (s), 2855 (s), 2243 (w), and 1647 cm^{-1} (w); δ_H 6.18 (2H, d J=1.5 Hz, HC=CH), 5.85 (2H, ddt J=17.2, 10.4, 5.8 Hz, C*H*=CH_2), 5.25 (2H, dd J=17.2, 1.6 Hz, =CH_{2trans}), 5.16 (2H, dd J=10.4, 1.50 Hz, =CH_{2cis}), 4.21–4.20 (2H, m, CH–O), 4.20 (4H, t J=1.7 Hz, ≡CCH_2O), 4.14 (4H, t J=1.7 Hz, ≡CCH_2O), 4.00 (4H, dt J=5.7, 1.2 Hz, CH_2CH=), 3.05 (2H, bs, =CHC*H*), 1.44 (1H, dt J=9.6, 2.2 Hz, CHCH_2CH), 1.30 (1H, d J=8.9 Hz, CHCH_2CH); δ_C 133.4 (=CH), 132.9 (=CH), 116.9 (=CH_2), 81.6 (≡C), 81.2 (≡C), 76.9 (CHO), 69.7 (CH_2O), 56.5 (CH_2O), 56.4 (CH_2O), 44.8 (CH), 40.8 (CH_2); m/z (CI) 360 ($M+NH_4^+$, 100), 343 (MH^+, 2). Found (CI) 360.2169, ($M+NH_4^+$) $C_{21}H_{30}NO_4$ requires 360.2175.

4.1.2. Metathesis of compound 7 using catalyst 1. A solution of compound **7** (100 mg, 0.29 mmol) in dry dichloromethane (22 ml) was cooled to −78 °C and ethene was passed through the solution for 10 min. A solution of catalyst **1** (12.0 mg, 0.015 mmol) in dry dichloromethane (2 ml) was then added and after 15 min the mixture was warmed to room temperature and stirred for 20 h. The solvent was then removed in vacuo and the residue subjected to flash chromatography (CH_2Cl_2/EtOAc 70/30) to give products **13**–**15**. Compound **13**, colourless oil: yield

(20 mg, 18%); ν_{max} 3074 (m), 2934 (s), 2852 (s), 1640 (m), and 1604 cm^{-1} (w); δ_H 6.00–5.90 (2H, m, C*H*=CH_2), 5.88–5.87 (2H, m, HC=C), 5.24 (2H, s, C=CH_2), 4.92 (2H, dd J=17.3, 1.5 Hz, CH=CH_{2trans}), 4.90 (2H, dd J=10.1, 2.0 Hz, CH=CH_{2cis}), 4.82 (2H, s, C=CH_2), 4.71–4.68 (8H, m, CH_2OCH_2), 4.26 (2H, d J=12.7 Hz, CH_2OCH), 4.19 (2H, d J=12.7 Hz, CH_2OCH), 3.77 (2H, dd J=1.5, 5.2 Hz, CHO), 2.61–2.57 (2H, m, C*H*CH=), 2.00 (1H, dt J=13.3, 8.5 Hz, CHCH_2CH), 1.52 (1H, dt, J=13.4, 4.4 Hz, CHCH_2CH); δ_C 140.5 (=CH), 137.8 (=C), 137.5 (=C), 122.6 (=CH), 115.0 (=CH_2), 114.5 (=CH_2), 83.7 (CHO), 77.1 (CH_2O), 75.6 (CH_2O), 71.6 (CH_2O), 44.6 (CH), 36.2 (CH_2); *m/z* (CI) 388 ($M+NH_4^+$, 50), 371 (MH^+, 7), 370 (M^+, 3), 211 (100). Found (CI) 388.2485, ($M+NH_4^+$) $C_{23}H_{34}NO_4$ requires 388.2488. Compound **14**, colourless oil: yield (14 mg, 14%); ν_{max} 3076 (m), 2941 (s), 2852 (s), 2246 (m), and 1640 cm^{-1} (s); δ_H 6.09–5.99 (2H, m, 2×=CH), 5.60 (1H, bs, C=C*H*CH_2), 5.57 (1H, d J=5.5 Hz, CHC*H*=C), 5.24 (1H, s, C=CH_2), 4.90–4.86 (2H, m, CH=CH_2), 4.86 (1H, s, C=CH_2), 4.71–4.67 (8H, m, CH_2OCH_2), 4.43 (1H, d J=14.2 Hz, =CCH_2O), 4.2–4.1 (3H, m, =CCH_2O), 3.91–3.89 (1H, m, CHO), 3.84 (1H, dd J=8.5, 4.2 Hz, CHO), 2.82 (1H, ddd J=18.5, 8.7, 5.8 Hz, CH_2CH), 2.26–2.24 (1H, m, CH_2CH), 2.15 (1H, dt J=13.0, 9.0 Hz CHCH_2CH), 1.47 (1H, ddd J=13.0, 9.2, 5.7 Hz, CHCH_2CH); δ_C 141.1 (=CH), 137.3 (=C), 137.2 (=C), 136.4 (=C), 129.2 (=C), 125.8 (=CH), 123.4 (=CH), 119.8 (=CH), 115.6 (=CH_2), 114.8 (=CH_2), 81.6 (CHO), 77.3 (CHO), 77.2 (CH_2O), 77.0 (CH_2O), 75.6 (CH_2O), 75.1 (CH_2O), 71.3 (CH_2O), 65.2 (CH_2O), 45.6 (CH), 36.7 (CH), 36.0 (CHCH_2CH); *m/z* (CI) 360 ($M+NH_4^+$, 12), 343 (MH^+, 3), 211 (100). Found (CI) 360.2169, ($M+NH_4^+$) $C_{21}H_{30}NO_4$ requires 360.2175. Compound **15**, white solid: yield (30 mg, 33%); mp 148–165 °C (decomp.); ν_{max} 2930 (m), 2852 (s), 2246 (m), and 1644 cm^{-1} (m); δ_H 5.60 (2H, s, C=C*H*CH_2), 5.55 (2H, d J=4.2 Hz, C=C*H*CH), 4.72–4.66 (8H, m, CH_2OCH_2), 4.48 (2H, d J=15.0 Hz, =CCH_2O), 4.20–4.14 (4H, m, CHOCH_2), 2.31 (2H, bs, CH_2CH=), 1.98 (1H, dt J=11.9, 6.4 Hz, CHCH_2CH), 1.50 (1H, q J=12.1 Hz, CHCH_2CH); δ_C 136.4 (=C), 130.3 (=C), 124.3 (=CH), 120.0 (=CH), 77.2 (CHO), 77.0 (CH_2O), 75.1 (CH_2O), 65.8 (CH_2O), 39.6 (CH), 36.4 (CH_2); *m/z* (CI) 332 ($M+NH_4^+$, 100), 315 (MH^+, 22), 314 (M^+, 11), 211 (35). Found (ES) 315.1592, (MH^+) $C_{19}H_{23}O_4$ requires 315.1596.

4.1.3. Metathesis of compound 7 using catalysts 1 and 2. A solution of compound **7** (100 mg, 0.292 mmol) in dry dichloromethane (22 ml) was cooled to −78 °C and ethene was passed through the solution for 10 min. A solution of catalyst **1** (12.0 mg, 0.015 mmol) and catalyst **2** (12.4 mg, 0.015 mmol) in dry dichloromethane (3 ml) was then added and after 15 min the mixture was warmed to 35 °C and stirred for 24 h. The solvent was then removed in vacuo and the residue subjected to flash chromatography (CH_2Cl_2/EtOAc 70/30) to give compounds **13** (16.2 mg, 15%), **14** (6.0 mg, 6%) and **15** (39.5 mg, 43%). Analytical data for these compounds was reported in experiment 4.1.2.

4.1.4. 5-Oxa-octa-2,7-diyn-1-ol 10. To a suspension of KOH (46.4 g, 827 mmol), in DMSO (400 ml) were added propargyl bromide (19.7 g, 165 mmol) and but-2-yne-1,4-diol (70.3 g, 827 mmol). The mixture was then stirred for 60 min, poured into water and extracted with dichloromethane (3×200 ml). The aqueous phase was then acidified with aqueous HCl (6 N, 80 ml) and further extracted with dichloromethane (3×200 ml). The combined organic phases were reduced in volume to 500 ml, washed with H_2O (6×150 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in ether (300 ml) and washed with water (6×40 ml). The organic layer was dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by distillation (120 °C at 17 mm Hg) to give alcohol **10** (11.5 g, 56%) as a colourless oil. ν_{max} 3400 (s), 3288 (s), 2909 (s), 2860 (s), 2117 (m), and 1632 cm^{-1} (m); δ_H 4.35 (2H, s, $OCH_2C{\equiv}CCH_2O$), 4.24 (2H, s, $OCH_2C{\equiv}CCH_2O$), 4.19 (2H, d J=2.4 Hz, O$CH_2C{\equiv}$CH), 2.41 (1H, t J=2.4 Hz, ≡CH), 2.22 (1H, bs, OH); δ_C 85.8 (≡C), 81.0 (≡C), 79.1 (≡C), 75.6 (≡CH), 57.2 (CH_2O), 56.9 (CH_2O), 51.3 (CH_2O); *m/z* (CI) 142 ($M+NH_4^+$, 100). Found (CI) 142.0870, ($M+NH_4^+$) $C_7H_{12}NO_2$ requires 142.0868.

4.1.5. 1-Bromo-5-oxa-octa-2,7-diyne 12. To a solution of alcohol **10** (11.3 g, 93.1 mmol) in ether (250 ml), were added CBr_4 (6.2 g, 186 mmol) and PPh_3 (48.8 g, 186 mmol). After 4 h, the mixture was filtered through Celite and evaporated in vacuo. The residue was purified by column chromatography (1:9 Et_2O/hexane) to give compound **12** (9.3 g, 55%) as a colourless oil. ν_{max} 3293 (s), 2954 (s), 2903 (s), 2858 (s), and 2118 cm^{-1} (m); δ_H 4.26 (2H, t J=2.0 Hz, $CH_2C{\equiv}CCH_2O$), 4.18 (2H, d J=2.3 Hz, $CH_2C{\equiv}$CH), 3.89 (2H, t J=2.0 Hz, CH_2Br), 2.41 (1H, t J=2.4 Hz, ≡CH); δ_C 85.8 (≡C), 81.0 (≡C), 79.1 (≡C), 75.6 (≡CH), 57.2 (CH_2O), 57.1 (CH_2O), 14.5 (CH_2Br); *m/z* (EI) 187 (($^{81}Br)M^+$, 100), 185 (($^{79}Br)M^+$, 90). Found (ES) 185.9681, (M^+) $C_7H_7O^{79}Br$ requires 185.9680.

4.1.6. Compound 8. To a solution of 2,3-norbornen-5,6-diol[11] (1.50 g, 11.9 mmol), in dimethylformamide (15 ml) at 0 °C was added NaH (60% in mineral oil; 1.4 g, 35.7 mmol). The mixture was stirred for 1 h at 0 °C, then bromide **12** (6.7 g, 35.7 mmol) was added. The mixture was warmed to room temperature and stirred for 40 h. After hydrolysis at 0 °C with water (20 ml), the mixture was extracted with diethyl ether (4×120 ml) and evaporated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O 30/70) to give compound **8** (3.9 g, 95%) as an off white oil. ν_{max} 3296 (s), 3059 (m), 2974 (s), 2901 (s), 2857 (s), 2116 (m), and 1712 cm^{-1} (m); δ_H 6.18 (2H, t J=1.4 Hz, =CH), 4.26–4.18 (10H, m, $OCH_2C{\equiv}CCH_2OCH$), 4.19 (4H, d J=2.35 Hz, $CH_2C{\equiv}$CH), 3.05 (2H, bs, =CHC*H*), 2.40 (2H, t J=2.35 Hz, ≡CH), 1.44 (1H, dt J=9.6, 2.2 Hz, CHCH_2CH), 1.16–1.12 (1H, m, CHCH_2-CH); δ_C 134.8 (=CH), 83.7 (≡C), 81.7 (≡C), 79.2 (≡C), 78.4 (CHO), 75.5 (≡CH), 57.7 (OCH_2), 57.2 (OCH_2), 56.9 (OCH_2), 46.2 (CH), 42.2 (CH_2); *m/z* (CI) 356 ($M+NH_4^+$, 100), 336 (MH^+, 6); 272 (8), 250 (20). Found (CI) 356.1857, ($M+NH_4^+$) $C_{21}H_{26}NO_4$ requires 356.1862.

4.1.7. Metathesis of compound 8 to form compounds 17–19. A solution of compound **8** (100 mg, 0.30 mmol) in dry dichloromethane (22 ml) was cooled to −78 °C and ethene was passed through the solution for 10 min. A solution of catalyst **1** (12.2 mg, 0.015 mmol) in dry dichloromethane (3 ml) was then added and after 15 min the mixture was

warmed to room temperature and stirred for 48 h. A solution of catalyst **1** (12.2 mg, 0.015 mmol) in dry dichloromethane (3 ml) was then added and the reaction stirred for a further 48 h until all the starting material had been consumed. The solvent was then removed in vacuo and the residue subjected to flash chromatography (CH_2Cl_2/EtOAc) to give products **17**–**19**. Compound **17**, yellow oil: yield (10 mg, 11%); ν_{max} 3286 (m), 2934 (m), 2859 (m), 2114 (w), 1641 (w), and 1610 cm^{-1} (w); δ_H 6.02 (2H, d J=3.9 Hz, CH=C), 5.10 (2H, s, C=CH_2), 4.98 (2H, s, C=CH_2), 4.50 (2H, d J=15.0 Hz, CH_2OCH), 4.23–4.02 (8H, m, CH_2OCH+=C–CH_2O), 4.07 (4H, d J=2.4 Hz, ≡C–CH_2O), 2.38 (2H, t J=2.3 Hz, HC≡), 2.31 (2H, m, CH–CH=), 1.99 (1H, dt J=12.1, 6.1 Hz, CHCH_2CH), 1.52 (1H, q J=12.3 Hz, CHCH_2CH); δ_C 140.2 (=C), 134.1 (=C), 124.0 (=CH), 114.0 (=CH_2), 79.6 (≡C), 77.0 (CHO), 75.0 (≡CH), 71.0 (CH_2O), 66.0 (CH_2O), 57.2 (CH_2O), 40.0 (CH), 36.4 (CH_2); *m/z* (CI) 384 ($M+NH_4^+$, 32); 372 (29), 297 (37), 278 (84), 266 (46), 250 (100). Found (CI) 384.2172, ($M+NH_4^+$) $C_{23}H_{30}NO_4$ requires 384.2175. Compound **18**, colourless oil: yield (21 mg, 20%); ν_{max} 3301 (s), 2914 (s), 2850 (s), 2245 (m), 2115 (w), 1725 (m), 1641 (m), and 1610 cm^{-1} (w); δ_H 6.49 (1H, dd J=17.6, 10.9 Hz, H_2C=CH), 6.03–6.02 (1H, m, HC=C–C=CH_2), 5.72 (1H, m, HC=C–C=C), 5.12 (1H, d J=10.1 Hz, HC=CH_{2cis}), 5.11 (1H, s, C=CH_2), 4.98 (1H, s, C=CH_2), 4.93 (1H, d J=17.6 Hz, HC=CH_{2trans}), 4.75–4.71 (4H, m, =CCH_2OCH_2C=), 4.49 (1H, d J=18.7 Hz, H_2-C=CCCH_2OCH), 4.45 (1H, d J=18.7 Hz, CHOCH_2C–C=C), 4.26–4.11 (6H, m, 2×$CHOCH_2$ +H_2C=C–CH_2O), 4.07 (2H, d J=2.4 Hz, ≡CCH_2O), 2.38 (1H, t J=2.3 Hz, ≡CH), 2.4–2.3 (2H, m, CHCH_2CH), 2.04 (1H, m, CHCH_2CH), 1.58–1.52 (1H, m, CHCH_2CH); δ_C 139.9 (=C), 133.8 (=C), 132.9 (=C), 131.8 (=C), 131.4 (=C), 128.3 (=CH), 126.6 (=CH), 123.6 (=CH), 117.0 (=CH_2), 113.4 (=CH_2), 79.6 (≡C), 77.6 (CH_2O), 76.8 (CH_2O), 76.7 (CHO), 76.6 (CHO), 74.6 (≡CH), 70.7 (CH_2O), 66.9 (CH_2O), 65.7 (CH_2O), 56.9 (CH_2O), 39.6 (CH), 39.5 (CH), 36.2 (CH_2); *m/z* (CI) 384 ($M+NH_4^+$, 16), 356 (M^+, 57), 297 (100), 278 (20), 250 (32). Found (CI) 384.2173, ($M+NH_4^+$) $C_{23}H_{30}NO_4$ requires 384.2175. Compound **19**, white solid: yield (16 mg, 15%); mp 125 °C (decomp.); ν_{max} 2934 (s), 2850 (s), 2244 (w), 1621 (w), and 1610 cm^{-1} (w); δ_H 6.49 (2H, dd J=17.5, 11.0 Hz, H_2C=CH), 5.71 (2H, d J=3.7 Hz, CH–CH=C), 5.13 (2H, d J=11.2 Hz, HC=CH_{2cis}), 4.94 (2H, d J=17.6 Hz, HC=CH_{2trans}), 4.8–4.7 (8H, m, CH_2OCH_2), 4.44 (2H, d J=15.0 Hz, CH_2OCH), 4.24 (2H, d J=15.0 Hz, CH_2OCH), 4.20 (2H, d J=4.7 Hz, CHO), 2.4–2.3 (2H, m, CH–CH=), 2.02 (1H, dt J=12.2, 6.2 Hz, CHCH_2CH), 1.53 (1H, q J=12.1 Hz, CHCH_2CH); δ_C 131.7 (=C), 130.8 (=C), 130.4 (=C), 127.2 (=CH), 125.3 (=CH), 116.1 (=CH_2), 76.6 (OCH_2), 75.7 (OCH_2), 75.6 (CHO), 65.8 (OCH_2), 38.3 (CH), 35.3 (CH_2); *m/z* (CI) 384 ($M+NH_4^+$, 12), 351 (30), 319 (15), 297 (100).

4.1.8. Metathesis of compound 8 to form compounds 18 and 19. A solution of bis-diyne **8** (100 mg, 0.296 mmol) in dry dichloromethane (22 ml) was cooled to −78 °C and ethene was passed through the solution for 10 min. A solution of catalyst **1** (12.2 mg, 0.015 mmol) in dry dichloromethane (3 ml) was then added and after 15 min the mixture was warmed to room temperature and stirred for 24 h. The addition of catalyst **1** (12.2 mg, 0.015 mmol) in dry dichloromethane (3 ml) and subsequent stiring for 24 h was repeated a further 5 times. The solvent was then removed in vacuo and the residue subjected to column chromatography (CH_2Cl_2/EtOAc 70/30) to give compounds **18** (19.5 mg, 18%) and **19** (38 mg, 35%). Analytical data is given in experiment 4.1.7.

4.1.9. 1-Bromo-5-oxa-nona-2,7-diyne 27. To a solution of alcohol **26**[15] (2.66 g, 19.3 mmol) in Et_2O (50 ml), were added CBr_4 (12.8 g, 38.5 mmol) and PPh_3 (10.1 g, 38.5 mmol). After 4 h the mixture was filtered through Celite and evaporated. The residue was purified by column chromatography (1:9 Et_2O/hexane) to give 1-bromo-5-oxa-nona-2,7-diyne **27** (2.85 g, 69%) as a colourless oil. ν_{max} 3007 (s), 2954 (s), 2919 (s), 2854 (s), 2293 (m), and 2226 cm^{-1} (m); δ_H 4.29 (2H, t J=2.0 Hz, H_2CC≡CCH_2O), 4.19 (2H, q J=2.2 Hz, H_3CC≡CCH_2O), 3.95 (2H, t J=2.0 Hz, CH_2Br), 1.87 (3H, t J=2.3 Hz, CH_3); δ_C 83.0 (≡C), 82.0 (≡C), 81.2 (≡C), 73.8 (≡C), 56.7 (CH_2O), 56.2 (CH_2O), 13.8 (CH_2Br), 3.3 (CH_3); *m/z* (CI) 220 ($M(^{81}Br)+NH_4^+$, 92), 218 ($M(^{79}Br)+NH_4^+$, 90), 172 (100), 170 (63), 156 (52). Found (ES) 222.97206 and 224.97009, ($M+Na^+$) C_8H_9OBrNa requires 222.97290 (^{79}Br) and 224.97085 (^{81}Br).

4.1.10. Compound 25. To a solution of 2,3-norbornen-5,6-diol[11] (0.50 g, 3.97 mmol), in dimethylformamide (5 ml) at 0 °C was added NaH (60% in mineral oil; 0.48 g, 11.9 mmol). The mixture was stirred for 1 h at 0 °C, then bromide **27** (2.01 g, 9.96 mmol) was added. The mixture was warmed to room temperature and stirred for 40 h. After hydrolysis at 0 °C with water (10 ml), the mixture was extracted with diethyl ether (4×15 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O: 30/70) to give compound **25** (0.65 g, 45%) as a colourless oil. ν_{max} 3146 (w), 3067 (m), 2970 (s), 2855 (s), 2293 (m), 2248 (m), and 1667 cm^{-1} (m); δ_H 6.25 (2H, t J=1.6 Hz, =CH), 4.29 (4H, t J=1.6 Hz, CHOCH_2), 4.27 (4H, t J=1.6 Hz, CHOCH_2C≡CCH_2O), 4.29–4.25 (2H, m, CHO), 4.21 (4H, q J=2.3 Hz, CH_3-C≡CCH_2O), 3.12 (2H, bs, CHCH=), 1.87 (6H, t J=2.3 Hz, CH_3), 1.50 (1H, dt J=9.7, 2.2 Hz, CHCH_2CH), 1.20 (1H, d J=9.4 Hz, CHCH_2CH); δ_C 134.8 (=CH), 83.6 (≡C), 83.4 (≡C), 82.1 (≡C), 78.4 (CHO), 74.6 (≡C), 57.8 (OCH_2), 57.6 (OCH_2), 57.1 (OCH_2), 46.2 (CH), 42.2 (CH_2), 4.0 (CH_3); *m/z* (CI) 384 ($M+NH_4^+$, 100), 367 (MH^+, 5), 280 (33), 264 (67). Found (CI) 384.2172, ($M+NH_4^+$) $C_{23}H_{30}NO_4$ requires 384.2175.

4.1.11. Metathesis of compound 25 to form compound 28. Bis-diyne **25** (100 mg, 0.27 mmol) was dissolved in dry toluene (20 ml) and ethene was passed through the solution for 20 min. A solution of catalyst **2** (23.2 mg, 0.027 mmol) in dry toluene (7 ml) was then added and the mixture was stirred at 60 °C for 24 h. The solvent was then removed in vacuo and the residue was purified by column chromatography (CH_2Cl_2/EtOAc 90/10) to give compound **28** as a transparent oil: yield (14 mg, 11%); ν_{max} 2868 (s), 1939 (w), 1725 (m), 1676 (w), and 1599 cm^{-1} (m); δ_H 6.00 (2H, d J=3.8 Hz, =CH), 5.19 (4H, s, =CH_2), 5.09 (2H, s, =CH_2), 5.05 (2H, s, =CH_2), 4.94 (4H, s, =CH_2), 4.50 (2H, d J=15.0 Hz, CH_2OCH), 4.2–4.0 (12H, m, $CH_2OCH+CH_2OCH_2$), 2.3–2.2 (2H, m, CH–CH=), 1.85 (6H, s,

CH_3), 1.51 (2H, dt $J=12.1$, 6.1 Hz, CHCH_2CH); δ_C 144.2 (=C), 141.3 (=C), 141.1 (=C), 134.3 (=C), 123.8 (=CH), 114.9 (=CH_2), 113.8 (=CH_2), 112.7 (=CH_2), 77.0 (CHO), 71.7 (OCH_2), 71.4 (OCH_2), 66.0 (OCH_2), 40.0 (CH), 36.4 (CH_2), 21.4 (CH_3); *m/z* (CI) 473 ($M+Na^+$, 100), 468 ($M+NH_4^+$, 95), 451 (MH^+, 5). Found (ES) 468.3103, $C_{29}H_{42}NO_4$ ($M+NH_4^+$) requires 468.3108.

4.1.12. 5,10-Dioxa-tridec-12-ene-2,7-diyn-1-ol 30. To a suspension of KOH (17.5 g, 312 mmol), in DMSO (65 ml) were added bromide **11**[9,10] (11.8 g, 62.5 mmol) and but-2-yne-1,4-diol (26.9 g, 312 mmol). The mixture was stirred for 60 min, poured into water and extracted with dichloromethane (3×120 ml). The aqueous phase was acidified with aqueous HCl (4 N, 100 ml) and further extracted with dichloromethane (3×120 ml). The combined organic phases were washed with H_2O (2×100 ml), then dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in Et_2O (250 ml), washed with brine (3×40 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by distillation (136 °C, 17 mm Hg) to give alcohol **30** as a colourless oil (8.8 g, 72.5%). ν_{max} 3400–3200 (br), 3082 (w), 2908 (s), 2856 (s), and 1647 cm^{-1} (m); δ_H 5.90 (1H, ddt $J=17.2$, 10.4, 4.7 Hz, =CH), 5.30 (1H, dd $J=17.2$, 1.6 Hz, =CH_{2trans}), 5.22 (1H, dd $J=10.4$, 1.2 Hz, =CH_{2cis}), 4.29–4.28 (6H, m, $CH_2OCH_2C{\equiv}CCH_2OCH_2$), 4.19 (2H, t $J=1.7$ Hz, CH_2OH), 4.05 (2H, dt $J=4.8$, 1.2 Hz, OCH_2CH=), 2.40 (1H, bs, OH); δ_C 134.2 (=CH), 118.4 (=CH_2), 85.7 (≡C), 83.6 (≡C), 81.9 (≡C), 81.3 (≡C), 71.1 (OCH_2), 57.8 (OCH_2), 57.4 (OCH_2), 57.3 (OCH_2), 51.4 (OCH_2); *m/z* (CI) 212 ($M+NH_4^+$, 100), 182 (15), 172 (29). Found (CI) 212.1285, ($M+NH_4^+$) $C_{11}H_{18}NO_3$ requires 212.1287.

4.1.13. 1-Bromo-5,10-dioxa-tridec-12-ene-2,7-diyne 31. To a solution of alcohol **30** (3.66 g, 18.9 mmol) in Et_2O (60 ml), were added CBr_4 (12.5 g, 37.7 mmol) and PPh_3 (9.89 g, 37.7 mmol). After 4 h the mixture was filtered through Celite and evaporated in vacuo. The residue was purified by column chromatography (1:9 Et_2O/hexane) to give bromide **31** (2.47 g, 51%) as a colourless oil. ν_{max} 3080 (s), 3008 (s), 2852 (s), 2276 (w), and 1650 cm^{-1} (m); δ_H 5.89 (1H, ddt $J=17.2$, 10.5, 5.7 Hz, =CH), 5.31 (1H, dd, $J=17.2$, 1.5 Hz, =CH_{2trans}), 5.22 (1H, dd $J=10.4$, 1.2 Hz, =CH_{2cis}), 4.30 (2H, t $J=1.9$ Hz, $OCH_2C{\equiv}CCH_2O$), 4.28 (2H, t $J=1.6$ Hz, $OCH_2C{\equiv}CCH_2O$), 4.20 (2H, t $J=1.8$ Hz, $BrCH_2C{\equiv}CCH_2O$), 4.06–4.05 (2H, m, CH_2CH=), 3.95 (2H, t $J=2.0$ Hz, CH_2Br); δ_C 134.3 (=CH), 118.3 (=CH_2), 83.5 (≡C), 82.4 (≡C), 82.3 (≡C), 81.7 (≡C), 71.1 (OCH_2), 57.7 (OCH_2), 57.3 (OCH_2), 57.2 (OCH_2), 14.4 (CH_2Br); *m/z* (CI) 276 ($M(^{81}Br)+NH_4^+$, 82), 274 ($M(^{79}Br)+NH_4^+$, 87), 196 (100), 179 (49), 164 (45). Found (CI) 274.0444, ($M+NH_4^+$) $C_{11}H_{17}NO_2Br$ requires 274.0443.

4.1.14. Compound 29. To a solution of 2,3-norbornen-5,6-diol[11] (0.50 g, 3.97 mmol), in dimethylformamide (5 ml) at 0 °C was added NaH (60% in mineral oil; 0.48 g, 11.9 mmol). The mixture was stirred for 1 h at 0 °C, then bromide **31** (2.55 g, 9.92 mmol) was added. The mixture was warmed to room temperature and stirred for 40 h. After hydrolysis at 0 °C with water (15 ml), the mixture was extracted with diethyl ether (4×15 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (hexane/Et_2O 30/70) to give compound **29** (1.96 g, 96%) as an off-white oil. ν_{max} 3070 (m), 2975 (s), 2938 (s), 2854 (s), and 1647 cm^{-1} (m); δ_H 6.18 (2H, t $J=1.7$ Hz, CHCH=), 5.83 (2H, ddt $J=17.2$, 10.4, 5.7 Hz, HC=CH_2), 5.24 (2H, ddd $J=17.2$, 3.2, 1.7 Hz, =CH_{2trans}), 5.16 (2H, dd $J=10.4$, 1.4 Hz, =CH_{2cis}), 4.3–4.2 (8H, m, ≡CCH_2OCH_2C≡), 4.20 (4H, t $J=1.7$ Hz, $CHOCH_2$), 4.18–4.17 (2H, m, CHO), 4.14 (4H, t $J=1.7$ Hz, CH_2-OCH_2CH=), 3.99 (4H, dt $J=5.8$, 1.3 Hz, OCH_2CH=), 3.05 (2H, bs, CHCH=), 1.44 (1H, dt $J=9.6$, 2.2 Hz, $CHCH_2CH$), 1.35 (1H, d $J=9.6$ Hz, $CHCH_2CH$); δ_C 134.8 (CH=), 134.3 (CH=), 118.3 (=CH_2), 83.7 (≡C), 83.3 (≡C), 81.9 (≡C), 81.8 (≡C), 78.4 (CHO), 71.1 (OCH_2), 57.8 (OCH_2), 57.7 (OCH_2), 57.3 (OCH_2), 57.2 (OCH_2), 46.2 (CH), 42.2 (CH_2); *m/z* (CI) 496 ($M+NH_4^+$, 100), 479 (MH^+, 16), 320 (20). Found (CI) 496.2695, ($M+NH_4^+$) $C_{29}H_{38}NO_6$ requires 496.2699.

Acknowledgements

The authors thank the EPSRC mass spectrometry service at the University of Wales, Swansea for recording low and high resolution mass spectra. The help and advice of Professor V. C. Gibson and Dr. E. Marshall (Imperial College London) on the synthesis of catalyst **1** is much appreciated.

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A route for preparing new neamine derivatives targeting HIV-1 TAR RNA

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Received 28 April 2004; revised 21 June 2004; accepted 24 June 2004
Available online 27 July 2004

Abstract—In the search for molecules possessing antibiotic or antiviral properties and ribonuclease like activity, that is, able to induce the cleavage of bacterial or viral RNA targets, we report a new route for preparing selectively neamine derivatives modified at their 4′- and/or 5-hydroxyl functions. Using trityl protective groups for the amino functions and 4-methoxybenzyl groups for the hydroxyl functions, new neamine derivatives, such as histidine, phenanthroline, flavin, adenine conjugates were efficiently obtained after a single deprotection step under acid conditions. For the first time, 4′-modified neamine derivatives were prepared. Most of the 4′-derivatives showed affinity and selectivity for TAR RNA close to those of the corresponding 5-derivatives. The most potent compound is the 4′-histidine derivative **31** which binds more tightly to TAR RNA compared to its 5-isomer and neamine and recognizes selectively TAR oligonucleotides having a bulge.

1. Introduction

Ribosomal RNA (rRNA) is the target of clinically important antibiotics. Among them, aminoglycosides (aminosides) constitute a large family of natural antibiotics that are effective against a broad range of microorganisms.[1] They are multiple positive charged molecules of high flexibility that bind specifically in the bacterial ribosome to the A-site of the decoding region of 16S rRNA and induce the synthesis of modified proteins.[2]

The aminoglycoside antibiotic neomycin B (**1**) (Scheme 1) also binds to other RNA targets[3] such as the HIV RNA recognition elements, RRE (Rev Responsive Element)[4a–d] and TAR (*trans*-acting responsive sequence)[4e] and blocks the HIV-Rev and HIV-Tat protein bindings necessary to viral RNA transactivation.

Unfortunately, neomycin B is toxic and high level antibiotic resistances that involve enzymatic modifications have been reported.[5] Detailed comparative NMR study and biochemical experiments have shown that rings I and II of neomycin-class aminoglycosides (Scheme 1) are sufficient to confer specificity for the binding to a model A-site RNA and can serve as a minimal structural motif for the binding to the 16S subunit of rRNA.[6] Therefore, in the search for new antibiotic or antiviral drugs, less toxic than neomycin, neamine **2** (Scheme 1) appears an attractive starting molecule.

In the last years, neamine derivatives have been prepared in modifying the amino groups, or the 3′-, the 5- or the 6-hydroxyl function in order to increase the affinity for the RNA targets and/or to induce a resistance to aminoglycoside-modifying enzymes.[7a] Combinatorial chemistry has been used to generate neamine libraries of neomycin B 'mimetics' by selective modifications at the 5 position.[8a,b] In such of a strategy, interesting dimers of neamine in which the two subunits are linked by an amino chain attached at the 5-positions, that target rRNA and inhibit resistance causing enzymes have been obtained.[8c] Aminoglycosides and neamine have also been modified in order to decrease the strength of their electrostatic interactions with aminoglycoside 3′-phosphotransferases types Ia and IIa, responsible for the resistance.[7b,c] More recently, 6-modified neamine derivatives possessing an amino side chain have been designed and synthesised efficiently. Some of these compounds have been found to be very poor substrates for two important purified resistance enzymes and showed interesting antibiotic properties.[7d]

Keywords: Neamine; Neomycin; Aminoglycosides; Conjugates; TAR RNA; HIV.
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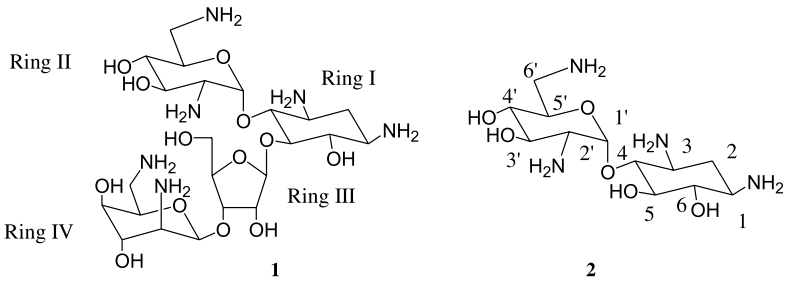
doi:10.1016/j.tet.2004.06.122



Scheme 1. Structure of neomycin B **1** and neamine **2**.

In the search for molecules possessing antibiotic or antiviral properties and ribonuclease like activity, that is, able to induce the cleavage of the bacterial or the viral RNA targets, we report here a new route for preparing selectively neamine derivatives modified at their 4′- and/or 5-hydroxyl functions. Previously, for modifying neamine at the 5- or 6-position, different protective groups for the amino functions have been used such as *t*-butoxycarbonyl,[7b,c] benzyloxycarbonyl[7d,8a] and azido groups.[8b,c] Acetyl,[8a] benzyl[8b,c] or MOM[7d] groups have been used for protection of the hydroxyl functions. A library of $N^{6'}$-modified neamine derivatives has also been obtained using a temporary trityl protecting group for the 6′-amino function.[9]

Using trityl protective groups for the four amino functions and 4-methoxybenzyl groups for the hydroxyl functions in the neamine core, the synthesis of new neamine conjugates at the 5- and/or 4′-positions, such as histidine, phenanthroline and adenine conjugates, is described here. We report here for the first time the synthesis of 4′-modified neamine derivatives and a comparison of their affinity and selectivity for HIV-1 TAR RNA with those of the corresponding 5-isomers.

Using the same protective groups and a single deprotection step under acid conditions, we synthesised a conjugate in which the neamine core is attached at the 5-position to the *N*-terminus of a 16-mer peptide nucleic acid that targets and cleaves HIV-1 TAR RNA and inhibits viral replication.[10]

2. Results and discussion

2.1. Protection of the amino and hydroxyl functions

The neamine amino groups are essential elements in the binding of HIV-1 and ribosomal RNAs and, thus, hexyl arms carrying new recognition elements or reactive groups were introduced from hydroxyl functions. For preparing these neamine conjugates, protective groups that can be easily removed under acid conditions were used such as hindered trityl protective groups for the amino functions. The presence of these trityl groups allowed a selective protection of two or three hydroxyl functions with 4-methoxybenzyl groups and hexyl arm(s) could be introduced from the remaining hydroxyl function(s).

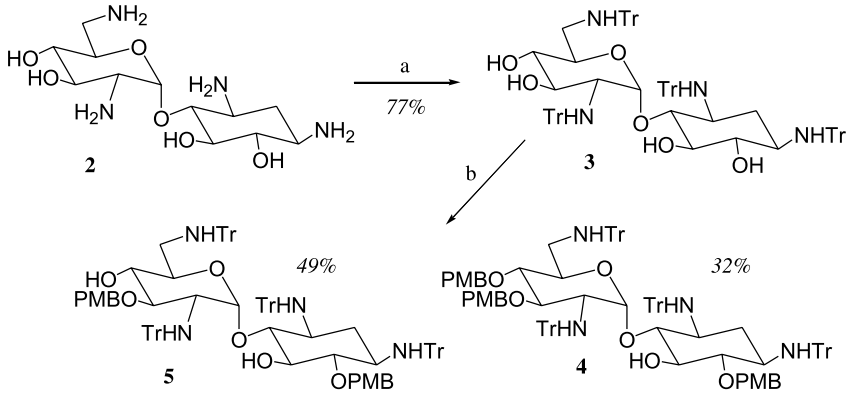
Remarkably, it appeared possible to protect the four amino functions with hindered 4-methoxytrityl or trityl groups through the reaction of the corresponding trityl chloride with neamine tetrahydrochloride[11] in triethylamine/DMF at room temperature. The trityl derivative **3** was obtained in a 77% yield after chromatography on alumina gel.

The presence of the trityl groups confers to the neamine derivative **3** an interesting high solubility in low polarity organic solvents (CH_2Cl_2, THF…) which was useful in the next steps.

The previous observation of the poor reactivity of the 5-hydroxyl function in neamine derivatives in which the amino groups have been protected with Boc or Cbz groups let us suppose a possible selectivity in a benzylation step.[7b–d,8a] Thus, the reactivity of compound **3** with benzyl bromide or 4-methoxybenzyl chloride in the presence of an excess of sodium hydride was studied. The chemistry developed with 4-methoxybenzyl chloride is described here, similar results were obtained with benzyl bromide.[12]

The reaction of the tetratritylated derivative **3** in DMF with three equivalents of 4-methoxybenzyl chloride in the presence of NaH and tetrabutylammonium iodide at room temperature gave the tribenzylated derivative **4** as the major product in 47% yield. As previously reported,[7,8a] the 5-hydroxyl function appeared less reactive than the 3′, 4′ and 6-hydroxyl functions due to steric effects. The remaining free hydroxyl function in the tribenzylated derivative **4** was used for preparing a first series of conjugates. Its location at the 5-position was confirmed by NMR experiments on the deprotected derivatives **9**, **28**–**30** and **36** prepared from compound **4** (see next parts and Supporting information).

For synthesizing conjugates in which the linking arm is attached at a position different from the 5-position and obtaining dibenzylated derivative(s), the velocity of the *O*-benzylation was decreased in a THF/DMF mixture (90:10). The reaction was conducted with 2.5 equiv of 4-methoxybenzyl chloride or benzyl bromide in the presence of an excess of sodium hydride and tetrabutylammonium iodide at room temperature. HPLC analysis revealed that only one dibenzyl derivatives was formed under these conditions. Formation of the tribenzyl derivative **4** was always observed under different conditions (one addition of the benzyl halide or addition by part). Finally, this derivative **4** and the dibenzylated derivative **5** (Scheme 2) were easily isolated after chromatography on alumina gel in 32 and 49% yields, respectively. The ^{13}C NMR spectrum of the isolated compound **5** confirmed the presence of only one dibenzylated derivative. For instance, the signals corresponding to the methylene groups in the two 4-methoxylbenzyl groups were detected at 75.6 and 73.7 ppm, respectively.



Scheme 2. Protection of the amino and hydroxyl functions of neamine **2**. Key: (a) TrCl, Et_3N, DMF; (b) PMBCl, NaH, TBAI, THF or THF/DMF 90:10.

From this compound possessing free 4′ and 5-hydroxyl groups, the deprotected amino derivative **13** and the conjugates **31**, **32** and **38** resulting from selective alkylation of the 4′-hydroxyl group were prepared. Their structures were determined by NMR spectrometry to assign the structure **5** to the starting dibenzylated derivative (tetra-*N*-trityl-di-*O*-3′,6-(4-methoxybenzyl) derivative; see next parts).

2.2. Selective functionalization of the neamine core

For preparing neamine conjugates from the protected tetratrityl tri(methoxybenzylated) and tetratrityl di(methoxybenzylated) neamine derivatives **4** and **5**, respectively, compounds **8**, **12**, **16**, possessing one or two flexible *n*-hexyl arms introduced from the free hydroxyl functions and bearing terminal amino function(s) were synthesised. Their synthesis involved three steps: (1) introduction of one or two bromohexyl chains (synthesis of compounds **6**, **10** and **14**), (2) substitution of the bromine atom(s) for azido group(s) for obtaining compounds **7**, **11**, **15** and (3) reduction of the azido groups to amino functions. These highly functionalized intermediates were characterized by HRMS and, then, the corresponding deprotected amines were characterized by NMR spectrometry and HRMS.

The bromo derivatives **6**, **10**, **14** were prepared by reaction of compounds **4** and **5** with 1,6-dibromohexane in the presence of sodium hydride in DMF at 60 °C. Using an excess of alkylating reagent (5 equiv) and of NaH, the tri(methoxybenzylated) derivative **4** gave the 5-bromohexyl derivative **6** in a 76% yield after chromatography on alumina (Scheme 3). Under different conditions of reaction, formation of the neamine dimer was not observed. Alkylation of the 3′,6-di(methoxybenzylated) derivative **5** in DMF at 60 °C in the presence of 1.5 equiv of 1,6-dibromohexane led to the 4′-monobromohexyl derivative **10** isolated in a 60% yield after chromatography (Scheme 4). The reaction selectivity may be explained by the low reactivity of the 5-hydroxyl function (steric effects).[7b–d,8a]

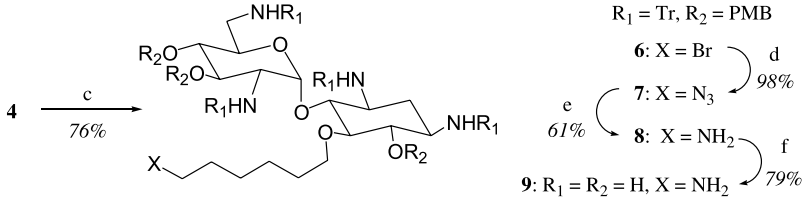
The 4′,5-dibromohexyl derivative **14** was also prepared from compound **5** in a 73% yield in increasing the 1,6-dibromohexane excess (10 equiv) and the reaction time (Scheme 4).

In order to substitute the terminal bromine atom for an amino group, compounds **6**, **10** and **14** were transformed to the corresponding azido derivative **7**, **11** and **15**, in high yields (98–93%, respectively) through reaction with sodium azide in excess in DMF (Schemes 3 and 4). Reduction of the azido group with triphenylphosphine in THF/H_2O gave, after chromatography on alumina, the corresponding amino derivatives **8**, **12** and **16**, respectively (61–75% yields).

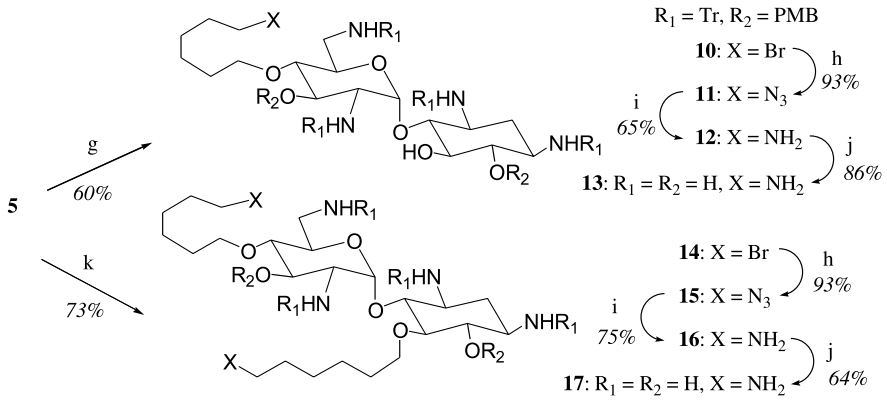
2.3. Deprotection of the amino derivatives 8, 12, 16

The amino derivatives **8**, **12**, **16** were deprotected in a TFA/anisole mixture (1:1) at room temperature. The corresponding amines **9**, **13**, **17** (Schemes 3 and 4) were purified by chromatography on C18 reversed phase eluting with water and, then, were passed through an ion exchange resin column (ammonium carboxylate form). These neamine derivatives were finally isolated as hydrochloride salts which were characterized by NMR spectrometry (D_2O) and HRMS. The ^1H and ^{13}C NMR spectra confirmed the purity of the isolated products (see Supporting data).

The position of the introduced hexyl arm was finally determined from the ^{13}C NMR spectra in comparison to neamine (Table 1). Attachment of the linking chain at the 5-position in the amino derivative **9** was confirmed by a strong deshielding effect (≈7.5 ppm) observed for the carbon atom 5 in comparison to neamine and to the amino



Scheme 3. Introduction of the linking chain on the 5-hydroxyl function of the neamine core. Key: (c) 1,6-dibromohexane (5 equiv), NaH, DMF, 60 °C; (d) NaN_3, DMF; (e) triphenylphosphine, H_2O, THF; (f) TFA, anisole.



Scheme 4. Introduction of the linking chain on the 4′-hydroxyl or the 4′,5-hydroxyl functions of the neamine core. Key: (g) 1,6-dibromohexane (1.5 equiv), NaH, DMF, 60 °C; (h) NaN_3, DMF; (i) triphenylphosphine, H_2O, THF; (j) TFA, anisole; (k) 1,6-dibromohexane (10 equiv), NaH, DMF, 60 °C.

derivative **13**. The shifts ($\Delta\delta$) measured for the C3′ and the C6 signals are not higher than 0.2 ppm. The chemical shifts of these carbon atoms and the C4′ are close to those described for neomycin.[13]

In the amino derivative **13**, only the C4′ signal is strongly deshielded ($\approx$9 ppm) in comparison to neamine and to the 5-amino isomer **9** (Table 1). This effect revealed that the linking chain is attached at the 4′-position.

2.4. Synthesis of the conjugates

The conjugates were prepared from the protected amino derivatives **8**, **12** and **16**.

From starting reagents possessing a carboxylic acid function carrying a bioactive element, conjugates were prepared through peptide bond formation (Scheme 5). The coupling reactions were conducted with 1.5–3 equiv of the carboxylic acid in dichloromethane or DMF at room temperature in the presence of EDC and HOBt as coupling reagents. The conjugates obtained were purified by chromatography on alumina gel.

In the search for molecules possessing ribonuclease like activity, three histidine conjugates were synthesized (Scheme 5). Histidine residues are involved in RNA hydrolysis catalysed by the enzyme ribonuclease A.[14] Reaction of amino derivatives **8**, **12** and **16** with the protected histidine derivative **18** gave selectively, after treatment with piperidine to remove the Fmoc protecting group, the corresponding conjugates **21**, **24** and **26** (Scheme 5).

Copper 1,10-phenanthroline complexes are reported to be able to induce cleavage of DNA or RNA through redox chemistry.[15a,b] Copper(II) derivatives of aminoglycosides such as neomycin B are also efficient hydrolytic cleaving agents for cognate RNA motifs[15c,d] and DNA.[15e]

For preparing the phenanthroline–neamine conjugates **22**, **25** and **27** which should cleave the target RNA under different conditions, 4-carboxylic phenanthroline acid **19** and the corresponding amino derivatives **8**, **12** and **16** were coupled (Scheme 5).

Flavin-dependent photocleavage of RNA at G-U base pairs has been reported.[16] In order to prepare tools for the study of the binding of neamine derivatives to RNA targets, the flavin **20** carrying a carboxylic acid function at the end of the side chain was reacted with the 6-aminohexyl neamine derivative **8** in the presence of EDC/HOBt (Scheme 5). The corresponding conjugate **23** was obtained as a yellow powder which led after deprotection to the conjugate **30** (60% yield for two steps).

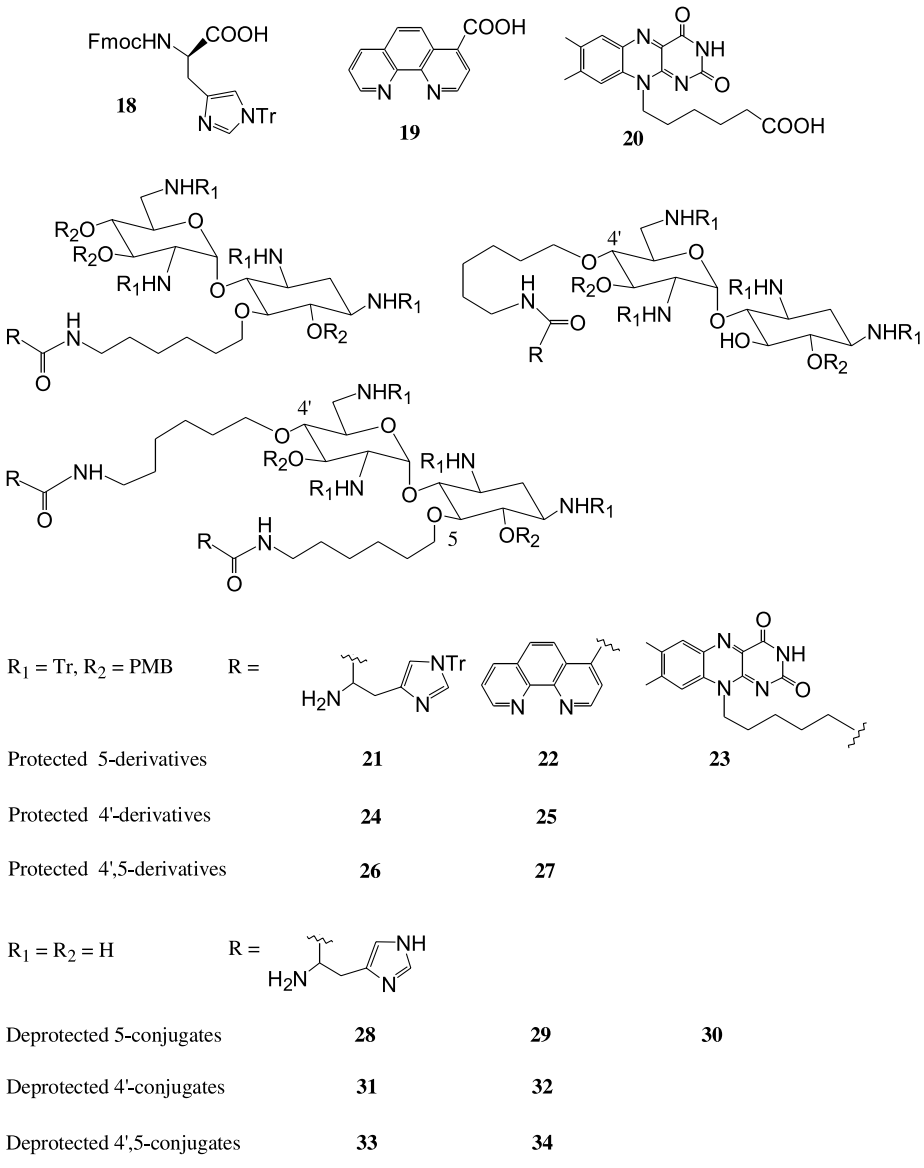
The adenine ring was also conjugated to the neamine core through an aromatic nucleophilic substitution. Reaction of 6-chloropurine in excess with the amino derivative **8**, **12** or **16** in the presence of triethylamine in ethanol at reflux afforded cleanly the corresponding conjugates **35**, **37** and **39** in good yields (75, 73 and 63%, overall yields in deprotected conjugates **36**, **38** and **40**, respectively; Scheme 6).

NMR spectrometry gave poor information on the structures of the protected conjugates which were confirmed from the corresponding deprotected conjugates.

Table 1. Comparison of ^{13}C NMR chemical shifts (100 MHz, D_2O) of neamine **3** and its amino derivatives **9** and **13** (between 65 and 85 ppm)

	Neamine	5-Derivative **9**		4'-Derivative **13**	
	δ ppm	δ ppm	Δ δppm/neamine	δ ppm	Δδ ppm /neamine
C 3'	68.1	68.2	0.1	68.3	0.2
C 4'	70.6	70.2	-0.4	79.0	8.8
C 5'	69.1	69.9	0.8	68.7	- 0.4
C 4	77.4	73.1	-4.3	77.2	- 0.2
C 5	75.1	82.5	7.4	75.2	0.1
C 6	72.4	72.6	0.2	72.5	0.1

A strong deshielding effect is observed for the carbon atom 5 in compound **9** and for the carbon atom 4′ in compound **13**.



Scheme 5. Preparation of the neamine conjugates through amide bond formation in two steps: (1) coupling reaction of the neamine derivatives **8**, **12** or **16** to compounds **18**, **19** or **20** for obtaining the corresponding conjugates **21**–**27**: EDC, HOBt, CH_2Cl_2 or DMF; (2) deprotection to lead to the neamine conjugates **28**–**34**: TFA, anisole (58, 46, 60, 59, 59, 27 and 22% overall yields, respectively).

2.5. Deprotected conjugates 28–34, 36, 38, 40

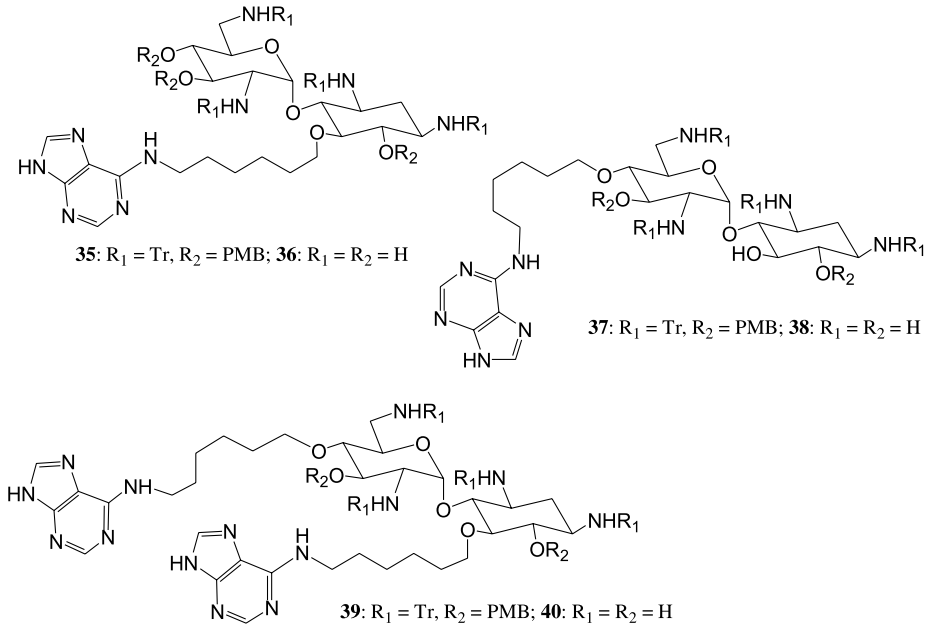
The conjugates **21**–**27**, **35**, **37**, **39** were deprotected in a mixture TFA/anisole at room temperature to lead to the conjugates **28**–**34** (Scheme 5) and **36**, **38**, **40** (Scheme 6) under the conditions used to prepare the amines **9**, **13**, **17**. The corresponding hydrochloride salts were characterized by NMR spectrometry and HRMS.

The ^1H and ^{13}C NMR spectra confirmed the purity and the structure of all the deprotected conjugates. The chemical shifts observed for the protons and the carbon atoms of the neamine core and the linking chain are close to those of the corresponding characterised amino derivatives (deshielding effects as in Table 1). For the 5-neamine derivatives, a NOE correlation was also observed between the $1'$-protons and the methylene protons of the chain attached to the 5-oxygen atom.

The HMR spectra of these neamine conjugates (electrospray mode) also confirmed the previously determined structures. For the conjugates **28**-**30** and **36** in which the linking chain is attached at the 5-position, ions corresponding to the modified deoxystreptamine core were detected confirming the expected structure. Such ions were also detected from the conjugates **33**, **34** and **40** possessing two linking chains. Fragments derived from the aminoglucopyranoside core were not observed. For the conjugates **31**, **32** and **38** in which the linking chain was expected to be attached on the aminoglucopyranoside core ($4'$-position), no modified deoxystreptamine fragments were observed in the HRM spectra. This observation confirms that the linking chain is attached on the sugar moiety.

2.6. Affinity and selectivity for TAR RNA

We compared the ability of neamine, neomycin and the



Scheme 6. Preparation in two steps of the neamine conjugates carrying the adenine ring **36**, **38**, **40** from the neamine derivatives **8**, **12** and **16**, respectively: (1) coupling reaction with 6-chloropurine for obtaining the protected conjugates **35**, **37**, **39**: ethanol, Et_3N, reflux; (2) deprotection: TFA, anisole.

neamine derivatives substituted at positions 4′, 5 or 4′,5 to alter the thermal denaturation profile of a 27-bases oligonucleotide corresponding to the upper part of the TAR RNA (Fig. 1). This oligonucleotide, designated TAR-1, includes the apical CUGGGA loop and the lateral UUU bulge characteristic of the TAR RNA. To investigate the selectivity of the different compounds, their effects were also tested with three other related RNA oligonucleotides: TAR-2, a 24-bp oligonucleotide lacking the UUU bulge; TAR-3 and TAR-4, both 27-bases long, for which the UUU bulge has been replaced with a CCC or AAA bulge (Fig. 1). Under our experimental conditions (BPE buffer, 16 mM Na^+), the four RNA melt at 51, 77, 55 and 57 °C for TAR1-4, respectively. As expected, the deletion of the U bulge in TAR-2 stabilizes the double stranded structure of the stem part of the RNA and therefore increases its thermal stability significantly. Each compound was incubated with the different RNA at a fixed ratio (0.5 μM RNA-5 μM ligand)

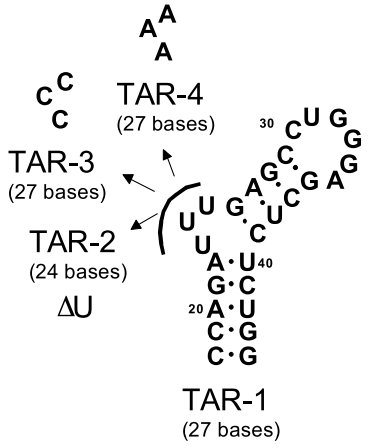


Figure 1. Structures of the 27-bases oligonucleotide TAR-1 coresponding to the upper part of TAR RNA model and the modified oligonucleotides TAR-2 to -4 used to study the affinity and selectivity of the synthesised neamine derivatives for TAR RNA.

and the temperature corresponding to the helix-to-coild transition was determined from the first derivative of the melting curves. The ΔT_m values ($\Delta T_m = T_m^{complex} - T_m^{RNA}$) values are collated in Table 2. All compounds tested induce a shift of the T_m value to a higher temperature but the effects vary considerably from one RNA to another and there are also large variations among compounds. The highest ΔT_m values were obtained with the amino compounds **9**, **13**, **17**. Incorporation of the NH_2 group at position 4′ and/or 5 strongly stabilizes the RNA structure. The 4′,5-disubstituted amino compound **17** shows a high affinity for TAR-1 but it also stabilizes the bulge-less derivative TAR-2 suggesting a low level of selectivity. The situation is more interesting with the histidine derivatives because in this case little or no effect was detected with TAR-2 whereas a marked stabilization of TAR-1 was detected. The most potent compound is the 4′-histidine derivative **31** which binds more tightly to TAR-1 compared to neamine but shows no detectable interaction with TAR-2. A similar behavior was observed with the monosubstituted phenanthroline and adenine derivatives which also interact with TAR-1 but not TAR-2, suggesting thus that a bulge is needed for the formation of a stable complex. But in these two cases the ΔT_m values drop considerably with the disubstituted compounds **34** and **40** most likely due to a steric hindrance, the phenanthroline and adenine substituents being bulkier than the histidine group.

The use of TAR-3 and TAR-4 RNA models also provided useful information. Neamine strongly stabilizes TAR-1 but not TAR-3 and TAR-4 suggesting that the compound recognizes selectively the UUU bulge. Neomycin exhibits a much higher affinity for TAR than neamine but its bulge selectivity is low. In contrast to neamine, the amino compounds **9**, **13** and **17** bind equally well to the three RNA carrying a trinucleotide bulge composed of U, C or A residues. It is the same thing for the histidine derivatives **28**, **31** and **33** which also show little difference with TAR-2, -3

Table 2. Shifts of the melting temperatures ΔT_m °C $= T_m^{complex} - T_m^{RNA}$ measured for TAR-1 to -4RNA in the presence of neomycin, neamine and the synthesised neamine derivatives

Aminoglycoside	Additional group(s)	Position(s) of the linking chain(s)	TAR-1 ΔT_m (°C)	TAR-2 ΔT_m (°C)	TAR-3 ΔT_m (°C)	TAR-4 ΔT_m (°C)
Neomycin **1**			21	12	15	17
Neamine **2**			8	1	1	1
9	NH_2	5	13	4	14	13
13	NH_2	4′	13	4	15	13
17	NH_2	5 and 4′	14	8	16	18
28	Histidine	5	5	1	6	1
31	Histidine	4′	10	0	8	11
33	Histidine	5 and 4′	8	0	10	4
29	Phenanthroline	5	9	0	10	3
32	Phenanthroline	4′	9	0	11	10
34	Phenanthroline	5 and 4′	3	0	0	2
30	Flavin	5	9	1	9	6
36	Adenine	5	8	0	10	4
38	Adenine	4′	9	1	9	7
40	Adenine	5 and 4′	0	0	1	1

The thermal denaturation curves corresponding to the helix-to-coiled transition were recorded at 260 nm with a heating rate of 1 °C/min using 0.5 μM RNA molecule and 5 μM ligand in 1 mL quartz cuvettes (BPE buffer pH 7.1, 6 mM Na_2HPO_4, 2 mM NaH_2PO_4, 1 mM EDTA).

or -4. These results suggest that the substituted compounds interact with (or close to) the lateral bulge of the TAR RNA but the exact sequence of the bulge is not essential. One of the most interesting compound, histidine **31**, stabilizes equally well the two TAR oligonucleotides having a pyrimidine (UUU) or a purine (AAA) bulge. We therefore believe that the substituent introduced at position 4′ or 5 on the neamine core points to a site close to but not directly involved in the bulge structure.

3. Conclusion

Remarkably, the four amino groups in neamine could be selectively protected with trityl groups leading to a very hindered intermediate. Steric effects in this intermediate are probably responsible for the observed selective benzylation step leading to the di-*O*-3′,6-(4-methoxybenzyl) intermediate **5**. In this compound possessing two 4′,5-hydroxyl functions, the low reactivity of the hindered 5-hydroxyl function allowed to efficiently prepare for the first time 4′-neamine derivatives using a single deprotection step under acid conditions.

Various 4′-, 5- and 4′,5-neamine conjugates were prepared in seven steps and good yields through different coupling reactions (peptide bond formation or aromatic nucleophilic substitution).

Surprisingly, we show here that most of the 4′ derivatives have affinity and selectivity for TAR RNA (TAR-1) close to those of the corresponding 5-derivatives. The most potent compound is the 4′-histidine derivative **31** which binds more tightly to TAR-1 compared to its 5-isomer and neamine and shows no detectable interaction with TAR-2.

4. Experimental

All oligoribonucleotides were purchased from Eurogentec (Liège, Belgium).

4.1. General procedures

Melting points are reported uncorrected. Chemical shifts are in parts per million relative to the residual signal of the solvent.

4.2. Synthesis

The imidazole derivative **18** was purchased from Bachem. 4-Carboxylic phenanthroline acid **19** was prepared in two steps from the corresponding 4-methyl derivative.[17] The flavin carboxylic acid derivative **20** was prepared according to a procedure previously developed.[18]

Thin-layer chromatographic data (R_f values) were obtained with Macherey Nagel Alugram® SIL G/UV_{254} analytical sheets (layer: 0.25 mm) developed with dichloromethane–methanol 95:5 (R_f^A) or 90:10 (R_f^B), pentane–dichloromethane 60:40 (R_f^C) or 50:50 (R_f^D).

4.2.1. Protection of the amine functions, preparation of compound 3. A solution of neamine tetrahydrochloride (5.0 g, 10.6 mmol) in DMF/triethylamine (60:8 mL) under Ar was stirred at room temperature for 1 h and then a solution of trityl chloride (13.6 g, 48.6 mmol) in DMF/triethylamine (130:8 mL) was added. After 4 h at room temperature, dichloromethane (200 mL) was added. The resulting solution was washed with water (2×250 mL), dried over Na_2SO_4 and evaporated. The residue was precipitated in pentane and then chromatographed on alumina gel in CH_2Cl_2–methanol (95:5) to lead to tetratritylated derivative **3** (10.6 g, 8.2 mmol, 77%, R_f^A 0.60): mp 178–179 °C; ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.5–145.7 (CPh), 129.5–125.5 (CHPh), 98.0 (C1′), [82.6, 77.1, 75.6, 73.4, 72.3, 71.6] (6CH nea), [71.0, 70.6, 70.5, 69.6] (4C$(Ph)_3$), [57.6, 54.2, 52.7] (3CH Nea), 45.2 (C6′), 34.6 (C2); LRMS (FAB$^+$, NBA) $m/z = 1313$ $[M+Na]^+$, 1291 $[M+H]^+$, 1047 $[M-Tr+H]^+$; HRMS (electrospray) Calcd for $C_{88}H_{82}N_4O_6Na$ $[M+Na]^+$: 1313.6132, found: 1313.6139, Calcd for $C_{88}H_{82}N_4O_6K$ $[M+K]^+$: 1329.5872, found: 1329.5811.

4.2.2. Protection of the hydroxyl functions, preparation of compounds 4 and 5. To a solution of compound **3** (9.0 g, 6.9 mmol) in THF/DMF (90:10 mL) under Ar, sodium hydride (60%, 800 mg, 21 mmol), tetrabutylammonium iodide (2.6 g, 6.9 mmol) and 4-methoxybenzyl chloride (2.4 mL, 17.4 mmol) were added. The mixture was stirred at room temperature for 12 h, then dichloromethane (200 mL) and a saturated aqueous ammonium chloride solution (150 mL) were added. The organic layer was washed twice with water (200 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on alumina gel in pentane–CH_2Cl_2 (7:3) for obtaining compounds **4** (tribenzylated product, 3.7 g, 2.24 mmol, 32%, R_f^D 0.78) and **5** (dibenzylated product, 5.2 g, 3.4 mmol, 49%, R_f^D 0.31).

4.2.3. Tribenzylated derivative 4. Mp 152–153 °C; ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 159.0 ($COCH_3$), 147.2–146.1 (CPh), 131.1–125.7 (CHPh), 113.9–113.6 (CH *o*-OCH_3), 94.6 (C1′), [86.0, 81.9, 81.1, 77.1, 76.0, 73.1] (6CH nea), 75.6, 74.5, 73.9 ($BnCH_2$), [71.0, 70.9, 70.5, 70.0] (4C$(Ph)_3$), [58.1, 53.0, 52.7] (3CH nea), 55.2 (CH_3O), 45.3 (C6′), 34.6 (C2); LRMS (FAB^+, NBA) m/z=1651 $[M+H]^+$, 1674 $[M+Na]^+$, 1047 $[M-Tr+H]^+$; HRMS (electrospray) Calcd for $C_{112}H_{106}N_4O_9Na$ $[M+Na]^+$: 1673.7858, found: 1673.7858, Calcd for $C_{112}H_{106}N_4O_9K$ $[M+K]^+$: 1689.7597, found: 1689.7596.

4.2.4. Dibenzylated derivative 5. Mp 134–135 °C; ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1–159.0 ($COCH_3$), 147.0–146.1 (CPh), 131.0–125.7 (CHPh), 113.7 (CH *o*-OCH_3), 95.2 (C1′), [85.6, 81.9, 81.5, 77.2, 76.9] (6CH nea), 75.6, 73.7 ($BnCH_2$), [71.0, 70.6, 70.5, 70.0] (4C$(Ph)_3$), [58.1, 53.0, 52.7] (3CH nea), 55.1 (CH_3O), 46.2 (C6′), 35.3 (C2); LRMS (FAB^+, NBA) m/z=1553 $[M+Na]^+$, 1289 $[M-Tr+H]^+$; HRMS (electrospray) Calcd for $C_{104}H_{99}N_4O_8$ $[M+H]^+$: 1531.7463, found: 1531.7407, Calcd for $C_{104}H_{98}N_4O_8Na$ $[M+Na]^+$: 1553.7282, found: 1553.7290, Calcd for $C_{104}H_{98}N_4O_8K$ $[M+K]^+$: 1569.7022, found: 1569.7013.

4.3. Synthesis of the bromo derivatives 6, 10 and 14

To a solution of compound **4** or **5** in DMF under Ar, were added successively sodium hydride (60% suspension) and 1,6-dibromohexane. The mixture was stirred for 12 h at 60 °C. After cooling, dichloromethane (200 mL) and then an aqueous saturated ammonium chloride solution (150 mL) were added. The organic layer was washed twice with water (100 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on alumina gel in pentane–CH_2Cl_2 (7:3) to lead to the corresponding bromo derivatives **6**, **10** or **14**.

4.3.1. Compound 6. Starting neamine derivative **4** (5.0 g, 3.03 mmol), DMF (60 mL), NaH (580 mg, 15.0 mmol), 1,6-dibromohexane (2.33 mL, 15.1 mmol), bromo derivative obtained **6** (4.2 g, 2.31 mmol, 76%, R_f^C 0.54): mp 120–121 °C; LRMS (FAB^+, NBA) m/z=1837 $[M+Na]^+$; HRMS (electrospray) Calcd for $C_{118}H_{117}N_4O_9^{79}BrNa$ $[M+Na]^+$: 1835.7902, found: 1835.7908, Calcd for $C_{118}H_{117}N_4O_9^{79}BrK$ $[M+K]^+$: 1851.7641, found: 1851.7642.

4.3.2. Compound 10. Starting neamine derivative **5** (15.0 g, 9.79 mmol), DMF (150 mL), NaH (980 mg, 24.5 mmol), 1,6-dibromohexane (2.27 mL, 14.7 mmol), bromo derivative obtained **10** (10.0 g, 5.90 mmol, 60%, R_f^C 0.28): mp 91–92 °C; HRMS (electrospray) Calcd for $C_{110}H_{110}N_4O_8^{79}Br$ $[M+H]^+$: 1693.7507, found: 1693.7504, Calcd for $C_{110}H_{109}N_4O_8^{79}BrNa$ $[M+Na]^+$: 1715.7326, found: 1715.7297.

4.3.3. Compound 14. Starting neamine derivative **5** (6.70 g, 4.37 mmol), DMF (80 mL), NaH (822 mg, 20 mmol), 1,6-dibromohexane (6.74 mL, 43.7 mmol), bromo derivative obtained **14** (5.60 g, 3.01 mmol, 69%, R_f^C 0.71): mp 112–113 °C; HRMS (electrospray) Calcd for $C_{116}H_{121}N_4O_8^{79}Br_2$ $[M+H]^+$: 1855.7551, found: 1855.7566, Calcd for $C_{116}H_{120}N_4O_8^{79}Br_2Na$ $[M+Na]^+$: 1877.7371, found: 1877.7380, Calcd for $C_{116}H_{120}N_4O_8^{79}Br_2K$ $[M+K]^+$: 1893.7110, found: 1893.7118.

4.4. Synthesis of the azido derivatives 7, 11 and 15

To a solution of the bromo derivative **6**, **10** or **14** in DMF, was added sodium azide. The mixture was stirred at room temperature for 2 h and then dichloromethane was added (60 mL). The resulting solution was washed twice with water (50 mL), dried over Na_2SO_4 and evaporated. The residue was chromatographed on alumina gel in pentane–CH_2Cl_2 (6:4) for obtaining the corresponding azido derivative **7**, **11** or **15**.

4.4.1. Compound 7. Bromo derivative **6** (2.50 g, 1.37 mmol), DMF (30 mL), NaN_3 (447 mg, 6.80 mmol), azido derivative obtained **7** (2.40 g, 1.35 mmol, 98%, R_f^C 0.31): IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2095; mp 118–119 °C; HRMS (electrospray) Calcd for $C_{118}H_{118}N_7O_9$ $[M+H]^+$: 1776.8991, found: 1776.8976, Calcd for $C_{118}H_{117}N_7O_9Na$ $[M+Na]^+$: 1798.8810, found: 1798.8721.

4.4.2. Compound 11. Bromo derivative **10** (3.00 g, 1.77 mmol), DMF (30 mL), NaN_3 (230 mg, 3.50 mmol), azido derivative obtained **11** (2.80 g, 1.69 mmol, 93%, R_f^C 0.20): IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2095; mp 120–121 °C; HRMS (electrospray) Calcd for $C_{110}H_{110}N_7O_8$ $[M+H]^+$: 1656.8415, found: 1656.8407, Calcd for $C_{110}H_{109}N_7O_8Na$ $[M+Na]^+$: 1678.8223, found: 1678.8211.

4.4.3. Compound 15. Bromo derivative **14** (4.00 g, 2.15 mmol), DMF (40 mL), NaN_3 (1.40 g, 21.0 mmol), azido derivative obtained **15** (3.60 g, 2.02 mmol, 93%, R_f^C 0.34): IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2095; mp 117–118 °C; HRMS (electrospray) Calcd for $C_{116}H_{121}N_{10}O_8$ $[M+H]^+$: 1781.9369, found: 1781.9394, Calcd for $C_{116}H_{120}N_{10}O_8Na$ $[M+Na]^+$: 1803.9188, found: 1803.9183, Calcd for $C_{116}H_{120}N_{10}O_8K$ $[M+K]^+$: 1819.8928, found: 1819.8895.

4.5. Synthesis of the amino derivatives 8, 12 and 16

To a solution of the azido derivative **7**, **11** or **15** in THF/H_2O (95:5, 30 mL), triphenylphosphine was added. The solution was refluxed for 3 h and then evaporated. The residue was chromatographed on alumina gel in CH_2Cl_2–methanol (98:2 to 95:5) for obtaining the corresponding amino derivative **8**, **12** or **16**.

4.5.1. Compound 8. Azido derivative **7** (2.20 g,

1.24 mmol), triphenylphosphine (1.62 g, 6.18 mmol), amino derivative obtained **8** (1.30 g, 0.74 mmol, 60%, R_f^A 0.51): mp 120–121 °C; HRMS (electrospray) Calcd for $C_{118}H_{120}N_5O_9$ $[M+H]^+$: 1750.9086, found: 1750.9075.

4.5.2. Compound 12. Azido derivative **11** (2.00 g, 1.21 mmol), triphenylphosphine (1.58 g, 6.03 mmol), amino derivative obtained **12** (1.30 g, 0.79 mmol, 66%, R_f^A 0.35): mp 133–134 °C; HRMS (electrospray) Calcd for $C_{110}H_{112}N_5O_8$ $[M+H]^+$: 1630.8510, found: 1630.8505, Calcd for $C_{110}H_{111}N_5O_8Na$ $[M+Na]^+$: 1652.8330, found: 1652.8341.

4.5.3. Compound 16. Azido derivative **15** (1.50 g, 0.84 mmol), triphenylphosphine (1.10 g, 4.21 mmol), amino derivative obtained **16** (1.10 g, 0.63 mmol, 75%, R_f^B 0.65): mp 114–115 °C; HRMS (electrospray) Calcd for $C_{116}H_{125}N_7O_8$ $[M+H]^+$: 1729.9558, found: 1729.9548, Calcd for $C_{110}H_{111}N_5O_8Na$ $[M+Na]^+$: 1751.7326, found: 1751.7317.

4.6. Synthesis of the conjugates through formation of an amide function

Coupling reaction with a carboxylic acid. The carboxylic acid was dissolved in dichloromethane or DMF under Ar, then 1-[3-(dimethylaminopropyl)]-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) were added. The mixture was stirred for 30 min and the neamine derivative was added. The mixture was stirred at room temperature for 1 h. For the histidine conjugates, at the end of the reaction, piperidine was added and the resulting solution was stirred at room temperature for 30 min until complete removal of the Fmoc protective group. Dichloromethane was added and the resulting solution was washed twice with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on alumina gel in CH_2Cl_2–MeOH (100:0 to 95:5) for obtaining the protected conjugate.

Deprotection. A solution of the protected conjugate in anisole–TFA (1:1) was stirred at room temperature for 12 h and then methanol was added. The resulting solution was evaporated, then the crude residue was taken up in water, washed with CH_2Cl_2, and the water phase was concentrated. The residue was chromatographed on C_{18} reversed-phase in water. After concentration, the residue was chromatographed on an ion-exchange resin (Amberlite CG-50, NH_4^+ form) in aqueous ammonia (6%) to afford the deprotected conjugate as the free base. This base was dissolved in 1 M aqueous HCl and the solution was lyophilised to afford the hydrochloride salt of the conjugate.

4.7. Deprotected amino derivatives 9, 13, 17

4.7.1. Amino derivative 9. Neamine derivative **8** (600 mg, 0.34 mmol), deprotected hydrochloride **9** (166 mg, 0.27 mmol, 79%): mp 230 °C dec; ^{1}H NMR (400 MHz, D_2O) δ 5.76 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 3.82–4.10 (m, 4H, H3′, H4, CH_2O, H5′), 3.60–3.78 (m, 3H, H5, H6, CH_2O), 3.40–3.60 (m, 4H, H3, H2′, H6′, H4′), 3.20–3.38 (m, 2H, H6′, H1), 2.90 (m, 2H, CH_2N), 2.42 (ddd, $J_{2eq-1}=J_{2eq-3}=$ 4.1 Hz, $J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{eq}$), 1.85 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{ax}$), 1.50–1.62 (m, 4H, CH_2 chain), 1.22–1.38 (m, 4H, CH_2 chain); ^{13}C NMR (100 MHz, D_2O) δ 92.9 (C1′), 82.6 (C-5), 73.1 (C-4), 72.6 (C-6), 72.2 (*C*H_2O), 70.2 (C-4′), 69.9 (C-5′), 68.3 (C-3′), 53.3 (C-2′), 49.8 (C-1), 48.9 (C-3), 40.2 (C-6′), 39.4 (*C*H_2NH), 29.1, 27.8 (C-2), 26.6, 25.5, 24.6 (4CH_2 chain); LRMS (electrospray) $m/z=444.3$ $[M+Na]^+$, 262.2 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray), Calcd for $C_{18}H_{40}N_5O_6$ $[M+H]^+$: 422.2979, found: 422.2979.

4.7.2. Amino derivative 13. Neamine derivative **12** (600 mg, 0.37 mmol), deprotected hydrochloride **13** (188 mg, 0.31 mmol, 86%): mp 220 °C dec; ^{1}H NMR (400 MHz, D_2O) δ 5.91 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 3.92–4.08 (m, 3H, H3′, H5′, H4), 3.78–3.88 (m, 1H, CH_2O), 3.60–3.70 (m, 2H, H5, CH_2O), 3.38–3.58 (m, 4H, H6, H3, H6′, H2′), 3.20–3.38 (m, 3H, H1, H4′, H6′), 2.92 (m, 2H, CH_2N), 2.49 (ddd, $J_{2eq-1}=J_{2eq-3}=4.1$ Hz, $J_{2eq-2ax}=$ 12.6 Hz, 1H, $H2_{eq}$), 1.90 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}=$ 12.6 Hz, 1H, $H2_{ax}$), 1.50–1.68 (m, 4H, 2CH_2 chain), 1.28–1.38 (m, 4H, 2CH_2 chain); ^{13}C NMR (100 MHz, D_2O) δ 95.7 (C-1′), 79.0 (C-4′), 77.2 (C-4), 75.2 (C-5), 73.8 (*C*H_2O), 72.5 (C-6), 68.7 (C-5′), 68.3 (C-3′), 53.6 (C-2′), 49.8 (C-1), 48.6 (C-3), 40.3 (C-6′), 39.1 (*C*H_2NH), 29.4, 28.6 (C-2′), 27.0, 25.8, 25.0 (4CH_2 chain); HRMS (electrospray) Calcd for $C_{18}H_{39}N_5O_6Na$ $[M+Na]^+$: 444.2798, found: 444.2796.

4.7.3. Amino derivative 17. Neamine derivative **16** (600 mg, 0.35 mmol), deprotected hydrochloride **17** (166 mg, 0.22 mmol, 64%): mp 220 °C dec; ^{1}H NMR (400 MHz, D_2O) δ 5.60 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 3.99–4.03 (m, 1H), 3.87–4.92 (m, 2H), 3.75–3.95 (m, 1H), 3.59–3.62 (m, 2H), 3.47–3.54 (m, 3H), 3.34–3.40 (m, 2H), 3.18–3.25 (m, 4H), 2.76–2.80 (m, 4H, 2CH_2N), 2.30 (ddd, $J_{2eq-1}=$ $J_{2eq-3}=4.1$ Hz, $J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{eq}$), 1.72 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{ax}$), 1.38–1.48 (m, 8H, 4CH_2 chain), 1.17–1.19 (m, 8H, 4CH_2 chain); ^{13}C NMR (50 MHz, D_2O) δ 96.9 (C1′), [83.3, 79.4, 79.0, 74.3, 72.8, 72.1, 68.2] (6CH nea, CH_2O), [54.7, 50.1, 49.1] (3CH nea), [40.3, 39.0] (C6′, CH_2NH), [32.0, 28.7, 28.6, 26.1, 25.0, 24.9, 24.2] (8CH_2 chain, C2); LRMS (electrospray) $m/z=543.4$ $[M+Na]^+$, 262.2 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{24}H_{52}N_6O_6Na$ $[M+Na]^+$: 543.3846, found: 543.3846.

4.8. Conjugates at the 5-position

4.8.1. Histidine conjugate 28. Histidine derivative **18** (540 mg, 0.46 mmol), CH_2Cl_2 (6 mL), EDC (178 mg, 0.93 mmol), HOBt (126 mg, 0.93 mmol), neamine derivative **8** (540 mg, 0.31 mmol), deprotected conjugate hydrochloride **28** (133 mg, 0.18 mmol, 58%): mp 220 °C dec; ^{1}H NMR (500 MHz, D_2O) δ 8.60 (s, 1H, H Im), 7.33 (s, 1H, H Im), 5.76 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 4.11 (t, $J=7.0$ Hz, 1H, CH His), 3.95–4.01 (m, 2H, H3′, H4), 3.84–3.95 (m, 2H, CH_2O, H5′), 3.60–3.75 (m, 3H, H5, H6, CH_2O), 3.40–3.55 (m, 4H, H3, H2′, H6′, H4′), 3.22–3.35 (m, 4H, CH_2 His, H6′, H1), 3.01–3.15 (m, 2H, CH_2N), 2.40 (ddd, $J_{2eq-1}=$ $J_{2eq-3}=4.1$ Hz, $J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{eq}$), 1.82 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{ax}$), 1.46–1.58 (m, 2H, CH_2 chain), 1.30–1.40 (m, 2H, CH_2 chain),

1.10–1.30 (m, 4H, $2CH_2$ chain); ^{13}C NMR (50 MHz, D_2O) δ 167.8 (CO), [134.7, 126.4, 118.7] (3C Im), 93.3 (C1′), [82.9, 73.6, 73.0, 72.6, 70.5, 70.4, 68.6] (6CH nea, CH_2O), [53.6, 52.7, 50.2, 49.3] (3CH nea, CH His), [40.5, 39.9] (C6′, CH_2NH), [29.6, 28.3, 28.2, 26.5, 26.2, 25.0] ($4CH_2$ chain, C2, CH_2 His); LRMS (electrospray) m/z=581.3 $[M+Na]^+$, 421.2 [5-modified deoxystreptamine+Na]$^+$; HRMS (electrospray) Calcd for $C_{24}H_{46}N_8O_7Na$ $[M+Na]^+$: 581.3387, found: 581.3380.

4.8.2. Phenanthroline conjugate 29. 4-Carboxylic phenanthroline acid **19** (77 mg, 0.34 mmol), DMF (6 mL), EDC (131 mg, 0.68 mmol), HOBt (92 mg, 0.68 mmol), neamine derivative **8** (400 mg, 0.22 mmol), deprotected conjugate hydrochloride **29** (78 mg, 0.10 mmol, 46%): mp 210 °C dec; ^1H NMR (600 MHz, D_2O) δ 9.22–9.30 (m, 2H, Ar), 9.12–9.16 (m, 1H, Ar), 8.24–8.34 (m, 3H, Ar), 8.02 (d, 1H, Ar), 5.88 (d, $J_{1'-2'}$=3.8 Hz, 1H, H1′), 4.02–4.08 (m, 3H, H4, H3′,CH_2O), 3.94 (m, 1H, H5′), 3.82 (m, 1H, CH_2O), 3.70–3.77 (m, 3H, H2, H5, H6), 3.48–3.62 (m, 6H, H3, H2′, H6′, H4′, CH_2N), 3.32–3.42 (m, 2H, H1, H6′), 2.50 (ddd, 1H, $H2_{eq}$), 1.90 (ddd, 1H, $H2_{ax}$), 1.66–1.76 (m, 4H, $2CH_2$ chain), 1.40–1.52 (m, 4H, $2CH_2$ chain); ^{13}C NMR (75 MHz, D_2O) δ 168.8 (CO), [151.0, 145.9, 144.5, 143.2, 139.8, 137.65, 130.1, 127.2, 126.3, 126.1, 125.4, 123.7] (C phen), 93.4 (C1′), [83.0, 73.6, 73.1, 72.8, 70.5, 70.4, 68.7] (6CH nea, CH_2O), [53.1, 50.2, 49.3] (3CH nea), [40.5, 39.9] (C6′, CH_2NH), [29.7, 28.6, 28.2, 26.5, 25.2] ($4CH_2$ chain, C2); LRMS (electrospray) m/z=650.3 $[M+Na]^+$, 468.5 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{31}H_{45}N_7O_7Na$ $[M+Na]^+$: 650.3278, found: 650.3280.

4.8.3. Flavine conjugate 30. Flavin carboxylic acid **20** (120 mg, 0.34 mmol), DMF (6 mL), EDC (126 mg, 0.66 mmol), HOBt (89 mg, 0.66 mmol), neamine derivative **8** (400 mg, 0.22 mmol), deprotected conjugate hydrochloride **30** (120 mg, 0.13 mmol, 60%): mp 200 °C dec; ^1H NMR (400 MHz, D_2O) δ 7.47 (s, 1H, H Fl), 7.43 (s, 1H, H Fl), 5.69 (d, $J_{1'-2'}$=3.8 Hz, 1H, H1′), 4.41 (m, 1H, CH_2–Fl), 3.88–3.94 (m, 2H, H3′, H4), 3.78–3.87 (m, 2H, CH_2O, H5′), 3.52–3.63 (m, 3H, CH_2O, H5, H6), 3.33–3.50 (m, 4H, H3, H2′, H6′, H4′), 3.17–3.28 (m, 2H, H6′, H1), 2.92 (t, J=6.9 Hz, 2H, CH_2N), 2.32–2.36 (m, 4H, H2eq, CH_3Fl), 2.23 (s, 3H, CH_3Fl), 2.08 (t, 2H, J=7.2 Hz, CH_2CO), 1.76 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}$=12.6 Hz, 1H, $H2_{ax}$), 1.63–1.70 (m, 2H, CH_2 chain), 1.45–1.53 (m, 2H, CH_2 chain), 1.35–1.45 (m, 2H, CH_2 chain), 1.18–1.33 (m, 4H, $2CH_2$ chain), 1.05–1.15 (m, 4H, $2CH_2$ chain); ^{13}C NMR (50 MHz, D_2O) δ 176.0 (CO), [160.7, 157.3, 150.3, 148.7, 138.7, 134.0, 133.5, 130.5, 130.1, 115.8] (10C Fl), 92.5 (C1′), [82.1, 72.9, 72.2, 71.8, 69.7, 67.8] (6CH nea, CH_2O), [52.8, 49.4, 48.5] (3CH nea), 45.2 (CH_2N Fl), [39.6, 38.6] (CH_2N, C6′), 35.1 (CH_2–CO), [28.6, 27.7, 27.4, 25.7, 25.4, 24.8, 24.5, 24.2] ($7CH_2$, C2), 20.3, (CH_3), 18.2 (CH_3); LRMS (electrospray) m/z=782.4 $[M+Na]^+$, 600.3 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{36}H_{57}N_9O_9Na$ $[M+Na]^+$: 782.4176, found: 782.4178.

4.9. Conjugates at the 4′-position

4.9.1. Histidine conjugate 31. Histidine derivative **18** (743 mg, 1.20 mmol), CH_2Cl_2 (6 mL), EDC (460 mg, 2.4 mmol), HOBt (324 mg, 2.4 mmol), neamine derivative **12** (650 mg, 0.39 mmol), deprotected conjugate hydrochloride **31** (170 mg, 0.23 mmol, 59%): mp 225 °C dec; ^1H NMR (500 MHz, D_2O) δ 8.60 (s, 1H, H Im), 7.33 (s, 1H, H Im) 5.86 (d, $J_{1'-2'}$=3.8 Hz, 1H, H1′), 4.11 (t, J=6.7 Hz, 1H, H His), 3.97–4.02 (m, 1H, H3′), 3.85–3.97 (m, 2H, H5′, H4), 3.78–3.83 (m, 1H, CH_2O), 3.58–3.67 (m, 2H, H5, CH_2O), 3.35–3.55 (m, 4H, H6, H3, H6′, H2′), 3.18–3.32 (m, 4H, H1, H4′, H6′), 3.03–3.18 (m, 2H, CH_2N), 2.43 (ddd, $J_{2eq-1}=J_{2eq-3}$=4.1 Hz, $J_{2eq-2ax}$=12.6 Hz, 1H, $H2_{eq}$), 1.83 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}$=12.6 Hz, 1H, $H2_{ax}$), 1.48–1.58 (m, 2H, CH_2 chain), 1.28–1.38 (m, 2H, CH_2 chain), 1.18–1.28 (m, 2H, CH_2 chain), 1.08–1.18 (m, 2H, CH_2 chain); ^{13}C NMR (100 MHz, D_2O) δ 167.5 (CO), [134.2, 126.2, 118.2] (3C Im), 95.5 (C1′), [79.0, 77.4, 75.1, 74.0, 72.4, 68.6, 68.3] (6CH nea, CH_2O), [53.5, 52.3, 49.6, 48.4] (3CH nea, CH His), [40.1, 39.5] (C6′, CH_2NH), [29.1, 28.2, 27.9, 26.1, 25.7, 24.6] ($4CH_2$ chain, C2, CH_2 His); HRMS (electrospray) Calcd for $C_{24}H_{46}N_8O_7Na$ $[M+Na]^+$: 581.3387, found: 581.3388.

4.9.2. Phenanthroline conjugate 32. 4-Carboxylic phenanthroline acid **19** (82 mg, 0.36 mmol), DMF (6 mL), EDC (140 mg, 0.73 mmol), HOBt (99 mg, 0.73 mmol), neamine derivative **12** (400 mg, 0.22 mmol), deprotected conjugate hydrochloride **32** (110 mg, 0.14 mmol, 59%): mp 220 °C dec; ^1H NMR (600 MHz, D_2O) δ 9.22–9.30 (m, 2H, Ar), 9.12–9.16 (m, 1H, Ar), 8.24–8.34 (m, 3H, Ar), 8.02 (d, 1H, Ar), 5.94 (d, $J_{1'-2'}$=3.8 Hz, 1H, H1′), 4.09 (m, 1H, H3′), 4.02 (m, 1H, H5′), 3.92–4.00 (m, 2H, H4, CH_2O), 3.76 (m, 1H, CH_2O), 3.70 (m, 1H, H5), 3.53–3.62 (m, 4H, H3, H6, CH_2N), 3.48–3.52 (m, 2H, H6′, H2′), 3.40 (m, 1H, H4′), 3.30–3.38 (m, 2H, H6′, H1), 2.52 (ddd, 1H, $H2_{eq}$), 1.90 (ddd, 1H, $H2_{ax}$), 1.62–1.78 (m, 4H, $2CH_2$ chain), 1.40–1.54 (m, 4H, $2CH_2$ chain); ^{13}C NMR (75 MHz, D_2O) δ 168.8 (CO), [151.0, 146.0, 144.4, 143.3, 139.7, 137.5, 130.1, 127.2, 126.35, 126.1, 125.4, 123.7] (C Phen), 96.1 (C1′), [79.4, 77.9, 75.5, 74.5, 72.9, 69.1, 68.7] (6CH nea, CH_2O), 53.9, 50.0, 48.8 (3CH nea), [40.51, 40.47] (C6, CH_2NH), [29.6, 28.6, 28.55, 26.4, 25.2] ($4CH_2$ chain, C2); HRMS (electrospray) Calcd for $C_{31}H_{46}N_7O_7$ $[M+H]^+$: 628.3458, found: 628.3452, Calcd for $C_{31}H_{45}N_7O_7Na$ $[M+Na]^+$: 650.3278, found: 650.3267.

4.10. Conjugates at the 4′- and 5-positions

4.10.1. Histidine conjugate 33. Histidine derivative **18** (682 mg, 1.10 mmol), CH_2Cl_2 (15 mL), EDC (432 mg, 2.20 mmol), HOBt (305 mg, 2.20 mmol), neamine derivative **16** (650 mg, 0.37 mmol), deprotected conjugate hydrochloride **33** (106 mg, 0.10 mmol, 27%): mp 210 °C dec; ^1H NMR (400 MHz, D_2O) δ 8.36 (s, 1H, H Im), 8.34 (s, 1H, H Im), 7.18 (s, 2H, H Im), 5.62 (d, $J_{1'-2'}$=3.8 Hz, 1H, H1′), 3.99–4.01 (m, 2H, H His), 3.77–4.95 (m, 3H), 3.45–3.68 (m, 6H), 3.33–3.43 (m, 2H), 3.13–3.32 (m, 6H), 2.92–3.11 (m, 6H), 2.30 (ddd, 1H, $H2_{eq}$), 1.72 (ddd, 1H, $H2_{ax}$), 1.38–1.53 (m, 4H, $2CH_2$), 1.20–1.30 (m, 4H, $2CH_2$), 1.10–1.20 (m, 4H, $2CH_2$), 1.00–1.10 (m, 4H, $2CH_2$); ^{13}C NMR (100 MHz, D_2O) δ 168.3 (CO), [135.0, 127.5, 118.4] (C Im), 92.79 (C1′), [83.1, 78.1, 74.6, 73.7, 73.3, 73.1, 70.6, 68.2] (6CH nea, $2CH_2O$), [53.3, 52.9, 50.2, 49.2] (3CH nea, CH His), [40.2, 40.0, 39.9] (C6′, $2CH_2NH$), [29.7, 29.5, 28.4, 27.1, 27.1, 26.3, 26.2, 25.1, 25.1, 23.6] ($8CH_2$ chain, C2, $2CH_2$

His); LRMS (electrospray) $m/z=817.5$ $[M+Na]^+$, 399.2 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{36}H_{66}N_{12}O_8Na$ $[M+Na]^+$: 817.5024, found: 817.5016.

4.10.2. Phenanthroline conjugate 34. 4-Carboxylic phenanthroline acid **19** (136 mg, 0.61 mmol), DMF (6 mL), EDC (236 mg, 1.20 mmol), HOBt (164 mg, 1.20 mmol), neamine derivative **16** (350 mg, 0.20 mmol), deprotected conjugate hydrochloride **34** (110 mg, 0.04 mmol, 22%): mp 220 °C dec; ^{1}H NMR (600 MHz, D_2O) δ 9.10–9.18 (m, 4H, Ar), 8.96–9.99 (m, 2H, Ar), 8.06–8.21 (m, 6H, Ar), 7.92–7.98 (m, 4H, Ar), 5.81 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 4.18–4.22 (m, 1H), 4.04–4.14 (m, 3H), 3.80–3.86 (m, 2H), 3.68–3.78 (m, 3H), 3.50–3.62 (m, 6H), 3.34–3.50 (m, 4H), 2.52 (ddd, 1H, $H2_{eq}$), 1.90 (ddd, 1H, $H2_{ax}$), 1.62–1.78 (m, 8H, CH_2), 1.40–1.54 (m, 8H, CH_2); ^{13}C NMR (75 MHz, D_2O) δ 168.6 (CO), [151.0, 150.9, 145.6, 144.6, 143.2, 143.1, 139.7, 137.5, 129.8, 127.2, 127.1, 126.4, 126.2, 126.1, 126.0, 125.9, 125.4, 123.74, 123.65, 123.62] (Ar), 92.8 (C1′), [82.9, 78.0, 74.7, 73.6, 73.4, 73.2, 70.9, 68.3] (6CH nea, $2CH_2O$), [55.7, 53.3, 50.1, 49.2] (CH nea), [40.4, 40.2, 40.1] (C6′, $2CH_2NH$), [29.8, 29.4, 28.6, 28.5, 28.2, 26.5, 26.3, 25.3, 25.1] ($8CH_2$ chain, C2); LRMS (electrospray) $m/z=955.5$ $[M+Na]^+$, 468.3 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{50}H_{64}N_{10}O_8Na$ $[M+Na]^+$: 955.4806, found: 955.4805.

4.11. Adenine conjugates

4.11.1. Coupling reaction. To a solution of the neamine derivative **8**, **12** or **16** in EtOH/THF/Et_3N (10:0.5:0.6 mL), 6-chloropurine was added and the mixture was refluxed for 4 h. After cooling, dichloromethane was added (50 mL). The resulting solution was washed twice with water (50 mL), dried over Na_2SO_4 and evaporated. The residue obtained was treated for deprotection according to the work-up described for the conjugates possessing an amide function.

4.11.2. Conjugate at the 5-position 36. Neamine derivative **8** (490 mg, 0.28 mmol) in EtOH/THF/Et_3N (10:0.5:0.6 mL), 6-chloropurine (441 mg, 2.85 mmol), deprotected conjugate hydrochloride **36** (151 mg, 0.21 mmol, 75%): mp 210 °C dec; ^{1}H NMR (400 MHz, D_2O) δ 8.36 (s, 1H, H Pu), 8.25 (s, 1H, H Pu), 5.77 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 3.83–4.03 (m, 4H, H3′,H4, H5′, CH_2O), 3.61–3.75 (m, 3H, H5, H6, CH_2O), 3.49–3.58 (m, 2H, CH_2N), 3.39–3.48 (m, 4H, H3, H2′, H6′, H4′), 3.22–3.35 (m, 2H, H6′, H1), 2.40 (ddd, $J_{2eq-1}=J_{2eq-3}=4.1$Hz, $J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{eq}$), 1.85 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{ax}$), 1.63–1.71 (m, 2H, CH_2 chain), 1.51–1.60 (m, 2H, CH_2 chain), 1.28–1.42 (m, 4H, $2CH_2$ chain); ^{13}C NMR (50 MHz, D_2O) δ [144.8, 142.6] (C Pu), 92.6 (C1′), [82.6, 72.9, 72.2, 71.8, 69.7, 67.6] (CH nea, CH_2O), [52.8, 49.4, 48.5] (3CH nea), 39.6 (C6′, CH_2NH), [28.8, 27.4, 25.4, 24.3] (CH_2 chain, C2); LRMS (electrospray) $m/z=540.3$ $[M+H]^+$, 380.2 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{23}H_{42}N_9O_6$ $[M+H]^+$: 540.3258, found: 540.3252, Calcd for $C_{23}H_{41}N_9O_6Na$ $[M+Na]^+$: 562.3077, found: 562.3091.

4.11.3. Conjugate at the 4′-position 38. Neamine derivative **12** (500 mg, 0.31 mmol) in EtOH/THF/Et_3N (10:0.5:0.6 mL), 6-chloropurine (473 mg, 3.05 mmol), deprotected conjugate hydrochloride **38** (160 mg, 0.22 mmol, 73%): mp 220 °C dec; ^{1}H NMR (500 MHz, D_2O) δ 8.34 (s, 1H, H Pu), 8.24 (s, 1H, H Pu), 5.86 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 3.97–4.01 (m, 1H, H3′), 3.88–3.95 (m, 2H, H5′, H4), 3.78–3.83 (m, 1H, CH_2O), 3.58–3.67 (m, 2H, H5, CH_2O), 3.43–3.58 (m, 4H, H6, H3, CH_2N), 3.37–3.43 (m, 2H, H2′, H3) 3.18–3.31 (m, 3H, H4′, H1, H6′) 2.43 (ddd, $J_{2eq-1}=J_{2eq-3}=4.1$Hz, $J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{eq}$), 1.83 (ddd, $J_{2ax-1}=J_{2ax-3}=J_{2eq-2ax}=12.6$ Hz, 1H, $H2_{ax}$), 1.63–1.71 (m, 2H, CH_2 chain), 1.51–1.60 (m, 2H, CH_2 chain), 1.28–1.42 (m, 4H, $2CH_2$ chain); ^{13}C NMR (100 MHz, D_2O) δ 143.4 (C Pu), 96.1 (C1′), [79.4, 77.9, 75.5, 74.4, 72.9, 69.0, 68.7] (6CH nea, CH_2O), [53.9, 50.0, 48.8] (3CH nea), [40.5, 40.3] (C6′, CH_2NH), [29.6, 28.6, 28.1, 26.1, 25.2] ($4CH_2$ chain, C2); HRMS (electrospray) Calcd for $C_{23}H_{42}N_9O_6$ $[M+H]^+$: 540.3258, found: 540.3282, Calcd for $C_{23}H_{41}N_9O_6Na$ $[M+Na]^+$: 562.3077, found: 562.3078, Calcd for $C_{23}H_{41}N_9O_6K$ $[M+K]^+$: 578.2816, found: 578.2823.

4.11.4. Conjugate at the 4′- and 5-positions 40. Neamine derivative **16** (500 mg, 0.29 mmol) in EtOH–THF–Et_3N (10:0.5:0.6 mL), 6-chloropurine (447 mg, 2.89 mmol), deprotected conjugate hydrochloride **40** (180 mg, 0.18 mmol, 63%): mp 230 °C dec; ^{1}H NMR (400 MHz, D_2O) δ 8.30 (bs, 2H, H Pu), 8.20 (bs, 2H, H Pu), 5.68 (d, $J_{1'-2'}=3.8$ Hz, 1H, H1′), 4.05–4.10 (m, 1H), 3.88–4.01 (m, 3H), 3.65–3.75 (m, 2H), 3.43–3.62 (m, 9H), 3.22–3.38 (m, 4H), 2.40 (ddd, 1H, $H2_{eq}$), 1.82 (ddd, 1H, $H2_{ax}$), 1.62–1.73 (m, 4H, $2CH_2$ chain), 1.50–1.60 (m, 4H, $2CH_2$ chain), 1.25–1.42 (m, 8H, $4CH_2$); ^{13}C NMR (100 MHz, D_2O) δ 142.9 (C Pu), 92.8 (C1′), [83.0, 78.0, 74.6, 73.6, 73.3, 73.1, 70.8, 68.2] (CH nea, CH_2O), [53.2, 50.1, 49.2] (3CH nea), 40.1 (C6′, CH_2NH), [29.7, 29.4, 28.2, 28.18, 26.2, 26.1, 25.24, 25.20] ($8CH_2$ chain, C2); LRMS (electrospray) $m/z=779.4$ $[M+Na]^+$, 380.2 [5-modified deoxystreptamine+H]$^+$; HRMS (electrospray) Calcd for $C_{34}H_{57}N_{14}O_6$ $[M+H]^+$: 757.4585, found: 757.4595, Calcd for $C_{34}H_{56}N_{14}O_6Na$ $[M+Na]^+$: 779.4405, found: 779.4404, Calcd for $C_{34}H_{56}N_{14}O_6K$ $[M+K]^+$: 795.4144, found: 795.4133.

Acknowledgements

We thank B. Baldeyrou for expert assistance with the T_m measurements, Dr. S. Chambert and Dr. F. Thomasson for NMR experiments and fruitful discussions and the 'Centre National de la Recherche Scientifique' (CNRS) for financial support (Programme 'Physique et Chimie du Vivant').

Supporting data

Supplementary data associated with this article can be found at doi:10.1016/j.tet.2004.06.122.

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Intermolecular 'oxidative' aromatic substitution reactions of the imidazol-5-yl radical mediated by the 'reductant' Bu_3SnH

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Received 26 April 2004; revised 7 June 2004; accepted 24 June 2004
Available online 22 July 2004

Abstract—The reactivity of the imidazol-5-yl in comparison to the imidazol-2-yl and phenyl radical under the reductive conditions of Bu_3SnH, in intermolecular substitution reactions onto various aromatic substrates is reported. The directing effect of the hetero atom or methyl substituent in aromatic substrates was found to be more important than the polarity of the attacking σ-radical in determining the major product isomer.

1. Introduction

Over the past 15 years, there have been many reported syntheses of heterocyclic compounds using intramolecular homolytic aromatic substitutions mediated by tributyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN).[1–9] Such reactions have become a mechanistic curiosity, since upon radical addition an intermediate cyclohexadienyl radical is generated, which loses a hydrogen atom to regenerate aromaticity, and thus represent a formal oxidation in the presence of the reductant Bu_3SnH. However, using the reducing radical initiators Bu_3SnH and tris(trimethylsilyl)silane $[(CH_3)_3Si]_3SiH$, there are relatively few examples of the intermolecular oxidative reaction; Minisci and co-workers[10] and Togo and co-workers[11] demonstrated the influence of polar effects on the regioselective substitution of nucleophilic alkyl radicals onto heteroaromatic bases, and more recently Alvarez-Builla and co-workers[12] reported the synthesis of biaryl compounds using radical substitution of phenyl and pyridyl radicals onto arenes. The following paper details our investigations into the intermolecular substitution of the σ-imidazol-5-yl radical onto aromatic substrates, and comparisons are made with the reactivity of σ-imidazol-2-yl and phenyl radicals. We are aware of only two reported reactions of σ-imidazole radicals; the imidazol-5-yl radical has been shown to undergo an efficient intramolecular 5-*exo* radical cyclization,[13] and a facile photochemical arylation of the imidazole-2-position has been demonstrated.[14]

Keywords: Free radicals; Heterocycles; Imidazoles; Tributyltin hydride.
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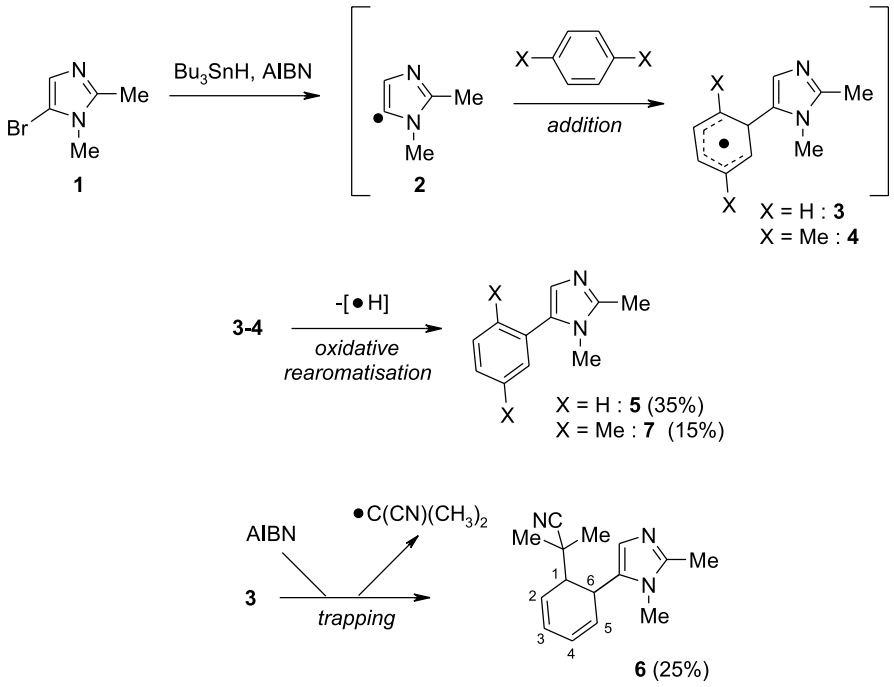
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.120

2. Results and discussion

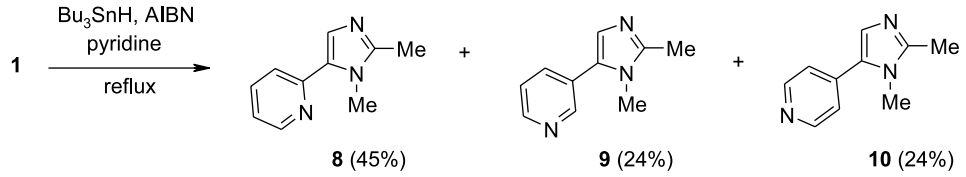
The imidazol-5-yl radical **2** was generated from 5-bromo-1,2-dimethylimidazole **1** using Bu_3SnH and azo-initiators AIBN or 1,1′-azobis(cyclohexanecarbonitrile) (ACN). The rate of addition of σ-aryl radicals, such as **2** onto aromatics should be between 1000 and 2000 times slower than reduction by Bu_3SnH (or at least it is for phenyl radicals[15,16]), however we made the addition process favourable by having the aromatic substrate as the reaction solvent and by keeping the concentration of Bu_3SnH low during the course of the reaction. In the case of benzene and *p*-xylene optimal yields of rearomatised products were obtained, when Bu_3SnH (1.5 equiv.) and AIBN (4.0 equiv.) in benzene or *p*-xylene were added over 18 h to the refluxing solution of **1** (1.0 equiv., 0.06 M) and AIBN (1.0 equiv.) in the same aromatic solvents. The requirement for a large excess of AIBN is in agreement with literature conjecture[3–5,8–12] that AIBN or an AIBN derived radical is implicated in the oxidative rearomatisation of the intermediated cyclohexadienyl radicals **3**–**4** to yield 5-arylimidazoles **5** and **7** in a non-chain process (Scheme 1). The reaction with benzene gave rearomatised product **5** in isolated yield of 35% along with significant amounts of the unexpected conjugated 2,4-cyclohexadiene **6** in 25% yield. Cyclohexadiene **6** was isolated as a single isomer, as confirmed by GC analysis and NMR spectra. The vicinal H-1 and H-6 atoms of **6** showed no coupling to one another in ^1H NMR spectra indicating that they are effectively at 90° with each other. Using this conformation, molecular geometry optimisations were carried out; however, we were unable to unequivocally establish whether the *cis* or *trans* isomer had been isolated. Therefore no stereochemistry is shown for 2,4-cyclohexadiene **6**. Substituting Bu_3SnH for the weaker reductant



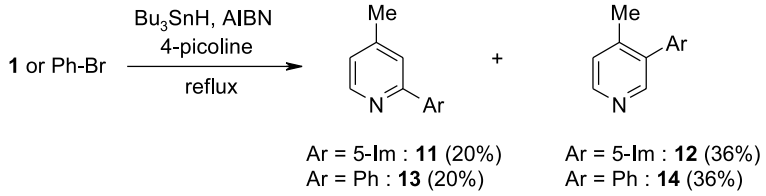
Scheme 1.

$[(CH_3)_3Si]_3SiH$ did not result in any improvement in yields of **5** and **6**, which were both isolated in 21% yield, and using ACN in place of AIBN resulted in lower yields of 5-phenyl-1,2-dimethylimidazole **5** (20%), along with an inseparable mixtures of dienes which were difficult to characterise. The formation of **6** can be rationalized by the trapping of the relatively long-lived resonance stabilized π-cyclohexadienyl radical **3** by the AIBN derived 2-cyano-2-propyl radical. Although, non-conjugated 2,5-cyclohexadienes are normally the major products of homolytic aromatic substitution reactions carried out under non-oxidative conditions,[17] only traces of such diene were detected in the ^{1}H NMR of the crude reaction mixtures and the amounts were too small for isolation by column chromatography. However, the efficient rearomatisation of non-conjugated dienes in the presence of radical initiators is well documented.[18] There are however other accounts of AIBN derived initiator radicals being incorporated into the products of radical reactions.[5,8,9] Motherwell and co-workers[5] have isolated products of the trapping of π-cyclohexadienyl radicals by 2-cyano-2-propyl radicals, when large amounts of AIBN were added, but these were all aromatised products. Bennasar and co-workers[8] have reported the trapping of an intramolecular 5-*endo* cyclization product radical by the 2-cyano-2-propyl radical to yield an unstable tetracycle that was partially converted into an oxidized rearomatised product upon column chromatography. In contrast, diene **6** is a stable crystalline compound isolated after an acid–base work up and column chromatography. We confirmed that diene **6** was not an intermediate in the formation of **5** by independently refluxing benzene solutions of **6** for several days, in which negligible decomposition of **6** was observed. However, diene **6** could be converted into rearomatised product **5** in quantitative yield by refluxing the former at much higher temperatures of refluxing xylene (bp 140–145 °C) for 48 h. This increased the overall isolated yields to 60% for 5-phenylimidazole **5**. The reaction with *p*-xylene (bp 138 °C) gave low yields of rearomatised product **7** of only 15%, with no dienes observed in the ^{1}H NMR of the crude reaction mixtures. For this reaction, we can assume that any dienes formed as a result of the trapping of π-radical **4** by the 2-cyano-2-propyl radical would be thermally unstable, and rapidly rearomatise to **7**. GC analysis of the crude reaction mixture indicated that 1,2-dimethylimidazole was the major product formed via the reduction of σ-radical **2** by Bu_3SnH. It can therefore be assumed that the addition of **2** onto *p*-xylene is slow, and analogous to the addition of phenyl radicals, which has been previously described as reversible.[19]

In these reactions, other possible rearomatisation pathways for π-radicals **3**–**4** including their disproportionation or hydrogen atom transfer from Bu_3SnH are considered unlikely. In view of the fact that the resultant cyclohexadienes should have been stable enough for detection or isolation prior to oxidation to the 5-arylimidazoles **5** and **7**. Experimental evidence[9] has also most recently been provided to disprove hydrogen atom transfer from Bu_3SnH, oxidation of cyclohexadienyl radicals by $Bu_3Sn^{\cdot}$, along with an earlier mechanism proposed by Bowman and co-workers[2,6] based on the $S_{RN}1$ pathway. According to the latter chain-reaction mechanism Bu_3SnH acts as a base, as well as an initiator to produce hydrogen gas from cyclohexadienyl radicals **3**–**4**, along with their respective oxidizable radical-anions. We confirmed the latter mechanism was not operational by refluxing bromide **1** in benzene with catalytic amounts (0.2 equiv.) of Bu_3SnH and AIBN in the presence of the base DABCO (1,4-diazabicyclo[2.2.2]octane, 1.5 equiv.). DABCO would thus replace Bu_3SnH as the base, and only catalytic amounts of Bu_3SnH would therefore be required for the initiation of the proposed chain reaction. This led to the isolation of products **5** and **6** in poor respective yields of 5 and 2%



Scheme 2.

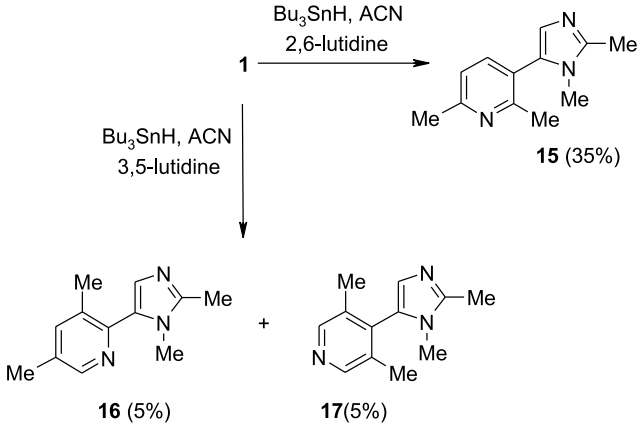


Scheme 3.

with 46% of **1** recovered. Furthermore, whenever less than full equivalents of AIBN were used, a significant amount of unaltered imidazole **1** was always recovered, indicating that a greater amount of AIBN was required to support the non-chain reaction.

Higher overall isolated yields were obtained for substitutions of σ-radical **2** onto pyridine. This clearly indicated that addition of imidazol-5-yl radical **2** onto certain heteroaromatic bases competed more effectively with radical reduction by Bu_3SnH, since these reactions also contained higher concentrations of Bu_3SnH. For example, the reaction with pyridine led to the clean isolation of the 2-substituted pyridine **8** in 45% yield along with an inseparable 1:1 mixture of 3- and 4-substituted isomers **9** and **10** in 48% yield (Scheme 2). The absence of any dienes analogous to **6** in the reactions with pyridines may be explained by the electrophilic nature of the 2-cyano-2-propyl radical (due to the proximity of the cyano group to its radical centre), which may have prevented it from reacting with π-radicals derived from heteroaromatic bases. Another explanation is the elevated reaction temperatures for pyridine reactions compared to the benzene reaction would have led to the thermal rearomatisation of any dienes analogous to **6**.

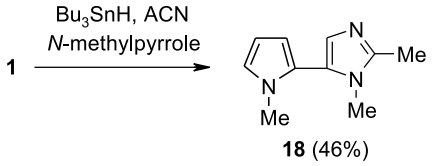
The isolation of 2-substituted pyridine isomer **8** as the major product may have inferred that σ-radical **2** was nucleophilic in character, however when 4-picoline was the substrate the 3-substituted isomer **12** was the predominate product (Scheme 3). An identical substitution pattern was observed when bromobenzene was used in place of 5-bromoimidazole **1** in the reaction with 4-picoline (bp 145 °C) carried out under identical reaction conditions indicating that the reactivity of the phenyl and imidazol-5-yl radicals **2** was equivalent. Furthermore, the reaction of **1** with 2,6-lutidine (bp 143–145 °C) led to the exclusive isolation of the 3-substituted isomer **15** in 35% yield (Scheme 4). The reaction with 3,5-lutidine (bp 169–170 °C) was not regioselective, and led to the formation of an inseparable 1:1 mixture of the 2- and 4-substituted isomers **16** and **17** in only 10% isolated yield. The high temperatures used for the lutidine reactions may have made the initial addition of radical **2** reversible in analogy with the reaction of **1** with *p*-xylene. The results with methyl substituted pyridines inferred that the philicity



Scheme 4.

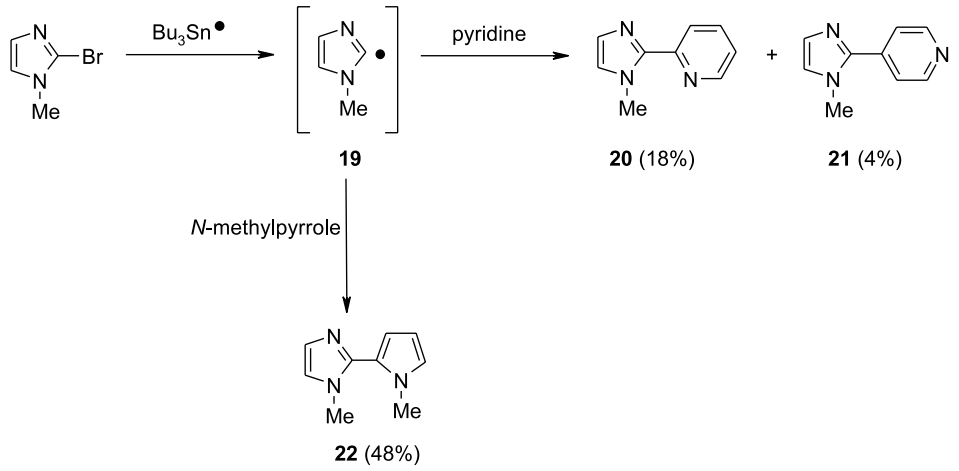
of σ-radical **2** is only weak and comparable to that of the phenyl radical, and demonstrated that inductive stabilization of the π-single-electron pyridyl intermediate (analogous to **3**–**4**) by the methyl substituents was more important.

The reaction with *N*-methylpyrrole gave exclusively the 2-substituted isomer **18** in 46% yield (Scheme 5). The reactions with *N*-methylpyrrole and pyridine are therefore in agreement with literature reactions of heterocycles with phenyl radicals produced under non-reductive conditions, which have been shown to predominately substitute at positions adjacent to the heteroatom.[20]



Scheme 5.

For comparison purposes, the reactivity of the imidazol-2-yl radical **19** generated from 2-bromo-*N*-methylimidazole was also investigated by reacting it with pyridine and *N*-methylpyrrole under reaction conditions identical to those used for the reaction with 5-bromoimidazole **1**. Substitution at the 2-position of pyridine and *N*-methylpyrrole was preferred with compounds **20**, and **22** isolated in 18 and



Scheme 6.

48% yield, respectively (Scheme 6). From the pyridine reaction, a small amount of the 4-isomer **21** was also isolated in 4% yield. The smaller yields indicate that the imidazol-2-yl radical **19** is less reactive towards pyridine than imidazol-5-yl **2** and phenyl radicals, which may be as a result of an inductive electron-withdrawing effect on the radical by the adjacent imidazole nitrogen atoms. However this increased electrophilic character for the imidazol-2-yl in comparison to the imidazol-5-yl radical did not give significantly higher yields of substitution product for reaction with *N*-methylpyrrole indicating that the inductive effect may be small.

There are reports of σ-heteroaromatic radicals generated from photolysis and thermolysis reactions being regarded as electrophilic in character,[21–24] however in such cases further oxidation of these radicals to the respective cations cannot be ruled out.[24] The reactivity of the σ-imidazole radical **2** is very similar to that of the phenyl[25] radical and other σ-heteroaromatic radicals,[12,23,24] which have been shown to be more reactive towards the *ortho* and *para* than the *meta* position of substituted benzenes irrespective of the polarity of the attacking radical. Thus, the difference in polarity of all these σ-aromatic radicals does not appear to be great enough to influence selectivity. This may be expected since the unpaired electron occupies an orbital orthogonal to the π-system.

3. Conclusion

We have reported the first intermolecular oxidative aromatic substitutions of σ-imidazole radicals in the presence of the reductant Bu_3SnH. Such reactions require an excess of azo-initiator, which has been implicated in the oxidative rearomatization of the intermediate π-cyclohexadienyl radical to give aromatized products in modest yields. For the reaction with benzene, along with the rearomatized 5-phenylimidazole, a significant amount of 2,4-cyclohexadiene was isolated, as a result of the trapping of the π-cyclohexadienyl radical by an AIBN derived 2-cyano-2-propyl radical. We have also established previously unknown reactivity patterns for σ-imidazole radicals towards various aromatics. The reaction was found to give the lowest yield of substitution products at the highest reaction temperatures. The imidazol-5-yl radical was more reactive towards pyridine than benzene with reactivity comparable to that of the phenyl radical. The imidazol-2-yl radical was less reactive than the imidazol-5-yl radical towards pyridine, but had a similar reactivity towards *N*-methylpyrrole. However in determining product selectivity the directing effect of the aromatic substrate methyl-substituents was found to be more important than the polarity of the attacking radical. For unsubstituted nitrogen-containing heterocyclic substrates, substitution at the position adjacent to the nitrogen atom is preferred.

4. Experimental

4.1. General

Melting points were measured on a Stuart Scientific melting point apparatus SMP3, and are uncorrected. IR spectra were determined using a Perkin–Elmer Spec 1 with ATR attached. ^1H NMR (400 Hz) and ^{13}C NMR (100 Hz) spectra were recorded in $CDCl_3$ on a Jeol 400 instrument. Chemical shifts are given in parts per million (ppm). EI-mass spectra were obtained on a Micro Mass GCT GC–MS. TLC using silica gel as absorbent was carried out using aluminium backed plates coated with silica gel (Merck Kieselgel 60 F254). Column chromatography using alumina was carried out with Aldrich aluminium oxide, activated, neutral, Brockmann, STD Grade 3, 150 mesh size.

4.2. Materials

All reactions were carried out using dried solvents under an argon atmosphere, however without rigorous freeze–thaw solvent deoxygenations. Bu_3SnH, AIBN and ACN were obtained commercially and the azo-initiators were recrystallized from methanol at 0 °C prior to use. 5-Bromo-1,2-dimethylimidazole **1** was obtained cleanly in 65% yield by stirring 1,2-dimethylimidazole for 2 h with *N*-bromosuccimide (NBS, 1 equiv.) in CH_2Cl_2 at 0 °C, and 2-bromo-*N*-methylimidazole was obtained according to a literature

procedure[26] in 62% yield from the reaction of cyanogen bromide with *N*-methylimidazole.

4.3. Intermolecular radical reactions

4.3.1. General procedure for reactions of the imidazol-5-yl radical 2 with benzene and *p*-xylene; 5-phenyl-1,2-dimethylimidazole 5 and 2-[1,6-*trans*-6-(1,2-dimethylimidazol-5-yl)-2,4-cyclohexadien-1-yl]-2-methylpropanenitrile 6. Bu_3SnH (2.2 ml, 8 mmol) and AIBN (3.51 g, 21.4 mmol) in benzene (50 ml) was added over 18 h via a syringe pump to 5-bromo-1,2-dimethyimidazole **1** (0.96 g, 5.3 mmol) and AIBN (0.88 g, 5.3 mmol) in benzene (90 ml). The reaction was refluxed for a further 1 h, cooled and evaporated to dryness. 2 M HCl (50 ml) added, and tin residues were eliminated by repeated washing with hexane ($\approx 20\times 50$ ml). The acidic solution was neutralised with solid Na_2CO_3 and the pH brought up to 14 by addition of NaOH pellets. The solution was extracted with CH_2Cl_2 ($2\times$ 50 ml), dried ($MgSO_4$) and evaporated to dryness to yield a yellow residue, which was purified by column chromatography on neutral alumina using mixtures of ethyl acetate and hexane as eluent. The first product eluted was **5** (0.32 g, 35%) as white crystals, mp 71–75 °C (lit.[27] 74 °C). (Found M^+, 172.1003, $C_{11}H_{12}N_2$ requires M^+ 172.1000), ν_{max}/cm^{-1} 3372, 1604, 1638, 1506, 1145; δ_H 2.45 (s, 3H, Im-2-Me), 3.50 (s, 3H, *N*–Me), 6.95 (s, 1H, Im-4-H), 7.40 (m, 5H, Ar-H); δ_C 13.6 (Me), 31.2 (*N*–Me), 125.8 (Im-4-CH), 127.5, 128.5, 128.6, 130.5, 133.4, 145.9 (Im-2-C); *m*/*z* 172 (M^+, 100%), 130 (5), 118 (8). The second product eluted was **6** (0.32 g 25%) as white crystals; mp 105–106 °C. (Found: M^+, 241.1579. $C_{15}H_{18}N_3$ requires M, 241.1573); ν_{max}/cm^{-1} 2233 (CN), 1411, 1182; δ_H 1.32 (s, 3H, C*Me*CN), 1.36 (s, 3H, C*Me*CN), 2.31 (s, 3H, Im-2-Me), 2.49 (d, $J=5.6$ Hz, 1H, diene-1-H), 3.53 (s, 3H, *N*–CH_3), 3.69 (d, $J=5.6$ Hz, 1H, diene-6-H), 5.47 (dd, $J=5.6$, $J=9.6$ Hz, 1H, diene-2-H), 5.71 (dd, $J=5.6$, 9.2 Hz, 1H, diene-5-H), 5.97 (dd, $J=5.2$, 9.2 Hz, 1H, diene-4-H), 6.17 (dd, $J=5.2$, 9.6 Hz, 1H, diene-3-H), 6.62 (s, 1H, Im-4-H); δ_C 13.5 (Im-2-Me), 21.6 (C*Me*CN), 24.3 (C*Me*CN), 29.0 (*N*–Me), 31.9 (*C*CN), 38.9 (diene-CH), 45.5 (diene-CH), 120.27 (CH), 123.1 (CN), 125.3 (CH), 126.1 (Im-5-C), 126.5 (CH), 127.1 (CH), 128.5 (CH), 145.7 (Im-2-C); *m*/*z* 241 (M^+, 100%), 226 (39), 173 (87), 147 (39), 132 (32), 117 (29), 91 (10).

The above procedure was repeated with *p*-xylene replacing benzene. 5-(2,5-Dimethylphenyl)-1,2-dimethylimidazole **7** (0.16 g, 15%) was isolated as a yellow oil. (Found M^+, 200.1311, $C_{13}H_{16}N_2$ requires M^+ 200.1313), ν_{max}/cm^{-1} 2920, 1613, 1559, 1505, 1435, 1403; δ_H 2.13 (s, 3H, Me), 2.33 (s, 3H, Me), 2.43 (s, 3H, Me), 3.29 (s, 3H, *N*–Me), 6.81 (s, 1H, Im-4-H), 7.00 (s, 1H, Ar-H), 7.11 (d, $J=7.8$ Hz, 1H, Ar-H), 7.17 (d, $J=7.8$ Hz, 1H, Ar-H); δ_C 13.3 (Im-Me), 19.3 (Me), 20.6 (Me), 30.6 (*N*–Me), 125.3, 127.5, 128.5, 128.6, 130.5 133.4, 145.9 (Im-2-C); *m*/*z* 200 (M^+, 100%), 158 (33).

4.3.2. General procedure for reactions of the imidazol-5-yl 2, imidazol-2-yl 19 and phenyl radicals with pyridines; 2-(1,2-dimethylimidazol-5-yl)-pyridine 8, 3-(1,2-dimethylimidazol-5-yl)pyridine 9 and 4-(1,2-dimethylimidazol-5-yl)pyridine 10. Bu_3SnH (2.5 ml, 9 mmol) and AIBN (2.46 g, 15 mmol) in pyridine (50 ml) was added over 1 h via a syringe pump to 5-bromo-1,2-dimethyimidazole **1** (1.09 g, 6 mmol) and AIBN (0.98 g, 6 mmol) in pyridine (90 ml). The reaction was refluxed for a further 1 h, cooled and evaporated to dryness. The work-up and purification procedure used for the benzene reaction was repeated. The first product eluted by column chromatography was **8** (0.47 g, 45%) as a yellow oil. (Found M^+, 173.0954, $C_{10}H_{11}N_3$ requires M^+ 173.0953), ν_{max}/cm^{-1} 1658, 1589, 1562, 1501, 1437, 1401; δ_H 2.39 (s, 3H, Im-2-Me), 3.85 (s, 3H, *N*–Me), 7.08 (m, 1H, py-H-5), 7.24 (s, 1H, Im-4-H), 7.46 (d, $J=7.8$ Hz, 1H, py-3-H), 7.62 (m, 1H, py-H-4), 8.53 (d, $J=2.4$ Hz, 1H, py-6-H); δ_C 13.5 (Me), 32.4 (*N*–Me), 121.0 (py-CH), 121.5 (py-CH), 128.3 (Im-4-CH), 132.0 (C), 136.4 (CH), 147.5 (C), 148.7 (py-6-CH), 150.6 (C); *m*/*z* 173 (M^+, 100%), 172 (90), 158 (10). The second products eluted were an inseparable 1:1 mixture (by ^1H NMR) of **9** and **10** (0.50 g, 48%) as a yellow oil. (Found M^+, 173.0952, $C_{10}H_{11}N_3$ requires M^+ 173.0953); **9**, δ_H 2.47 (s, 3H, Im-2-Me), 3.55 (s, 3H, *N*–Me), 7.02 (s, 1H, Im-4-H), 7.37 (dd, $J=$ 4.8, 8.2 Hz, 1H, Py-5-H), 7.68 (d, $J=8.2$ Hz, 1H, Py-4-H), 8.59 (d, $J=4.8$ Hz, 1H, Py-H-6), 8.64 (s, 1H, Py-2-H); **10**, δ_H 2.36 (s, 3H, Im-2-Me), 3.63 (s, 3H, *N*–Me), 7.14 (s, 1H, Im-4-H), 7.29 (d, $J=6.0$ Hz, 2H, Py-3,5-H), 8.63 (d, $J=$ 6.0 Hz, 2H, Py-2,6-H).

The above procedure was repeated with 4-picoline replacing pyridine. The first product eluted by column chromatography was 2-(1,2-dimethylimidazol-5-yl)-4-methylpyridine **11** (0.22 g, 20%) as a yellow oil. (Found M^+, 187.1108. $C_{11}H_{13}N_3$ requires M^+ 187.1109); ν_{max}/cm^{-1} 1659, 1604, 1507, 1436, 1401; δ_H 2.36 (s, 3H, Im-2-Me), 2.44 (s, 3H, Py-Me), 3.88 (s, 3H, *N*–Me), 6.96 (d, $J=5.2$ Hz, 1H, Py-5-H), 7.29 (s, 1H, Im-4-H), 7.34 (s,1H, Py-3-H), 8.44 (d, $J=$ 5.2 Hz, 1H, Py-6-H); δ_C 13.5 (Im-2-Me), 20.9 (Py-Me), 32.4 (*N*–Me), 113.4 (C), 122.2 (CH), 122.4 (CH), 128.0 (CH), 131.6 (C), 147.5 (C), 148.8 (Py-6-CH), 150.6 (C); *m*/*z* 187 (M^+, 100%). The second product eluted was 3-(1,2-dimethylimidazol-5-yl)-4-methylpyridine **12** (0.39 g, 36%) as a yellow oil. (Found M^+, 187.1110, $C_{11}H_{13}N_3$ requires M^+ 187.1109); ν_{max}/cm^{-1}1659, 1604, 1507, 1436, 1401; δ_H 2.24 (s, 3H, Im-2-Me), 2.47 (s, 3H, Py-Me), 3.34 (s, 3H, *N*–Me), 6.90 (s, 1H, Im-4-H), 7.24 (d, $J=5.7$ Hz, 1H, Py-5-H), 8.41 (s, 1H, Py-2-H), 8.49 (d, $J=5.7$ Hz, 1H, Py-6-H); δ_C 13.4 (Im-2-Me), 19.3 (Py-Me), 30.5 (*N*–Me), 124.9 (CH), 126.4 (C), 127.1 (CH), 128.1 (C), 145.9 (C), 1473 (C), 149.4 (CH), 151.0 (CH); *m*/*z* 187 (M^+, 100%).

The above procedure was repeated with bromobenzene replacing **1**. The first product eluted by column chromatography was 4-methyl-2-phenylpyridine **13**[28] (0.21 g, 20%) as a yellow oil. (Found M^+ 169.0895, $C_{12}H_{11}N$ requires 169.0891), ν_{max}/cm^{-1} 3026, 1590, 1556, 1478, 1444, 1401; δ_H 2.38 (s, 3H, Me), 7.03, (d, $J=4.8$ Hz, 1H, Py-5-H), 7.43 (m, 3H, Ph-H), 7.53, (s, 1H, Py-3-H), 7.96 (m, 2H, Ph-H), 8.53 (d, $J=4.8$ Hz, 1H, Py-6-H); δ_C 21.1 (Me), 121.4 (CH), 123.0 (CH), 126.9 (CH), 128.7 (CH), 139.5 (C), 147.6 (C), 149.3 (Py-6-CH), 157.3 (Py-2-C); *m*/*z* 170 (MH^+, 2%), 169 (81), 168 (100), 167 (19), 154 (3). The second product eluted was 4-methyl-3-phenylpyridine **14** (0.35 g, 36%) as a yellow oil. (Found M^+ 169.0889, $C_{12}H_{11}N$ requires 169.0891), ν_{max}/cm^{-1} 3026, 1590, 1556, 1478, 1444, 1401; δ_H 2.28 (s, 3H, Me), 7.18 (d, $J=4.9$ Hz, 1H, Py-5-H), 7.31–7.46 (m, 5H, Ph-H), 8.44 (bs, 2H, Py-2 and 6-H);

δ_C 19.8 (Me), 124.7 (CH), 127.6 (CH), 128.4 (CH), 129.2 (CH), 137.8 (C), 144.5 (C), 148.2 (Py-CH), 149.9 (Py-CH); *m/z* 170 (2%), 169 (M^+, 81), 168 (100), 154 (3).

The above procedure was repeated with 2-bromo-*N*-methylimidazole and pyridine. The first product eluted by column chromatography was 2-(1-methylimidazol-2-yl)pyridine **20**[23] (0.17 g, 18%) as a yellow oil. (Found M^+ 159.0797, $C_9H_9N_3$ requires 159.0796); ν_{max}/cm^{-1} 1588, 1491, 1464, 1278, 1034; δ_H 4.11 (s, 3H, Me), 6.96 (s, 1H, Im-5-H), 7.11 (s, 1H, Im-4-H), 7.21 (dd, $J=0.8$, 4.8 Hz, 1H, Py-5-H), 7.73 (m, 1H, Py-4-H), 8.16 (d, $J=8.0$ Hz, 1H, Py-3-H), 8.57 (d, $J=4.8$ Hz, 1H, Py-6-H); δ_C 36.1 (Me), 122.2 (CH), 122.5 (CH), 124.3 (CH), 128.0 (CH), 136.4 (CH), 148.1 (Py-6-CH), 150.62 (C); *m/z* 159 (M^+, 100%). The second product eluted was 4-(1-methylimidazol-2-yl)pyridine **21**[29] (30 mg, 4%), which contained inseparable traces of *N*-methylimidazole; δ_H 3.81 (s, 3H, Me), 7.02 (s, 1H, Im-5-H), 7.13 (s, 1H, Im-4-H), 7.34 (d, $J=5.8$ Hz, 2H, Py-3,5-H), 8.57 (d, 1H, $J=5.8$ Hz, 2H, Py-2,6-H); δ_C 36.7 (Me), 120.6 (Im-5-CH), 124.3 (Im-4-CH), 131.8 (Py-3,5-CH), 150.5 (Py-2,6-CH).

The above procedure was repeated using **1**, 2,6-lutidine and ACN in place of AIBN. Purification by column chromatography led to the isolation of 2,6-dimethyl-3-(1,2-dimethylimidazol-5-yl)pyridine **15** (0.42 g, 35%) as a yellow oil. (Found M^+, 201.1268, $C_{12}H_{15}N_3$ requires M^+ 201.1266); ν_{max}/cm^{-1} 1659, 1604, 1507, 1436,1401; δ_H 2.31 (s, 3H, Me), 2.36 (s, 3H, Me), 2.50 (s, 3H, Me), 3.22 (s, 3H, *N*–Me), 6.88 (s, 1H, Im-4-H), 6.98 (d, $J=7.8$ Hz, Py-4 or 5-H), 7.30 (1H, d, $J=7.8$ Hz, Py-4 or 5-H); δ_C 13.6 (Im-2-Me), 22.9 (Py-Me), 24.5 (Py-Me), 30.6 (*N*–Me), 118.6 (C), 120.3 (Py-CH),122.3 (C), 126.5 (Im-4-CH) 139.1 (Py-CH), 145.5 (Im-2-C), 157.5 (Py-C), 158.2 (Py-C); *m/z* 201 (M^+, 100%), 159 (79).

The above procedure was repeated using **1**, 3,5-lutidine and ACN in place of AIBN. Purification by column chromatography led to the isolation of an inseparable 1:1 mixture (by GC and ^1H NMR) of 2-(1,2-dimethylimidazol-5-yl)-3,5-dimethylpyridine **16** and 4-(1,2-dimethylimidazol-5-yl)-3,5-dimethylpyridine **17** (0.12 g, 10%) as a yellow oil. (Found M^+, 201.1265, $C_{12}H_{15}N_3$ requires M^+ 201.1266); **16** and **17**, δ_H 2.08 (s, 6H, Me), 2.34 (s, 3H, Me), 2.37 (s, 3H, Me), 2.45 (s, 3H, Me), 2.46 (s, 3H, Me), 3.22 (s, 3H, *N*–Me), 3.59 (s, 3H, *N*–Me), 6.81 (s, 1H, Im-4-H), 7.06 (s, 1H, Im-4-H), 7.42 (s, 1H, Py-4-H, **16**), 8.34 (s, 1H, Py-6-H, **16**), 8.40 (s, 2H, Py-2,6-H, **17**); δ_C 13.5 (Im-2-Me), 17.0, 17.9, 19.8, 30.2 (*N*–Me), 31.6 (*N*–Me), 125.6 (Im-4-CH), 128.2 (Im-4-CH), 131.4 (C), 132.4 (C), 139.1 (Py-4-CH, **16**), 147.1 (Py-CH), 148.5 (Py-CH); *m/z* 201 (M^+, 100%), 159 (20), 145 (2).

4.3.3. General procedure for reactions of the imidazol-5-yl 2 and imidazol-2-yl 19 radicals with *N*-methylpyrrole; 1,2-dimethyl-5-(1-methylpyrrol-2-yl)imidazole 18. Bu_3SnH (1.1 ml, 4 mmol) and ACN (1.51 g, 6 mmol) in *N*-methylpyrrole (40 ml) was added over 18 h via a syringe pump to 5-bromo-1,2-dimethyimidazole **1** (0.54 g, 3 mmol) and ACN (2.27 g, 9 mmol) in *N*-methylpyrrole (70 ml). The reaction was refluxed for a further 1 h, cooled and evaporated to dryness. The work-up and purification procedure used for the benzene reaction was repeated. Purification by column chromatography led to the isolation of **18** (0.24 g, 46%) as a brown oil. (Found M^+ 175.1108, $C_{10}H_{13}N_3$ requires 175.1109); ν_{max}/cm^{-1} 2940, 1700, 1666, 1520, 1401, 1301; δ_H 2.42 (s, 3H, Im-2-Me), 3.49 (s, 3H, *N*–Me), 3.51 (s, 3H, *N*–Me), 6.17 (m, 1H, Pyl-3-H), 6.20 (m, 1H, Pyl-4-H), 6.76, (s, 1H, Pyl-5-H), 6.92 (s, 1H, Im-4-H); δ_C 13.6 (Im-2-Me), 30.7 (*N*–Me), 34.3 (*N*–Me), 107.7 (Pyl-3-CH), 111.1 (Pyl-4-CH) 122.0 (C) 123.4 (CH) 127.9 (CH) 132.5 (C) and 145.4 (Im-2-C); *m/z* 176 (5%), 175 (M^+, 100), 174 (5), 119 (5).

The above procedure was repeated with 2-bromo-*N*-methylimidazole replacing **1**. Purification by column chromatography led to the isolation of 1-methyl-2-(1-methylpyrrol-2-yl)-imidazole **22** (0.24 g, 48%), as a brown oil. (Found M^+ 161.0953, $C_9H_{11}N_3$ requires 161.0953); ν_{max}/cm^{-1} 3104, 2930, 1579, 1443, 1407, 1281, 1137; δ_H 3.71 (s, 3H, *N*–Me), 3.81 (s, 3H, *N*–Me), 6.20 (m, 1H, Pyl-3-H), 6.31 (m, 1H, Pyl-4-H), 6.74, (m, 1H, Pyl-5-H), 6.94 (s, 1H, Im-5-H), 7.12 (s, 1H, Im-4-H); δ_C 34.2 (Me), 35.5 (Me), 107.4 (Pyl-3-CH) 111.8 (Pyl-4-CH) 121.1 (Im-5-CH) 122.6 (C) 124.4 (Py-5-CH), 128.8 (Im-4-CH), 141.4 (C). *m/z* 161 (M^+, 100%).

4.4. Molecular geometry optimizations

Molecular geometry optimizations and molecular mechanics calculations were performed with Hyperchem 5.1 with Polak–Ribiere as the minimization algorithm under root-mean-square gradient conditions of 0.1 kcal/(Å) or 420 calculation cycles.

Acknowledgements

We thank Enterprise Ireland for a Basic Research Grant and a Postgraduate Research Fellowship for Padraig McLoughlin.

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Cinchona alkaloids in the asymmetric synthesis of 2-(phenylsulfanyl)aziridines

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Received 23 April 2004; revised 1 June 2004; accepted 24 June 2004

Available online 23 July 2004

Abstract—Enantioselective aza-Michael initiated ring closure (MIRC) additions of ethyl nosyloxycarbamate to 2-(phenylsulfanyl)-2-cycloalkenones catalysed by *Cinchona* alkaloids were studied. The results suggest that the enantioselectivity obtained is influenced by the structure of the catalyst and the different amination conditions. Substrate ring size also plays an important role.

1. Introduction

Asymmetric synthesis of optically active compounds from prochiral substrates by using chiral catalysts is a very attractive methodology in organic chemistry.[1] Several natural chiral amines have been considered as efficient enantioselective catalysts under phase-transfer conditions in many cases. Initially, *Cinchona* alkaloids were used mainly as resolving agents. Later, their role in asymmetric synthesis increased substantially after the publication of the first examples of their use as chiral catalysts.[2] These organic phase-soluble chiral bases were reported to catalyse an array of asymmetric phase-transfer reactions.[3]

New features of this class of derivatives of natural amines in various asymmetric syntheses continue to be published. Quaternary salts of *Cinchona* alkaloids are divided according to their generation. We chose **1** as the most recent third generation catalyst and **2** as one of the simplest first generation catalyst (Fig. 1).

Chiral quaternary *N*-(9-anthracenylmethyl)cinchonidinium cations such as **1** have been shown to be effective and useful catalysts for example in enantioselective alkylation,[4] Michael[5] and epoxidation[6] reactions.

In the past, no asymmetric induction was obtained in olefin aziridination reactions with sulfonyloxycarbamates either in the presence of (−)-*N*-benzylcinchonidinium chloride as a chiral phase-transfer catalyst in a two-phase system or in a homogenous system by using a chiral base.[7] On the contrary, it is known that using different aminating agents, a highly enantioselective induction takes place during aziridination reactions performed in the presence of enantiopure ligands as catalysts in a homogenous system.[8] Recently chiral quaternary *N*-(*p*-trifluorobenzyl)cinchoninium cation **2** was used in the aziridination of methyl acrylate with aryl hydroxamic acids under phase-transfer conditions (5–61% ee).[9]

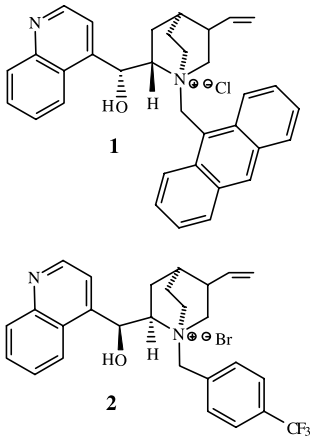

Figure 1. Chiral quaternary salts of *Cinchona* alkaloids.

Continuing our studies on the direct stereoselective aziridination, especially of α,β-unsaturated ketones,[10] α-carbonyl enoates[11] and 2-(phenylsulfinyl)-2-cycloalkenones,[12] we performed aza-Michael initiated ring closure (MIRC) reactions[13] under asymmetric phase-transfer

Keywords: Aza-Michael initiated ring closure (MIRC) reactions; Aziridination; *Cinchona* alkaloids; Heterogenous catalysis; Chiral catalyst.
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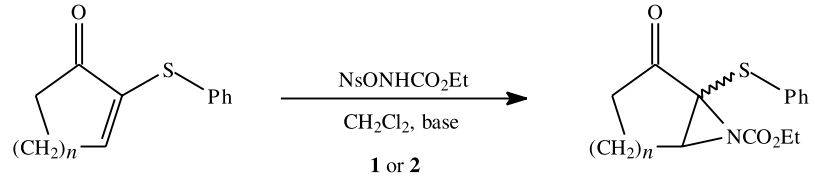
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.119

Table 1. Enantioselective aziridinations with $NsONHCO_2Et$ in the presence of quaternary salts of *Chincona* alkaloids **1** and **2**



3a n = 1; **3b** n = 2
3c n = 3; **3d** n = 4

4a-d

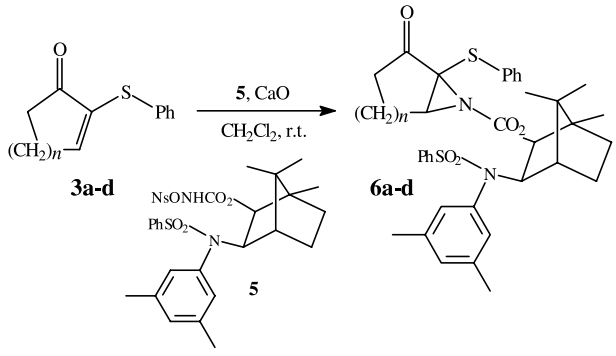
Entry	Aziridine	Catalyst	Method A				Method B			
			Molar ratio[a]	Time (h)	Yield (%)	ee[b] (%)	Molar ratio[c]	Time (h)	Yield (%)	ee[b] (%)
1	**4a**	—	—	—	—	—	1:6:4	24	54	—
2	**4a**	**1**	1:3:2	3	65	35	1:4:4	24	25	48
3	**4a**	**2**	1:3:3	4	98	17	1:2:2	3	18	25
4	**4b**	—	—	—	—	—	1:3:3	24	31	—
5	**4b**	**1**	1:5:5	22	77	21	1:4:4	24	25	71
6	**4b**	**2**	1:3:3	4	96	61	1:6:5	9	93	75
7	**4c**	**1**	1:7:7	29	34	24	1:6:6	6	43	48
8	**4c**	**2**	1:5:5	23	94	37	1:7:7	23	29	60
9	**4d**	**1**	1:7:7	30	50	N.d.[d]	1:8:8	28	44	N.d.
10	**4d**	**2**	1:5:5	24	53	N.d.	1:7:7	23	17	N.d.

[a] Substrate:$NaHCO_3$:$NsONHCO_2Et$.
[b] Determined by conversion into corresponding diastereomeric ketals.[18]
[c] Substrate:CaO:$NsONHCO_2Et$.
[d] N.d.: not determined.

catalysis to synthesise the chiral *N*-acyloxy 2-acyl-2-(phenylsulfanyl)aziridines, important synthetic analogues of several biologically interesting sulfur containing compounds,[14] by using ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = 4-nitrophenylsulfonyl).[15]

2-(Phenylsulfanyl)-2-cycloalkenones **3a-d** were reacted under two different heterogeneous conditions, using an aqueous $NaHCO_3$ solution as base[16] (liquid/liquid heterogeneous conditions, Method A) or calcium oxide[17] (solid/liquid heterogeneous conditions, Method B). The results are listed in Table 1, including yields obtained without catalyst for **4a** and **4b** (entries 1 and 4).

Table 2. Diastereoselective aziridinations with **5**



Aziridine	Molar ratio[a]	Time (h)	Yield (%)	de[b] (%)
6a	1:5:2.5	48	90	26
6b	1:6:1.5	28	71	20
6c	1:6:2.5	22	77	22
6d	1:8:4	22	83	24

[a] Substrate:CaO:**5**.
[b] Determined by ^1H NMR spectroscopy on the crude mixture.

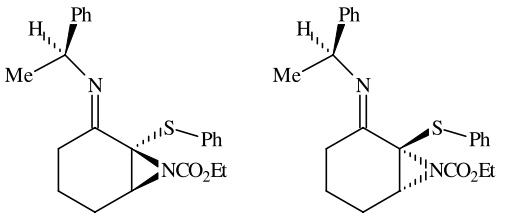
According to collected data, catalyst **2** seems to be more effective than catalyst **1** in the considered reaction conditions. Moreover, higher yields were obtained in the aza-MIRC reactions run under liquid/liquid heterogeneous conditions (Method A). On the contrary, in the presence of a solid phase (Method B), the expected aziridines **4** were obtained mostly in higher enantiomeric excesses. An increase in the internal temperature of reactions was always observed working under solid conditions[19] (Method B) and therefore these reactions must be carried out at 0 °C. This could reasonably explain the lower yields but also the higher ee obtained. From a stereochemical point of view, the best result (75% ee) was obtained in the aziridination performed following Method B on 2-(phenylsulfanyl)-2-cyclohexenone **3b** (entry 6) where the yield too is good (93%). Probably, the ring size also plays a role in controlling the reaction outcome.

The considered salts usually behave as pseudoenantiomeric catalysts in many stereocontrolled reactions.[2b] Surprisingly, we observed that **1** and **2** led to the same major enantiomer. A similar behaviour was already found in other aza-Michael reactions and explained on the basis of steric hindrance on the substrate.[9] Similarly, this anomaly could be due to steric hindrance effects on the catalyst itself as it seems to be in our aziridinations.

In order to compare the present data and our results concerning the aziridination of related sulfoxides,[12] we considered a different approach to synthesise chiral *N*-acyloxy 2-acyl-2-(phenylsulfanyl)aziridines **6a-d** namely by addition of the chiral nosyloxycarbamate **5** derived from Helmchen's auxiliary[20] to the same prochiral 2-(phenylsulfanyl)-2-cycloalkenones **3a-d** (Table 2). Contrary to our

expectations, the diastereomeric excesses are lower than those obtained in aziridinations on other prochiral olefins.

Moreover as a possible development of this work, we considered to use optically pure primary amines for the generation of interesting imino derivatives starting from the synthesised chiral aziridines. By reacting (*S*)-(−)-1-phenylethylamine with **4b** (75% ee), **7b** were obtained as a diastereomeric mixture (dr=88:12) and then purified by HPLC to give optically pure compounds (Fig. 2).



7b

Figure 2. Imino derivatives.

Starting from these first encouraging results,[21] we hope to optimise a general protocol for a parallel synthesis of a large number of highly functionalised aziridines.[22]

In summary two approaches towards the asymmetric synthesis of *N*-acyloxy 2-acyl-2-(phenylsulfanyl)aziridines have been considered. The one using *Cinchona* alkaloids as catalyst under different phase-transfer conditions gave in several cases satisfactory yields (up to 98%) and ee (up to 75%). Furthermore, observed high chemoselectivity is remarkable when compared with previous data concerning amination of simple vinyl sulfides[23] or cephem derivatives.[24]

2. Experimental

GC analyses were performed on a HP 5890 Series II gas chromatograph with a capillary column (methyl silicone, 12.5 m×0.2 mm). GC-MS were carried out on a HP G1800A GCD System with a capillary column (phenyl methyl silicone, 30 m×0.25 mm). ESI-MS analyses were performed using a commercial API 365 triple-quadrupole mass spectrometer from Perkin Elmer Sciex Instruments, equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. The analyses by HPLC were performed with a Varian 9001 instrument equipped with a Varian RI-4 differential refractometer. Solvents were HPLC-grade. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 or 300 and 50 or 75 MHz, respectively. $CDCl_3$ was used as solvent and $CHCl_3$ as internal standard. Optical rotations were recorded at the Sodium D line with a polarimeter at room temperature. Catalysts **1** and **2** are commercially available. Substrates **3a-d**,[25] $NsONHCO_2Et$[15] and **5**[20] were prepared following reported procedures. Enantiomeric excesses of **4a-c** were determined by transforming them with (*R*,*R*)-2,3-butanediol into corresponding ketals and by HPLC analyses.[18]

2.1. General procedure for the synthesis of aziridines 4a-d

Liquid/liquid conditions. Method A. To a stirred solution of substrates **3a-d** (10 mmol) and catalysts **1** or **2** (2–5 mmol) in CH_2Cl_2 (10 mL), $NsONHCO_2Et$ and an aqueous solution of $NaHCO_3$ were added portionwise at room temperature during 1 h up to the molar ratios reported in Table 1. After stirring, reaction mixtures were diluted with H_2O (50 mL) extracted with CH_2Cl_2 (50 mL) and dried on Na_2SO_4. Then solvent was evaporated and aziridines **4a-d** were obtained by HPLC (hexane/ethyl acetate, 6:4) in the yields reported in Table 1. The products do not survive to silica gel chromatography.

Solid/liquid conditions. Method B. To a stirred solution of substrates **3a-d** (10 mmol) and of catalysts **1** or **2** (2–5 mmol) in CH_2Cl_2 (10 mL) at 0 °C, $NsONHCO_2Et$ and CaO were added portionwise during 1 h up to the molar ratios reported in Table 1. After stirring, reaction mixtures were diluted with CH_2Cl_2 (50 mL) and filtered. The solvent was evaporated and aziridines **4a-d** were obtained by HPLC (hexane/ethyl acetate, 6:4) in the yields reported in Table 1.

2.1.1. Ethyl 2-oxo-1-(phenylsulfanyl)-6-azabicyclo-[3.1.0]hexane-6-carboxylate (4a). Viscous oil; $[\alpha]_D$=+30.0 (*c* 3.6, $CHCl_3$, 48% ee). IR: 1735 cm^{-1}; ^{1}H NMR: δ 1.18 (t, *J*=7.2 Hz, 3H), 1.90–2.61 (m, 4H), 3.45 (d, *J*=3.0 Hz, 1H), 4.07–4.24 (m, 2H), 7.27–7.56 (m, 5H). ^{13}C NMR: δ 14.2, 19.4, 32.0, 52.0, 57.0, 63.2, 128.0, 128.7 (two), 132.9 (two), 143.8, 157.9, 202.3. GC-MS *m/z*: 277 (M^+, 100), 168 (61), 162 (30), 140 (20), 121 (24), 109 (29), 96 (21), 77 (21). Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.56; H, 5.43; N, 5.04; S, 11.54%.

2.1.2. Ethyl 2-oxo-1-(phenylsulfanyl)-7-azabicyclo-[4.1.0]heptane-7-carboxylate (4b). Viscous oil; $[\alpha]_D$=+9.2 (*c* 2.7, $CHCl_3$, 75% ee). IR: 1735 cm^{-1}; ^{1}H NMR: δ 1.30 (t, *J*=7.2 Hz, 3H), 1.64–2.69 (m, 6H), 3.28 (d, *J*=2.4 Hz, 1H), 4.23 (q, *J*=7.2 Hz, 2H), 7.27–7.50 (m, 5H). ^{13}C NMR: δ 14.4, 18.3, 23.2, 37.6, 48.6, 54.2, 63.4, 127.9, 129.0 (two), 132.0 (two), 134.5, 158.9, 199.5. GC-MS *m/z*: 291 (M^+, 100), 182 (23), 162 (20), 154 (58), 121 (32). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; S, 11.01. Found: C, 61.77; H, 5.86; N, 4.78; S, 10.99%.

2.1.3. Ethyl 2-oxo-1-(phenylsulfanyl)-8-azabicyclo-[5.1.0]octane-8-carboxylate (4c). Viscous oil; $[\alpha]_D$=−14.4 (*c* 2.5, $CHCl_3$, 60% ee). IR: 1736 cm^{-1}; ^{1}H NMR: δ 1.32 (t, *J*=7.2 Hz, 3H), 1.66–2.86 (m, 8H), 3.05 (dd, *J*=1.8, 6.3 Hz, 1H), 4.03–4.26 (m, 2H), 7.00–7.56 (m, 5H). ^{13}C NMR: δ 14.0, 23.5, 25.2, 28.0, 39.8, 44.9, 53.8, 63.2, 126.8, 128.7 (two), 129.7 (two), 132.6, 159.6, 202.8. GC-MS *m/z*: 305 (M^+, 39), 196 (73), 168 (100), 121 (30), 109 (23), 84 (28), 77 (36), 67 (27), 51 (20). Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.86; H, 6.26; N, 4.57; S, 10.47%.

2.1.4. Ethyl 2-oxo-1-(phenylsulfanyl)-9-azabicyclo-[6.1.0]nonane-9-carboxylate (4d). Viscous oil. IR: 1736 cm^{-1}; ^{1}H NMR: δ 1.37 (t, *J*=7.2 Hz, 3H), 1.70–2.79 (m, 10H), 3.29 (dd, *J*=6.0, 6.6 Hz, 1H), 4.25 (q, *J*=

7.2 Hz, 2H), 7.26–7.57 (m, 5H). ^{13}C NMR: δ 13.8, 20.2, 22.1, 25.0, 27.1, 42.0, 46.8, 51.0, 63.2, 127.3, 129.0 (two), 129.6 (two), 133.9, 162.8, 201.6. GC-MS *m/z*: 319 (M^+, 32), 210 (100), 182 (86), 121 (37), 110 (23), 109 (32), 91 (24), 81 (23), 77 (38), 55 (27), 41 (30). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.04. Found: C, 63.84; H, 6.62; N, 4.37; S, 10.01%.

2.2. General procedure for the synthesis of aziridines 6a-d

To a stirred solution of substrates **3a-d** (10 mmol) in CH_2Cl_2 (10 mL), chiral nosyloxycarbamate **5** and CaO were added portionwise during 1 h up to the molar ratios reported in Table 2. After stirring at room temperature, reaction mixtures were diluted with CH_2Cl_2 (50 mL) and filtered. Then solvent was evaporated and aziridines **6a-d** were obtained as diastereomeric mixtures by HPLC (hexane/ethyl acetate, 7:3) in the yields reported in Table 2.

2.2.1. (1*R*,2*S*,3*R*)-3-[(3,5-Dimethylphenyl) (phenylsulfonyl)amino]-2-bornanyl 2-oxo-1-(phenylsulfanyl)-6-azabicyclo[3.1.0]hexane-6-carboxylate (6a). Viscous oil. IR: 1742 cm^{-1}; ^{1}H NMR: δ 0.56 (s, major), 0.58 (s), 3H; 0.89 (s, major), 0.90 (s), 3H; 0.96 (s), 0.98 (s, major), 3H; 1.28–2.58 (m, 15H); 3.47 (d, J=7.8 Hz), 3.52 (d, J=6.0 Hz, major), 1H; 3.61 (d, J=3.0 Hz), 3.75 (d, J=2.7 Hz, major), 1H; 5.02 (d, J=6.6 Hz, major), 5.20 (d, J=7.2 Hz), 1H; 5.66 (s), 5.81 (s, major), 1H; 6.81 (s, major), 6.83 (s), 1H; 6.88 (s, major), 6.97 (s), 1H; 7.27–7.75 (m, 10H). ^{13}C NMR: δ 11.1, 11.6, 20.8 (two), 21.1 (four), 21.3, 21.8, 27.4, 27.5, 27.9, 29.3, 29.7, 32.0, 33.1, 34.7, 47.4, 48.2, 48.5, 48.9, 50.1 (two), 50.5 (aziridine ring CH, major), 50.8 (aziridine ring CH, minor), 60.3 (aziridine ring C, two), 66.9, 67.3, 82.3, 82.4, 121.2, 124.3, 128.0 (six), 128.4 (four), 128.8 (four), 129.1 (two), 129.3, 129.5, 132.3, 132.5, 132.9, 133.1, 133.3, 134.3, 135.3, 136.6 (two), 137.1 (two), 137.8, 138.0 (two), 138.6, 138.7, 155.1, 156.7, 203.3, 204.5. HR-MS (ES Q-TOF) Calcd for $C_{36}H_{41}N_2O_5S_2$ $(M+H)^+$: 645.2457. Found: 645.2453.

2.2.2. (1*R*,2*S*,3*R*)-3-[(3,5-Dimethylphenyl) (phenylsulfonyl)amino]-2-bornanyl 2-oxo-1-(phenylsulfanyl)-7-azabicyclo[4.1.0]heptane-7-carboxylate (6b). Viscous oil. IR: 1742 cm^{-1}; ^{1}H NMR: δ 0.61 (s, major), 0.63 (s), 3H; 0.89 (s, major), 0.90 (s), 3H; 0.93 (s), 0.95 (s, major), 3H; 1.02–2.75 (m, 17H); 3.46 (d, J=2.7 Hz, major), 3.49 (d, J=3.0 Hz), 1H; 3.90 (d, J=6.9 Hz, major), 3.93 (d, J=6.9 Hz), 1H; 5.08 (d, J=6.9 Hz, major), 5.18 (d, J=7.2 Hz), 1H; 5.87 (s), 6.27 (s, major), 1H; 7.22 (s, major), 7.23 (s), 1H; 7.24 (s), 7.25 (s, major), 1H; 7.27–7.53 (m, 10H). ^{13}C NMR: δ 11.2 (two), 21.0 (two), 21.1 (six), 27.1, 27.7, 28.2, 28.7, 29.2, 29.6, 31.0, 31.8, 32.0, 38.6, 47.3 (two), 48.4, 48.7, 50.3 (two), 56.4 (aziridine ring CH, minor), 59.1 (aziridine ring CH, major), 61.5 (aziridine ring C, major), 61.7 (aziridine ring C, minor), 67.2 (two), 82.2, 82.9, 127.0 (four), 127.3 (four), 128.0 (four), 128.9 (four), 129.2, 131.5, 131.8, 132.1 (two), 132.3 (two), 133.3, 133.6 (two), 136.3, 136.8 (two), 137.2 (two), 137.4, 138.1 (two), 138.6, 139.1, 155.3, 156.8, 193.5, 194.8. HR-MS (ES Q-TOF) Calcd for $C_{37}H_{43}N_2O_5S_2$ $(M+H)^+$: 659.2613. Found: 659.2618.

2.2.3. (1*R*,2*S*,3*R*)-3-[(3,5-Dimethylphenyl) (phenylsulfonyl)amino]-2-bornanyl 2-oxo-1-(phenylsulfanyl)-8-azabicyclo[5.1.0]octane-8-carboxylate (6c). Viscous oil. IR: 1743 cm^{-1}; ^{1}H NMR: δ 0.58 (s), 0.59 (s, major), 3H; 0.87 (s), 0.88 (s, major), 3H; 0.97 (s), 0.98 (s, major), 3H; 1.25–2.68 (m, 19H); 3.62 (d, J=7.2 Hz, major), 3.70 (d, J=7.2 Hz), 1H; 3.75 (d, J=2.7 Hz, major), 3.86 (d, J=3.0 Hz), 1H; 5.03 (d, J=6.9 Hz, major), 5.18 (d, J=7.2 Hz), 1H; 5.67 (s), 5.82 (s, major), 1H; 6.58 (s), 6.62 (s, major), 1H; 6.82 (s), 6.88 (s, major), 1H; 7.27–7.80 (m, 10H). ^{13}C NMR: δ 11.1, 11.8, 21.1 (six), 21.8 (two), 22.8, 23.3, 25.0, 27.1, 27.7 (two), 27.9, 28.8, 29.7, 32.1 (two), 33.1, 45.3 (aziridine ring CH, major), 45.8 (aziridine ring CH, minor), 46.9, 47.3, 48.4, 48.9, 49.8, 50.2, 65.8 (aziridine ring C, two), 67.2, 67.3, 82.3, 82.5, 124.3, 126.8, 127.5, 128.0 (two), 128.1 (two), 128.6 (two), 128.8 (two), 129.1 (two), 129.4 (two), 129.6, 130.4 (two), 131.0, 131.2, 131.6, 132.1, 132.4 (two), 132.9, 133.3, 135.3, 135.9, 136.5, 137.2, 137.5, 137.9, 138.4, 138.6, 138.8, 139.5, 151.1, 151.4, 204.2 (two). HR-MS (ES Q-TOF) Calcd for $C_{38}H_{45}N_2O_5S_2$ $(M+H)^+$: 673.2770. Found: 673.2764.

2.2.4. (1*R*,2*S*,3*R*)-3-[(3,5-Dimethylphenyl) (phenylsulfonyl)amino]-2-bornanyl 2-oxo-1-(phenylsulfanyl)-9-azabiciclo[6.1.0]nonane-9-carboxylate (6d). Viscous oil. IR: 1743 cm^{-1}; ^{1}H NMR:δ 0.61 (s, major), 0.64 (s), 3H; 0.81 (s, major), 0.85 (s), 3H; 0.97 (s), 0.99 (s, major), 3H; 1.19–2.39 (m, 21H); 3.62 (d, J=6.9 Hz), 3.79 (d, J=7.2 Hz, major), 1H; 3.75 (d, J=2.7 Hz), 3.88 (d, J=3.0 Hz, major), 1H; 4.89 (d, J=6.9 Hz), 5.04 (d, J=7.5 Hz, major), 1H; 5.67 (s, major), 5.83 (s), 1H; 6.83 (s, major), 6.89 (s), 1H; 6.98 (s), 7.04 (s, major), 1H; 7.27–7.76 (m, 10H). ^{13}C NMR: δ 11.2, 11.9, 21.2 (six), 21.8 (two), 27.8 (three), 28.0 (two), 28.2, 29.8, 30.5, 32.1 (four), 33.2, 34.2, 47.0, 47.4, 48.0 (aziridine ring CH, minor), 48.5, 49.0, 49.5 (aziridine ring CH, major), 50.2, 50.7, 65.4 (aziridine ring C, minor), 65.6 (aziridine ring C, major), 67.2, 67.4, 82.3, 82.5, 123.9 (two), 124.3, 127.1, 128.0 (two), 128.1 (four), 128.7, 128.9 (two), 129.2 (two), 129.4 (two), 129.6, 130.8, 131.3 (two), 131.7, 131.9, 132.3, 132.6, 132.9, 136.3, 136.7, 137.1, 137.2, 138.1, 138.5, 138.7, 138.9, 139.0, 139.6, 155.0, 156.7, 205.0 (two). HR-MS (ES Q-TOF) Calcd for $C_{39}H_{47}N_2O_5S_2$ $(M+H)^+$: 687.2926. Found: 687.2931.

2.3. Synthesis of (7b) Ethyl (2*E*)-[(1*S*)-(1-phenylethyl) imino]-1-(phenylsulfanyl)-7-azabicyclo[4.1.0]heptane-7-carboxylate

A solution of **4b** (0.38 g, 1.13 mmol) and (*S*)-(−)-1-phenylethylamine (0.17 mL, 1.13 mmol) in anhydrous benzene (20 mL) was refluxed in a Dean Stark apparatus for 2 h. After solvent evaporation, the obtained diastereomeric mixture of **7b** (0.31 g, 0.79 mmol, 60% yield) was separated by HPLC (hexane/ethyl acetate, 8:2). Viscous oil. Major. IR: 1728, 1680 cm^{-1}; ^{1}H NMR: δ 1.20–1.29 (m, 3H), 1.44 (d, J=6.9 Hz, 3H), 2.07–2.80 (m, 6H), 4.07–4.27 (m, 2H), 4.12 (q, J=6.9 Hz, 1H), 4.69 (br, 1H), 7.16–7.33 (m, 10H). ^{13}C NMR: δ 14.7, 17.5, 25.0, 31.5, 44.1, 47.3, 53.2, 61.1, 62.3, 125.5 (two), 125.9, 126.8 (two), 128.5 (two), 129.0 (two), 131.8, 139.5, 144.3, 155.5, 193.2. GC-MS *m/z*: 213 (M^+−181, 13), 212 (23), 197 (32), 151 (10), 106 (14), 105 (100), 103 (19), 91 (13), 80 (12), 79 (22), 78 (10), 77 (30), 54 (22). HR-MS (ES Q-TOF) Calcd for

$C_{23}H_{27}N_2O_2S$ $(M+H)^+$: 395.1793. Found: 395.1801. Minor. ^1H NMR: δ 1.20–1.29 (m, 3H), 1.31 (d, $J=7.2$ Hz, 3H), 2.07–2.80 (m, 6H), 4.07–4.27 (m, 2H), 4.23 (q, $J=7.2$ Hz, 1H), 4.85 (br, 1H), 7.16–7.33 (m, 10H). GC-MS *m/z*: 212 ($M^+ -182$, 17), 197 (21), 109 (32), 106 (13), 105 (100), 104 (11), 103 (23), 91 (13), 80 (12), 79 (28), 78 (17), 77 (44), 54 (17), 51 (19).

Acknowledgements

We thank the Italian Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) and the Università degli Studi di Roma La Sapienza (National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni') for financial support.

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Copper(I) and silver(I) complexes of 1,5-methylene- and diethylmethylene-bridged bis(oxazoline) ligands. In situ Cu(II)-catalyzed oxidation of methylene bridge

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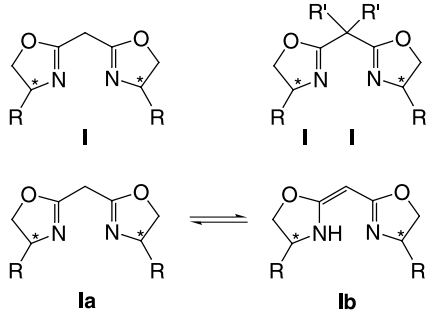
Received 23 April 2004; revised 28 May 2004; accepted 24 June 2004

Available online 29 July 2004

Abstract—Silver(I) and copper(I) complexes of C_2-symmetric bis(oxazoline) ligands were studied by UV, NMR, IR, EPR and ES-MS spectroscopies. The stability constants of the Ag–**1a** and Ag–**1b** complexes with 1:1 and 1:2 stoichiometries in acetonitrile were determined by NMR spectrometric titrations. The evidence of tetrahedral coordination for complex (Ag(**1a**)$_2$($^+$ was obtained from the complexation induced shifts (CIS) and NOEs. Mass spectra revealed the Cu(II) mediated oxidation of methylene bridge in copper complexes of **1a** and **1b**, which was in accordance with the UV, NMR, IR and EPR findings. The efficiency of Cu(I) complexes of methylene-bridged 1,5-bis(oxazoline)s **1** as chiral catalysts in stereoselective cyclopropanation of styrene with ethyl diazoacetate, was compared to that of the dialkylmethylene-bridged 1,5-bis(oxazoline)s **2**.

1. Introduction

Over the last years a wide variety of chiral, C_2-symmetric bis(oxazoline) ligands has been synthesized and their metallic complexes used as stereoselective catalysts in different reactions,[1–4] including cyclopropanations[5–8] and aziridinations of olefins and imines,[9–11] Diels–Alder and hetero Diels–Alder reactions,[12–14] 1,3-dipolar cycloadditions,[15] allylic displacement,[16,17] addition of dialkylzinc to aldehydes,[18] organolithium addition to imines,[19] hydrosilylative reduction,[20,21] allylic oxidation of olefins,[22] hydrosilylation of ketones,[23] Friedel–Crafts reaction,[24] diene cyclization/hydrosilylation,[25] glyoxylate–ene reaction,[26] Canizzaro reaction[27] etc. The Lewis basicity of the nitrogen donor atoms and the conformational rigidity of chelates formed represent important structural features of C_2-symmetric bis(oxazoline) ligands. Among 1,5-bis(oxazoline) ligands, the most frequently used ones in catalytic transformations can be divided into two groups: the bis(oxazolines) with methylene spacer (**I**) and the bis(oxazolines) with the dialkylmethylene spacer (**II**) (Scheme 1).



Scheme 1.

Both types of the ligands are capable to form six-membered metal chelates, which fixes their conformation in nearly planar geometry. Recently, we have prepared a series of macrocyclic[28] and acyclic[29] 1,5-bis(oxazoline) derivatives, the latter possessing elongated aromatic arms of variable length and flexibility attached on chiral centres. We have also performed a detailed study of the structure, stoichiometry and conformation of Cu(I) and Ag(I) complexes with type II bis(oxazoline) ligands in solution.[30] In the type **II** of the 1,5-bis(oxazoline) ligands, the presence of dialkylmethylene spacer fixes two oxazoline double bonds in an isolated position. However, if the type **I** ligands are

Keywords: Bis(oxazoline); Metal complex; Chiral catalysts.
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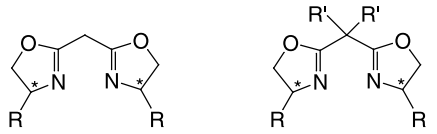
doi:10.1016/j.tet.2004.06.117



1a R = -C_6H_4-OBzl
1b R = -CH_2-C_6H_4-OBzl
1c R = -CH_2-C_6H_4-OMe
1d R = -CH_2-C_6H_4-O*t*Bu
1e R = -C_6H_4-O*t*Bu
1f R = -Ph
1g R = -CH_2-Ph
1h R = -*t*Bu

2a R = -C_6H_4-OBzl, R' = Et
2b R = -CH_2-C_6H_4-OBzl, R' = Et
2c R = -Ph, R' = Me
2d R = -CH_2-Ph, R' = Me
2e R = -*t*Bu, R' = Me

Chart 1.

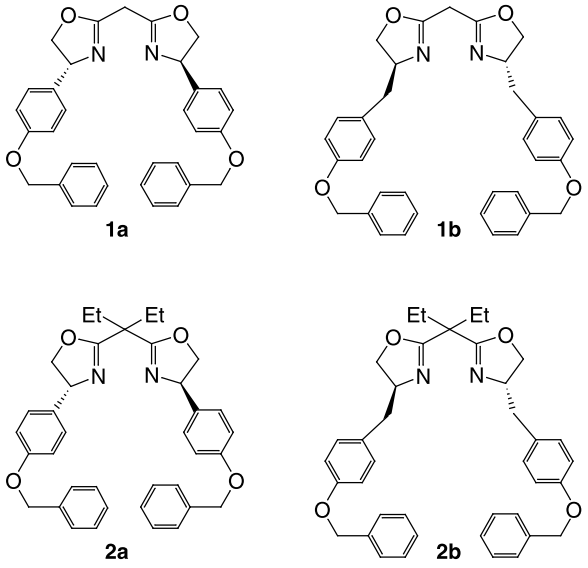


Chart 2.

considered, the presence of the methylene bridge allows formation of two tautomeric forms, **Ia** and **Ib**, the latter possessing 4π conjugated system (Scheme 1). It should be noted that removal of the NH proton in **Ib** may give an anionic ligand which should exhibit different affinity toward metal cations and as the consequence the properties of such catalytic complex may also be altered. PE and NMR spectra of bis(oxazolines) **1f** and **1 h** (Chart 1) revealed that the **Ia** tautomeric form presents the dominant species in the gas phase as well as in the solution. On the other hand, a UV spectroscopic investigation of ligand **1h**, indicated the presence of a small amount of the enamine **Ib** in solution.[31] To investigate possible differences between methylene- (**1a**, **1b**) and the previously studied diethylmethylene (**2a**, **2b**)[30] bridged 1,5-bis(oxazoline) ligands (Chart 1) we undertook a detailed spectroscopic study of **1a**, **1b**–Ag(I) and Cu(I) complexes and the comparative study of the catalytic properties of type **I** and type **II** (Chart 2) Cu(I) complexes in the cyclopropanation of styrene with ethyl diazoacetate.

For comparison, the cyclopropanations were also performed by using the Cu(I) catalytic complexes of alkoxyphenyl substituted ligands **1c**, **1d**, **1e**[29] and commercially available ligands **1f**, **1g**, **1h** and **2c**, **2d**, **2e** lacking long substituents on chiral centres. All of the 1,5-bis(oxazoline) ligands studied are based on *S*-tyrosine and *R*−4-hydroxyphenylglycine. The aromatic arms of variable length and flexibility attached onto stereogenic centers of the ligands may influence both their complexation and catalytic properties and may result by different stereochemical outcome.

2. Results and discussion

2.1. Spectroscopic studies of 1a and 1b silver(I) and copper(I) complexes in solution

2.1.1. Silver(I) complexes. The UV spectral changes in the titrations of **1a** and **1b** with Ag^+ in MeCN were insufficient

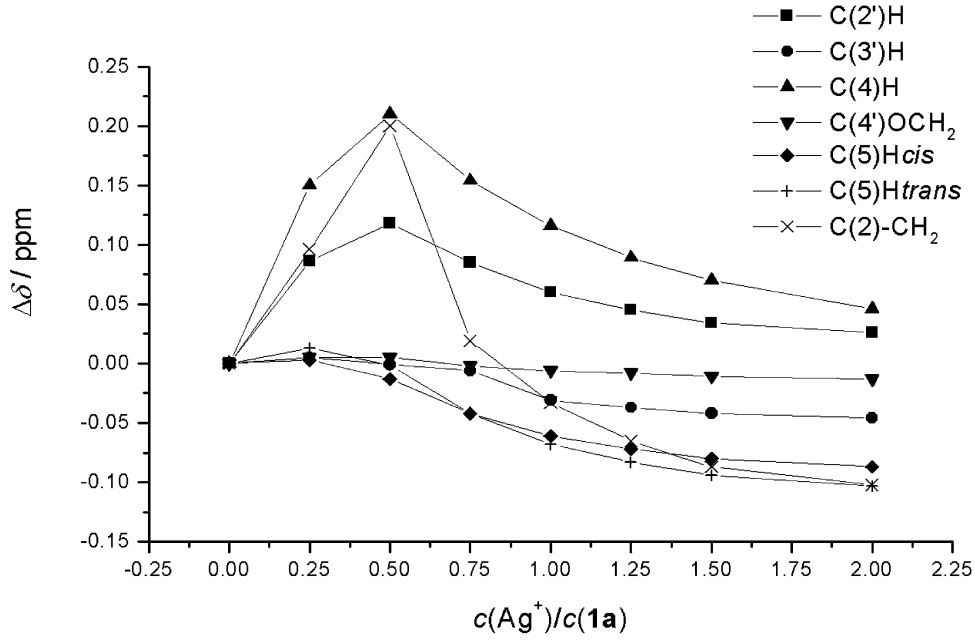


Figure 1. Complexation-induced shifts (CIS) for **1a**–Ag^+ complexes.

to enable accurate analysis, and changes remained only very slight over longer period of time. Therefore, the formation of Ag^+ complexes of **1a** and **1b** in MeCN-d_3 was studied by ^1H NMR. The spectra of the free ligands were found concentration-independent in the concentration range of 2×10^{-3} to 2×10^{-2} mol dm^{-3} showing lack of ligand self-association.

Addition of Ag^+ produced significant shifts in all of the ligand resonances, without significant line broadening, indicating fast equilibrium kinetics on the NMR time scale. The observed complexation induced shifts (CIS; $\Delta\delta=\delta Hi_{lig}-\delta Hi_{compl}$, ppm), were plotted against the $c(Ag^+)/c$(**1a**,**1b**) ratio (Fig. 1). In the case of ligand **1a**, additions of Ag^+ induced upfield shifts of C(2)–CH_2 (methylene bridge), C(4)–H and C(2′)–H (aromatic) signals, until the ratio of 0.5 was reached followed by downfield shifts of all resonances at higher ratios. The upfield shifts observed up to the molar ratio of 0.5 suggests formation of the (Ag(**1a**)$_2$)$^+$ complex, whereas downfield shifts of all of the ligand resonances in the $c(Ag^+)/c$(**1a**) range of 0.5–2.0 shows transformation of the first complex into (Ag(**1a**))$^+$ one. Strong deshielding effects were observed for C(4)–H, C(5)–H*cis* and C(2′)–H protons (see Figure 2 for numeration) on going from 1:2 to 1:1 complex (Fig. 1). Also the methylene bridge protons experienced the strongest deshielding effect on going from the (Ag(**1a**)$_2$)$^+$ towards the (Ag(**1a**))$^+$ complex. This suggests that the same protons

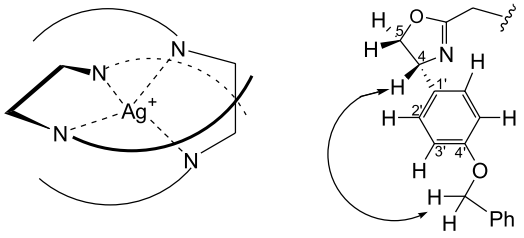


Figure 2. Schematic presentation of (Ag(**1a**)$_2$)$^+$ pseudotetrahedral complex and intermolecular NOE interaction between C(4)H and OCH_2–Ph observed in the NOESY spectrum of [Ag(**1a**)$_2$]$^+$.

are strongly shielded in (Ag(**1a**)$_2$)$^+$ complex. In the 1:1 complex the protons close to the metal centre [C(4)–H, C(5)–H and C(2′)–H] should be strongly deshielded upon Ag^+ coordination by the through bond effects; in the 1:2 Ag^+–ligand complex, such effects are less pronounced being distributed between two bis(oxazoline) units. Exactly the same trend of induced shifts was observed for (Ag(**2a**)$_2$)$^+$ and (Ag(**2a**))$^+$ complexes and explained by formation of the pseudotetrahedral Ag^+ complex of 1:2 stoichiometry, with the cation bound to four nitrogen atoms of two orthogonally oriented bis(oxazoline) units.[30] In such a complex, each bis(oxazoline) unit is located between two C(4)–phenyl groups of the second ligand molecule, which results through shielding of C(4)–H and C(2′)–H. The bridging methylene protons are shielded by two distant phenyls of the C(4′)–*O*-benzyl arms in the 1:2 complex. Additional support for the structure of the 1:2 complex comes from the analysis of the NOESY spectrum taken at the $c(Ag^+)/c$(**1a**) ratio of 0.5.

Examination of the CPK model of **1a** shows that the majority of the observed NOE crosspeaks could be explained by the favourable distances between respective hydrogen atoms in a single **1a** molecule. However, a clear crosspeak corresponding to NOE interaction between C(4′)–OCH_2 and C(4)–H is observed. The closest possible distance between these protons in the model of **1a** is over 6 Å, well exceeding the limiting value of 2.2–5 Å,[32] necessary for observation of the NOE effect. Thus, this crosspeak could be explained only by mutual interaction of two **1a** ligands in the pseudotetrahedral [Ag(**1a**)$_2$]$^+$ complex (Fig. 2).

The additions of Ag^+ to ligand **1b** also induced upfield shifts of C(4)–H, C(4)–CH*a*, C(2′)–H (aromatic), and C(4′)–OCH_2 signals until the ratio of 0.5 was reached; further additions of the cation produced downfield shifts of all resonances (Fig. 3). A clear maximum at the $c(Ag^+)/c$(**1b**) ratio of 0.5 suggests initial formation of the Ag^+–**1b** complex of a 1:2 stoichiometry (Fig. 4) which at higher ratios transforms to the 1:1 complex. The strongest

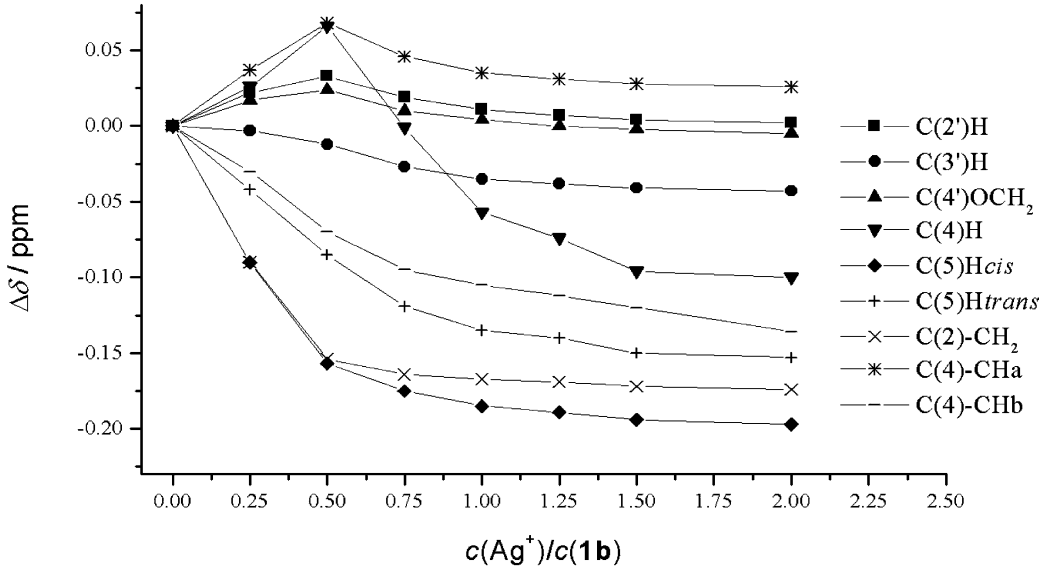


Figure 3. Complexation induced shifts for **1b**–Ag^+ complexes.

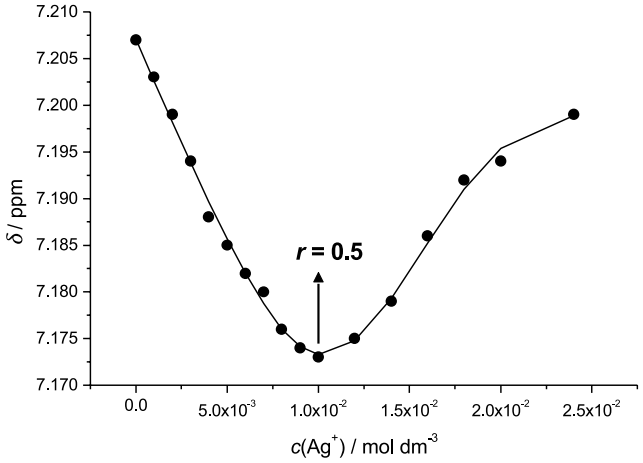


Figure 4. Experimental (dots) and calculated (line) chemical shifts of C(2′)–H of **1b** induced by addition of $AgBF_4$ (solvent: MeCN-d_3), $r=c(Ag^+)/c(\mathbf{1b})$.

shielding effects upon formation of $(Ag(\mathbf{1b})_2)^+$ showed C(4)–H, C(4)–CH*a*, the aromatic C(2′)–H proton, as well as the benzylic methylene group protons. The observed downfield trend of the complexation induced shifts at the $c(Ag^+)/c(\mathbf{1b})$ range between 0.5 and 2.0, could be explained by the disappearance of the $[Ag(\mathbf{1b})_2]^+$ complex and predominant formation of $[Ag(\mathbf{1b})]^+$ complex.

2.1.1.1. Stability constants.. Among several chemically reasonable speciations used in the fitting of the spectrometric data, two (set by assuming the presence of $[AgL]^+$ and $[AgL_2]^+$ or $[AgL_2]^+$ and $[Ag_2L_2]^+$; L standing for either **1a** or **1b**) gave satisfactory results. As the electrospray mass spectrometry (ES-MS) of **1a** and **1b** Ag^+ complexes unambiguously indicated the formation of $[AgL]^+$ and $[AgL_2]^+$, and no evidence of the presence of $[Ag_2L_2]^{2+}$ species, we could exclude the formation of $[Ag_2L_2]^{2+}$ (see Figures 1 and 2 in the Supplementary Material). The electrospray mass spectra of $Ag^+(\mathbf{1a})$ and $Ag^+(\mathbf{1b})$ solutions in MeCN showed peaks at $m/z=625$ for $[Ag(\mathbf{1a})]_n^{n+}$ and 1145 for $[Ag(\mathbf{1a})_2]^+$ and 653 for $[Ag(\mathbf{1b})]_n^{n+}$ and 1201 for $[Ag(\mathbf{1b})_2]^+$ (Figs. 1 and 2, Supplementary Material). The isotopic abundances of the peaks at $m/z=625$ and 653 showed peak separation of 1 Da, corresponding to the singly charged species $[Ag(\mathbf{1a})]^+$ and $[Ag(\mathbf{1b})]^+$, respectively. The stability constants of the Ag^+ complexes calculated from the ^{1}H NMR titration data are collected in Table 1. Both, **1a** and **1b** form quite stable 1:1 ($K_{AgL}\approx 10^5$ M^{-1}) and 1:2 ($K_{AgL2}\approx 10^3-10^4$ M^{-1})

Table 1. Stability constants of Ag^+ complexes with **1a**, **1b**, **2a** and **2b** in MeCN determined by ^{1}H NMR titrations

	log K[a]
Ag(**1a**)	4.8±0.4
Ag(**1a**)$_2$	4.1±0.2
Ag(**1b**)	5.0±0.2
Ag(**1b**)$_2$	2.8±0.2
Ag(**2a**)	3.5[b]
Ag(**2a**)$_2$	3.3[b]
Ag(**2b**)	3.9[b]
Ag(**2b**)$_2$	3.1[b]

[a] $K=[AgL_n]/[AgL_{n-1}][L]$, L standing for **1a**, **1b**, **2a** or **2b**; $n=1,2$.
[b] See Ref. 30.

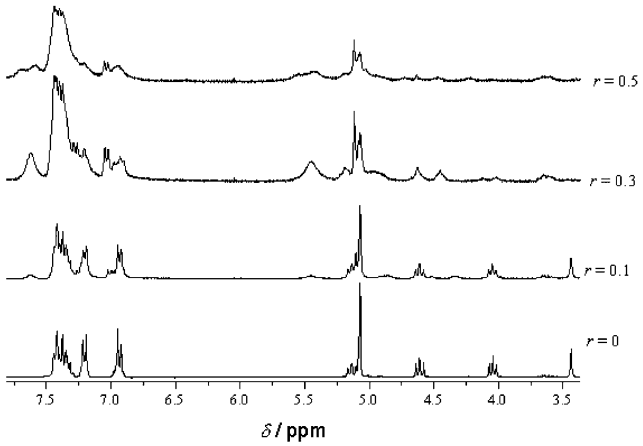


Figure 5. ^{1}H NMR spectra of **1a** in CD_3CN at different $c(Cu+)/c(\mathbf{1a})$ ratios.

complexes with Ag^+ in MeCN; generally, their stability constants are for more than one order of magnitude higher than those of the corresponding diethylmethylene bridged derivatives **2a** and **2b** (except that of $Ag(\mathbf{1b})_2$ being somewhat lower than that of $Ag(\mathbf{2b})_2$).[30]

2.1.2. Copper(I) complexes. ^{1}H NMR spectroscopic titrations of **1a** and the corresponding diethylmethylene bridged **2a** with $(Cu(MeCN)_4(PF_6$ showed significant differences. The methylene bridged bis(oxazoline) **1a** gave at least two sets of signals upon addition of Cu(I) salt indicating formation of mixture of complexes (Fig. 5). In contrast, ligand **2a** showed a single set of signals with significant downfield shifts of the oxazoline protons in accord with fast complex formation and simultaneous coordination of the cation with both nitrogens (Fig. 6). In addition, Cu(I) salt induced severe broadening of **1a** lines (as shown in Figure 5) and besides the signals of the free ligand, new resonances shifted downfield for 0.3 ppm could be observed. In the spectrum at $c(Cu^+)/c(\mathbf{1a})$ molar ratio of only 0.1 new resonances with integrals approximately 20% of those of the free ligand indicated the initial formation of $(Cu(\mathbf{1a})_2(^+$ complex. However, further additions of Cu^+, (Fig. 5; $c(Cu^+)/c(\mathbf{1a})=0.3$) resulted in

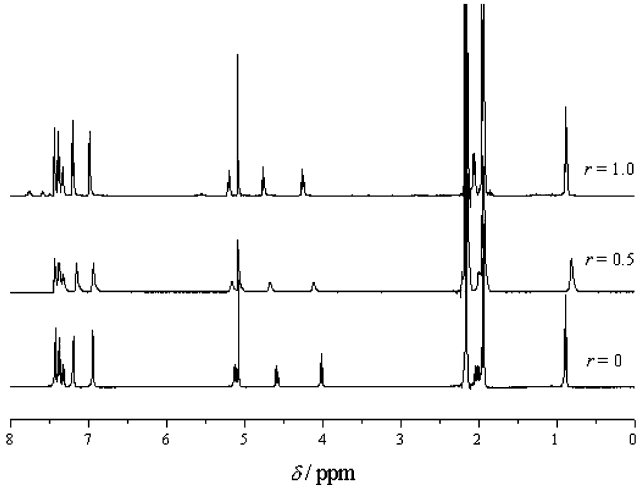


Figure 6. ^{1}H NMR spectra (600 MHz) obtained by titration of **2a** in CD_3CN with $[Cu(MeCN)_4]PF_6$ at different ratios $r=c(Cu^+)/c(\mathbf{2a})$.

severe line broadening and diminished intensity of oxazoline proton resonances, being characteristic for the presence of a paramagnetic species; presumably air oxidation of Cu^{+} to paramagnetic Cu^{2+} occurred. The process can be also observed visually through appearance of violet-blue colour. The corresponding diethylmethylene bridged ligand **2a** could be titrated with Cu^{+} up to the $c(Cu^{+})/c(\mathbf{2a})$ molar ratio of 1.0 lacking any line broadening (Fig. 6) or colour change.

In order to shed more light on the transformations of copper complexes of **1a** and **1b** the IR- and MS-investigations were performed. The IR spectra of freshly prepared and aged (four weeks) Cu–**1a** complexes showed changes (broadening of the band) in the region of carbon–heteroatom double bonds (about 1670 cm^{-1}) indicating an oxidative process on methylene bridge of **1a** to carbonyl group by air-oxygen, thus generating the new chromophore with three conjugated double bonds. All other bands remained unaffected. Opposite to this, IR spectra of Ag^{+} complexes did not show any change during 4 weeks of standing.

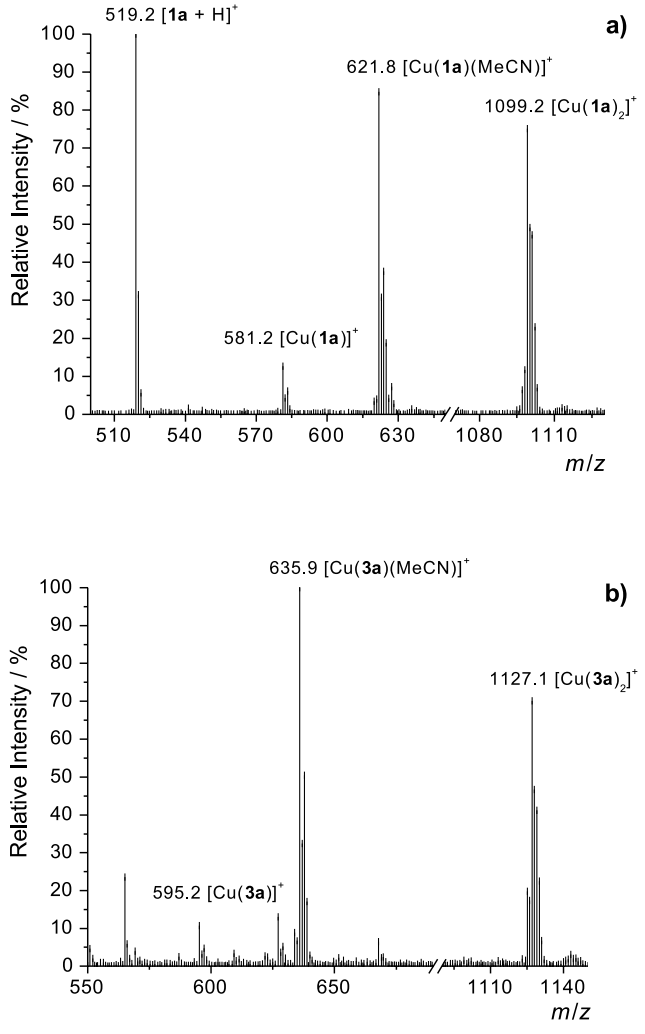


Figure 7. ES-MS spectra of Cu–**1a** complex in acetonitrile, freshly prepared (a) and after 24 h standing at room temperature (b).

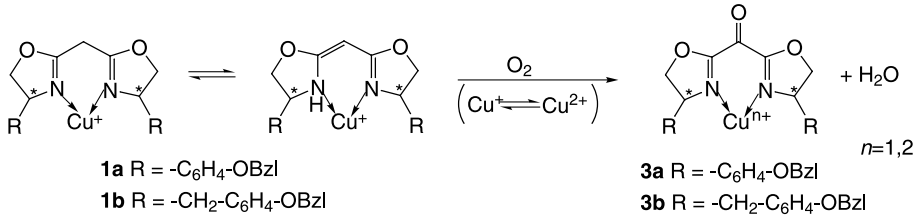
The FTIR spectra of the **1a**–Ag^{+} complex did not show any change during 4 weeks, showing that the presence of copper ions was necessary for oxidation. The mass spectra of the freshly prepared acetonitrile solutions of $(Cu(MeCN)_4(PF_6$ and **1a** and **1b**, respectively, show the simultaneous presence of the free ligand and 1:1 and 1:2 complexes (Fig. 7a here and Fig. 3a in Supplementary Material). However, the same solutions after standing for 24 h at room temperature gave different mass spectra; the peaks of free ligands and 1:1 and 1:2 complexes disappeared and new peaks corresponding to 1:1- and 1:2-complexes increased for 14 and 28 mass units, respectively, were observed (Fig. 7b, here and Fig. 3b, Supplementary Material). In contrast, the mass spectra of $AgBF_4$ and **1a** and **1b** acetonitrile solutions did not show any changes after 24 h at room temperature (see Figures 1 and 2 in Supplementary Material).

The increase of masses of the complexes for 14 and 28 mass units clearly show that oxidation of methylene bridge into carbonyl group took place accompanied presumably by the reduction of Cu(II) back to Cu(I), as outlined in Scheme 2. The presence of Cu(II) was additionally confirmed by EPR spectrum which showed the formation of a para-magnetic Cu(II) immediately after mixing the solutions of Cu(I) salt and ligand **1a**. These results are in agreement with those of NMR and FTIR experiments. Similar oxidation of methylene bridge in Cu(II)–benzimidazole complex was recently reported.[33]

All our attempts to avoid oxidation by working under argon atmosphere failed, since even the very small amount of residual oxygen was sufficient to initiate the deleterious oxidative processes.

The UV spectral changes observed upon mixing of equimolar amounts of **1a** and $[Cu(MeCN)_4]PF_6$ ($c=1\times10^{-4}$ mol dm^{-3}) in acetonitrile at 25 °C can be grouped into two types.

As can be seen in Figure 8, the addition of Cu^{+} to **1a** solution caused a rather significant hyperchromic effect on the ligand UV spectrum, accompanied by the occurrence of a shoulder at ≈300 nm. According to ES-MS results (Fig. 7) and the previously reported spectrophotometric



Scheme 2.

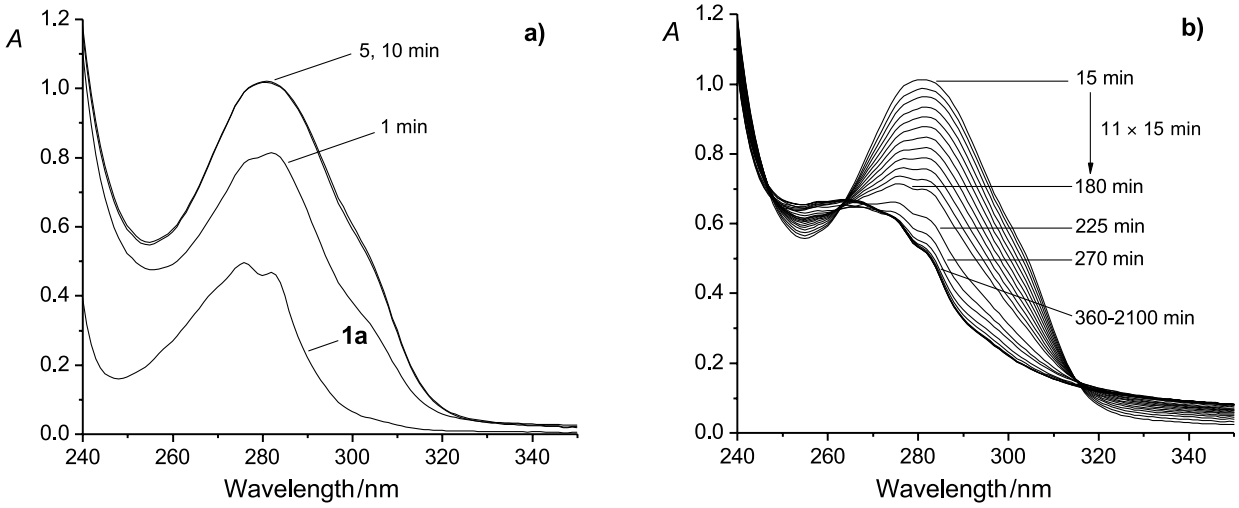


Figure 8. Time dependence of the UV spectra of acetonitrile solution containing **1a** ($c=1\times10^{-4}$ mol dm^{-3}) and $[Cu(MeCN)_4]PF_6$ ($c=1\times10^{-4}$ mol dm^{-3}). Spectra are labelled with the approximate times after mixing of **1a** and Cu^+. $l=1$ cm, $t=(25.0\pm0.1)$ °C. (a) Spectrum of the free ligand solution and its changes during the first 10 min after the addition of Cu^+. (b) Spectra corresponding to the 'second process', recorded in the period of several hours.

titrations of **2a** and **2b** with Cu^+,[30] these spectral changes can be attributed to the formation of $[Cu(\mathbf{1a})]^+$ and $[Cu(\mathbf{1a})_2]^+$ complexes. The initial increase in the spectrum intensity (up to approx. 5 min from mixing) was followed by a drop in absorbance at spectral maximum (at about 280 nm) of several hours, by a hypsochromic shift of the spectrum and its broadening, and by disappearance of a shoulder at ≈300 nm (Fig. 8).

This indicated that another process took place in the solution. We believe that it was the Cu^{2+} mediated oxidation of the methylene bridge in the $[Cu(\mathbf{1a})]^+$ and $[Cu(\mathbf{1a})_2]^+$ complexes, which is in accordance with the EPR results and the observed time-dependent changes of the corresponding ES-MS spectra. The $Cu^+ + \mathbf{1b}$ system showed a similar behaviour. The UV spectra recorded for this system can be found in the Supplementary Material (Fig. 4). As already mentioned, upon mixing of **1a** and $[Cu(MeCN)_4]PF_6$ at higher concentrations, the resulting acetonitrile solution appeared pronouncedly violet-blue. The colour changed with time to yellow-green, and finally became dark brown. The starting blue colour was assumed to be due to the presence of Cu^{2+} in the solution. For this reason, an experiment was performed in which a solution containing 5.5×10^{-3} mol dm^{-3} of both Cu^+ and **1a** was prepared, and its spectrum dependence on time was followed simultaneously in the UV and visible regions. Since the absorption coefficients in the UV region were about 100 times higher than in the visible one, the measuring cells of 0.01 and 1 cm path lengths were used, respectively. The spectra collected during three hours are displayed in Figure 9. The changes of the UV spectrum were faster, but basically similar to those described above for the case of the lower reactant concentrations. The visible absorption band recorded ≈1 min after mixing was centred at app. 620 nm. The spectrum then started to broaden, the

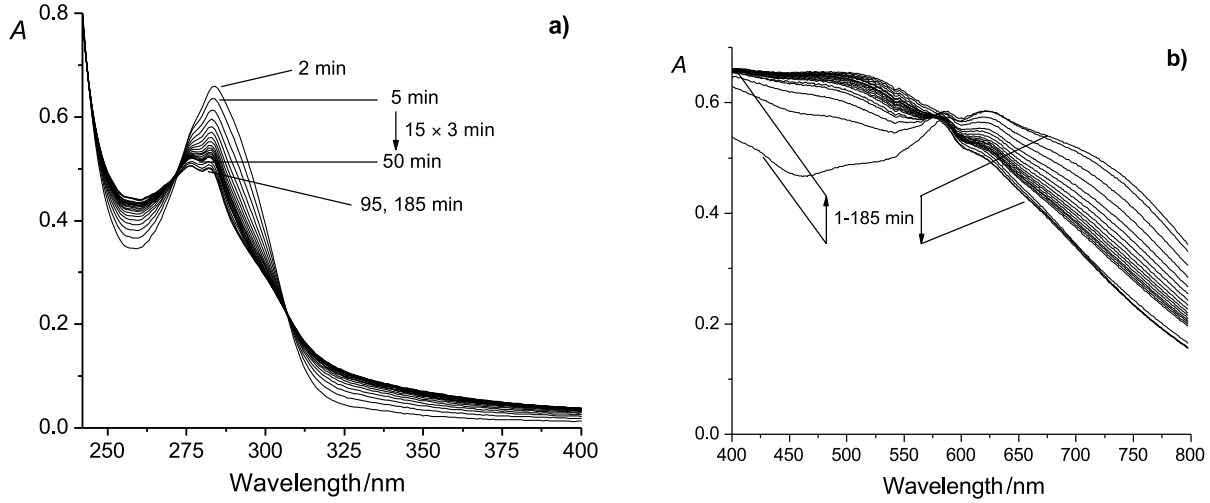


Figure 9. Time dependence of the absorption spectra of an equimolar acetonitrile solution of 1a and $[Cu(MeCN)_4]PF_6$ ($c=5.5\times10^{-3}$ mol dm^{-3}). Spectra are labelled with the approximate times after mixing of **1a** and Cu^+. $t=(25.0\pm0.1)$ °C. (a) Spectra recorded in the UV region; $l=0.01$ cm. (b) Spectra recorded in the visible region; $l=0.01$ cm.

absorbances at higher wavelengths decreased, whereas at lower wavelengths the spectrum intensity increased for a quite long period of time (Fig. 9). According to the NMR, EPR and ES-MS findings, these observations can be tentatively explained by the initial oxidation of coordinated Cu^{+} to Cu^{2+}, followed by the reversible reaction, i.e. reduction of copper and the oxidation of the ligand bridge from the methylene to the carbonyl one. Obviously, oxygen plays an important role in these reactions. The main final reaction products are Cu^{+} complexes with oxidized **1a** (stoichiometries 1:1 and 1:2), in agreement with the species observed by ES-MS (Fig. 7).

2.2. Catalytic cyclopropanation

The results of cyclopropanation of styrene with diazoacetate catalyzed by Cu(I) complexes of the ligands **1a–h** and **2a–e** are collected in Table 2. The results show that the catalytic complexes with the methylene bridged ligands **1** give somewhat better chemical yields of cyclopropanes than those with the dialkylmethylene bridged ligands **2**, while the *cis*/*trans* ratios are similar or slightly lower. However, ees achieved with ligands **2** are in all cases superior to those obtained with methylene bridged ligands **1**. The comparison of the ees of the *cis*- and *trans*-cyclopropanes by using *O*-benzyl substituted (**1a**, **1b**) and unsubstituted (**1f**, **1g**) ligand complexes revealed the significant increase of ee (18% for *cis*- and 10% for *trans*-products) for **1b** compared to **1g**. For the **1a/1f** pair of catalytic complexes lower ee increase for **1a** compared to **1f** was observed (15% for *cis*- and 4% for *trans*-products). The analysis of enantioselectivities obtained by ligands **2a–e** revealed that the ligands with *O*-benzyl substituents gave lower ees than the unsubstituted ligands (compare **2a/2b** and **2c/2d**). Taken together, the results of cyclopropanation studies reveal only a small influence of elongated substituents on stereogenic centres on the stereochemical outcome of the reaction. The most important result, arising from Table 2, are superior ees achieved by substituted ligands **2** in comparison to methylene-unsubstituted ligands **1**. This is in agreement with clearly evidenced mixtures of Cu complexes formed with methylene bridged ligands in solution, while the dialkylmethylene bridged ligands under the same conditions produce better defined Cu(I) catalytic complexes.

3. Conclusion

Combined spectroscopic studies of silver(I) and copper(I) complexes of 1,5-dinitrogen ligands with C_2-symmetric **1a** and **1b** have shown that they form stable 1:2 metal/ligand complexes with a pseudotetrahedral arrangement of coordinating N atoms around the central metal ion, which transform on ulterior addition of metal ions to 1:1 complexes. The stability constants (Table 1) were determined for $[Ag–\mathbf{1a}]^{+}$ and $[Ag–\mathbf{1b}]^{+}$ complexes of 1:2 and 1:1 stoichiometries. All spectroscopic investigations of copper complexes of **1a** and **1b** revealed the oxidative transformation of methylene bridge concomitant with oxidation of Cu(I) to Cu(II). C_2-Symmetric bis(oxazolines) with methylene bridge (**1**) and dialkylmethylene bridge (**2**) in the form of Cu(I) catalytic complexes were tested in enantioselective cyclopropanations of styrene with ethyl diazoacetate. Most of the ligands exhibited modest

Table 2. Enantioselectivity in cyclopropanation of styrene catalyzed by Cu(I) complexes of **1a–h** and **2a–2e**

Ligand	Molar ratio[a]	Yield (%)	*cis*/*trans*	*cis* (ee%)[b]	*trans* (ee%)[b]
1a	1.2	75	38/62	$45.7_{(1S,2R)}$	$45.6_{(1S,2S)}$
1a	2.0	81	36/64	$43.2_{(1S,2R)}$	$45.1_{(1S,2S)}$
1b	1.2	57	40/60	$53.2_{(1R,2S)}$	$55.8_{(1R,2R)}$
1b	2.0	67	42/58	$52.7_{(1R,2S)}$	$53.4_{(1R,2R)}$
1c	1.2	87	36/64	$45.3_{(1R,2S)}$	$43.7_{(1R,2R)}$
1c	2.0	81	35/65	$46.3_{(1R,2S)}$	$50.3_{(1R,2R)}$
1d	1.2	58	40/60	$47.6_{(1R,2S)}$	$47.4_{(1R,2R)}$
1d	2.0	62	39/61	$46.1_{(1R,2S)}$	$47.7_{(1R,2R)}$
1e	1.2	72	35/65	$30.6_{(1S,2R)}$	$37.8_{(1S,2S)}$
1e	2.0	69	36/64	$34.2_{(1S,2R)}$	$40.2_{(1S,2S)}$
1f	1.2	78	36/64	$30.3_{(1R,2S)}$	$41.9_{(1R,2R)}$
1f	2.0	73	39/61	$38.7_{(1R,2S)}$	$47.1_{(1R,2R)}$
1f[5]	2.0	81	30/70	$52.0_{(1R,2S)}$	$60.0_{(1R,2R)}$
1g	1.2	71	39/61	$35.3_{(1R,2S)}$	$46.1_{(1R,2R)}$
1g	2.0	67	38/62	$31.3_{(1R,2S)}$	$49.4_{(1R,2R)}$
1g[5]	2.0	76	29/71	$15.0_{(1R,2S)}$	$36.0_{(1R,2R)}$
1h	1.2	85	37/63	$53.2_{(1R,2S)}$	$67.1_{(1R,2R)}$
1h	2.0	78	32/68	$65.9_{(1R,2S)}$	$78.5_{(1R,2R)}$
1h[5]	2.0	80	25/75	$77.0_{(1R,2S)}$	$90.0_{(1R,2R)}$
2a	1.2	62	37/63	$54.6_{(1S,2R)}$	$59.7_{(1S,2S)}$
2a	2.0	72	34/66	$54.8_{(1S,2R)}$	$59.7_{(1S,2S)}$
2b	1.2	59	40/60	$60.4_{(1R,2S)}$	$54.5_{(1R,2R)}$
2b	2.0	53	40/60	$62.0_{(1R,2S)}$	$55.8_{(1R,2R)}$
2c	1.2	77	30/70	$54.0_{(1S,2R)}$	$64.8_{(1S,2S)}$
2c	2.0	79	31/69	$54.2_{(1S,2R)}$	$65.3_{(1S,2S)}$
2d	1.2	76	33/67	$67.3_{(1S,2R)}$	$70.8_{(1S,2S)}$
2d	2.0	73	35/65	$67.8_{(1S,2R)}$	$71.3_{(1S,2S)}$
2e	1.2	75	28/72	$95.0_{(1R,2S)}$	$95.7_{(1R,2R)}$
2e	2.0	80	29/71	$94.9_{(1R,2S)}$	$96.2_{(1R,2R)}$
2e[6]	2.0	77	27/73	$97.0_{(1R,2S)}$	$99.0_{(1R,2R)}$

[a] $r = c(\text{ligand})/c(Cu^{+})$.
[b] Enantiomeric excesses were determined by gas chromatography using GLC chiral CP-Chirasil-Dex CB capillary column.

enantioselectivity with the highest enantioselectivity of 62% ee for *cis*- and 56% ee for *trans*-isomer obtained by the Cu(I) complex of **2b** (Table 2). The observed oxidative transformation of the Cu(I) complexes of methylene bridged ligands may account for the lower enantioselectivities obtained in the cyclopropanations with this type of catalytic complexes.

4. Experimental

Preparation of compounds **1a–e** and **2a**,**b** was reported previously,[29] and compounds **1f–h** and **2c–e** were obtained from Aldrich. Reagents were purchased from Aldrich and Fluka and were used without further purification. All solvents were purified and dried according to standard procedures. IR spectra were taken in KBr pellets on a Perkin Elmer 297 spectrometer. NMR spectra were recorded on the Bruker spectrometer, at 300 or 600 MHz. Mass spectra were recorded by means of Finnigan LCQ Deca instrument. EPR spectra were recorded at Varian E-9 spectrometer.

4.1. Spectrometry

The UV/Vis absorption spectra were recorded at (25.0±0.1) by means of a Varian Cary 5 spectrophotometer equipped with a thermostating device. Quartz cells of 0.01 and 1 cm path lengths were used. Absorbances were sampled at 1 nm intervals.

^{1}H NMR titrations of **1a**, **1b** and **2a** were carried out at ambient temperature in CD_3CN (data taken in $\Delta\delta$/ppm according to the signal of solvent used as internal standard) with Bruker 300 and 600 MHz. c(**1a**,**1b**,**2a**)$=2\times10^{-3}$ mol dm^{-3}), $V_0=0.5$ mL, $c(AgBF_4)=0$–4×10^{-2} mol dm^{-3}, $c[Cu(MeCN)_4]PF_6=0$–2×10^{-2} mol dm^{-3}. Aliquots of the metal ion solution were added into the solution of the ligand in a NMR probe with Hamilton syringe. The obtained spectrometric data were processed using the SPECFIT program.[34]

4.2. Catalytic cyclopropanation

To an excess of styrene (0.52 g, 0.57 ml, 5.0 mmol) the precatalytic Cu(I) trifluoromethanesulphonate benzene complex (15 μmol, available from Fluka) and the corresponding quantity of chiral oxazoline ligand were added. Then ethyl diazoacetate (1.0 mmol, 1.0 ml of 1 mol dm^{-3} solution in 1,2-dichlorethane) was added dropwise by a syringe pump over a period of 4.5 h. The reaction mixture was stirred under inert argon atmosphere overnight at room temperature. Diastereomeric mixture of *cis*/*trans* ethyl 2-phenylcyclopropan-1-carboxylates was isolated by chromatography on a silica gel column (1×15 cm) with ethylacetate–light petroleum (gradient 0–10%) as eluent. Diastereomeric composition and chemical yield were determined by gas chromatography on the HP-1 capillary column with biphenyl as an internal standard. Enantiomeric excesses were determined by gas chromatography using GLC chiral CP-Chirasil-Dex CB capillary column. Cyclopropanation products were characterized by independent synthesis as described.[6,35]

Acknowledgements

The financial support from the Croatian Ministry of Science and Technology (Programs 009807 and 0119620) is gratefully acknowledged. The authors thank Dr.sc. Vesna Nöthig-Laslo for EPR measurements, and Ms. Tamara Gopurenko for the help with mass spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.06.117

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Asymmetric synthesis of 3,4-dihydroxyglutamic acids via enantioselective reduction of cyclic *meso*-imide

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Received 14 April 2004; revised 17 June 2004; accepted 24 June 2004

Available online 21 July 2004

Abstract—Stereoselective synthesis of (3*S*,4*S*)- and (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids was investigated. The key reaction in this synthesis is asymmetric reduction of *meso*-imide derived from *meso*-tartaric acid. Lewis acid-promoted cyanation of the obtained optically active lactam via the acyliminium intermediate followed by standard deprotection procedure afforded the desired 3,4-dihydroxyglutamic acids.

1. Introduction

Much attention is being paid to the synthesis of non-proteinogenic as well as unusual amino acids of natural occurrence. 3,4-Dihydroxyglutamic acid is a natural glutamic acid derivative, which was isolated from the seeds of *Lepidum sativum* and the leaves of *Rheum rhaponticum* about 50 years ago.[1] However, nothing is known concerning the stereochemistry of the three consecutive chiral centers. Recently, two groups reported the stereoselective synthesis of (2*S*,3*S*,4*S*)- and (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid,[2,3] and the former compound was found to be a selective agonist of mGluR1. However, the methods require multistep synthesis from the commercially available compound and lack applicability to other diastereomers. Therefore, a simple and general approach to all stereoisomers of 3,4-dihydroxyglutamic acid must be explored.

We have previously reported a concise stereoselective synthesis of (2*S*,3*S*,4*R*)-, (2*R*,3*S*,4*R*)-, (2*S*,3*R*,4*S*)-, and (2*R*,3*R*,4*S*)-3,4-dihydroxyglutamic acid starting from L- or D-tartaric acid.[4] In order to obtain the corresponding (3*S*,4*S*)- and (3*R*,4*R*)-isomers, there are at least two ways including enantioselective symmetry breaking of *meso*-tartaric acid or utilization of a chiral starting material. Taking advantage of our previous work in this area, we planned to investigate enantioselective reduction of *meso*-imide derived from *meso*-tartaric acid. Such synthetic operation on the *meso*-imide can establish the absolute stereochemistry at three contiguous centers in a single step.

There are some reports on the enantioselective reduction of cyclic *meso*-imide.[5–8] Among them, optically active oxaborolidines mainly derived from L-amino acid have been widely used as a catalyst for borane reduction.[5] On the other hand, chiral BINAL-H is also recognized as an effective reducing agent for enantioselective desymmetrization of *meso*-imide;[6] however, reduction of *meso*-imide derived from *meso*-tartaric acid by the BINAL-H complex is not reported. In this paper, we examined the asymmetric synthesis of 3,4-dihydroxyglutamic acids via enantioselective reduction of cyclic *meso*-imide prepared from *meso*-tartaric acid with BINAL-H because both (*S*)-(−)- and (*R*)-(+)-binaphthol are commercially available.

2. Results and discussion

Scheme 1 shows the synthetic course of (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids. First of all, the enantioselective reduction of cyclic *meso*-imide **1**, derived from *meso*-tartaric acid, was carried out with 3 equiv. of (*R*)-BINAL-H reagent prepared in situ by mixing lithium aluminum hydride with equimolar amounts of (*R*)-(+)-binaphthol and ethanol in tetrahydrofuran.[9] The enantiomeric excess was assessed by HPLC analysis to be 83% ee using a chiral stationary column after conversion of the initially formed hydroxylactam into triacetoxylactam **2**. Among the simple alcohols such as methanol, 2-propanol, 2-methyl-2-propanol, and butanol tested as the additive,

Keywords: Asymmetric synthesis; 3,4-Dihydroxyglutamic acid; *meso*-Imide; Desymmetrization.
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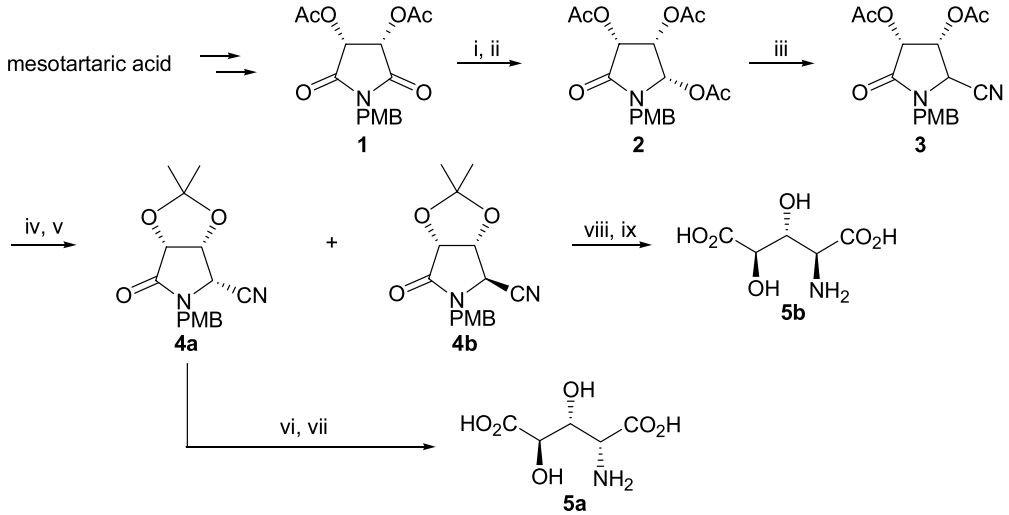
doi:10.1016/j.tet.2004.06.109

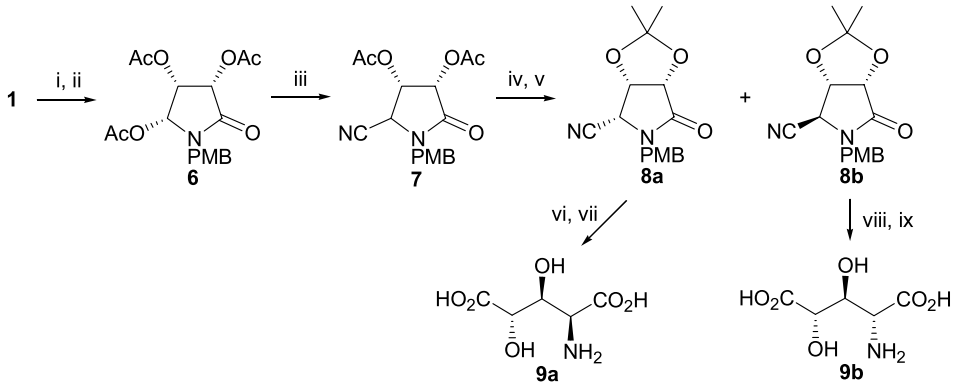


Scheme 1. (i) (*R*)-BINAL-H (EtOH), −78 °C; (ii) Ac_2O in pyridine, 61% (2 steps); (iii) BF_3–OEt_2, Me_3SiCN, toluene, 87%; (iv) AcCl, EtOH; (v) $Me_2C(OMe)_2$, *p*-toluenesulfonic acid, acetone, 36 and 60% yields for **4a** and **4b**, respectively (2 steps); (vi) $Ce(NH_4)_2(NO_3)_6$, acetonitrile–H_2O; (vii) 6 M HCl, reflux, 16 h, then Dowex 50W-X8, 75% (2 steps); (viii) as in vi; (ix) 1 M HCl, reflux, 3 h, then Dowex 50W-X8, 38% (2 steps).

ethanol afforded the best enantioselectivity. By comparing the sign of the specific rotation of the 3,4-dihydroxyglutamic acid **5a** formed from the triacetate **2** with that of known 3,4-dihydroxyglutamic acid, the (2*S*,3*S*,4*S*)-isomer,[2] the absolute configuration of the triacetate **2** was presumed as depicted in Scheme 1. The triacetate **2** was obtained as a single diastereomer and the stereochemical outcome suggests that the preferred trajectory of the (*R*)-BINAL-H reagent would be from the least hindered face of the carbonyl group attached to the *S* center of the cyclic *meso*-imide. Matsuki and co-workers reported that (*R*)-BINAL-H would attack the carbonyl carbon adjacent to the *R* center of the bicyclic *meso*-imide.[6] At the present stage, we cannot pinpoint the origin of enantioselective discrimination of the two enantiotopic imide carbonyl groups; however, the interaction of an acetoxy group with the (*R*)-BINAL-H reagent may be responsible for the observed reversal of the enantioselectivity.

The obtained triacetoxylactam **2** was then subjected to cyanation reaction. When a solution of triacetate **2** and trimethylsilyl cyanide (1.5 equiv.) in toluene was treated with boron trifluoride etherate (1.5 equiv.) at room temperature for 1 h, cyanolactam **3** was obtained in 87% yield as a 38:62 mixture of *syn* and *anti* adducts. The stereochemistry of the cyanolactam **3** was determined by comparison of the $J_{4,5}$ values, 5 and 1 Hz for the *syn* and *anti* adducts, respectively,[10] and was finally confirmed by transformation to 3,4-dihydroxyglutamic acid **5**. Several investigations were made on the diastereoselective cyanation; however, there was no improvement in diastereoselectivity.

Separation of the diastereomers was carried out after conversion of the diacetate **3** to the corresponding acetonide **4** because the diastereomeric mixture of **3** could not be separated by column chromatography. The cyanolactams **4a** and **4b** were isolated in 36 and 60% yields, respectively, and were independently treated with ammonium cerium (IV) nitrate followed by acidic hydrolysis to give novel (2*R*,3*R*,4*R*)- and (2*S*,3*R*,4*R*)-3,4-dihydroxyglutamic acid **5a** and **5b** in 75 and 38% yields, respectively. The transformation of the *anti* adduct **4b** to **5b** needed to be performed with care. The final acidic hydrolysis should be performed



Scheme 2. (i) (*S*)-BINAL-H (EtOH), −78 °C; (ii) Ac_2O in pyridine, 68% (2 steps); (iii) BF_3–OEt_2, Me_3SiCN, toluene, quant.; (iv) AcCl, EtOH; (v) $Me_2C(OMe)_2$, *p*-toluenesulfonic acid, acetone, 26 and 46% yields for **8a** and **8b**, respectively (2 steps); (vi) $Ce(NH_4)_2(NO_3)_6$, acetonitrile–H_2O; (vii) 6 M HCl, reflux, 16 h, then Dowex 50W-X8, 80% (2 steps); (viii) as in vi; (ix) 1 M HCl, reflux, 3 h, then Dowex 50W-X8, 63% (2 steps).

in refluxing 1 M HCl for 3 h. Refluxing in 6 M HCl overnight as in the synthesis of **5a** resulted in undesirable epimerization at the α-position.

3,4-Dihydroxyglutamic acids in another enantiomeric series, the (3*S*,4*S*)-isomers, were synthesized from a chiral triacetoxylactam **6** prepared by reduction of the *meso*-imide **1** with (*S*)-BINAL-H. The results are summarized in Scheme 2. Using the same procedure for the preparation of the corresponding (3*R*,4*R*)-isomers, the known (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid (**9a**)[2] and novel (2*R*,3*S*,4*S*)-isomer (**9b**) were obtained in good yields.

In conclusion, asymmetric synthesis of (3*S*,4*S*)- and (3*R*,4*R*)-series of 3,4-dihydroxyglutamic acids using enantioselective desymmetrization of *meso*-imide derived from *meso*-tartaric acid was achieved. Lewis acid-promoted cyanation of the obtained optically active lactam via the acyliminium intermediate followed by standard deprotection procedure afforded the 3,4-dihydroxyglutamic acids. Coupled with the results obtained in our previous work,[4] the present study provides a facile and versatile protocol for accessing all eight stereoisomers of 3,4-dihydroxyglutamic acids.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (δ_H 7.26), residual DMSO (δ_H 2.50), dioxane (δ_H 3.53 and δ_c 66.5), or the central peak of $CDCl_3$ (δ_c 77.0). High-resolution mass spectra (HRMS) were determined using perfluorokerosene as an internal standard. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. Enantiomeric excess was determined on an HPLC system (monitored at 254 nm) equipped with a chiral column (CHIRALPAK AS-H) using a mixture of hexane and ethanol (50:50) as an eluent.

3.1.1. (3*R,4*S**)-3,4-Diacetoxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione (1).** According to the procedure for the preparation of the corresponding *N*-benzyl derivative reported by Hiemstra and co-workers,[5] the title compound **1** was obtained as colorless needles (hexane–chloroform), mp 102–103 °C. ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6H), 3.77 (s, 3H), 4.66 (s, 2H), 5.53 (s, 2H), 6.83 (d, *J*=9 Hz, 2H), 7.31 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 19.95, 42.37, 55.23, 65.96, 114.08, 126.75, 130.49, 159.57, 168.99, 170.89. HRMS (EI, 70 eV) *m*/*z* 335.0970 (M^+, calcd for $C_{16}H_{17}NO_7$ 335.1005).

3.1.2. (3*R*,4*S*)-3,4,5-Triacetoxy-1-(4-methoxybenzyl)-2-pyrrolidinone (2). To a solution of (3*R**,4*S**)-3,4-diacetoxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione (**1**, 1.00 g, 3.00 mmol) in THF (90 mL) was added a solution of (*R*)-BINAL-H (EtOH) (9.00 mmol) in THF (25 mL) at −78 °C under an argon atmosphere. After it was stirred for 17 h, the reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to dryness to give a hydroxylactam. To a solution of the hydroxylactam in pyridine (60 mL) was added acetic anhydride (1.83 g, 18.0 mmol), and the reaction mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with 1 M HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel (hexane–ethyl acetate=50:50) to give the title compound **2** (690 mg, 61%) as an oil. ^{1}H NMR (DMSO-d_6) δ 1.91 (s, 3H), 1.97 (s, 3H), 2.07 (s, 3H), 3.70 (s, 3H), 4.20 (d, *J*=15 Hz, 1H), 4.49 (d, *J*=15 Hz, 1H), 5.45 (d, *J*=7 Hz, 1H), 5.50 (dd, *J*=7, 5 Hz, 1H), 6.11 (d, *J*=5 Hz, 1H), 6.87 (d, *J*=9 Hz, 2H), 7.15 (d, *J*=9 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 19.89, 20.08, 20.21, 43.03, 54.99, 64.78, 67.12, 79.49, 113.97, 126.97, 129.58, 159.21, 167.81, 168.87, 169.19, 169.52. HRMS (EI, 30 eV) *m*/*z* 379.1279 (M^+, calcd for $C_{18}H_{21}NO_8$ 379.1267).

3.1.3. (3*R*,4*R*)-3,4-Diacetoxy-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (3). To a solution of acetoxylactam **2** (3.03 g, 8.0 mmol) and trimethylsilyl cyanide (1.19 g, 12.0 mmol) in toluene (80 mL) was added a solution of boron trifluoride etherate (2.27 g, 12.0 mmol) in toluene (8 mL) at room temperature. After it was stirred for 1 h, the reaction mixture was quenched with saturated aqueous Na_2CO_3 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane–ethyl acetate=50:50) to give the title compound **3** (2.60 g, 87%) as a 62:38 mixture of diastereomers. HRMS (EI, 30 eV) *m*/*z* 346.1186 (M^+, calcd for $C_{17}H_{18}N_2O_6$ 346.1165). Major isomer: ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.17 (s, 3H), 3.80 (s, 3H), 3.98 (d, *J*=15 Hz, 1H), 4.07 (d, *J*=1 Hz, 1H), 5.12 (d, *J*=15 Hz, 1H), 5.61 (dd, *J*=6, 1 Hz, 1H), 5.63 (d, *J*=6 Hz, 1H), 6.98 (d, *J*=9 Hz, 2H), 7.19 (d, *J*=9 Hz, 2H). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.34 (s, 3H), 3.80 (s, 3H), 4.43 (d, *J*=15 Hz, 1H), 4.30 (d, *J*=5 Hz, 1H), 5.19 (d, *J*=15 Hz, 1H), 5.42 (d, *J*=5 Hz, 1H), 5.53 (dd, *J*=5, 5 Hz, 1H), 6.98 (d, *J*=9 Hz, 2H), 7.19 (d, *J*=9 Hz, 2H).

3.1.4. (3*R*,4*R*,5*S*)-3,4-*O*-Isopropylidene-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (4a) and (3*R*,4*R*,5*R*)-3,4-*O*-isopropylidene-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (4b). To a solution of cyanolactam **3** (3.42 g, 9.87 mmol) in ethanol (86 mL) was added acetyl chloride (2.02 g, 25.8 mmol), and the solution was stirred at 50 °C for 2.5 h. After evaporation of the solvent, the residue was dissolved in acetone (86 mL). To the solution was added 2,2-dimethoxypropane (4.47 g, 43.0 mmol) and *p*-toluenesulfonic acid (440 mg, 2.55 mmol), and the solution was stirred at 30 °C for 2 h. After removal of the solvent, the crude product was purified by column chromatography on silica gel (hexane–ethyl acetate=50:50) to give the title compound **4b** (1.80 g, 60%) as an oil, which solidified upon standing. Colorless powder (hexane–chloroform), mp 94–95 °C. ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.35 (s, 3H), 3.78 (s, 3H), 3.91 (d, *J*=15 Hz, 1H), 4.12 (s, 1H), 4.85 (s, 2H), 5.10 (d, *J*=15 Hz, 1H), 6.87 (d, *J*=9 Hz, 2H), 7.17 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 25.75, 26.84, 44.79, 51.24, 55.18, 74.81, 76.76, 113.92, 114.42, 114.93, 125.01, 139.88,

159.73, 169.69. HRMS (EI, 70 eV) *m/z* 302.1224 (M^+, calcd for $C_{16}H_{18}N_2O_4$ 302.1266).

Further elution with a mixture of hexane and ethyl acetate (50:50) gave the corresponding (3*R*,4*R*,5*S*)-isomer **4a** (1.09 g, 36%) as a pale yellow oil, which solidified upon standing. Colorless needles (hexane–chloroform), mp 174–175 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.52 (s, 3H), 3.78 (s, 3H), 3.95 (d, J=14 Hz, 1H), 4.30 (d, J=4 Hz, 1H), 4.70 (d, J=5 Hz, 1H), 4.77 (dd, J=5, 4 Hz, 1H), 5.18 (d, J=14 Hz, 1H), 6.86 (d, J=8 Hz, 2H), 7.22 (d, J=8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 25.79, 26.72, 44.89, 51.38, 55.19, 71.15, 76.90, 112.95, 114.06, 114.46, 125.63, 130.22, 159.76, 169.08. HRMS (EI, 70 eV) *m/z* 302.1273 (M^+, calcd for $C_{16}H_{18}N_2O_4$ 302.1266).

3.1.5. (2*R*,3*R*,4*R*)-3,4-Dihydroxyglutamic acid (5a). To a suspension of cyanolactam **4a** (302 mg, 1.00 mmol) and diammonium cerium (IV) nitrate (1.09 g, 2.00 mmol) in acetonitrile (15 mL) was added water (3 mL) at room temperature, and the resulting mixture was stirred for 4 h. The reaction mixture was then diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was hydrolyzed in refluxing 6 M HCl (20 mL) for 16 h. The cooled aqueous solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion exchange column chromatography on Dowex 50W-X8 to furnish the title compound **5a** (128 mg, 75%) as a colorless powder (EtOH–H_2O), mp 155–160 °C (dec). $[\alpha]_D^{25}=+0.7$ (c 1.0, H_2O). ^{1}H NMR (D_2O) δ 3.63 (d, J=0.4 Hz, 1H), 4.09 (d, J=3.5 Hz, 1H), 4.49 (dd, J=3.5, 0.4 Hz, 1H). ^{13}C NMR (D_2O) δ 56.96, 71.20, 76.21, 173.91, 178.33. HRMS (EI, 70 eV) *m/z* 135.0559 [$(M-CO_2)^+$, calcd for $C_4H_9NO_4$ 135.0532). MS (FAB) *m/z* 180 (MH^+).

3.1.6. (2*S*,3*R*,4*R*)-3,4-Dihydroxyglutamic acid (5b). To a suspension of cyanolactam **4b** (1.69 g, 5.60 mmol) and diammonium cerium (IV) nitrate (9.21 g, 16.8 mmol) in acetonitrile (56 mL) was added water (11 mL) at room temperature, and the resulting mixture was stirred for 4 h. The reaction mixture was then diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave deprotected cyanolactam (418 mg, 41%). The obtained crude cyanolactam (93.2 mg, 0.511 mmol) was hydrolyzed in refluxing 1 M HCl (30 mL) for 3 h. The cooled aqueous solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion exchange column chromatography on Dowex 50W-X8 to furnish the title compound **5b** (82.6 mg, 92%) as a colorless powder (EtOH–H_2O), mp 170–180 °C (dec). $[\alpha]_D^{25}=-1.6$ (c 1.0, H_2O). ^{1}H NMR (D_2O) δ 3.77 (d, J=4.4 Hz, 1H), 3.87 (d, J=3.7 Hz, 1H), 4.13 (dd, J=4.4, 3.7 Hz, 1H). ^{13}C NMR (D_2O) δ 56.96, 71.20, 72.82, 171.58, 177.46. HRMS (EI, 70 eV) *m/z* 135.0519 [$(M-CO_2)^+$, calcd for $C_4H_9NO_4$ 135.0532). MS (FAB) *m/z* 180 (MH^+).

3.1.7. (2*S*,3*S*,4*S*)-3,4-Dihydroxyglutamic acid (9a). According to the procedure for the preparation of compound **5a**, deprotection and hydrolysis of cyanolactam **8a** (532 mg, 1.76 mmol) gave the title compound **9a** (195 mg, 63%) as a white powder, $[\alpha]_D^{25}=-0.5$ (c 1.0, H_2O) (lit.[2] $[\alpha]_D^{28}=-0.8$ (c 1.0, H_2O)). The physical and spectral data of compound **9a** are identical with those of the compound **5a**.

3.1.8. (2*R*,3*S*,4*S*)-3,4-Dihydroxyglutamic acid (9b). According to the procedure for the preparation of compound **5b**, deprotection and hydrolysis of cyanolactam **8b** (958 mg, 3.17 mmol) gave the title compound **9b** (454 mg, 80%) as a white powder, $[\alpha]_D^{25}=+2.0$ (c 1.0, H_2O). The physical and spectral data of compound **9b** are identical with those of compound **5b**.

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10. In a similar system, the value of $J_{4,5}$ of the *syn* adduct is larger than that of the *anti* isomer. See Ref. 7.

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12-Substituted-13,14-dihydroretinols designed for affinity labeling of retinol binding- and processing proteins

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Received 22 March 2004; revised 7 June 2004; accepted 24 June 2004
Available online 29 July 2004

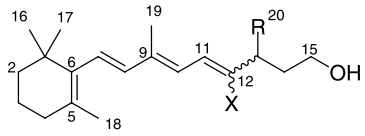
Abstract—All-*trans*- and 11-*cis*-retinol derivatives substituted with various electron-withdrawing groups at C_{12} were designed to be affinity labels for retinol binding and processing proteins. Unlike other non-selective highly reactive affinity labels, these compounds carry a Michael acceptor type substitution at C_{12} of the polyene chain. Therefore, they are expected to be highly selective towards such proteins that have a nucleophilic residue near the C_{11} position of their retinol ligand. The synthetic route for these compounds is based on the Emmons–Horner reaction of a C15 aldehyde with an appropriate phosphonate bearing the desired electron-withdrawing group to be incorporated at the C_{12} position of the retinol skeleton.

1. Introduction

Retinoids and their metabolites are essential for many physiological processes such as vision, gene transcription, cell proliferation and differentiation, hormone level regulation, immune function and morphogenesis.[1] The regulation of these processes is mediated via retinoid-binding proteins (RBP). RBP range from a variety of retinoid-processing and metabolizing enzymes via retinoid receptors, to different transport proteins designed to protect and transfer these sensitive and lipophilic compounds to their cell target, as well as mediators of retinoid action.[2] RBP can be found as soluble proteins both intra- and extracellularly, while others are present as integral membrane-bound minor constituents. The multiplicity of retinoid isomers and chemical forms (alcohols, aldehydes, acids and esters) requires different protein structures and binding sites, in order to bind the appropriate ligand with high selectivity and affinity.

Affinity labeling has been used as a tool in the study of these proteins' structure and function and for their isolation and purification. Most of the affinity labels of various RBPs were synthetic retinoids bearing highly reactive functional groups such as azide,[3] diazirene,[3a,4] allyl bromide,[5] haloketone and ester[6] or diazoketone and ester.[3a,4a,b,7] As such, they lack the specificity within the large family of RBPs, a major disadvantage when attempting to tag a specific minor constituent protein.[6a]

In a previous study, we synthesized a set of 13-substituted-13,14-dihydroretinols as potential affinity labels of retinol-binding proteins.[8] Most of these compounds were found to be not stable enough for biological studies. Thus, the present paper describes the design and synthesis of a family of stable 12-substituted all-*trans*- and 11-*cis*-retinol derivatives (Fig. 1) that would act as mild, highly specific affinity labels for retinol-binding proteins containing a nucleophilic residue in the binding pocket of the protein. One specific target in mind was the enzyme *trans* retinyl ester isomerohydrolase, which has been postulated to carry out its catalytic activity via a nucleophilic attack at the substrate C_{11} position.[1a,9]



	X	R
1	CN	H
2	CN	CH_3
3	CHO	H
4	CHO	CH_3
5	CO_2Et	H
6	CO_2Et	CH_3

Figure 1.

Keywords: Retinol analogs; Retinol binding proteins; *trans* Retinyl ester isomerohydrolase; Affinity labeling; Michael acceptors.
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doi:10.1016/j.tet.2004.06.116

2. Results and discussion

2.1. Design of the C_{12}-substituted retinol analogs

Substitution of an electron-withdrawing group at C_{12} of the retinol polyene skeleton can efficiently render the C_{11} position an electrophilic core of the molecule, yielding an electrophilic retinoid of a Michael acceptor type (Fig. 2).

The C_{13}–C_{14} bond in the synthetic retinol analogs is saturated, in contrast to the native ligand. This prevents cross-conjugation to the 12-substituted electron-withdrawing group, thus, increasing its electrophilicity. In addition, in the context of the *trans* retinyl ester isomerohydrolase, the saturated C_{13}–C_{14} bond prevents the natural isomerization from taking place, ensuring that the C_{12}-substituted compounds are not substrates for the enzyme.

Both 13-de-methyl and 13-methyl analogs were prepared, since this substitution may affect the isomeric distribution of the new synthetic 12-substituted retinol analogs. The 13-de-methyl analogs are expected to exhibit higher stability of their 11-*cis* isomer, relative to the corresponding 13-methyl counterparts (see below). This is especially relevant taking into account the fact that the 11-*cis* isomer of retinoids is of high biological importance. Thus, both the all-*trans* and the 11-*cis* isomers of the various new compounds were synthesized.

Since many 13-demethyl retinoids are biologically active[10] or bind their biological target,[11] the omission of this methyl in some of the new affinity label compounds should not prohibit their activity.

2.2. Synthesis

A convergent strategy for the synthesis of the 12-substituted retinol analogs **1**–**6** was employed, based on the assembly of two fragments, the all-*trans* isomer of the C15 aldehyde **15** and an appropriate four-carbon chain phosphonate, via the Emmons–Horner condensation (Fig. 3). The phosphonates contain the precursors of the electron-withdrawing group functionalities.

2.2.1. Preparation of the phosphonate units. Four different phosphonates were prepared for the synthesis of the six 12-substituted retinol analogs by a common synthetic strategy, i.e. condensation of an *O*-protected halo alcohol with an appropriate phosphonate bearing the desired substituent (Scheme 1).

Thus, 3-bromopropanol protected either with *tert*-butyldimethylsilyl or with tetrahydropyran was condensed with the sodium salt of diethyl cyanomethylphosphonate (producing

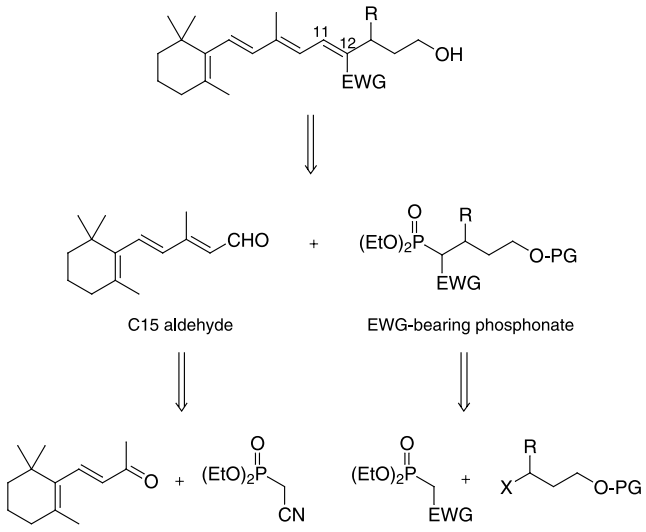


Figure 3.

cyano phosphonate **7**) or triethyl phosphonoacetate (yielding ester phosphonate **11**), respectively.

The corresponding methylated analogs **10** and **14** were prepared from 1,3-butanediol by protection of the primary alcohol (yielding also some secondary alcohol protection), substitution of the free secondary hydroxyl with iodide (**9** and **13**)[12] and condensation with the appropriate phosphonates. The condensation on the secondary alkyl iodides was more difficult and required drastic conditions: 55–60 °C for 5 days in the presence of HMPA in dry THF.

Phosphonates **10** and **14** have a few chiral centers, only one of which will remain in the corresponding final products. They were both synthesized as a mixture of diastereomers. These compounds are quite rigid, in respect to their C_3–C_4 bond. Their relative configurations and conformations were determined by the $^3J_{H,H}$ and $^3J_{P,C}$ coupling constants in the ^1H and ^{13}C NMR spectra. While the ester phosphonate **14** was present in solution as a mixture of both the *anti* and the *gauche* conformations (in both diastereomers), both diastereomers of the cyano phosphonate **10** were present mainly in the *gauche* conformation, without any significant contribution from the *anti* conformation (Fig. 4). This is probably due to the very small size of the cyano substituent.

2.2.2. Condensation. The synthesis of the 12-substituted retinol analogs from C15 aldehyde **15**[13] and the appropriate phosphonates is described in Scheme 2. All the condensation reactions between aldehyde **15** and the different phosphonates, as well as all subsequent reactions were carried out under dim red light, in order to avoid undesired isomerizations along the polyene skeleton.

The Emmons–Horner condensation between all-*trans*

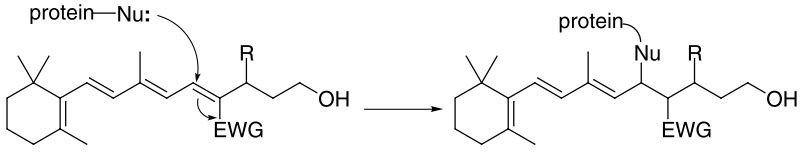
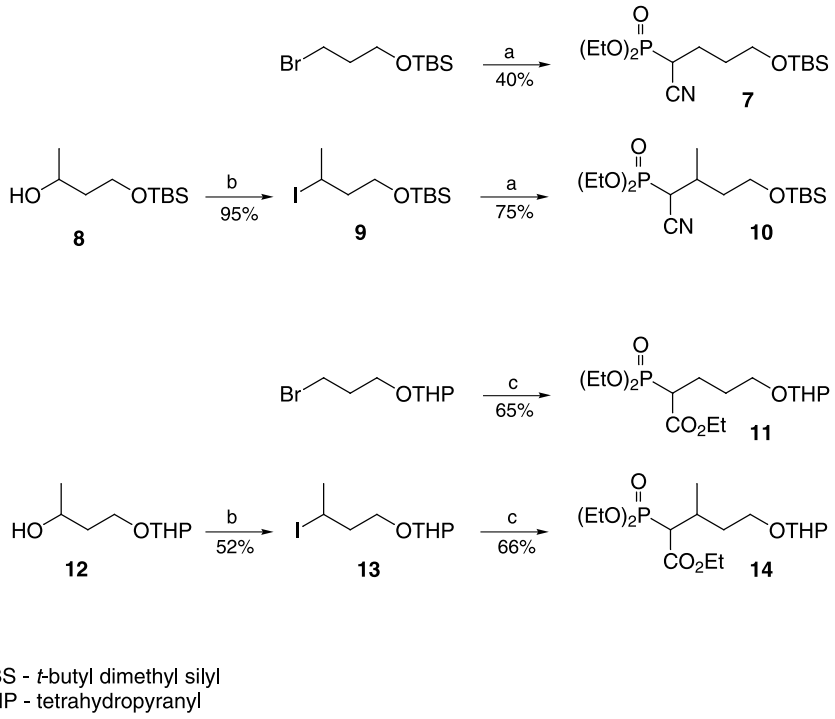


Figure 2.



Scheme 1. Reagents and conditions: (a) $(EtO)_2P(O)CH_2CN$, NaH, dry THF/HMPA. (b) I_2, PPh_3, imidazole, CH_2Cl_2. (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, dry THF/HMPA.

aldehyde **15** and either phosphonate **7** or **11** readily produced a mixture of two isomers about the newly formed C_{11}–C_{12} double bond of **16** and **20**: 11-*Z* (will be referred to as 'all-*trans*' in respect to the full length retinol skeleton) and 11-*E* (11-*cis* in the retinol terminology) (Scheme 2). Minor amounts of the 9-*cis* isomer of **20** were also isolated. Deprotection and separation of the isomers afforded the all-*trans* and the 11-*cis* isomers of retinol analogs **1** and **5**, respectively.

The isolation and purification of some of the all-*trans*-retinol analogs was problematic due to unconstrained isomerization about the C_{11}–C_{12} double bond. We therefore decided to re-introduce the Me-20 group to the retinol analogs. This should decrease the rate of isomerization, owing to steric hindrance between H-10 and the Me-20 group in the 11-*cis* isomer.[14] Furthermore, re-introduction of the methyl group to C_{13} makes these 12-substituted retinol analogs better mimics of the native substrate of the enzyme.

Thus, the 13-methyl substituted analogs were synthesized similarly, starting with phosphonates **10** and **14**, which carry both the nitrile and ester functionalities, respectively, and the future Me-20 groups. The condensation reaction of the

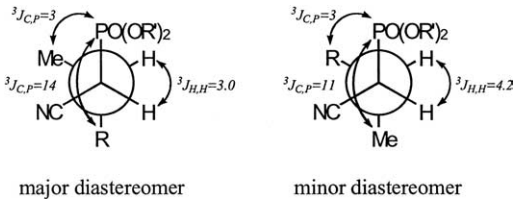
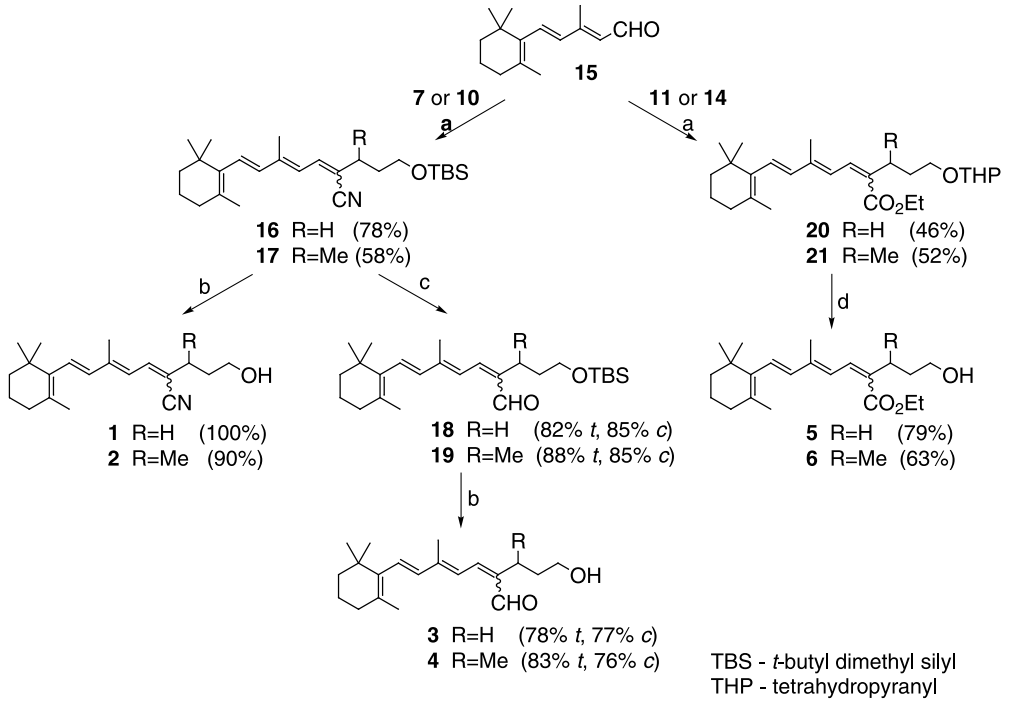


Figure 4.

phosphonates with aldehyde **15** produced mainly the all-*trans* isomer of **17** and **21**, with only minor amounts of the 11-*cis* isomer. Thus, the introduction of Me-20 indeed fulfilled the expectation of stabilizing the all-*trans* isomer due to increased steric repulsion in the 11-*cis* isomer. The all-*trans* and 11-*cis* isomers of the final products, 12-cyano-13,14-dihydroretinol **2** and 12-carbethoxy-13,14-dihydroretinol **6**, were readily obtained by mild deprotection of **17** and **21**, respectively.

During the synthesis of **21**, the basic conditions of the Emmons–Horner reaction promoted some dimerization of aldehyde **15** by the Robinson annulation reaction.[15]

Cyano intermediates **16** and **17** were also used for the synthesis of the 12-formyl retinol analogs **3** and **4**, respectively. In order to produce separately each isomer, the subsequent reduction of the nitrile group and deprotection were carried out separately for each isomer of **16** and **17**. DIBAL-H reduction followed by removal of the silyl protecting group successfully furnished the desired products 12-formyl-13-demethyl-13,14-dihydroretinol **3** and 12-formyl-13,14-dihydroretinol **4**. The above procedure preserved the isomeric integrity of the starting materials 11-*cis* **16**, 11-*cis* **17** and all-*trans* **17**. However, similar treatment of all-*trans* **16** yielded a mixture of all-*trans* and 11-*cis* *O*-protected-12-formyl retinol **18**, even when all reactions and workups were carried out in the dark at 4 °C. Deprotection of all-*trans* **18** again produced a mixture of all-*trans* and 11-*cis* **3**, along with some 9-*cis* product. The best results (a 1:1 mixture of all-*trans*: 11-*cis*) were obtained when the aldehyde reduction product was subjected to deprotection immediately, without any purification step. These results demonstrate once again the stabilizing effect



Scheme 2. Reagents and conditions: (a) NaH, dry THF. (b) $Bu_4N^+F^-$, dry THF. (c) (i) DIBAL-H, hexane, −78 °C. (ii) SiO_2/H_2O, ether. (d) PPTS, EtOH, 55 °C.

of the 13-methyl substitution on the all-*trans* isomer of the retinol analogs.

The chemical stability of aldehyde derivatives **3** and **4**, both in terms of isomerization and degradation, was poor. Only when kept dry at −20 °C, was the 11-*cis* isomer stable against isomerization for several months. The all-*trans*-isomer was much more labile. Nitriles **1** and **2** and esters **5** and **6** were quite stable under argon atmosphere at 20 °C.

3. Conclusions

In this paper we present the design and synthesis of a family of retinol analogs substituted at C_{12} with electron withdrawing groups as potential selective affinity labels for retinol binding- and processing proteins. Both 11-*cis* and all-*trans* isomers of aldehyde, cyano and ester substituted retinol analogs and 13-demethyl retinol analogs were prepared via an efficient convergent procedure, based on Emmons–Horner condensation reaction between C15 aldehyde and an appropriate phosphonate unit bearing the desired C_{12} functional group. These compounds are now being tested as inhibitors of the enzyme *trans* retinyl ester isomerohydrolase.

4. Experimental

4.1. General

All operations involving synthesis and manipulation of full-length retinoids were performed under dim red light. ^1H and ^{13}C NMR spectra were recorded at 300 or 600, and 75 or 150 MHz, respectively, in $CDCl_3$ (TMS as an internal standard), unless otherwise indicated. ^{31}P NMR spectra were recorded at 81 MHz in $CDCl_3$ (85% H_3PO_4 as an external reference). ^1H NMR assignments were supported by COSY and NOESY experiments, while ^{13}C NMR assignments were supported by distortionless enhancement by polarization transfer (DEPT), heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond connectivity (HMBC) experiments. *J* values are given in Hz. The NMR signals are assigned according to the atom numbering of the retinoid skeleton (Fig. 1). All-*trans*, 11-*cis* or 9-*cis* configurations refer to the configuration of the retinol skeleton. UV spectra were recorded on a diode array spectrophotometer in dichloromethane. Mass spectra were recorded in DCI mode with methane, unless otherwise stated. TLC was performed on E. Merck 0.2 mm precoated silica gel F-254 plates, and viewed by UV light and vanillin.[16] Chromatography refers to flash column chromatography,[17] carried out on silica gel 60 (230–400 mesh ASTM, E. Merck). Anhydrous solvents were dried and freshly distilled: THF and diethyl ether (referred to as ether) from sodium/benzophenone, CH_2Cl_2 from $CaCl_2$ and DMF from 4 Å molecular sieves.

4.2. Synthesis

1-*tert*-Butyldimethylsilanyloxy-3-butanol **8**[18] and C15 aldehyde **15**[13b] were prepared as previously described.

4.2.1. Diethyl 4-*tert*-butyldimethylsilanyloxy-1-cyanobutyl phosphonate (7). *General procedure A*. Diethyl cyanomethylphosphonate (7.7 g, 0.04 mol), was added dropwise to a suspension of NaH (80% in mineral oil, 1.42 g) and NaI (0.5 g) in dry THF (120 mL) and HMPA (20 mL) under Ar atmosphere. After full consumption of NaH, 1-(*tert*-butyldimethylsilanyloxy)-3-bromopropane

(5.0 g, 0.022 mol) was added and the reaction mixture was stirred at rt for 3 days. The solvent was evaporated and the residue was dissolved in ether and washed twice with water. The organic phase was dried ($MgSO_4$), filtered and evaporated. Chromatography ($CHCl_3$: ether, 1:3) afforded the product as colorless oil (40% yield). ^{1}H NMR δ 4.23 (m, J=7.2 Hz, 4H, CH_2OP), 3.70 (ddd, J=10.5, 5.5, 5.1 Hz, 1H, H-4), 3.64 (ddd, J=10.5, 6.5, 5.0 Hz, 1H, H-4), 3.04 (ddd, J=23.4, 10.5, 4.8 Hz, 1H, H-1), 2.12–1.79 and 1.73–1.64 (m, 4H, H-2, H-3), 1.38 (m, 6H, Me), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 116.2 (d, J=9.1 Hz, CN), 63.8 (d, J=7.0 Hz, COP), 63.5 (d, J=6.9 Hz, COP), 61.7 (C-4), 30.3 (d, J=11.9 Hz, C-3), 29.7 (d, J=143.8 Hz, C-1), 25.7 (*t*-Bu), 24.0 (d, J=4.2 Hz, C-2), 18.1 (C-*t*-Bu), 16.2 (d, J=5.6 Hz, 2×Me), −5.6 (C–Si). ^{31}P NMR δ 18.8. HRMS *m/z* calcd for $C_{16}H_{35}NO_4SiP$ (MH^+) 364.2073, found 364.2053.

4.2.2. *tert*-Butyl-3-iodobutoxy dimethylsilane (9). *General procedure B*. **8** (3.0 g, 0.015 mol) in dry CH_2Cl_2 (16 mL) was added to a solution of triphenylphosphine (5.9 g, 0.022 mol), imidazole (1.6 g, 0.023 mol) and iodine (5.7 g, 0.022 mol) in dry CH_2Cl_2 (60 mL). After 3 h at rt, the solvent was evaporated. The residue was triturated with *n*-hexane and the organic phase was washed with sat. $Na_2S_2O_3$, dried ($MgSO_4$), filtered and evaporated to give **9** as colorless oil (95% yield). ^{1}H NMR δ 4.35 (dqd, J=9.6, 6.9, 4.5 Hz, 1H, H-3), 3.76 (ddd, J=10.5, 5.7, 4.5 Hz, 1H, H-1), 3.65 (ddd, J=10.2, 8.1, 4.8 Hz, 1H, H-1), 1.99 (ddt, J=14.7, 9.6, 4.8 Hz, 1H, H-2), 1.97 (d, J=6.9 Hz, 3H, Me-4), 1.79 (dddd, J=18.6, 8.1, 5.4, 4.5 Hz, 1H, H-2), 0.91 (s, 9H, *t*-Bu), 0.08 and 0.07 (s, 3H, SiMe). ^{13}C NMR δ 68.2 (C-3), 62.7 (C-1), 39.9 (C-2), 25.8 (*t*-Bu), 23.3 (C-4), 18.1 (C-*t*-Bu), −5.6 (C–Si). MS (CI/ isobutane) *m/z* 315 (MH^+), 257 ($MH^+ - t$-Bu).

4.2.3. Diethyl 4-*tert*-Butyldimethylsilanyloxy-1-cyano-2-methylbutyl phosphonate (10). Compound **10** was prepared according to general procedure A with diethyl cyanomethylphosphonate (5.7 g, 0.032 mol), NaH (60% in mineral oil, 1.2 g) and **9** (5.4 g, 0.017 mol) in dry THF (160 mL) and HMPA (24 mL) at 55 °C for 5 days. Chromatography (hexane/ether 1:1) afforded the product as a 2:1 diastereomeric mixture of colorless oil (75% yield, 20% recovery of SM). ^{1}H NMR δ 4.23 (m, 4H, CH_2OP), 3.70 (m, 2H, CH_2-4), 3.39 (dd, J=25.2, 3.0 Hz, 1H, H-1), 2.98 (dd, J=24.6, 4.2 Hz, 1H, H-1), 2.39 and 2.10 (bm, 1H, H-2), 1.62 (m, 2H, CH_2-3), 1.38 (m, 6H, CH_3CH_2O), 1.22 (d, J=6.9 Hz, 3H, 2-Me), 1.18 (dd, J=6.9, 0.9 Hz, 3H, 2-Me), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 115.0 (d, J=9.0 Hz, CN), 63.8, 63.7, 63.42 and 63.37 (d, J=6.7 Hz, COP), 60.7 and 60.1 (C-4), 38.4 (d, J=13.5 Hz, C-3), 36.9 (d, J=143.2 Hz, C-1), 35.9 (d, J=3.3 Hz, C-3), 35.2 (d, J=143.2 Hz, C-1), 29.6 and 29.2 (d, J=3.3 Hz, C-2), 25.8 (*t*-Bu), 18.7 (d, J=11.2 Hz, 2-Me), 18.1 (C-*t*-Bu), 17.2 (2-Me), 16.3 (d, J=5.9 Hz, CH_3CH_2O), −5.4, −5.5, −5.6 (C–Si). ^{31}P NMR δ 18.8 and 18.2. HRMS *m/z* calcd for $C_{16}H_{35}NO_4PSi$ (MH^+) 364.2073, found 364.2053.

4.2.4. Ethyl 2-diethoxyphosphoryl-5-(tetrahydropyran-2-yloxy)-pentanoate (11). The product was obtained according to general procedure A with triethyl phosphonoacetate (1.0 g, 4.5 mmol), NaH (80% in mineral oil, 0.17 g) and 2-(3-bromopropoxy)-tetrahydropyran (0.5 g, 2.2 mmol) in dry THF (8 mL) at rt for 2 days. Chromatography (*n*-hexane/ether 1:1) afforded the product (a diastereomeric mixture) as colorless oil (65% yield). ^{1}H NMR δ 4.57 (t, J=3.3 Hz, 1H, H-2′), 4.18 (m, 6H, CH_2OCO and CH_2OP), 3.84 (ddd, J=11.4, 7.8, 3.6 Hz, 1H, H-6′), 3.74 (m, 1H, H-5), 3.48 (m, 1H, H-6′), 3.38 (m, 1H, H-5), 3.00 (ddd, J=22.5, 10.5, 4.5 Hz, 1H, H-2), 2.1–1.5 (m, 10H, H-3, H-4, H-3′, H-4′, H-5′), 1.34 and 1.33 (t, J=7.2 Hz, 3H, phosphonate-Me), 1.29 (t, J=7.2 Hz, 3H, ester-Me). ^{13}C NMR δ 169.0 (d, J=4.5 Hz, C-1), 98.6 and 98.5 (C-2′), 66.5 and 66.4 (C-6′), 62.5 (d, J=6.6 Hz, COP), 62.4 (d, J=6.8 Hz, COP), 62.0 (C-5), 61.2 (CH_2OCO), 45.33 and 45.30 (d, J=131.3 Hz, C-2), 30.5 (C-3′), 28.2 (d, J=14.5 Hz, C-4), 28.1 (d, J=14.8 Hz, C-4), 25.3 (C-5′), 23.89 and 23.86 (d, J=4.8 Hz, C-3), 19.3 (C-4′), 16.2 (d, J=5.4 Hz, phosphonate-Me), 14.0 (ester-Me). ^{31}P NMR δ 23.3. HRMS *m/z* calcd for $C_{11}H_{24}O_6P$ (MH^+-THP) 283.1311, found 283.1317, calcd for $C_{11}H_{22}O_5P$ (MH^+ − THP-H_2O) 265.1146, found 265.1148.

4.2.5. 1-(Tetrahydropyran-2-yloxy)-3-butanol (12).[19] 1,3-Dihydroxybutane (1.0 g, 11 mmol), 3,4-dihydro-2*H*-pyran (1.0 g, 12 mmol) and catalytic amount of PPTS (0.28 g, 1.1 mmol) were stirred in dry CH_2Cl_2 (25 mL) at rt for 4 h. Evaporation and chromatography (*n*-hexane/ether 1:1 and then 3:1) afforded the product **12** (about 1:1 diastereomeric mixture) as colorless oil (45% yield), along with some 3-protected (5%) byproduct. ^{1}H NMR δ 4.50 and 4.49 (t, J=4.5 Hz, 1H, H-2′), 3.87, 3.78 and 3.55–3.39 (m, 5H, H-1, H-3, H-6′), 3.16 (s, 1H, OH), 1.63 and 1.44 (m, 8H, H-2, H-3′, H-4′, H-5′), 1.11 (d, J=6.3 Hz, 3H, Me-4). ^{13}C NMR δ 98.8 and 98.6 (C-2′), 66.8 and 66.2 (C-3), 65.7 and 65.6 (C-1), 62.4 and 61.9 (C-6′), 38.1 and 38.0 (C-2), 30.5 and 30.3 (C-3′;), 25.1 (C-5′), 23.12 and 23.07 (C-4), 19.4 and 19.2 (C-4′). HRMS *m/z* calcd for $C_9H_{17}O_3$ ($(M-H)^+$) 173.1178, found 173.1183.

4.2.6. 2-(3-Iodobutoxy)-tetrahydropyran (13). Compound **13** was prepared according to general procedure B with triphenylphosphine (5.24 g, 0.02 mol), imidazole (1.36 g, 0.02 mol), iodine (5.1 g, 0.02 mol) in dry CH_2Cl_2 (27 mL) and **12** (2.9 g, 0.017 mol, contaminated with about 10% of the 3-protected isomer) in dry CH_2Cl_2 (13 mL). The product, a 1:1 diastereomeric mixture contaminated by 17% of a 1:1 diastereomeric mixture of *O*-THP-1-iodo-3-butanol, was obtained as colorless oil (52% overall yield). ^{1}H NMR δ 4.61 (t, J=3.0 Hz, 1H, H-2), 4.59 (dd, J=4.2, 2.7 Hz, 1H, H-2), 4.37 (dqd, J=9.3, 6.9, 4.5 Hz, 1H, H-3′), 4.35 (dqd, J=10.8, 6.9, 4.5 Hz, 1H, H-3′), 3.90 (m, 2H, H-6, H-1′), 3.85 (ddd, J=12, 7, 3 Hz, 1H, H-6), 3.81 (ddd, J=9.9, 7.8, 5.4 Hz, 1H, H-1′), 3.52 (m, 3H, 2×H-6, H-1′), 3.45 (ddd, J=9.9, 8.1, 4.8 Hz, 1H, H-1′), 2.08 (m, 1H, H-2′), 1.97 (d, J=6.9 Hz, 3H, Me-4′), 1.91 (m, 1H, H-2′), 1.81 (m, 1H, H-4), 1.71 (m, 1H, H-3), 1.60–1.50 (m, 4H, H-3, H-4, 2×H-5,). ^{13}C NMR δ 99.4 and 98.4 (C-2), 67.1 and 66.8 (C-1′), 62.5 and 62.0 (C-6), 42.6 (C-2′), 30.6 and 30.5 (C-3), 29.0 and 29.0 (C-4′), 26.6 and 26.2 (C-3′), 25.38 and 25.36 (C-5), 19.4 and 19.2 (C-4). MS (CI/NH_3) *m/z* 285 (MH^+), 155 (M − HI). HRMS *m/z* calcd for $C_9H_{16}O_2I$ (M − H) 283.0195, found 283.0196.

4.2.7. Ethyl 2-diethoxyphosphoryl-3-methyl-5-(tetrahydropyran-2-yloxy)-pentanoate (14). Compound **14**

was obtained according to general procedure A with triethyl phosphonoacetate (4.9 g, 0.022 mol), NaH (80% in mineral oil, 0.81 g) and **13** (2.5 g, 8.8 mmol, with 17% impurity of the 3-protected isomer) in dry THF (40 mL) and HMPA (10 mL) at 70 °C for 5 days. Chromatography (ether) afforded the product as a diastereomeric mixture (colorless oil, 66% yield). ^{1}H NMR δ 4.59 (dd, J=4.5, 2.7 Hz, 1H, H-2′), 4.57 (dd, J=4.1, 2.9 Hz, 1H, H-2′), 4.20 (q, J=7.1 Hz, 2H, CH_2OCO), 4.16 (m, 4H, CH_2OP), 3.88 (m, 1H, H-6′), 3.80 (m, 1H, H-5), 3.52 (m, 1H, H-6′), 3.42 (m, 1H, H-5), 2.98 (dd, J=21.3, 7.1 Hz, 1H, H-2), 2.96 (dd, J=21.2, 7.2 Hz, 1H, H-2), 2.85 (dd, J=28.2, 5.3 Hz, 1H, H-2), 2.50 and 2.42 (m, 1H, H-3), 2.01 (m, 2H, H-4), 1.83 (m, H-4′), 1.70 (m, H-3′), 1.6–1.5 (m, H-4, H-3′, H-4′, H-5′), 1.33 (m, 3H, phosphonate-Me), 1.30 (t, J=7.1 Hz, 3H, ester-Me), 1.20 and 1.10 (d, J=6.8 Hz, 3H, 3-Me). ^{13}C NMR δ 169.0, 168.8 and 166.7 (d, J=5.3 Hz, CO), 98.9, 98.8 and 98.6 (C-2′), 65.2 and 64.8 (C-5), 63.6 and 62.8 (d, J=7 Hz, COP), 62.4 and 62.1 (C-6′), 59.9 (CH_2OCO), 51.1 and 51.0 (d, J=134.5 Hz, C-2), 48.4 (d, J=128.0 Hz, C-2), 47.6 (d, J=131.6 Hz, C-2), 35.0 (d, J=11.6 Hz, C-4), 34.9 (d, J=11.3 Hz, C-4), 30.7 (C-3′), 28.7 (d, J=3.9 Hz, C-3), 25.5 (C-5′), 22.6 (d, J=6.6 Hz, 2-Me), 19.8 and 19.5 (C-4′), 16.4 (d, J=5.6 Hz, phosphonate-Me), 14.2 (ester-Me). ^{31}P NMR δ 23.3. HRMS *m/z* calcd for $C_{17}H_{34}O_7P$ (MH^+) 381.2042, found 381.1960.

4.2.8. *O*-TBS-12-cyano-13-demethyl-13,14-dihydroretinol (16). Compound **16** was prepared according to general procedure A with phosphonate **7** (0.42 g, 1.2 mmol), NaH (60% in mineral oil, 0.04 g) and aldehyde **15** (0.54 g, 2.5 mmol) in dry THF (35 mL) at rt for 18 h. Chromatography (*n*-hexane/ether 25:1) afforded the two separated clean isomers (all-*trans*: 11-*cis* 3:1) as yellow oils in 78% yield. All -*trans*. ^{1}H NMR δ 6.98 (d, J=12.0 Hz, 1H, H-11), 6.43 (d, J=12.0 Hz, 1H, H-10), 6.38 (d, J=16.2 Hz, 1H, H-7), 6.19 (d, J=16.2 Hz, 1H, H-8), 3.64 (t, J=6.0 Hz, 2H, CH_2-15), 2.39 (t, J=7.5 Hz, 2H, CH_2-13), 2.03 (t, J=6.0 Hz, 2H, CH_2-4), 1.97 (s, 3H, Me-19), 1.75 (m, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.46 (m, 2H, CH_2-2), 1.03 (s, 6H, Me-16, 17), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 142.5 (C-9), 140.4 (C-11), 137.3, (C-6), 136.6 (C-8), 130.9 (C-7 and C-5), 125.5 (C-10), 118.5 (CN), 111.1 (C-12), 61.3 (C-15), 39.6 (C-2), 34.2 (C-1), 33.1 (C-4), 31.2 (C-13), 30.9 (C-14), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.7 (C-18), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.9 (C-19), −5.4 (C–Si). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{26}H_{44}NOSi$ (MH^+) 414.3192, found 414.3202. 11-*cis*. ^{1}H NMR δ 7.13 (d, J=12.3 Hz, 1H, H-11), 6.41 (d, J=15.9 Hz, 1H, H-7), 6.26 (d, J=12.3 Hz, 1H, H-10), 6.14 (d, J=16.2 Hz, 1H, H-8), 3.63 (t, J=6.0 Hz, 2H, CH_2-15), 2.43 (t, J=7.5 Hz, 2H, CH_2-13), 2.03 (t, J=6.0 Hz, 2H, CH_2-4), 1.99 (d, J=0.9 Hz, 3H, Me-19), 1.77 (m, 2H, CH_2-14), 1.70 (d, J=0.9 Hz, 3H, Me-18), 1.60 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.02 (s, 6H, Me-16, 17), 0.89 (s, 9H, *t*-Bu), 0.04 (s, 6H, $SiMe_2$). ^{13}C NMR δ 143.6 (C-9), 139.6 (C-11), 137.4, (C-6), 136.6 (C-8), 131.4 (C-7), 130.9 (C-5), 122.9 (C-10), 121.5 (CN), 111.1 (C-12), 61.3 (C-15), 39.5 (C-2), 34.2 (C-1), 33.1 (C-4), 31.2 (C-14), 28.8 (C-16, C-17), 25.9 (*t*-Bu), 24.9 (C-13), 21.7 (C-18), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.8 (C-19), −5.4 (C–Si). HRMS *m/z* calcd for $C_{26}H_{44}NOSi$ (MH^+) 414.3192, found 414.3203.

4.2.9. *O*-TBS-12-cyano-13,14-dihydroretinol (17). Compound **17** was prepared according to general procedure A with phosphonate **10** (0.88 g, 2.4 mmol), NaH (60% in mineral oil, 0.09 g) and aldehyde **15** (1.05 g, 4.8 mmol) at rt for 3 days. The isomeric mixture (all-*trans* and 11-*cis* in a 9:1 ratio, and some 9-*cis* which was formed upon standing) was purified by chromatography (hexane/ether 25:1), yielding yellow oil in 58% yield. All-*trans*. ^{1}H NMR δ 6.99 (d, J=11.7 Hz, 1H, H-11), 6.45 (d, J=11.7 Hz, 1H, H-10), 6.39 (d, J=16.2 Hz, 1H, H-7), 6.21 (d, J=16.2 Hz, 1H, H-8), 3.65 (dt, J=10.2, 5.4 Hz, 1H, H-15), 3.55 (ddd, J=10.2, 7.8, 5.4 Hz, 1H, H-15), 2.67 (sextet, J=6.9 Hz, 1H, H-13), 2.04 (t, J=6.0 Hz, 2H, CH_2-4), 1.98 (s, 3H, Me-19), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.66 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.19 (d, J=6.9 Hz, Me-20), 1.04 (s, 6H, Me-16, 17), 0.90 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR δ 142.5 (C-9), 139.3 (C-11), 137.3 (C-6), 136.6 (C-8), 130.84 (C-5), 130.8 (C-7), 125.5 (C-10), 117.3 (CN), 116.9 (C-12), 60.2 (C-15), 39.6 (C-2), 38.2 (C-14), 35.6 (C-13), 34.2 (C-1), 33.1 (C-4), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.7 (C-18), 20.0 (C-20), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.9 (C-19), −5.4 (C–Si). UV λ_{max} 332 nm. HRMS *m/z* calcd for $C_{27}H_{46}NOSi$ (MH^+) 428.3349, found 428.3350. 11-*cis*. ^{1}H NMR δ 7.11 (d, J=12.0 Hz, 1H, H-11), 6.41 (d, J=15.6 Hz, 1H, H-7), 6.32 (d, J=12.3 Hz, 1H, H-10), 6.15 (d, J=15.9 Hz, 1H, H-8), 3.65 (dt, J=10.5, 5.4 Hz, 1H, H-15), 3.53 (m, 1H, H-15), 3.11 (dq, J=14.1, 6.9 Hz, 1H, H-13), 2.04 (t, J=6.0 Hz, 2H, CH_2-4), 1.99 (d, J=0.9 Hz, 3H, Me-19), 1.71 (s, 3H, Me-18), 1.68 (m, 2H, CH_2-14), 1.62 (m, 2H, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.16 (d, J=6.9 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.88 (s, 9H, *t*-Bu), 0.04 (s, 6H, $SiMe_2$). ^{13}C NMR δ 143.6 (C-9), 138.9 (C-11), 137.4 (C-6), 138.7 (C-8), 131.2 (C-7), 129.1 (C-5), 122.9 (C-10), 120.1 (CN), 117.1 (C-12), 61.1 (C-15), 39.5 (C-2), 38.3 (C-14), 34.2 (C-1), 33.1 (C-4), 28.9 (C-16, C-17), 28.5 (C-13), 25.9 (*t*-Bu), 21.7 (C-18), 19.5 (C-20), 19.1 (C-3), 18.2 (C-*t*-Bu), 12.8 (C-19), −5.8 (C–Si). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{27}H_{46}NOSi$ (MH^+) 428.3349, found 428.3320. 9-*cis*. ^{1}H NMR δ 7.06 (d, J=11.7 Hz, 1H, H-11), 6.55 (d, J=15.6 Hz, 1H, H-8), 6.35 (d, J=12 Hz, 1H, H-10), 3.62 (dt, J=10.2, 5.4 Hz, H-15), 3.57 (m, H-15), 2.67 (sextet, J=6.6 Hz, 1H, H-13), 2.04 (d, J=1.2 Hz, 3H, Me-19), 2.03 (t, J=6.0 Hz, 2H, CH_2-4), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.66 (m, 4H, CH_2-14, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.17 (d, J=6.9 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.90 (s, 9H, *t*-Bu), 0.05 (s, 6H, $SiMe_2$).

4.2.10. All-*trans*-*O*-TBS-12-formyl-13-demethyl-13,14-dihydroretinol (18). *General procedure C*. All-*trans* **16** (0.29 g, 0.7 mmol) was dissolved in *n*-hexane (10 mL) under Ar atmosphere. The solution was cooled to −78 °C and DIBAL-H (1 M in hexane, 1.2 mL) was added. The reaction was stirred at −78 °C for 35 min. Wet silica gel and ether were added and the reaction mixture was stirred at 0 °C overnight. The mixture was filtered through Celite. The Celite was then washed with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and evaporated. The obtained isomeric mixture (11-*cis* and all-*trans* in 1:3.5 ratio) was separated by chromatography (*n*-hexane/ether/ethyl acetate 4:2:1) (yellow oils, 82% yield). ^{1}H NMR (acetone-d_6) δ 10.40 (s, 1H, CHO), 7.46 (d, J=12.6 Hz, 1H, H-11), 7.25 (d, J=12.9 Hz, 1H, H-10), 6.48 (d, J=16.2 Hz, 1H, H-7), 6.32 (d, J=16.2 Hz, 1H, H-8), 3.64 (t, J=6.3 Hz,

2H, CH_2-15), 2.35 (dd, J=8.1, 7.2 Hz, 2H, CH_2-13), 2.07 (d, J=1.2 Hz, 3H, Me-19), 2.03 (m, CH_2-4), 1.73 (d, J=0.6 Hz, 3H, Me-18), 1.64 (m, 4H, CH_2-14 and CH_2-3), 1.49 (m, 2H, CH_2-2), 1.06 (s, 6H, Me-16, 17), 0.92 (s, 9H, *t*-Bu), 0.07 (s, 6H, $SiMe_2$). ^{13}C NMR δ 189.8 (CHO), 142.5 (C-9), 140.1 (C-11), 137.5 (C), 137.4 (C-8), 137.36 (C), 130.0 (C-7), 129.9 (C), 122.3 (C-10), 62.0 (C-15), 39.4 (C-2), 33.9 (C-1), 32.7 (C-4), 32.1 (C-14), 28.4 (C-16, C-17), 26.9 (C-13), 25.4 (*t*-Bu), 21.1 (C-18), 18.9 (C-3), 17.9 (C-*t*-Bu), 11.4 (C-19), −6.1 (C–Si). UV λ_{max} 352 nm. HRMS *m/z* calcd for $C_{26}H_{45}O_2Si$ (MH^+) 417.3189, found 417.3243.

4.2.11. 11-*cis*-*O*-TBS-12-formyl-13-demethyl-13,14-dihydroretinol (18). The 11-*cis* isomer was similarly prepared according to general procedure C with 11-*cis* **16** (0.09 g, 0.22 mmol) and DIBAL-H (1 M in hexane, 0.35 mL) in *n*-hexane (5 mL). Chromatography (*n*-hexane/ether/ethyl acetate 4:2:1) provided pure 11-*cis* **18** (yellow oil, 85% yield). ^{1}H NMR δ 9.47 (s, 1H, CHO), 7.24 (d, J=12.3 Hz, 1H, H-11), 6.52 (d, J=11.7 Hz, 1H, H-10), 6.49 (d, J=16.2 Hz, 1H, H-7), 6.27 (d, J=15.9 Hz, 1H, H-8), 3.61 (t, J=6.3 Hz, 2H, CH_2-15), 2.45 (dd, J=8.1, 7.5 Hz, 2H, CH_2-13), 2.10 (d, J=1.2 Hz, 3H, Me-19), 2.05 (t, J=6.3 Hz, 2H, CH_2-4), 1.74 (d, J=0.9 Hz, 3H, Me-18), 1.61 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.06 (s, 6H, Me-16, 17), 0.91 (s, 9H, *t*-Bu), 0.06 (s, 6H, $SiMe_2$). ^{13}C NMR δ 194.6 (CHO), 145.4 (C-9), 144.9 (C-11), 141.0, (C-6), 137.4 (C-5 or C-12), 137.0 (C-8), 131.7 (C-7), 131.2 (C-12 or C-5), 124.5 (C-10), 62.6 (C-15), 39.6 (C-2), 34.3 (C-1), 33.2 (C-4), 32.1 (C-14), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.8 (C-18), 20.5 (C-13), 19.1 (C-3), 18.3 (C-*t*-Bu), 12.9 (C-19), −5.3 (C–Si). UV λ_{max} 354 nm. HRMS *m/z* calcd for $C_{26}H_{45}O_2Si$ (MH^+) 417.3189, found 417.3184.

4.2.12. All-*trans*-*O*-TBS-12-formyl-13,14-dihydroretinol (19). All-*trans* **19** was prepared according to general procedure C with all-*trans* **17** (0.33 g, 0.77 mmol) and DIBAL-H (1 M in Hexane, 1.4 mL) in *n*-hexane (10 mL). The product was obtained as yellow oil (88% yield). ^{1}H NMR δ 10.32 (s, 1H, CHO), 7.26 (d, J=12.6 Hz, 1H, H-11), 7.00 (d, J=12.9 Hz, 1H, H-10), 6.42 (d, J=16.2 Hz, 1H, H-7), 6.20 (d, J=15.9 Hz, 1H, H-8), 3.56 (t, J=6.6 Hz, 1H, CH_2-15), 2.88 (sextet, J=6.9 Hz, 1H, H-13), 2.03 (d, J=1.2 Hz, and t, J=6 Hz, 5H, Me-19 and CH_2-4), 1.76 (m, 1H, H-14), 1.72 (d, J=0.9 Hz, 3H, Me-18), 1.62 (m, 3H, H-14, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.10 (d, J=6.9 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.88 (s, 9H, *t*-Bu), 0.02 (s, 6H, $SiMe_2$). ^{13}C NMR δ190.2 (CHO), 143.3 (C-4°), 141.6 (C-4°), 138.9 (C-11), 137.5 (C-4°), 137.2 (C-8), 130.9 (C-7), 130.7 (C-4°), 122.0 (C-10), 61.5 (C-15), 39.5 (C-2), 39.1 (C-14), 34.2 (C-1), 33.1 (C-4), 30.4 (C-13), 28.9 (C-16, C-17), 25.9 (*t*-Bu), 21.7 (C-18), 20.6 (C-20), 19.1 (C-3), 18.3 (C-*t*-Bu), 12.3 (C-19), −5.3 (C–Si). UV λ_{max} 354 nm. HRMS *m/z* calcd for $C_{27}H_{46}O_2Si$ ($M^{\cdot+}$) 430.3267, found 430.3223.

4.2.13. 11-*cis*-*O*-TBS-12-formyl-13,14-dihydroretinol (19). 11-*cis* **19** was prepared according to general procedure C with 11-*cis* **17** (0.69 g, 1.6 mmol) and DIBAL-H (1 M in Hexane, 2.9 mL) in *n*-hexane (21 mL). The product was obtained as yellow oil in 85% yield. ^{1}H NMR δ 9.43 (d, J=2 Hz, 1H, CHO), 7.19 (d, J=12.0 Hz, 1H, H-11), 6.53 (d, J=12.0 Hz, 1H, H-10), 6.46 (d, J=15.9 Hz, 1H, H-7), 6.22 (d, J=16.2 Hz, 1H, H-8), 3.55 (dt, J=10.8, 5.7 Hz, 1H, H-15), 3.43 (ddd, J=10.4, 7.8, 5.4 Hz, 1H, H-15), 3.09 (m, 1H, H-13), 2.08 (d, J=1.2 Hz, 3H, Me-19), 2.03 (CH_2-4), 1.77 (m, 1H, H-14), 1.71 (d, J=0.9 Hz, 3H, Me-18), 1.64 (m, 3H, H-14, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.19 (d, J=7.2 Hz, Me-20), 1.03 (s, 6H, Me-16, 17), 0.87 (s, 9H, *t*-Bu), 0.00 and −0.02 (s, 3H, SiMe). ^{13}C NMR δ 195.1 (CHO), 145.8 (C-11), 145.3 (C-4°), 144.0 (C-4°), 137.4 (C-4°), 137.1 (C-8), 131.6 (C-7), 131.1 (C-4°), 124.5 (C-10), 61.2 (C-15), 39.2 (C-2), 36.7 (C-14), 34.2 (C-1), 32.8 (C-4), 28.9 (C-16, C-17), 27.9 (C-13), 25.9 (*t*-Bu), 21.7 (C-18), 19.1 (C-3), 18.7 (C-20), 18.2 (C-*t*-Bu), 12.9 (C-19), −5.3 (C–Si). UV λ_{max} 356 nm.

4.2.14. *O*-THP-12-carbethoxy-13-demethyl-13,14-dihydroretinol (20). Compound **20** was prepared according to general procedure A with phosphonate **11** (0.84 g, 2.3 mmol), NaH (60% in mineral oil, 0.085 g) and aldehyde **15** (1.0 g, 4.6 mmol) in dry THF at rt for 2 days. The obtained isomeric mixture (11-*cis* as a major product, along with some all-*trans* and 9-*cis*) was purified and partially separated by chromatography (*n*-hexane/ether, 20:1) (yellow oil, 46% yield). 11-*cis*. ^{1}H NMR δ 7.63 (d, J=12.3 Hz, 1H, H-11), 6.35 (d, J=16.2 Hz, 1H, H-7), 6.33 (d, J=12.0 Hz, 1H, H-10), 6.18 (d, J=16.2 Hz, 1H, H-8), 4.55 (dd, J=4.5, 3.0 Hz, H, H-2′), 4.22 (q, J=7.2 Hz, 2H, CH_2OCO), 3.86 (ddd, J=11.1, 7.5, 3.3 Hz, 1H, H-6′), 3.74 (dt, J=9.9, 6.3 Hz, 1H, H-15), 3.47 (m, 1H, H-6′), 3.37 (dt, J=9.9, 6.3 Hz, 1H, H-15), 2.58 (dt, J=13.5, 7.5 Hz, 1H, H-13), 2.50 (dt, J=13.5, 6.9 Hz, 1H, H-13), 2.03 (d, J=1.2 Hz, 3H, Me-19), 2.02 (t, J=6.3 Hz, 2H, CH_2-4), 1.80–1.48 (m, CH_2-3, CH_2-14, CH_2-3′, CH_2-4′, CH_2-5′), 1.70 (d, J=0.9 Hz, 3H, Me-18), 1.46 (m, 2H, CH_2-2), 1.31 (t, J=7.2 Hz, 3H, ester-Me), 1.03 (s, 6H, Me-16, 17). ^{13}C NMR δ 168.3 (CO_2), 142.9 (C-9), 137.5 (C-6), 137.3 (C-8), 134.5 (C-11), 130.3 (C-12), 130.2 (C-5), 129.8 (C-7), 124.6 (C-10), 98.8 (C-6′), 66.6 (C-15), 62.1 (C-2′), 60.3 (C-21), 39.5 (C-2), 34.1 (C-1), 33.0 (C-4), 30.7 (C-5′), 29.4 (C-14), 28.8 (C-16, 17), 25.4 (C-3′), 23.4 (C-13), 21.6 (C-18), 19.5 (C-4′), 19.1 (C-3), 14.2 (C-22), 12.8 (C-19). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{27}H_{42}O_4$ ($M^{\cdot+}$) 430.3083, found 430.3073. All-*trans*. ^{1}H NMR δ 7.03 (d, J=12.0 Hz, 1H, H-10), 6.79 (d, J=12.0 Hz, 1H, H-11), 6.34 (d, J=15.6 Hz, 1H, H-7), 6.01 (d, J=15.6 Hz, 1H, H-8), 4.57 (dd, J=3.9, 2.7 Hz, 1H, H-2′), 4.22 (q, J=7.2 Hz, 2H, CH_2OCO), 3.86 (m, 1H, H-6′), 3.75 (m, 1H, H-15), 3.49 (m, 1H, H-6′), 3.36 (dt, 1H, H-15), 2.46 (m, 2H, CH_2-13), 1.94 (s, 3H, Me-19). 9-*cis*. ^{1}H NMR δ 7.69 (d, J=12.3 Hz, 1H, H-11), 6.88 (d, J=15.3 Hz, 1H, H-8), 6.28 (d, J=12.0 Hz, 1H, H-10), 6.09 (d, J=15.9 Hz, 1H, H-7). HRMS *m/z* calcd for $C_{27}H_{42}O_4$ ($M^{\cdot+}$) 430.3083, found 430.3054.

4.2.15. *O*-THP-12-carbethoxy-13,14-dihydroretinol (21). Compound **21** was prepared according to general procedure A with phosphonate **14** (1.2 g, 3.2 mmol), NaH (60% in mineral oil, 0.12 g) and aldehyde **15** (0.65 g, 3.0 mmol) in dry THF at rt for 3 days. Chromatography (*n*-hexane/ether 25:1) afforded a complex diastereoisomeric mixture of the all-*trans* and 11-*cis* isomers, as well as minor amounts of a product derived from the phosphonate of the 3-protected butanediol (yellow oil, 52% yield). ^{1}H NMR δ 7.60, 7.58 and 7.57 (d, J=12.3 Hz, 1H, H-11), 6.79 (J=

12.0 Hz, 2H-10), 6.73 (dd, J=12.0, 0.9 Hz, 1H, H-11), 6.71 (dd, J=12.0, 0.9 Hz, 1H, H-11), 6.42 (d, J=12.3 Hz, 1H, H-10), 6.41–6.30 (m, 2H-10, 4H-7), 6.27 (d, 12 Hz, 1H, H-10), 6.25 (d, J=16.2 Hz, 1H, H-7), 6.19 (d, J=16.2 Hz, 1H, H-8), 6.17 (d, J=15.9 Hz, 1H, H-8), 6.16 (d, J=16.2, 1H, H-8), 6.15 (d, J=15.9 Hz, 1H, H-8), 6.13 (d, J=15.6 Hz, 1H, H-8), 4.71 (dd, J=4.2, 3 Hz, 1H, H-2′), 4.63 (dd, J=4.8, 3.0 Hz, 1H, H-2′), 4.54 (t, J=3.3 Hz, 1H, H-2′), 4.52 (dd, J=4.7, 2.7 Hz, 1H, H-2′), 4.40 (dd, J=4.5, 2.7 Hz, 1H, H-2′), 4.23, 4.20, 4.19, 4.18, (q, J=6.9 Hz, 2H, ester-CH_2), 3.95–3.10 (m, H-13, CH_2-15 and CH_2-6′), 2.78 (m, 1H, H-13), 2.63 (ddd, J=13.8, 10.8, 6 Hz, 1H, H-13), 2.45 (m, 1H, H-13), 2.02, 2.01, 2.00, 1.95 and 1.94 (d, J=1.2 Hz, 3H, Me-19), 1.98 (m, 2H, CH_2-4), 1.9–1.4 (m, 12H, CH_2-2, CH_2-3, CH_2-14, CH_2-3′, CH_2-4′, CH_2-5′), 1.70 (d, J=0.9 Hz, 3H, Me-18), 1.70, 1.69 and 1.68 (s, 3H, Me-18), 1.317, 1.29 (t, J=6.9 Hz, 3H, ester-Me), 1.25 (d, J=6.3 Hz, 3H, Me-20), 1.21 (d, J=7.2 Hz, 3H, Me-20), 1.18 (t, J=6.9 Hz, 3H, ester-Me), 1.15 (d, J=6.9 Hz, 3H, Me-20), 1.13 (d, J=6.0 Hz, 3H, Me-20), 1.02, 1.02, 1.01, 1.00 and 0.99 (s, 6H, Me-16, 17). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{28}H_{44}O_4$ 444.3240, found 444.3214.

4.2.16. 12-Cyano-13-demethyl-13,14-dihydroretinol (1). *General procedure D*. A mixture of all-*trans* and 11-*cis* (2.6:1) **16** (0.34 g, 0.8 mmol) was dissolved in dry THF (10 mL). A solution of $Bu_4N^+F^-$ (1 M in THF, 0.88 ml) was added and the reaction mixture was stirred at rt for 1 h. After evaporation of the solvent, the isomers were separated by chromatography (ethyl acetate/hexane 1:2) (yellow oils, 100% yield). All-*trans*. ^{1}H NMR δ 7.02 (d, J=11.9 Hz, 1H, H-11), 6.43 (d, J=11.9 Hz, 1H, H-10), 6.39 (d, J=16.1 Hz, 1H, H-7), 6.20 (d, J=16.1 Hz, 1H, H-8), 3.71 (t, J=6.2 Hz, 2H, CH_2-15), 2.43 (t, J=7.5 Hz, 2H, CH_2-13), 2.03 (t, J=6.2 Hz, 2H, CH_2-4), 1.99 (s, 3H, Me-19), 1.84 (quintet, J=7.4 Hz, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.03 (s, 6H, Me-16, Me-17). ^{13}C NMR δ 142.8 (C-9), 140.6 (C-11), 137.2 (C-6), 136.4 (C-8), 131.0 (C-7), 130.8 (C-5), 125.3 (C-10), 118.4 (CN), 110.6 (C-12), 61.0 (C-15), 39.5 (C-2), 34.1 (C-1), 33.0 (C-4), 31.1 (C-14), 30.8 (C-13), 28.8 (C-16, C-17), 21.6 (C-18), 19.0 (C-3), 12.9 (C-19). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{20}H_{30}NO$ (MH^+) 300.2327, found 300.2310. 11-*cis*. ^{1}H NMR δ 7.15 (d, J=12.1 Hz, 1H, H-11), 6.43 (d, J=16.1 Hz, 1H, H-7), 6.26 (d, J=12.1 Hz, 1H, H-10), 6.16 (d, J=16.1 Hz, 1H, H-8), 3.71 (t, J=6.1 Hz, 2H, CH_2-15), 2.47 (t, J=7.4 Hz, 2H, CH_2-13), 2.03 (t, J=6.6 Hz, 2H, CH_2-4), 2.00 (s, 3H, Me-19), 1.85 (quintet, J=7.6 Hz, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.03 (s, 6H, Me-16, Me-17). ^{13}C NMR δ 144.1 (C-9), 139.8 (C-11), 137.4 (C-6), 136.5 (C-8), 131.7 (C-7), 131.0 (C-5), 122.6 (C-10), 121.5 (CN), 110.6 (C-12), 61.4 (C-15), 39.5 (C-2), 34.2 (C-1), 33.1 (C-4), 30.9 (C-14), 28.9 (C-16, C-17), 24.9 (C-13), 21.7 (C-18), 19.1 (C-3), 12.9 (C-19). UV λ_{max} 336 nm. HRMS *m/z* calcd for $C_{20}H_{30}NO$ (MH^+) 300.2327, found 300.2311.

4.2.17. 12-Cyano-13,14-dihydroretinol (2). Retinol analog **2** was prepared according to general procedure D with **17** (0.3 g, 0.7 mmol, a mixture of isomers) and $Bu_4N^+F^-$ (1 M in THF, 0.8 ml) in dry THF (10 mL). The product isomeric mixture was purified and separated by chromatography (ethyl acetate/hexane 1:2) (yellow oils, 90% yield). All-*trans*. ^{1}H NMR δ 7.04 (d, J=11.7 Hz, 1H, H-11), 6.44 (d, J=11.7 Hz, 1H, H-10), 6.38 (d, J=15.9 Hz, 1H, H-7), 6.20 (d, J=15.9, 1H, H-8), 3.67 (m, 1H, H-15), 3.62 (m, 1H, H-15), 2.66 (dquintet, J=8.1, 6.6 Hz, 1H, H-13), 2.49 (t, J=7.8 Hz, 1H, OH), 2.03 (t, J=6.3 Hz, 2H, CH_2-4), 1.99 (d, J=1.2 Hz, 3H, Me-19), 1.75 (m, 2H, CH_2-14), 1.72 (s, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.47 (m, 2H, CH_2-2), 1.23 (d, J=6.6 Hz, 3H, Me-20), 1.03 (s, 6H, Me-16, 17). ^{13}C NMR δ 142.9 (C), 139.4 (C-11), 137.3 (C), 136.5 (C-8), 131.0 (C-7), 130.8 (C), 125.3 (C-10), 117.2 (CN), 116.6 (C), 59.9 (C-15), 39.5 (C-2), 38.1 (C-14), 35.5 (C-13), 34.1 (C-1), 33.0 (C-4), 28.8 (C-16, 17), 21.6 (C-20), 20.0 (C-18), 19.1 (C-3), 13.0 (C-19). UV λ_{max} 334 nm. HRMS *m/z* calcd for $C_{21}H_{31}NO$ (M^+) 313.2406, found 313.2410. 11-*cis*. ^{1}H NMR δ 7.13 (d, J=12.3 Hz, 1H, H-11), 6.42 (d, J=15.9 Hz, 1H, H-7), 6.33 (d, J=12.1 Hz, 1H, H-10), 6.16 (d, J=15.9, 1H, H-8), 3.71 (dt, J=10.7, 5.4 Hz, 1H, H-15), 3.60 (dt, J=10.7, 6.6 Hz, 1H, H-15), 3.08 (sextet, J=6.9 Hz, 1H, H-13), 2.04 (d, J=5.4 Hz, 2H, CH_2-4), 2.00 (d, J=1 Hz, 3H, Me-19), 1.76 (td, J=6.9, 5.7 Hz, 2H, CH_2-14), 1.71 (d, J=1 Hz, 3H, Me-18), 1.62 (m, 2H, CH_2-3), 1.48 (m, 2H, CH_2-2), 1.19 (d, J=6.9 Hz, 3H, Me-20), 1.033 (s, 3H, Me-16), 1.026 (s, 3H, Me-17). ^{13}C NMR δ 144.2 (C-9), 139.0 (C-11), 137.4 (C-6), 136.6 (C-8), 131.6 (C-7), 131.1 (C-5), 125.6 (CN), 116.9 (C-12), 60.2 (C-15), 39.6 (C-2), 37.9 (C-14), 34.3 (C-1), 33.1 (C-4), 29.0 (C-16), 28.9 (C-17), 28.8 (C-13), 21.8 (C-18), 19.6 (C-20), 19.1 (C-3), 12.9 (C-19). HRMS *m/z* calcd for $C_{21}H_{31}NO$ (M^+) 313.2406, found 313.2395. 9-*cis*. ^{1}H NMR δ 7.10 (d, J=11.7 Hz, 1H, H-11), 6.56 (d, J=15.9 Hz, 1H, H-8), 6.38 (d, J=15.9 Hz, 1H, H-7), 6.37 (d, J=11.7, 1H, H-10), 3.71 (dt, J=10.8, 6.0 Hz, 1H, H-15), 3.62 (ddd, J=10.8, 7.5, 1.8 Hz, 1H, H-15), 2.65 (dquintet, J=8.1, 6.9 Hz, 1H, H-13), 2.06 (d, J=0.9 Hz, 3H, Me-19), 2.05 (t, J=6 Hz, 2H, CH_2-4), 1.76 (m, 2H, CH_2-14), 1.74 (d, J=0.9 Hz, 3H, Me-18), 1.64 (m, 2H, CH_2-3), 1.49 (m, 2H, CH_2-2), 1.21 (d, J=6.9 Hz, 3H, Me-20), 1.04 (s, 6H, Me-16, 17). ^{13}C NMR δ 142.0 (C-9), 138.1 (C-11), 137.7 (C-6), 132.2 (C-8), 130.6 (C-5), 128.8 (C-7), 123.8 (C-10), 117.1 (CN), 116.1 (C-12), 60.1 (C-15), 39.4 (C-2), 38.0 (C-14), 35.5 (C-13), 34.2 (C-1), 33.0 (C-4), 28.9 (C-16, 17), 21.8 (C-18), 20.9 (C-20), 19.9 (C-19), 19.1 (C-3).

4.2.18. All-*trans*-12-formyl-13-demethyl-13,14-dihydroretinol (3). All-*trans* **3** was prepared according to general procedure D with all-*trans* **18** (0.11 g, 0.26 mmol) and $Bu_4N^+F^-$ (1 M in THF, 0.26 mL) in dry THF (7 mL). It was purified by chromatography (hexane/ethyl acetate 5:1), providing a mixture of 1:1 all-*trans* and 11-*cis* **3**, along with small amounts of the 9-*cis* congener (yellow oil, 78% yield). ^{1}H NMR δ 10.34 (s, 1H, CHO), 7.38 (d, J=12.6 Hz, 1H, H-11), 6.99 (d, J=12.6 Hz, 1H, H-10), 6.44 (d, J=16.2 Hz, 1H, H-7), 6.20 (d, J=16.2 Hz, 1H, H-8), 3.59 (t, J=6 Hz, 2H, CH_2-15), 2.38 (t, J=7.2 Hz, 2H, CH_2-13), 2.03 (m, 5H, Me-19 and CH_2-4), 1.73 (s, 3H, Me-18), 1.64 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.04 (s, 6H, Me-16, 17). ^{13}C NMR δ 190.7 (CHO), 144.0 (C-9), 142.0 (C-11), 137.5 (C), 136.9 (C-8), 131.4 (C-7), 131.0 (C), 121.5 (C-10), 61.4 (C-15), 39.5 (C-2), 34.2 (C-1), 33.1 (C-4), 32.6 (C-14), 28.9 (C-16, C-17), 26.5 (C-13), 21.8 (C-18), 20.2 (C-13), 19.1 (C-3), 12.4 (C-19). UV λ_{max} 354 nm. HRMS *m/z* calcd for $C_{20}H_{30}O_2$ (M^+) 302.2246, found 302.2283.

4.2.19. 11-*cis*-12-Formyl-13-demethyl-13,14-dihydroretinol (3). 11-*cis* **3** was prepared from 11-*cis* **18** according to general procedure D as yellow oil in 77% yield. It was further purified by HPLC on a 5μ PVA-Sil (250×4.6 mm, 1.20 Å, YMC) column, using a mixture of 7% dioxane in hexane at a flow rate of 1.5 mL/min. Retention time: 26.3 min. 98% purity. λ_{max} (hexane)=342 nm, ε=18600. ^{1}H NMR δ 9.48 (s, 1H, CHO), 7.30 (d, J=12.3 Hz, 1H, H-11), 6.51 (d, J=15.9 Hz, 1H, H-7), 6.49 (d, J=12.3 Hz, 1H, H-10), 6.27 (d, J=16.2 Hz, 1H, H-8), 3.53 (t, J=6.0 Hz, 2H, CH_2-15), 2.52 (t, J=7.2 Hz, 2H, CH_2-13), 2.12 (s, 3H, Me-19), 2.05 (t, J=6.0 Hz, 2H, CH_2-4), 1.75 (s, 3H, Me-18), 1.66 (m, 4H, CH_2-14 and CH_2-3), 1.49 (m, 2H, CH_2-2), 1.06 (s, 6H, Me-16, 17). ^{13}C NMR δ 195.5 (CHO), 146.5 (C-9), 146.0 (C-11), 140.2 (C), 137.4 (C), 136.8 (C-8), 132.4 (C-7), 131.5 (C), 124.0 (C-10), 60.9 (C-15), 39.5 (C-2), 34.2 (C-1), 33.2 (C-4), 31.7 (C-14), 28.9 (C-16, C-17), 21.8 (C-18), 19.5 (C-13), 19.1 (C-3), 13.0 (C-19). UV λ_{max} 354 nm. MS m/z 303 (MH^+).

4.2.20. All-*trans*-12-formyl-13,14-dihydroretinol (4). All-*trans* **4** was prepared according to general procedure D with all-*trans* **19** and (0.52, 1.2 mmol) $Bu_4N^+F^-$ (1 M in THF, 1.2 mL) in dry THF (14 mL). The product, all-*trans* isomer, was obtained as a yellow oil (83%). ^{1}H NMR (acetone-d_6) δ 10.33 (s, 1H, CHO), 7.38 (d, J=12.6 Hz, 1H, H-11), 7.15 (d, J=12.9 Hz, 1H, H-10), 6.48 (d, J=16.2 Hz, 1H, H-7), 6.28 (d, J=16.2 Hz, 1H, H-8), 3.45 (td, J=6.5, 2.4 Hz, 1H, H-15), 3.43 (td, J=6.5, 2.4 Hz, 1H, H-15), 2.89 (sextet, J=7.2 Hz, 1H, H-13), 2.06 (d, J=1.2 Hz, 3H, Me-19), 2.03 (t, J=6.6 Hz, 2H, CH_2-4), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.63 (m, 4H, CH_2-14 and CH_2-3), 1.48 (m, 2H, CH_2-2), 1.12 (d, J=6.3 Hz, Me-20), 1.03 (s, 6H, Me-16, 17). ^{13}C NMR δ 192.1 (CHO), 144.8 (C), 143.4 (C), 140.5 (C-11), 139.0 (C), 138.6 (C-8), 131.7 (C-7), 130.4 (C), 123.8 (C-10), 61.3 (C-15), 40.8 (C-2), 38.3 (C-14), 35.4 (C-1), 34.2 (C-4), 30.8 (C-13), 29.7 (C-16, C-17), 22.5 (C-18), 21.1 (C-20), 20.4 (C-3), 12.9 (C-19). UV λ_{max} 354 nm. HRMS m/z calcd for $C_{21}H_{32}O_2$ (M^+) 316.2402, found 316.2425.

4.2.21. 11-*cis*-12-Formyl-13,14-dihydroretinol (4). 11-*cis* **4** was similarly prepared. The product, 11-*cis* isomer exclusively, was obtained as a yellow oil (76%). It was purified by HPLC on a 5μ PVA-Sil (250×4.6 mm, 1.20 Å, YMC) column, using a mixture of 7% dioxane in hexane at a flow rate of 1.5 mL/min. Retention time: 23.1 min. 93% purity. λ_{max} (hexane)=336 nm, ε=22400. ^{1}H NMR (acetone-d_6) δ 9.48 (d, J=1.8 Hz, 1H, CHO), 7.39 (d, J=12.3 Hz, 1H, H-11), 6.72 (d, J=12.0 Hz, 1H, H-10), 6.55 (d, J=16.2 Hz, 1H, H-7), 6.35 (d, J=16.2 Hz, 1H, H-8), 3.42 (m, CH_2-15), 3.15 (dqd, J=6.9, 6.6, 1.8 Hz, 1H, H-13), 2.14 (d, J=1.2 Hz, 3H, Me-19), 2.05 (m, CH_2-4), 1.94 (m, H-14), 1.74 (d and m, J=0.9 Hz, Me-18 and H-14), 1.64 (m, CH_2-3), 1.48 (m, CH_2-2), 1.20 (d, J=7.2 Hz, 3H, Me-20), 1.064 and 1.056 (s, 3H, Me-16 and Me-17). HRMS m/z calcd for $C_{21}H_{32}O_2$ (M^+) 316.2402, found 316.2415.

4.2.22. 12-Carbethoxy-13-demethyl-13,14-dihydroretinol (5). *General procedure E.* PPTS (0.017 g, 0.07 mmol) was added to a solution of 11-*cis* **20** (0.3 g, 0.7 mmol) in ethanol (10 mL). The mixture was stirred at 55 °C for 1.5 h, cooled to rt and the solvent was evaporated to half its volume. The mixture was diluted with ether, washed with water, dried ($MgSO_4$) filtered and evaporated, providing a mixture of 11-*cis*, 9-*cis* and all-*trans* isomers in a ratio of 30:2:1, respectively. Chromatography (hexane/ether 2:1) afforded clean 11-*cis* **5** as yellow oil and a fraction containing the three isomers (79% overall yield). 11-*cis*. ^{1}H NMR δ 7.62 (d, J=12.3 Hz, 1H, H-11), 6.34 (d, J=15.9 Hz, 1H, H-7), 6.28 (d, J=12.3 Hz, 1H, H-10), 6.17 (d, J=15.9 Hz, 1H, H-8), 4.20 (q, J=7.2 Hz, 2H, ester-CH_2), 3.55 (t, J=6.3 Hz, 2H, CH_2-15), 2.52 (t, J=7.2 Hz, 2H, CH_2-13), 2.01 (d, J=0.9 Hz, 3H, Me-19), 1.98 (t, J=6.3 Hz, 2H, CH_2-4), 1.68 (m, 5H, CH_2-14 and Me-18), 1.58 (m, 2H, CH_2-3), 1.42 (m, 2H, CH_2-2), 1.29 (t, J=6.9 Hz, 3H, ester-Me), 1.00 (s, 6H, Me-16, 17). ^{13}C NMR δ 168.9 (CO_2), 143.5 (C-9), 137.4 (C-6), 137.2, (C-8), 134.9 (C-11), 130.3 (C-12), 130.2 (C-7), 129.7 (C-5), 124.3 (C-10), 61.3 (C-15), 60.6 (ester-CH_2), 39.5 (C-2), 34.1 (C-1), 33.0 (C-4), 32.3 (C-14), 28.8 (C-16, 17), 22.5 (C-13), 21.6 (C-18), 19.1 (C-3), 14.2 (ester-CH_3), 12.8 (C-19). UV λ_{max} 340 nm. HRMS m/z calcd for $C_{22}H_{34}O_3$ ($M^{\cdot+}$) 346.2508, found 346.2490. All-*trans*. ^{1}H NMR δ 6.99 (d, J=12.0 Hz, 1H, H-10), 6.82 (d, J=12.0 Hz, 1H, H-11), 6.33 (d, J=16 Hz, H-7), 6.13 (d, J=16.2 Hz, 1H, H-8), 4.21 (q, J=7.2 Hz, 2H, ester-CH_2), 3.62 (t, J=6.3 Hz, 2H, CH_2-15), 2.42 (t, J=7.2 Hz, 2H, CH_2-13), 2.01 (CH_2-4), 1.94 (d, J=1.2 Hz, 3H, Me-19), 1.70 (s, 3H, Me-18), 1.58 (m, 2H, CH_2-3), 1.42 (m, 2H, CH_2-2), 1.29 (t, J=7.2 Hz, 3H, ester-Me), 0.98 (s, 6H, Me-16, 17). ^{13}C NMR δ 169.1 (CO_2), 141.7 (C-9), 137.8 (C-8), 135.7 (C-11), 129.4 (C-7), 126.3 (C-10), 61.9 (C-15), 60.3 (ester-CH_2), 39.6 (C-2), 34.2 (C-1), 33.1 (C-4), 32.4 (C-14), 28.9 (C-16, 17), 22.3 (C-13), 21.8 (C-1O-8), 19.2 (C-3), 14.3 (ester-CH_3), 12.9 (C-19). UV λ_{max} 338 nm. HRMS m/z calcd for $C_{22}H_{34}O_3$ ($M^{\cdot+}$) 346.2508, found 346.2547. 9-*cis*. ^{1}H NMR δ 7.72 (d, J=12.3 Hz, 1H, H-11), 6.70 (d, J=15.9 Hz, 1H, H-8), 6.33 (d, J=15.9 Hz, 1H, H-7), 6.19 (d, J=12.3 Hz, 1H, H-10), 4.19 (q, J=6.9 Hz, 2H, ester-CH_2), 3.56 (t, J=6.3 Hz, 2H, CH_2-15), 2.51 (t, J=7.2 Hz, 2H, CH_2-13), 2.02 (CH_2-4), 2.02 (d, J=1.2 Hz, 3H, Me-19), 1.71 (d, J=0.9 Hz, 3H, Me-18), 1.58 (m, 2H, CH_2-3), 1.42 (m, 2H, CH_2-2), 1.28 (t, J=7.2 Hz, 3H, ester-Me), 1.01 (s, 6H, Me-16, 17).

4.2.23. 12-Carbethoxy-13,14-dihydroretinol (6). Compound **6** was prepared according to general procedure E with **21** (0.23 g, 0.5 mmol) and PPTS (0.014 g, 0.06 mmol) in ethanol (10 mL). The product isomeric mixture was separated by chromatography (*n*-hexane/ether 3:1 to 1:1), affording two fractions, of the all-*trans* and the 11-*cis* isomers of **6** (yellow oils, 63% yield). 11-*cis* **6** was further purified by HPLC (inertSil prep-sil, 20×250 mm column, 7% ethyl acetate in *n*-hexane, flow rate 35 mL/min, detection at 324 nm, retention time 37.3 min). All-*trans*. ^{1}H NMR δ 6.81 (d, J=12.1 Hz, 1H, H-10), 6.78 (d, J=11.9 Hz, 1H, H-11), 6.29 (d, J=15.9 Hz, 1H, H-7), 6.15 (d, J=16.1 Hz, 1H, H-8), 4.28 (q, J=7.1 Hz, 2H, ester-CH_2), 3.64 (m, 2H, CH_2-15), 2.85 (sextet, J=7.0 Hz, 1H, H-13), 2.02 (t, J=6.3 Hz, 2H, CH_2-4), 1.98 (s, 3H, Me-19), 1.74 (m, 1H, H-14), 1.70 (s, 3H, Me-18), 1.62 (m, 3H, H-14 and CH_2-3), 1.46 (m, 2H, CH_2-2), 1.35 (t, J=7.2 Hz, 3H, ester-Me), 1.18 (J=7.0 Hz, 3H, Me-20), 1.02 (s, 6H, Me-16, 17). ^{13}C NMR δ 169.0 (CO_2), 141.0 (C-9), 137.8 (C-8), 137.7 (C-6), 135.2, (C-12), 132.0 (C-11), 129.9 (C-5), 129.2 (C-7), 126.0 (C-10), 60.8 (C-15), 60.6 (ester-CH_2), 40.2 (C-14), 39.5 (C-2), 34.2 (C-1), 34.0 (C-13), 33.0 (C-4), 28.9 (C-16,

17), 21.7 (C-18), 20.8 (C-20), 19.2 (C-3), 14.3 (ester-Me), 12.4 (C-19). UV λ_{max} 330 nm. HRMS *m/z* calcd for $C_{23}H_{36}O_3$ ($M^{\cdot+}$) 360.2664, found 360.2671. 11-*cis*. ^{1}H NMR δ 7.61 (d, J=12.3 Hz, 1H, H-11), 6.42 (d, J=12.0 Hz, 1H, H-10), 6.38 (d, J=15.3 Hz, 1H, H-7), 6.19 (d, J=16.2 Hz, 1H, H-8), 4.23 (q, J=7.2 Hz, 2H, ester-CH_2), 3.62 (sextet, J=6.3 Hz, 1H, H-15), 3.55 (ddd, J=10.8, 8.1, 5.7 Hz, 1H, H-15), 3.18 (m, 1H, H-13), 2.04 (m, 5H, CH_2-4 and Me-19), 1.99 (m, 1H, H-14), 1.86 (m, 1H, H-14), 1.73 (d, J=0.9 Hz, 3H, Me-18), 1.61 (m, 2H, CH_2-3), 1.49 (m, 2H, CH_2-2), 1.33 (t, J=7.2 Hz, 3H, ester-Me), 1.25 (d, J=6.9 Hz, 3H, Me-20), 1.05 (s, 3H, Me-16), 1.04 (s, 3H, Me-17). ^{13}C NMR δ 168.5 (CO_2), 143.5 (C-9), 137.5 (C-6), 137.4 (C-8), 134.8 (C-11), 133.8 (C-12), 130.5 (C-5), 130.1 (C-7), 124.0 (C-10), 61.4 (C-15), 60.3 (ester-CH_2), 39.6 (C-2), 38.1 (C-14), 34.3 (C-1), 33.1 (C-4), 29.3 (C-13), 28.99 and 28.96 (C-16 and C-17), 21.8 (C-18), 19.7 (C-20), 19.2 (C-3), 14.3 (ester-Me), 12.9 (C-19). UV λ_{max} 338 nm.

Acknowledgements

This research was supported by a United States-Israel Binational Science Foundation grant no. 2000390.

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Ring strain energies: substituted rings, norbornanes, norbornenes and norbornadienes

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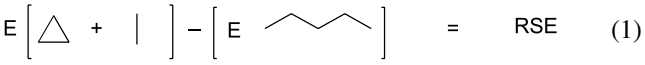
Received 19 February 2004; revised 10 June 2004; accepted 18 June 2004

Available online 21 July 2004

Abstract—Ring strain energies (RSEs) are predicted using homodesmotic reactions at the B3LYP/6-31G* level of theory. Substituents are conserved in the acyclic reference and any difference in energy between the ring and the acyclic reference corresponds exclusively to RSE. Small rings are stabilized by alkyl substituents and this stabilization decreases as the size of the ring increases. There is a destabilization of medium sized rings. Greater stabilization is found upon alkyl substitution at a double bond in an unsaturated ring and this stabilization decreases as ring size increases. The effects of *cis*-1,2-disubstitution on RSEs have been evaluated and indicate stabilization for both small and medium sized rings. RSEs of saturated and unsaturated polycyclic systems agree well with the RSEs derived from experimental thermochemical data. RSEs are reported for substituted norbornanes, norbornenes, and norbornadienes to complement experimental studies.

1. Introduction

Ring strain energy (RSE) may be defined as the destabilization or increase in energy created upon ring closure of an acyclic molecule. Traditional methods[1,2] established group increments which are summed to predict the energy of a hypothetical strain free molecule. The heat of formation of the real molecule is subtracted from the energy of the strain free reference molecule to predict the strain energy. Due to a lack of thermochemical data for many compounds, chemists have turned to schemes[4,5,8,16,17] based on theoretical models. Some recent approaches[6,7] employ an acyclic molecule as the strain free reference and RSE is the strain which results upon the bonding of two carbons in the acyclic reference. The homodesmotic scheme[3] in Eq. 1 ensures that the number of atom and bond types are conserved in the two terms on the left hand side



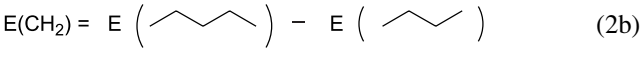
(1)

In both cyclopropane plus ethane and the acyclic reference compound, there are three secondary carbons and two primary carbons and the energy difference is the RSE. Unsubstituted all-*s*-*trans* alkanes are considered to be unstrained. The all-*s*-*trans* alkane is not strain free[1] but RSE cannot be present and therefore it is an appropriate reference molecule.

When using homodesmotic reactions, the difference in energy between the real molecule and the all-*s*-*trans* acyclic reference corresponds to the RSE for simple saturated monocyclic rings. In substituted rings energy corrections are made to ensure that the energy difference corresponds exclusively to RSE. George et al.[3] and Dill et al.[8] recognized the importance of maintaining the pattern of substitution in both the cyclic and acyclic species (as in Eqs. 2):

(2a)

$E(CH_2)$ is the energy difference between an $(n+1)$ and an (n) carbon alkane. In this work, the B3LYP/6-31G(d) energy difference between *n*-pentane and *n*-butane was used



(2b)

The use of longer chain alkanes does not alter the value of $E(CH_2)$. The $E(CH_2)$ term balances the number of secondary carbons in the two energy terms on the left hand side of the equation.

The presence of the tertiary carbon in the acyclic reference ensures that the energy difference is not affected by bond

Keywords: Ring strain; Substituents; Norbornanes; Norbornenes; Norbornadienes.

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doi:10.1016/j.tet.2004.06.100

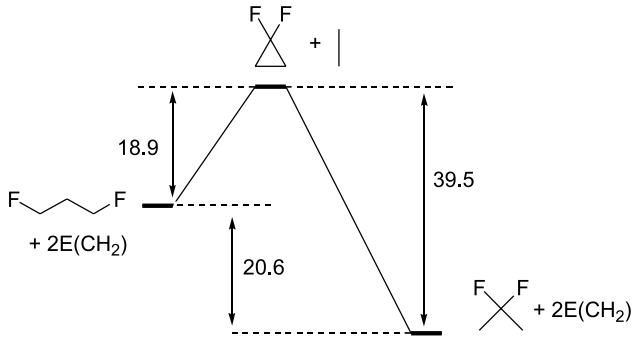
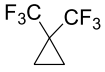


Figure 1. Two possible acyclic references for *gem*-1,1-difluorocyclopropane. Relative energies in kcal/mol.

energy differences which would result if an all-*s*-*trans* alkyl reference is used. Effects involving the substituent X and the tertiary carbon in the ring are included in the acyclic reference with X bonded to an unstrained tertiary carbon.

Bach and Dimitrenko[6] stressed the importance of replicating the substituent pattern in the acyclic reference. In the case of an electron-withdrawing group, the proper choice of the product of the ring opening will determine if the substituents decrease or increase the RSE of the reactant. For example, the RSE of cyclopropane is predicted to be 29.0 kcal/mol. Using the all-*s*-*trans* 1,3-difluoropropane acyclic reference, *gem*-1,1-difluoro substitution leads to an RSE 10 kcal/mol less than in cyclopropane and thus an RSE

Table 1. Ring strain energies (kcal/mol) of substituted and unsubstituted cycloalkanes and total strain energies from Ref. 1

		This work	Schleyer et al.	Others			This work	Schleyer et al.	Others
1		29.0	28.13	27.5[a]/27.4[b]	**16**		26.3	26.90	26.5[a]
2		27.6			**17**		25.7	27.0	
3		26.5	28.7		**18**		23.8		
4		26.0		27.2[b]	**19**		24.1		23.7[b]
5		24.6	30.85		**20**		22.3		
6		26.5			**21**		7.4	7.19	6.2[a]
7		26.1			**22**		6.7	7.23	
8		28.1			**23**		7.5	7.87	
9		26.2		26.4[b]	**24**		5.6	8.85	
10		22.2			**25**		1.3	1.35	0.0[a]
11		24.9			**26**		0.8		
12		33.3		40.7[b]	**27**		2.8	2.79	
13		39.5			**28**		0.9	3.79	
14		39.5/34.0[c]			**29**		8.0	7.57	6.3[a]
15		30.3							

[a] Experimental values of Wiberg.[20]
[b] G2(MP2) values from Bach and Dimitrienko.[6]
[c] Corrected value.

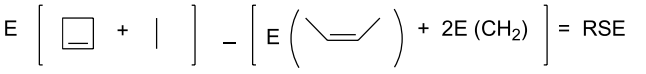
value of 18.9 kcal/mol (see Fig. 1). With a branched acyclic product as reference which conserves the *gem*-1,1-disubstitution pattern, an increase in RSE of 10 kcal/mol and an overall RSE of 39.5 kcal/mol are predicted. This RSE value is solely related to ring formation.

The homodesmotic approach is extended to 1,2-disubstituted rings and is applied to substituted rings, polycyclic systems and in particular to substituted norbornanes, norbornenes and norbornadienes. Substituent effects on ring strain energies have not been studied extensively with the work by Novak[9,10] being exceptional. The interest in syntheses based on substituted bicyclic alkenes, for example, the work by Mayo and Tam[11,12] motivates these theoretical studies of norbornenes and norbornadienes.

2. Results and discussion

2.1. Choice of reference compounds

2.1.1. Unsubstituted monocyclic rings. All-*s*-*trans* acyclic alkanes are used as the references for unsubstituted, saturated monocyclic rings as in Eq. 1 above. The energy of the acyclic reference is subtracted from the energy of the ring to ensure that the RSE is positive. Unsubstituted, unsaturated monocyclic rings are referenced to a *cis*-2-butene as in Eq. 3. The use of *cis*- instead of *trans*-2-butene is necessary to evaluate only RSE. Use of the *trans* species as the reference would predict the RSE plus the energy difference between *cis*- and *trans* 2-butene.

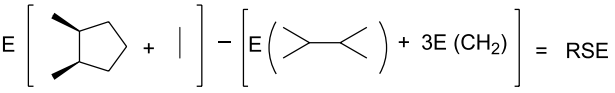


(3)

2.1.2. Rings with substituents. A substituent may be electron-withdrawing or electron-donating and may contribute to steic interactions. Any substituent effects are gauged relative to hydrogens. In the unsubstituted rings George et al.[3] conserved the pattern of substitution in the acyclic reference and predicted that cyclopropane is stabilized upon methyl substitution. For example, in Eqs. 2 with X=methyl, isobutane rather than *n*-butane is the appropriate reference. This stabilization is attributed to a stronger carbon–carbon bond between the strained carbon of cyclopropane and the carbon in the alkyl substituent. The shorter, stronger bond may be attributed to the higher s-character and subsequently increased electronegativity of the carbons in cyclopropane.[13] For example, the shorter cyclopropyl to methyl CC bond is estimated to be ~9 kcal/mol stronger than the isopropyl-methyl CC bond.[6,14]

Schemes that use 'strainless' group increments[1] from experimental data indicate increase in the total strain energy of small and medium saturated rings upon alkyl substitution (see the values from Ref. 1 in Table 1). An alkyl substituent increases the overall or total strain of the system due to steric effects.

For example, a scheme based on energy increments[1] indicates an increase in the total strain energy of 1.7 kcal/mol for *cis*-1,2-dimethyl-cyclopentane relative to cyclopentane. This increase in the overall strain can be ascribed to steric interactions between the two substituents. However, the present method which focuses on the ring strain energy predicts a decreased RSE of 1.8 kcal/mol. Any significant energy contributions found in the ring other than RSE, are duplicated in the reference compound and cancel. The appropriate homodesmotic reaction for the RSE of *cis*-1,2-dimethylcyclopentane is:



(4)

Similar increases in the total strain energies[1] but decreases in the RSEs may be observed for 1,2-dimethylcyclopropane, 1,2-dimethylcyclobutane, and 1,2-dimethylcyclohexane. Even for relatively small methyl substituents on small or medium rings an effect similar to the corset model discussed by Maier[23] for substituted tetrahedranes appears to be operative. Neighboring bulky substituents on rings interact with each other. Steric crowding is increased if the ring is broken in the scheme. Note for example in Eq. 4 the two interactions between the methyl groups attached to cyclopentane. In the acyclic reference, there are four skew interactions and the two 'extra' skew interactions result in a smaller RSE.

2.1.3. Polycyclic molecules. The all-*s*-*trans* conformations plus tertiary, *E*(Y), and quaternary, *E*(X), energy corrections are used as the acyclic references for polycyclic systems. This need for an all-*s*-*trans* reference is outlined for the tricyclo[2.2.2.0]octane shown in Figure 2. Sequence a. in Figure 2 involves an initial cleavage of the central carbon–carbon bond. Breakage of this bond alleviates the strain of three cyclobutane rings and would be an energetically favorable first step in this hypothetical ring opening of this system. Conceptually, the next two steps involve cleaving

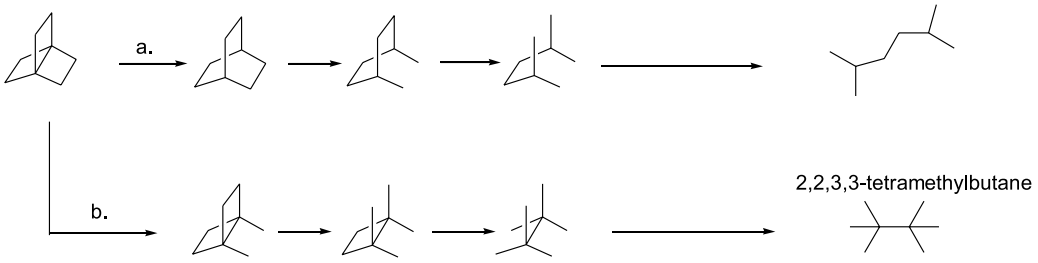


Figure 2. Two routes to an acyclic references for a propellane.

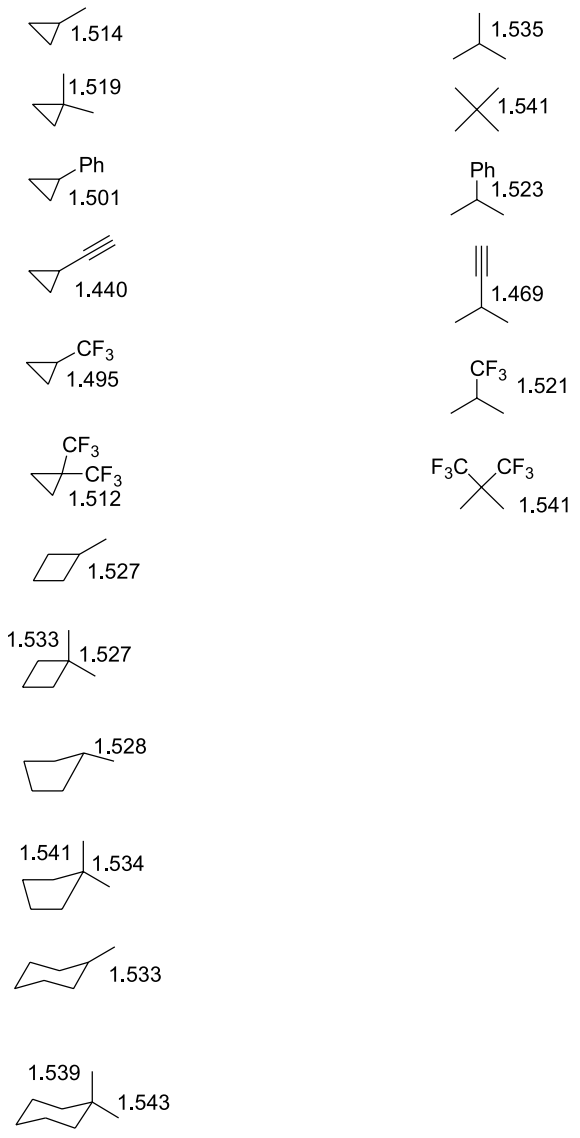


Figure 3. Ring-to-substituent bond lengths and acyclic reference-to-substituent bond lengths in Å (B3LYP/6-31G*).

the two remaining rings. The final structure has the all-*s-trans* conformation to avoid skew interactions. Experiment indicates that branching generally slightly stabilizes the alkane.[15] The all-*s-trans* acyclic reference is used as the minimum number of skew interactions which destabilize the acyclic reference molecule are present. Two quaternary energy corrections are added to balance the energy of the quaternary carbons found in the tricyclic system.

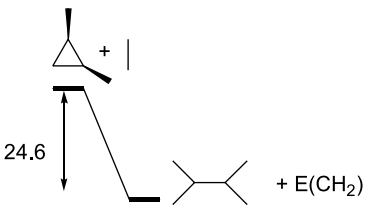
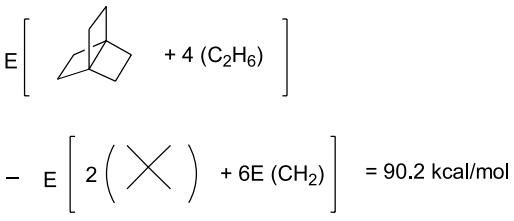


Figure 4. Acyclic references for 1,2-disubstitued cyclopropanes.

In the hypothetical sequence b. of Figure 2, the first step involves breakage of a carbon–carbon bond in a cyclobutane ring. The molecule remains significantly strained due to the two remaining cyclobutane rings (RSE of ca. 50 kcal/mol). Recall that in sequence a., ring strain was reduced greatly with the breakage of the central bond. The remaining two cyclobutane rings are cleaved in subsequent steps and the resulting acyclic reference is 2,2,3,3-tetramethylbutane.

The all-*s-trans* reference also is preferred over the branched for tricyclo[2.2.2.0] octane if the bond strengths are considered. For example, in the simplest four membered ring, the acyclic reference for cyclobutene is *cis*-2-butene. The hypothetical ring-cleavage occurs at the weakest sp^3–sp^3 carbon–carbon bond and the strongest, sp^2–sp^2 bond is preserved in the acyclic reference. The bond dissociation energy (BDE) of the central carbon–carbon bond of the 2,2,3,3-tetramethyl butane is ca. 11 kcal/mol weaker than the BDE of the all-*trans* acyclic product.[18] Therefore, the all-*trans* reference molecule with the stronger CC bond is chosen.

The acyclic reference with two corrections for the quaternary carbons in the propellane gives the equation:

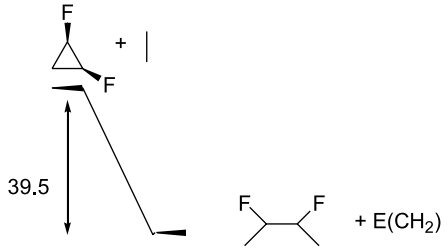


(5)

2.2. Ring strain energies of selected molecules

2.2.1. Unsubstituted rings: C_3H_6 to C_6H_{12}. The predicted RSEs compare well with those found by other computational methods (see Table 1). Differences are less than 1 kcal/mol in comparison with the values from Schleyer et al.[1] For unsubsitituted rings the total strain energies from Schleyer[1] are directly comparable with the ring strain energies of this work. Recall that for example, this work predicts the RSE of cyclohexane to be 1.3 kcal/mol in agreement with results based on experimental data.[2,6]

2.2.2. Rings with substituents. Ring strain energy decreases with alkyl substitution. The decreases are smaller as ring size increases. The ring strain energies of *gem*-1,1-dimethylcyclopropane and *gem*-1,1-dimethylcyclobutane are decreased relative to the unsubstituted rings by 3.0



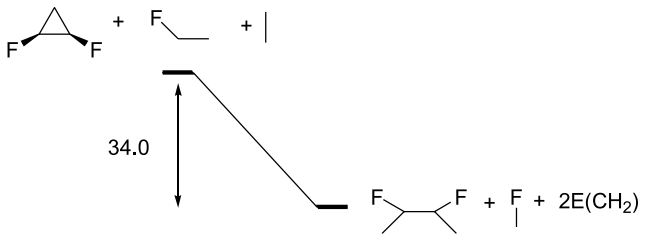
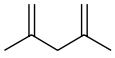
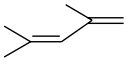
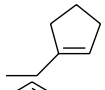
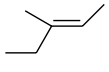


Figure 5. *cis*-1,2-Difluorocyclopropane: energy scheme with a balanced number of carbons interacting with fluorines.

and 2.2 kcal/mol, respectively (see Table 1). In *gem*-1,1-dimethyl-pentane, di-substitution leaves the RSE unchanged to within 0.1 kcal/mol. The RSE of *gem*-1,1-dimethylcyclohexane is increased by 1.5 kcal/mol relative to cyclohexane. As noted earlier, the carbons in the smallest rings, cyclopropane and cyclobutane, are more electronegative due to angle strain[13] than is a secondary carbon in *n*-propane. This increased electronegativity originates from the higher *s*-character in the carbons of cyclopropane and to a lesser extent in cyclobutane. The increased *s*-characters in cyclopropane and cyclobutane are manifested in the shorter bonds to the substituent carbons (see Fig. 3). Shorter bond lengths correlate with larger BDE[14] and the decreased RSEs correlate with shorter and stronger bonds from the ring to the substituent.

As the ring size and carbon angles increase (and subsequently the *s*-character of each carbon decreases) the methyl-to-ring carbon–carbon bond lengths increase. Total steric interactions increase as the ring size increases which also may lead to an increase in the bond lengths between the ring and substituent. In *gem*-1,1-dimethylcyclohexane the methyl-to-ring bond lengths are within 0.002 Å of the values in neopentane, the acyclic reference. No reduction in RSE results as the bond lengths in the ring and the acyclic

Table 2. Ring strain energies (kcal/mol) of unsaturated cyclic systems

		Schleyer[1]	Wiberg[20]	This Work	Main structure of acyclic reference
30		54.5	55.2	55.7	
31		40.9	40.9	38.8	
32		40.1		38.0	
33		54.5		51.6	
34		51.0		44.9	
35		30.6	28.4	30.2	
36		26.9	26.9	26.8	
37		30.4		26.6	
38		28.0		26.2	
39		29.6		21.5	
40		6.8	4.1	4.8	
41		6.1	6.1	6.6	
42		5.0		3.9	
43		5.9		3.6	
44		2.5	−0.3	0.3	
45		1.9	−1.1	1.6	
46		6.7	3.6	4.4	

Total strain energies from Ref. 1.

reference are equal. Increased intramolecular hydrogen repulsions may increase the total strain in the ring.

The choice of 2,3-dimethylbutane as a reference gives a RSE of 24.6 kcal/mol for *cis*-1,2-dimethylcyclopropane (see Fig. 4). This reference accounts for the two tertiary carbons found in *cis*-1,2-dimethylcyclopropane plus the bond joining the two tertiary carbons. Any electronic effects from the four bonds to the two tertiary carbons, as well as the bond between the two tertiary carbons are conserved in the reference. All B3LYP/6-31G* results indicate that alkyl branching at the central carbons destabilizes the alkane with respect to the all-*trans* isomer.[19]

In *cis*-1,2-difluorocyclopropane, the six-member acyclic reference yields an RSE of 39.5 kcal/mol and shows the strong influence of fluorine on the bond energies of the σ-framework in the alkanes.

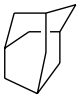
There is an additional carbon in the six-member reference which is influenced by these fluorine substituents. The six-member reference replicates the two tertiary carbons correctly. However, the extra methyl in the reference which is influenced by the fluorines ultimately produces a larger RSE than might be anticipated. A more complicated scheme to balance the number of carbons interacting with fluorine is outlined in Figure 5 and yields a smaller RSE.

Unlike fluorine and oxygen containing substituents, the data in Table 1 and earlier work[6] indicate that groups containing electronegative sp and sp^2 carbons do not lead to larger RSEs for the substituted cyclopropanes. Phenyl and acetylenyl substituents, respectively, decrease the RSE of cyclopropyl systems by ca. 2.5 and 2.9 kcal/mol. Trifluoromethyl substitution also decreases the RSE of the substituted cyclopropane by 0.9 kcal/mol.

2.2.3. Unsaturated rings. Table 2 illustrates the increase in RSEs upon introduction of a double bond into a small ring. The RSE decreases as the ring size increases: cyclopropene and cyclobutene have RSEs 26.7 and 3.9 kcal/mol larger, respectively, than their saturated analogues. The RSEs of the medium sized rings, cyclopentene, cyclohexene, and cycloheptene decrease by 2.6, 1.0, and 3.6 kcal/mol. Cyclohexene has a RSE near zero. These results compare well with the values from earlier methods based on experimental thermochemical data[1,20] (see Table 2).

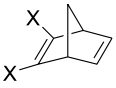
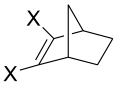
Methyl substitution at the double bond decreases the RSE in small rings. This trend reflects the relatively strong sp^2–sp^3

Table 3. Ring strain energies (kcal/mol) for polycyclic systems

		Wiberg[20]	This work			Wiberg[20] and others	This work
47		63.9[a]	66.3[b]	**58**		130[c]	123.6[d]
48		54.7[a]	54.7[b]	**59**		67.9[a]	68.6[e]
49		68[c]	67.0[b]	**60**		126[c]	117.4[d]
50		51.8[a]	52.1[b]	**61**		55.7[a]	55.5[e]
51		37[c]	38.4[b]	**62**		87[c]	84.2[d]
52		14.4[a]	16.6[b]	**63**		51[c]	51.7[e]
53		7.4[a]	11.6[b]	**64**		19.2[a]	21.6[e]
54		98[c]	98.2[f]	**65**		34.7[g]	32.3[h]
55		104[c]	98.1[f]	**66**		154.7[a]	153.8[i]
56		105[c]	96.9[f]	**67**		6.5[g]	6.0[j]
57		89[c]	90.2[f]				

[a] Values from experiment by Wiberg.[20]
[b] all-*trans* reference with two tertiary corrections.
[c] ab initio values from Wiberg.[20]
[d] See Eq. 9.
[e] See Eq. 8.
[f] all-*trans* reference with two quaternary corrections.
[g] Values from experiment by Schleyer.[1]
[h] See Eq. 10.
[i] See Eq. 6.
[j] See Eq. 7.

Table 4. Theoretical heats of hydrogenation for 7-norbornadienes, 7-norbornenes, 2,3-norbornadienes, and 2-norbornadienes

	Substituent	RSE		Substituent	RSE	Δ RSE
	**68**. OAc	24.8		**68a**. OAc	15.6	9.2
	69. OTBS	31.3		**69a**. OTBS	23.2	8.1
	70. O^{t}BU	31.1		**70a**. O^{t}BU	23.1	8.0
	65. H	32.3		**64a**. H	21.6	10.7
	71. ^{n}Hexyl	32.1		**71a**. ^{n}Hexyl	21.7	10.4
	72. Ph	33.1		**72a**. Ph	22.5	10.6
	**73**. OAc	13.3		**73a**. OAc	9.5	3.8
	74.OTBS	19.8		**74a**. OTBS	16.8	3.0
	75. O^{t}Bu	19.3		**75a**. O^{t}Bu	16.4	2.9
	64. H	21.6		**52a**. H	16.6	5.0
	76. ^{n}Hexyl	22.0		**76a**. ^{n}Hexyl	17.3	4.7
	**77**. COOMe	27.2		**77a**. COOMe	17.2	10.0
	78. $SiMe_3$	16.9		**78a**. $SiMe_3$	8.3	8.6
	79. Br	31.1		**79a**. Br	19.1	12.0
	65. H	32.3		**64a**. H	21.6	10.7
	80. ^{n}Hexyl	25.1		**80a**. ^{n}Hexyl	15.3	9.8
	**81**. COOEt	31.2		**81a**. COOEt	20.6	10.6
	65. H	32.3		**64a**. H	21.6	10.7
	82. ^{n}Hexyl	29.5		**82a**. ^{n}Hexyl	19.4	10.1
	83. Br	33.0		**83a**. Br	21.5	11.5
	84. $OSiMe_3$	31.3		**84a**. $OSiMe_3$	20.3	11.0

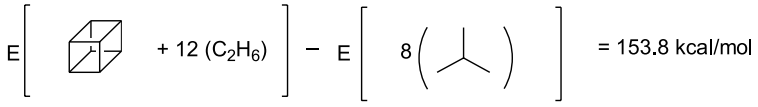
The heats of hydrogenation correspond to the difference in ring strain energy (kcal/mol) of the respective dienes and alkenes or alkenes and alkanes.

carbon–carbon bond. A single methyl substituent at the double bond is predicted to decrease the RSE of cyclopropene by 4.1 kcal/mol. Two methyl groups lead to an RSE smaller by 10.8 kcal/mol for cyclopropene. For methylcyclopropene, **33**, and dimethylcyclopropene, **34**, the reference compound has an extra carbon attached to the double bond. A greater RSE may result. Unlike the case shown in Figure 5, a simple correction has not been devised and the RSE values of **33** and **34** should be taken as approximate. This particular balancing problem vanishes in rings larger than cyclopropane.

The present work indicates that the decrease in RSE due to alkylation at the double bonds decreases as the ring size increases. The RSEs of methylene–cyclobutane and methylene–cyclohexane are within 0.5 kcal/mol of the values for their unsubstituted counterparts. Methylene–cyclopentane has an RSE which is 0.8 kcal/mol smaller than cyclopentane. These findings agree with those from earlier work.[20]

2.2.4. Polycyclic rings. The all-*trans* acyclic reference scheme for the saturated polycyclic systems in Table 3 produces RSEs in good agreement with the findings of Wiberg.[20] The RSEs for the tricyclo[2.1.1.0]hexane (**55**) and tricyclo[2.2.1.0]heptane (**56**) systems differ slightly from the values of Wiberg.[20] Tricyclo [1.1.1.0] pentane (**54**) is predicted to be more stable than the former propellanes as has been found experimentally.[21] The RSEs of structures **54** to **56** are predicted to be approximately equal and the large values reflect the three small three or four membered rings in each structure. Tricyclo[1.1.1.0]pentane might be expected to be the most highly strained ring because it is based on three fused cyclopropanes.

RSEs of cubane and adamantane agree well with the earlier findings of Wiberg[20] and Schleyer.[1] The relevant equations involving the polycyclic ring, ethanes, *t*-butanes and *E*(CH_2) are:



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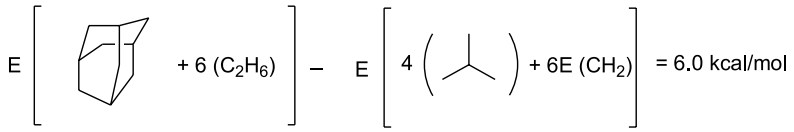
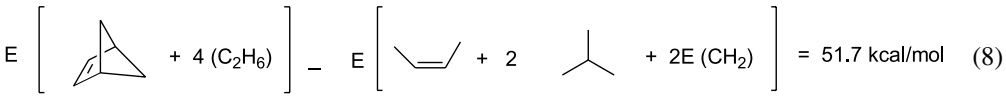
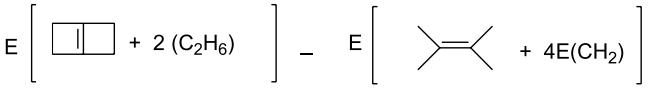


(7)

For unsaturated polycyclic rings, the *cis*-alkene reference is employed. The other carbons are maintained in the all-*trans* conformation. Two examples of the pattern of substitution for the 4-member (*cis*) and six-member acyclic reference are given in Eqs. 8 and 9, respectively. These two examples include the basic patterns related to the location of the double bonds in structures **58** to **64** in Table 3. The degree of substitution of the cyclic system is reproduced. The energies of the isobutanes balance the tertiary carbons in the cyclic system in Eq. 8.



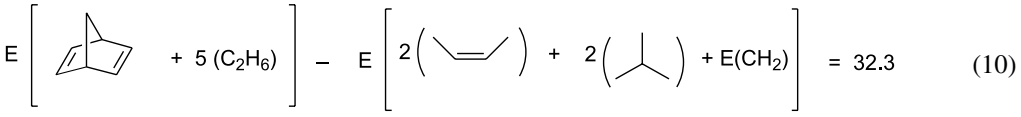
(8)



(9)

2.3. Substituted norbornanes, norbornenes and norbornadienes

The acyclic reference for norbornadiene (NBD) requires two *cis*-butene fragments to represent the double bonds in NBD, and two butanes



(10)

Table 4 reports theoretical heats of hydrogenation predicted as differences in the RSEs of the substituted bicyclic dienes and bicyclic alkenes or bicyclic alkenes and bicyclic alkanes. Including the parent systems with X and Y equal hydrogen, the RSEs of 42 substituted norbornanes, norbornenes, and norbornadienes are predicted and reported in Table 4. The effects of substituents on the RSEs will be discussed for the different bicyclic systems as well as comparisons of the norbornane, norbornene, and norbornadiene skeletons. The substituents are realistic from a chemical viewpoint, for example, OAc, O^{t}Bu, hexyl, and phenyl, as the reactivities of many of these species have been examined experimentally.[22]

2.3.1. 7-Substituted norbornadienes and norbornenes. Research by the Tam group[22,24] found that the rates of ruthenium catalyzed cycloaddition reactions of alkynes with bicyclic alkenes depend on the substituents on the norbornadienes and norbornenes. Electron-withdrawing groups at the 7-carbon in norbornadiene and norbornene decrease the electron density in the *anti*-π bond.[25] The electron deficient π bond leads to a slower rate of reaction. Electron-donating groups in the 7-position are associated with a faster relative rate of reaction. The ruthenium catalyzed cycloaddition reaction occurs by an oxidative-addition/reductive-elimination mechanism.[26] The height of the reaction barrier to the addition step which involves breakage of the *anti*-π bond of the norbornadiene or norbornene will be influenced by the character of that bond. If the reaction barriers to the oxidative addition steps are higher and thus overall rate-determining then the slower rate of reaction with an electron-withdrawing substituent corresponds to a higher reaction barrier. The reactivity of the norbornadiene or norbornene is related to the theoretical heat of hydrogenation (ΔRSE) upon reduction of the double bond.

The higher reactivity of the 7-substituted norbornadienes over the 7-substituted norbornenes is reflected in the larger ΔRSE values given in Table 4. ΔRSE values of the 7-substituted norbornenes are ca. 5 kcal/mol less than for the norbornadienes.

The OTBS and O^{t}Bu electron-withdrawing groups in **69** and **70** stabilize these norbornadienes by ca. 1 kcal/mol relative to norbornadiene, **65**. On the contrary, the same electron-withdrawing groups in the norbornenes **69a** and **70a** are destabilizing by ca. 1.5 kcal/mol. In **69** and **70** interactions of the electron withdrawing groups with the *anti*-double bond increases the stability slightly. This source of stability is absent in **69a** and **70a**. The small destabilization results from unfavorable interactions between the electron-withdrawing groups and the *syn*-double bond. OAc on **68a** substantially stabilizes, by 7.5 kcal/mol, this compound relative to norbornadiene, **65**. The OAc substituted norbornene **68a** is 6.0 kcal/mol more stable than norbornene itself, **64a**. The stability of **68** over **68a** is consistent with interactions of electron withdrawing groups with the double bonds mentioned above for OTBS and O^{t}Bu. However, OAc more strongly stabilizes both **68** and **68a** and the importance of σ-interactions may be inferred.

2.3.2. 7-Substituted norbornenes and norbornanes. Norbornenes **74** and **75** are 1.8 and 2.3 kcal/mol less strained than norbornene, **64a**. This is consistent with stabilizing interactions between the electron-withdrawing groups and the *anti* double bond. The RSEs of the substituted norbornanes **74a** and **75a** are nearly equal to that of norbornane, **52a**. Apparently OTBS and O^{t}Bu influence RSE through interactions with the π-bonds.

OAc again shows a large stabilizing effect which is enhanced further in **73** due to interactions with the *anti*-double bond.

2.3.3. 2,3-Disubstituted norbornenes and norbornadienes. Di-substitution with $SiMe_3$, **78**, and **78a** has by far the greatest stabilizing effect on norbornadiene, **65**, and norbornene **64a**, respectively. This effect is attributed to the large bulk of the substiuents and is analogous in principle to the corset effect[23] found in rings with large substituents. **77** and **77a**, with COOMe substituents as well as **80** and **80a** with hexyl groups are significantly less strained than their

unsubstituted parents. These stabilizations are due to carbon to sp^2 bonds as well as corset-type effects.

2.3.4. 2-Substituted norbornadienes and norrbornenes. The RSEs of **81**, **81a**, **82**, and **82a** are slightly smaller than unsubstituted norbornadiene, **65** and norbornene, **64a**. This small stabilization by alkyl substituents on a double bond is consistent with the RSE values predicted for alkyl substituted cyclopentenes in Table 2.

3. Conclusions

The homodesmotic approach to RSEs has been extended by including the effects of substituents in the acyclic reference. The resultant energy difference between the ring and the acyclic reference corresponds solely to the RSE which is one component of the total strain energy.

This is the first study to examine RSEs for 1,2-dimethyl substitution. The present method predicts smaller RSE for *cis*-1,2-di-substituted rings from cyclopropane through cyclohexane. The bulkier the substituent the greater the stabilization of the ring. This observation is consistent with the corset effect.[21] Balancing the types of carbons for substituted cyclopropanes and cyclopropenes creates an unresolved difficulty and the RSEs for these systems are somewhat approximate.

Introduction of a double bond into cyclopropane approximately doubles the RSE. However, for cyclobutene the RSE is only 4 kcal/mol greater than for cyclobutane. Cylopentene, cyclohexene, and cycloheptene all have smaller RSEs than their saturated analogues. Alkyl substitution at the double bond decreases the RSE. The change is greatest for the methyl-substituted cyclopropenes, and as with alkyl substitution in saturated rings decreases as the ring size increases.

Electron-withdrawing groups attached to the 7-carbon stabilize the norbornene or norbornadiene through interactions with the *anti* double bond. Such groups interact unfavorably with the *syn* double bonds. Alkyl groups have either a destabilizing or a negligible effect on these rings.

The present results indicate that the B3LYP/6-31G* level of theory can predict the RSEs of organic molecules. The chosen level of computation is modest so that large, substituted systems can be computed readily. The present schemes isolate RSE from the total strain in the true spirit of a homodesmotic reaction.

4. Computational methods

All predictions were made with Gaussian98.[27] The Becke three-parameter hybrid functional[28] combined with the Lee, Yang, Parr (LYP)[29] correlation functional, B3LYP, was used with the 6-31G(d) basis set. B3 as implemented in the Gaussian98 code was used.[30] All geometries were optimized and the structures had no imaginary vibrational frequencies indicating minimum energy forms. The zero-point vibrational energy corrections were not included in determining the energy differences as this would require a further balancing of the number of harmonic vibrational frequencies on the two sides of the basic energy difference equation.

5. Supporting information

Total energies and Cartesian coordinates for structures **1** to **84** follow this paper in the web version of this journal.

Acknowledgements

This research was supported in part by the Natural Sciences and Engineering Research Council of Canada (NSERC).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.06.100.

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19. Unlike the other branched alkanes, isobutane and neopentane are predicted to be stabilized relative to their acyclic isomers at the B3LYP level of theory. The tertiary and quaternary energy corrections are included in the reference energy so as to cancel the stabilization energy in the ring due to tertiary and quaternary carbons
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Synthesis of vinylcyclopentanes via samarium(II) mediated tandem reactions

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Received 16 February 2004; revised 8 June 2004; accepted 18 June 2004

Available online 4 August 2004

Abstract—In the presence of either visible light or HMPA, SmI_2 reacts with some carbohydrate derived ω-iodoallylic alcohols, and their acetylated derivatives, to give vinylcyclopentanediol and vinylcyclopentanetriol derivatives.

1. Introduction

Samarium(II) iodide is a versatile reducing reagent that has been the subject of a large number of scientific papers over the past two decades.[1] The reduction of organic halides by SmI_2 in THF was first described by Kagan's group[2] and several years later Inanaga and coworkers reported that these reactions are faster when hexamethylphosphoramide (HMPA) is added to the reaction mixtures.[3a] Electrochemical studies on SmI_2/THF/HMPA solutions[3b] and X-ray structures of $SmI_2(hmpa)_4$[3c] and $[Sm(hmpa)_6]I_2$[3d] have since been published. Kinetic studies comparing SmI_2 in THF with SmI_2 in THF/HMPA,[3e] and studies on the mechanism of electron transfer (inner-sphere-type versus outer-sphere-type) between Sm(II) and organic substrates,[3f,g] have been reported. An article describing the structure and energetics of the SmI_2–HMPA complex in THF has also appeared in the literature.[3h] Together these papers have given us an appreciation of the role HMPA plays in changing the redox properties of divalent samarium.

While the addition of HMPA to SmI_2 reaction mixtures is now fairly common, significant efforts have been directed towards finding safer promoters of SmI_2 reductions. Several years ago, the groups of Ogawa,[4a] Scaiano[4b] and Molander[5] reported that irradiation of SmI_2 reaction mixtures of organic halides with visible light results in a significant reactivity enhancement. Literature reports described the efficient reduction of organic chlorides by the photoirradiation of SmI_2 reaction mixtures;[4,5] the absorbance of visible light by SmI_2 in the 560–700 nm range was attributed to a $4f^6$ to $4f^5 5d^1$ electronic transition and the observed reactivity enhancement associated with an efficient electron transfer between photoexcited SmI_2 and the organic halides.[4a] More recently, Hilmersson and collaborators have found that mixtures of SmI_2/H_2O/amine can also be successfully used to reduce alkyl halides.[6]

As well as being a popular reducing reagent for individual transformations, samarium(II) iodide is useful in promoting sequential or tandem reactions.[1d,e] In a preliminary communication from our group we reported that *E* and *Z* ω-iodoallylic acetates **1a** and **1b** react with SmI_2 in a stereodivergent manner to give the vinylcyclopentanetriol derivatives **3a** and **3b** [Fig. 1 and Table 1 (entries g and h)].[7] The vinylcyclopentane derivatives **3a** and **3b** are formed by a sequence of Sm(II) mediated steps and, at the time of our first report, our best results were obtained for reactions run at low temperature with an excess of SmI_2 in the presence of both HMPA and MeOH. In contrast, the Bu_3SnH mediated reactions of **1a** and **1b** gave the reductive cyclization compounds **6a** and **6b** [Table 3, entries a and b]. Reaction of the corresponding ω-iodoallylic alcohol **2b** with SmI_2 in THF–HMPA–MeOH under similar conditions was incomplete (Table 1, entry d); initial attempts to improve the efficiency resulted in the formation of complex mixtures and in a lower overall mass balance[8] but we have since overcome these difficulties. We have expanded our investigation so as to establish the generality of this method and to identity the factors that are important with respect to the efficiency and selectivity of these transformations.

The synthesis of functionalized cyclopentane molecules

Keywords: Alkenyl halides; Cyclisation; Samarium and compounds; Tandem or sequential reactions.
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doi:10.1016/j.tet.2004.06.099

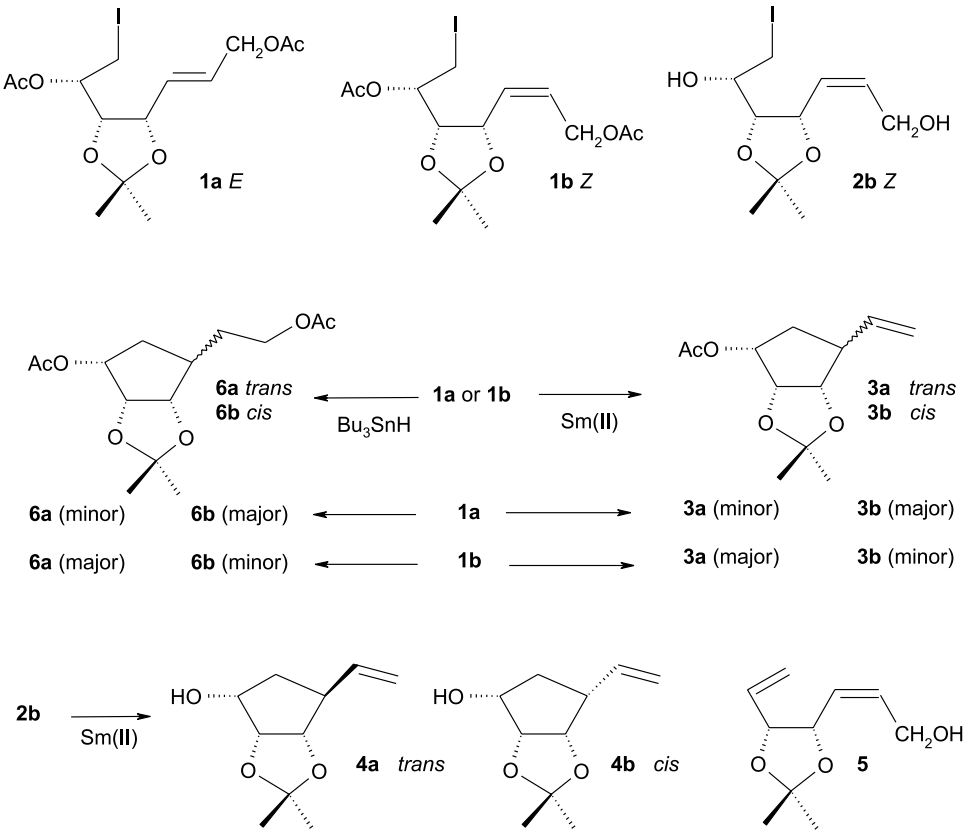


Figure 1. Reaction of **1a**, **1b** and **2b** with SmI_2 and Bu_3SnH.[7]

Table 1. SmI_2 reactions of ω-iodoallylic acetates **1a** and **1b** and ω-iodoallylic alcohols **2a** and **2b**

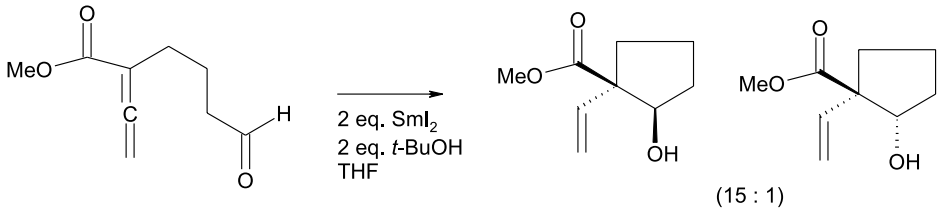
Exp.	S. mat and method[a]		SmI_2/MeOH/HMPA ratio	Isolated yields[b] (%)			
				$Tandem_{trans}$	$Tandem_{cis}$	Diene	S. mat.
a	**2b**	A2 (3 h)	3:0:0	**4a**:11	**4b**:3	**5**:3[c]	50
b	**2b**	A2 (4 h)	3:9:0	**4a**:34	**4b**:13	**5**:19[c]	36[c]
c	**2b**	D (2.5 h)	4:10:0	**4a**+**4b**:57[d] (**4a**/**4b**=89/11)		**5**:14	—[e,f]
d	**2b**	A1	5:11:20	**4a**:51	**4b** —[g]	—[g]	30
e	**2b**	B2	6:10:14.4	**4a**:76	**4b** —[e,f]	—[e,f]	—[e,f]
f	**2a**	B2	6:10:14.6	**4a**+**4b**:62[d] (**4a**/**4b**=53/47)		—[e,f]	—[e,f]
g	**1a**	A1	5:13:21	**3a**:26	**3b**:65	—[g]	—[g]
h	**1b**	A1	5:10:20	**3a**:76	**3b**:6	—[g]	—[g]
i	**1b**	A2 (o.night)	5:0:0	**3a**:34	**3b**:18	—[g]	39

[a] With the exception of entries a and i, reactions were run in THF with 1 equiv of substrate, 9–13 equiv of MeOH, 3–6 equiv of SmI_2 and 0–21 equiv of HMPA; entries a and i were run in the absence of MeOH. See Section 4 for details of Sm(II) methods.
[b] Compounds **4a** and **4b** are somewhat volatile and care must be taken to avoid loss during solvent removal steps.
[c] Isolated as a slightly impure sample as determined by NMR.
[d] In this experiment compounds **4a** and **4b** were isolated as a mixture; the *trans*/*cis* ratio was determined by ^1H NMR.
[e] Compound not detected by TLC analysis of crude products before chromatography.
[f] Not detected by GC–MS analysis of crude products before chromatography.
[g] Not detected by either TLC or NMR analysis of the crude products before chromatography.

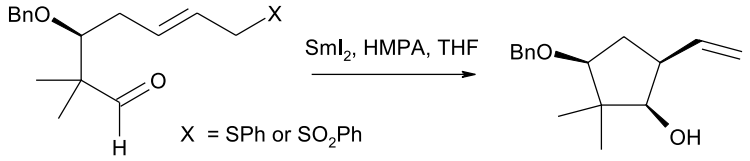
using SmI_2 mediated annulation reactions is a research objective that is shared by many groups. A number of excellent methods have been reported in the literature but only a few of these Sm(II) mediated cyclizations give direct access to vinylcyclopentanes.[1,9] Gillmann[9a] reported that intramolecular reductive coupling of an aldehyde with an allenic ester gives vinylcyclopentanols. The selectivity of the reaction was attributed to chelation with a samarium ion thus favoring formation of the diastereoisomer with the hydroxyl and ester groups *cis* to one another (Scheme 1).

Kan et al.[9b] found that aldehydes tethered to an allyl sulfide or sulfone are also reduced with samarium(II) iodide in the presence of HMPA to give vinylcyclopentanol products in a stereoselective fashion. Unsubstituted 7-(phenylthio)-5-heptenal or 7-(phenylsulfonyl)-5-heptenal substrates give the corresponding *trans* vinylcyclopentanol. Substrates with additional functional groups may react to give *cis* products preferentially as illustrated below (Scheme 2).

Molander and Harris[9c] have described the synthesis of



Scheme 1.



Scheme 2.

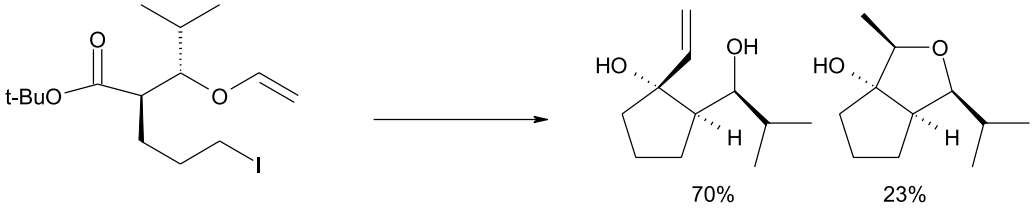
vinylcyclopentanes via a one pot, three step, nucleophilic acyl substitution/ketyl-olefin coupling/β-elimination sequence. Cyclopentanones with a pendant enol ether are generated after the first step. Samarium(II) initiated ketyl-olefin coupling is then either followed by β-elimination or by competitive protonation (Scheme 3).

Aurrecoechea and López[9d] found that ring contraction of 6-enopyranosides to form diastereomeric mixtures of vinylcyclopentanols is possible using SmI_2 and a catalytic amount of Pd(0); the major products are those in which the vinyl and hydroxyl groups of the newly formed stereocenters are *trans* to one another. A representative example is shown below. These reactions are thought to involve Pd(0)-mediated ring opening and formation of an aldehyde tethered to a π-allyl palladium complex. Reduction of the palladium complex with SmI_2 and coupling of the resulting allylsamarium species with the aldehyde function gives the vinylcyclopentanol reaction products (Scheme 4).

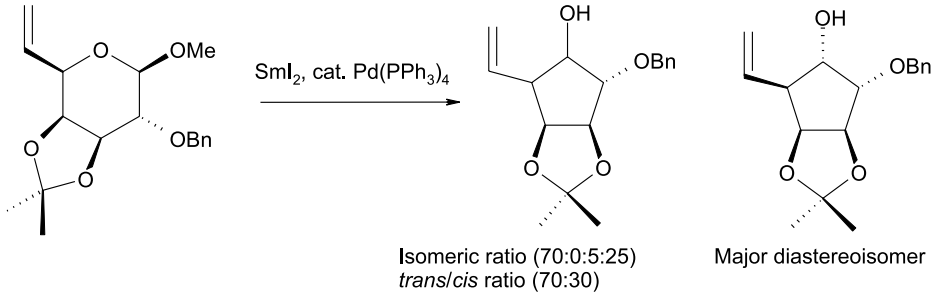
Our approach to vinylcyclopentanes differs from those of other groups (vide supra) in that our annulation reactions do not involve an addition to a carbonyl carbon. Because we have used primary alkyl iodides as substrates, our cyclization reactions result in the formation of only one new stereocenter. The following section describes the synthesis of vinylcyclopentanediol and vinylcyclopentanetriol derivatives from ω-iodoallylic alcohol substrates, or their acetylated derivatives, via a sequence of samarium(II) iodide mediated transformations using either visible light or HMPA as a promoter. The chemoselectivity and the stereoselectivity of these Sm(II) reactions were compared to those with Bu_3SnH. Reactions with Bu_3SnH gave the expected 5-*exo* radical cyclization products whereas vinylcyclopentanes were the major products of the Sm(II) mediated tandem reactions.

2. Results and discussion

The substrates for this present study were prepared by 1,2-reduction of known carbohydrate-derived conjugated *tert*-butyl esters with DIBAL.[10] After workup and chromatography the desired allylic alcohols **2a**, **2b**, **10a**, **10b** and **11**



Scheme 3.



Scheme 4.

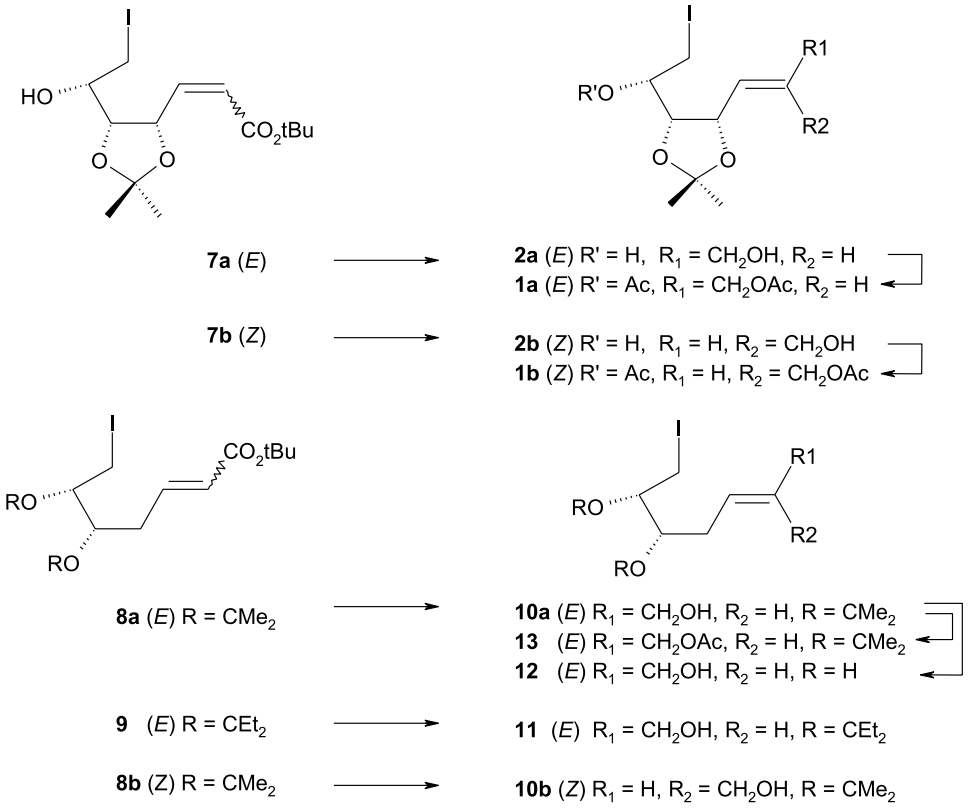


Figure 2. Preparation of ω-iodoallylic alcohols and acetates.

were isolated in moderate to good yields. Acetylation of the free hydroxyl groups of **2a**, **2b** and **10a** under standard conditions gave compounds **1a**, **1b** and **13**. The acetonide group of **10a** was removed by treatment with MeOH and an acidic resin to give the triol **12** in good yield (Fig. 2).

The experimental conditions and results of reactions with Sm(II) for **1a**, **1b**, **2a** and **2b** are shown in Table 1 and those for compounds **10a**, **10b**, **11**, **12** and **13** are summarized in Table 2. We used commercially available solutions of SmI_2 for our experiments. The SmI_2 solution was transferred dropwise, using a cannula, over ca. 10 min to a solution of the ω-iodoallylic alcohol in THF/MeOH or in THF/HMPA/MeOH under an argon atmosphere. The final concentration of the starting material was 0.015 M. It should be noted that, at the time reactions were quenched, the reaction mixtures were still either the deep blue color associated with SmI_2 in THF or the purple color associated with solutions of SmI_2 in THF/HMPA. This was also true for experiments where the reduction was incomplete, as judged by the presence of either unreacted starting material or simple reductive cyclization compounds.

Our initial investigations focused on compound **2b**. Room temperature reactions with an excess of SmI_2 in THF under ambient lighting conditions are incomplete after 3 h and gave complex mixtures of starting material, vinylcyclopentanes (**4a** and **4b**) and non-cyclized β-elimination product **5** (Table 1, entry a). The stereoselectivity of the tandem cyclization-reductive elimination process was poor. One of the reaction condition changes that we considered involved adding a proton source. We also considered either irradiating our reaction mixtures with a visible light source or changing the nature of the Sm(II) reductant by in situ coordination with HMPA ligands. Our mass balance improved when the reaction was run in the presence of MeOH but the reaction was non selective and still incomplete after 4 h at room temperature. There is an marked improvement in stereoselectivity when the Sm(II) reductions were run with either visible light or HMPA as a promoter. Photoirradiation of the reaction mixture, using a xenon lamp, allowed us to push the reduction to completion and to improve the stereoselectivity of the reaction. Unfortunately, an appreciable amount of compound **5** was formed under these conditions. We had more success using HMPA as a promoter for the sequenced reactions of **2b** but light was successfully used with some of the other substrates described in this paper (vide infra).

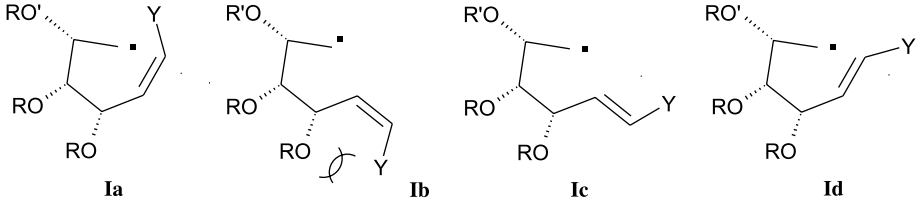
Reaction of **2b** at low temperature with 5 equiv of SmI_2 and 20 equiv of HMPA was stereoselective but incomplete (Table 1, entry d); attempts to push the reduction to completion by simply increasing the quantity of SmI_2 from 5 to 7 equiv, while keeping the SmI_2–HMPA ratio at ca. 1:4, resulted in the formation of some of compound **5**.[8] This loss of chemoselectivity is presumably due to an increase in the rate of the β-elimination reaction due to the increase in the Sm(II) concentration. This pathway, leading to **5**, is competitive with that leading to **4a** (Scheme 5). We have since found that a more successful and convenient approach is to run the reaction at room temperature with a different molar ratio of substrate, SmI_2, and HMPA (vide infra). The selectivity of the reaction was excellent and the isolated yield of **4a** was good (Table 1, entry e).

As one might expect, based on considerations of A-strain,[11]

Table 2. Reactions of 2-deoxy-D-ribose derived substrates with SmI_2–HMPA and SmI_2–hν

Exp.	S.mat.	Method[a] and SmI_2/HMPA ratio		Tandem (T_{trans},T_{cis}) and simple (S_{trans},S_{cis}) reaction product ratios[b]				Yield (%) of vinylcyclo-pentanes
				T_{trans}	T_{cis}	S_{trans}	S_{cis}	
a	**10a**	C	4:19	83	11	6	0	39[c]
b	**10a**	B1	4:19	85	13	2	0	91[d]
c	**10a**	B1	4:19	82	12	6	0	n.d.
d	**10a**	B1	4:9.5	87	2	11	0	72[d]
e	**10a**	C	4:9.5	58	7	32	3	46[d]
f	**10a**	B1	4:4.8	61	8	21	2	44[d,e]
g	**10a**	B1	4:0	16	2	9	0	n.d.[f]
h	**10a**	B2	4:0	28	11	13	3	n.d.[g]
i	**10a**	B2	4:19	90	3	7	0	58[d,h]
j	**10a**	B2	6:14	95	3	2	0	60[d,h]
k	**10a**	D	4:0	91	5	4	0	65[d]
l	**10b**	D	4:0	82	15	3	0	84[d]
m	**10b**	B2	6:14	83	10	7	0	90[d]
n	**10b**	B2	4:19	84	16	0	0	50[c]
o	**10b**	B1	4:19	83	8	9	0	56[d]
p	**13**	D	4:0	80	20	0	0	80[d]
q	**13**	B2	6:14	53	9	31	7	48[d]
r	**13**	B1	4:9.5	82	0	18	0	n.d.
s	**13**	B1	4:19	67	7	20	6	51[d]
t	**11**	D	4:0	78	22	0	0	79[c]
u	**11**	B2	6:14	92	8	0	0	77[c]
v	**11**	B2	4:19	84	14	2	0	74[c]
x	**12**	D	4:0	40	60	0	0	73[c]
y	**12**	B2[i]	6:14	28	51	7	13	56[c,j]

[a] With the exception of entry c, reactions were run in THF with 1 equiv of substrate, 10 equiv of MeOH, 4–6 equiv of SmI_2 and 0–19 equiv of HMPA; entry c was run in the absence of MeOH. See Section 4 for details on Sm(II) methods.
[b] Ratios determined by GC–MS after workup and before concentration of the dried organic phase.
[c] Isolated yield of purified compounds.
[d] GC yields are reported for **14a** and **14b** (volatile compounds); these values were determined after chromatography but before evaporation of solvents. The error associated with these values is less than or equal to 5%.
[e] Incomplete; GC–MS of crude indicated that **10a** accounted for 8% of reaction products.
[f] Incomplete; GC–MS of crude indicated that **10a** accounted for 71% of reaction products. Trace amounts of two unidentified compounds were also detected in the crude products.
[g] Incomplete; GC–MS of crude indicated that **10a** accounted for 45% of reaction products.
[h] The organic phase was washed several times with aq. $CuSO_4$ to remove residual HMPA.
[i] Reaction products for this experiment with **12** were isolated as their acetylated derivatives; product ratios were determined by ^{1}H NMR.
[j] Simple cyclization products **22a**+**22b** were also isolated (14%).



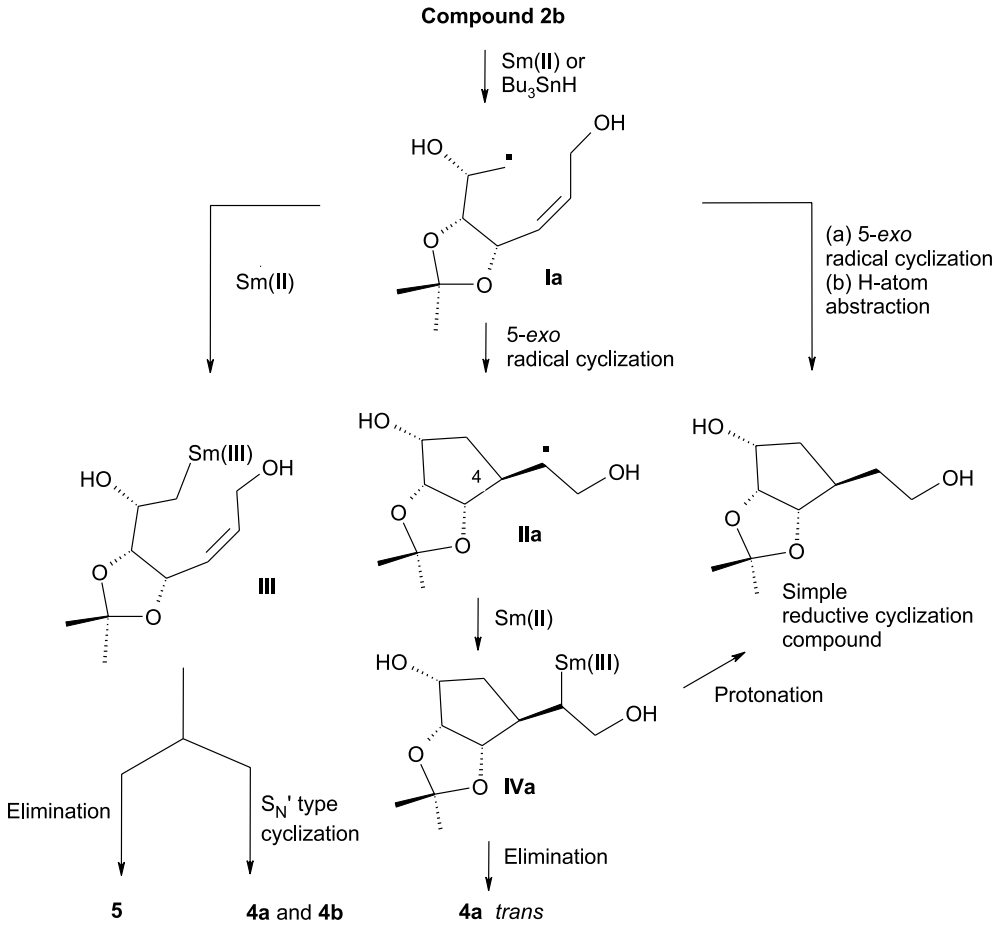
Ia **Ib** **Ic** **Id**

the Sm(II)-mediated cyclization of the *Z* ω-iodoallylic alcohol **2b** is more stereoselective than that of the corresponding *E* isomer **2a**. Cyclization via conformer **Ia** leads to the *trans* product while cyclization via conformer **Ib** is expected to be the minor pathway and leads to formation of the *cis* products. Reaction of **2a**, under the

Table 3. Reductive cyclizations with Bu_3SnH

Entry	S. mat. and method[a]		Simple reductive cyclization products	
			Diastereomeric ratios (*trans*/*cis*)[b]	Isolated yields (%)[c]
a	**1b**	Method E	79/21	**6a**+**6b**:72
b	**1a**	Method E	37/63	**6a**+**6b**:25; **1a**:10
c	**2b**	Method F[d]	93/7	**6a**+**6b**:61
d	**10a**	Method F	82/18	**18a**+**18b**:75
e	**10b**	Method F	90/10	**18a**+**18b**:63
f	**13**	Method F	76/24	**20a**+**20b**:86
g	**11**	Method F	89/11	**19a**+**19b**:73
h	**12**	Method F[d]	42/58	**22a**+**22b**:62

[a] Method E: Bu_3SnH, AIBN, refluxing benzene. Method F: Bu_3SnH, Et_3B, toluene (d–g) or THF (c, h), room temperature.
[b] Ratios determined by ^{1}H NMR and/or GC–MS after workup and chromatography.
[c] Isolated yield of purified compounds.
[d] Products of reactions of **12** and **2b** were isolated as their acetylated derivatives.



Scheme 5. Possible mechanistic pathways.

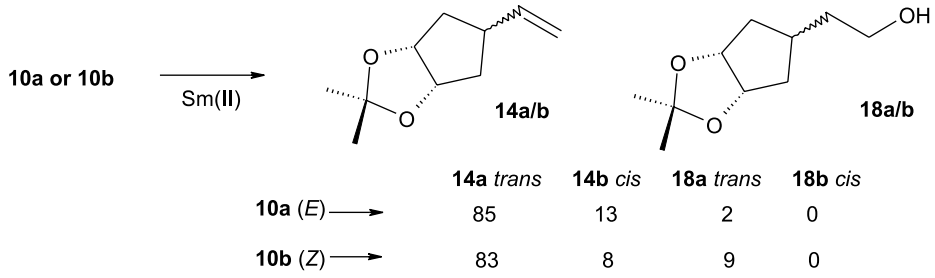
room temperature SmI_2–HMPA conditions, resulted in the formation of both *trans* and *cis*-cyclized products **4a** and **4b** in almost equal proportions (Table 1, entry f).

Reduction of the acetylated derivatives **1a** and **1b** with SmI_2 in the presence of HMPA also results in the formation of vinylcyclopentane products. While the stereoselectivity for the ω-iodoallylic acetate **1b** is slightly less than that observed for the ω-iodoallylic alcohol **2b**, both of these *Z* substrates give predominantly the *trans* tandem products. Once again, as expected, the double bond geometry has a marked effect on the stereoselectivity of these reactions and reduction of the *E* diastereoisomer **1a** gives predominantly the *cis* derivative **3b** (Table 1, entry g).

Two possible mechanisms, that may explain our observations for substrate **2b**, are illustrated in Scheme 5. They involve either a radical or a S_N' type cyclization.[12] It is relevant to note that reduction of **2b** with Bu_3SnH (Table 3, entry c) gives the 5-*exo* radical cyclization products; compounds **5**, **4a** and **4b** were not detected in our Bu_3SnH reaction mixture. This observation together with the requirement of an excess of Sm(II) suggests that organosamarium intermediates are involved at some stage in our reactions and result in the formation of β-elimination products.[13–15] Scheme 5 presents two possible pathways available to compound **2b**.

Sm(II) reduction of **2b** gives a primary radical which may either (1) cyclize in a 5-*exo* fashion to give the cyclic secondary radical **IIa** or (2) be reduced by a second equivalent of Sm(II) to give organosamarium species **III**. Cyclization via conformer **Ia** would eventually give the *trans* product in which the C-4 substituent is on the opposite side as all the other ring substituents. In the Bu_3SnH mediated reaction, H-atom abstraction allows for the transformation of **IIa** to the simple reductive cyclization compound. In the samarium(II) mediated conversion, this is also a possibility if H-atom abstraction from THF is competitive with further reduction. Alternatively, the cyclic secondary radical **IIa** may be reduced by Sm(II) to give an organosamarium intermediate **IVa**; β-elimination results in formation of **4a**. If intermediate **III** is formed, it may then either (1) undergo β-elimination to give diene **5** or (2) cyclize in a S_N' type fashion to give the vinylcyclopentane derivatives **4a** and **4b**. Elimination may be assisted by coordination of the departing hydroxyl groups with Sm(III).

Both the *Z* double bond geometry of **1b** and **2b** and the presence of a substituent at the γ-position are factors that favor formation of *trans* vinylcyclopentanetriol derivatives **3a** and **4a**. Reductions of the *E* isomer **1a** with Sm(II) were less stereoselective than those with **1b** and the major product was the *cis* derivative **3b**. The *E* ω-iodoallylic alcohol **2a** gave almost equal amounts of the *trans* and *cis* compounds **4a** and **4b**. This same tendency for stereodivergence was not, however, seen with the simpler compounds



Scheme 6.

10a and **10b**; these two ω-iodoallylic alcohols lack a substituent at the γ-position. Reduction of either **10a** or **10b** with Sm(II) gives the same *trans* vinylcyclopentane derivative **14a** as the major reaction product (Scheme 6).

Compound **14a** is the major product formed when Sm(II) reacts with either **10a**, **10b** or **13** (see Table 2). It is not the only product however and small quantities of other compounds were detected by GC–MS analysis of our crude reaction products before chromatography; one of these minor components is the expected *cis* isomer **14b**. Based on our results with compound **2b** we considered the possibility that uncyclized β-elimination products (Fig. 3) might be present as minor reaction products. This proved to be incorrect as the minor reaction products were actually the simple reductive cyclization compounds. Reactions run with Bu_3SnH and our substrates (Table 3) allowed us to prepare authentic samples of compounds **18**–**22**; NMR and GC–MS data for these compounds matched those of the minor reaction products of the Sm(II) reactions.

Crude and purified products were analyzed by TLC, GC–MS and by NMR. The product ratios were determined after reaction workup but before chromatography. The vinylcyclopentane derivatives **14a** and **14b** are somewhat volatile and so, with the exception of entries a and n of Table 2, the yields given for these compounds are GC yields determined after chromatography using a calibration curve. Reaction products of substrate **11** are less volatile and yields reported in entries t–v are for the isolated compounds **15a** and **15b**. The isolation of reaction products of substrate **12** with Sm(II)–HMPA was complicated by the solubility of compounds **16a** and **16b** in water and so the yield reported for the last entry of Table 2 corresponds to that of the peracetylated derivatives **17a** and **17b**.

Either visible light or HMPA can be used to facilitate these reactions. Reactions using visible light as a promoter were carried out at room temperature using a xenon lamp with appropriate filters. Reaction conditions involving the photoirradiation of SmI_2 reaction mixtures with a visible light source offered some practical advantages over the HMPA conditions. In addition to the obvious safety consideration of using visible light as a promoter, rather than HMPA, isolated yields of vinylcyclopentanediol derivatives were higher for substrates **11**–**13**. Isolation of the major reaction products was easier due, in part, to a simpler workup procedure and because reactions run under the SmI_2-hν conditions favored the exclusive (Table 2, entries p, t, x) or near exclusive (entries k and l) formation of the vinylcyclopentanediol compounds. The stereochemistry of the SmI_2–hν reactions, of the Figure 3 substrates, was equivalent or slightly less than that observed under our best Sm(II)–HMPA conditions.

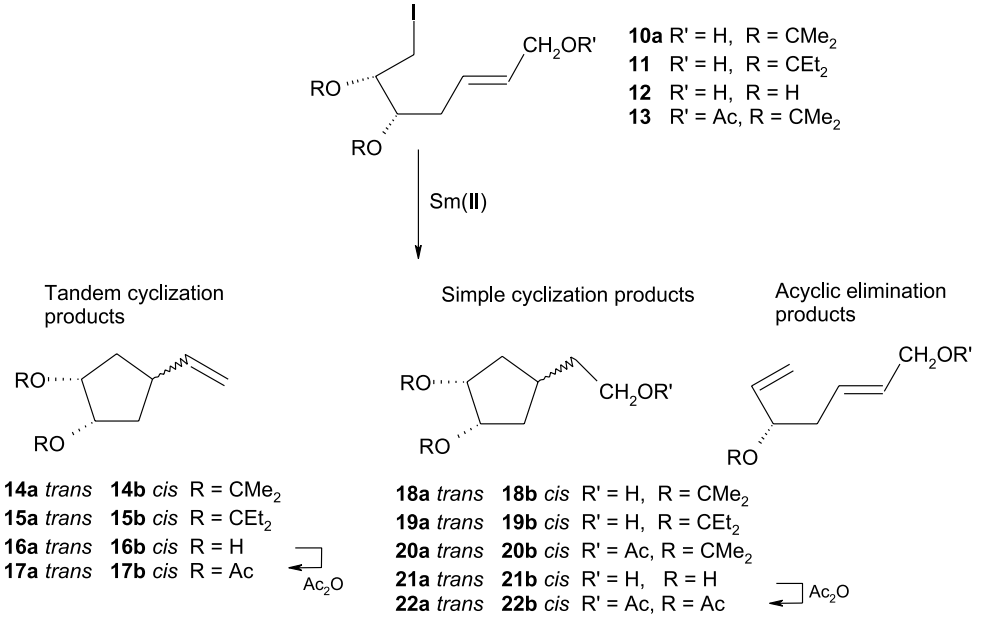


Figure 3. Conversion of ω-iodoallylic alcohols to tandem and simple cyclization products.

The results of the Sm(II)–HMPA mediated reactions of substrates **10**–**13** (Table 2) show that the diastereoselectivity and the product distribution vary with the reaction conditions and the substrate characteristics. Reactions with SmI_2-HMPA were run at either room temperature (Method B2) or at −78 °C (Methods B1 and C) under ambient lighting conditions in the presence of MeOH and with either 4 or 6 equiv of SmI_2 per equivalent of alkenyl iodide. Although the sequenced reactions formally require only 2 equiv of Sm(II), we routinely ran these reactions in the presence of excess reagent. We found that both the quantity of HMPA and its order of addition are key factors in the determining the outcome of these Sm(II)–HMPA mediated reductions. The proportion of unreacted starting material and simple reductive cyclization products increases as the quantity of HMPA is reduced for both the −78 °C and the room temperature reactions. As we decreased the quantity of HMPA (entries b, d, f, g) we observed a drop in the proportion of vinylcyclopentanediol products; in the absence of HMPA at −78 °C (entry g) the major reaction component is unreacted starting material **10a**. Removal of methanol from the reaction mixture does not have an appreciable effect on the ratio of tandem–simple cyclization products (entries b and c).

One might expect a decrease in the ratio of tandem–simple cyclization products under conditions where the Sm(II) reducing reagent is not reactive enough to ensure that reduction of the cyclized radical and β-elimination, to give vinylcyclopentanes, is favored over hydrogen-atom abstraction (Scheme 5). The redox potential of Sm(II)–HMPA complexes varies with the number of coordinated HMPA ligands[3] and so it is not surprising that our results vary with the SmI_2–HMPA ratios. The nature of the Sm(II)–HMPA complexes formed in solution, when SmI_2 in THF is mixed with HMPA, depends on the HMPA–SmI_2 molar ratio. It has been proposed that, in the presence of more than 10 equiv of HMPA, the species formed is $[Sm(HMPA)_6]I_2$. At 4 equiv, the principal species is $[Sm(HMPA)_4(THF)_2]I_2$ and at intermediate concentrations of HMPA (4–10 equiv) both species are present. The exact nature of the Sm(II)–HMPA complexes formed in solution in the presence of less than 4 equiv of HMPA is not well understood.[3f]

With the exception of entries a and e, all of the Sm(II)–HMPA reactions summarized in Table 2 involve the dropwise addition of SmI_2 in THF to solutions of our substrates in THF/MeOH/HMPA (Methods B1 and B2). The order of addition of HMPA had little effect on results of reactions of **10a** with SmI_2 when the **10a**–SmI_2–HMPA ratio was 1:4:19 (entries a and b). This was not true for reactions with a lower HMPA–SmI_2 ratio. If HMPA and the THF solution of SmI_2 were first pre-mixed, before transferring the resulting purple solution to a cooled solution of **10a** in THF–MeOH (Method C), we observed a decrease in the ratio of tandem–simple cyclization products and in the ratio of *trans*:*cis* products (entries d and e). Precomplexation, of Sm(II) with less than 4 equiv of HMPA per equivalent of SmI_2, should result in the formation of Sm(II)–HMPA complexes, with fewer HMPA ligands, that are weaker reducing reagents than the complex or complexes formed when the HMPA–SmI_2 ratio is greater than 4:1 (entry a). Why do we see an increase in the amount of vinylcyclopentanes formed if the THF solution of SmI_2 is added dropwise to a solution of **10a** in THF–MeOH–HMPA? We noticed that, during the initial phase of the transfer process, the deep blue color of the SmI_2/THF solution rapidly dissipates and the deep purple color associated with SmI_2/THF/HMPA solutions persisted only after addition of ca. two molar equivalents of Sm(II). One possible explanation for this observation and for the differences observed for Methods B1 and C (entries d and e) is that during the addition of the first 2 equiv of SmI_2, to the solution of the substrate in THF–MeOH–HMPA, the ratio of HMPA–SmI_2 is actually greater than 4:1 and so the Sm(II)–HMPA species that initially forms and rapidly reacts with **10a** has a greater number of HMPA ligands coordinated to Sm(II) than does the reagent formed under the Method C conditions.

Entry j (Table 2) summarizes a set of convenient reaction parameters for **10a** that allowed us to achieve both a high ratio of tandem–simple reductive cyclization products as well as a high level of diastereoselectivity. The reaction was run at room temperature and does not require premixing of SmI_2 and HMPA. These conditions, as well as the SmI_2–hν conditions, were then used for the reactions of the other substrates of this series. Both the isopropylidene and the isopentylidene substrates **10a** and **11** give excellent ratios of tandem–simple cyclization products under these conditions (entries j and u, Table 2) with a slightly better diastereoselectivity observed for **10a**. Acetylation of the hydroxyl group of **10a** to give **13** had a detrimental effect on the Sm(II)–HMPA sequenced reactions (entry q), however reaction of **13** under the SmI_2–hν conditions exclusively gave compounds **14a** and **14b** in an 80:20 ratio (entry p). Removal of the protecting group of the 1,2-diol group had a bigger impact on product distribution; reductions of **12** with either SmI_2–hν or Sm(II)–HMPA gave slightly more *cis* cyclization products than *trans* cyclization products. We observed a similar level of diastereoselectivity for the Bu_3SnH mediated reaction of **12** (entry h, Table 3). The *trans*/*cis* ratio was 42/58 for the reductive cyclization products of the Bu_3SnH reaction and 40/60 for the tandem products of the SmI_2–hν reaction of **12**.

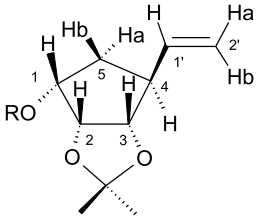
2.1. Structure assignment for tandem and simple cyclization products

The ω-iodoallylic alcohols that we used in this study originate from either D-(+)-ribonic γ-lactone (**1a**, **1b**, **2a**, **2b**) or 2-deoxy-D-ribose (**10**–**13**). The relative configuration of C_4 for compounds **4a** and **4b** was determined using the known configuration of C_1, C_2 and C_3 together with NMR data from NOE and COSY experiments, vicinal coupling constants, and simple ^1H–^1H decoupling experiments. Analysis of the coupling constants associated with the H_3 and H_4 protons is complicated by the fact that, for the ^1H NMR spectrum of **4a** in $CDCl_3$, H_4 appears as a complex multiplet and the H_3 and H_2 signals overlap to give an apparent doublet. ^1H NMR spectra of **4a** were also recorded in acetone-d_6 and benzene-d_6. Although the use of acetone-d_6 did give a better resolution of some signals (i.e. $H_{2a'}$, $H_{2b'}$, H_{5a} and H_{5b}) it did not allow us to resolve the H_2 and

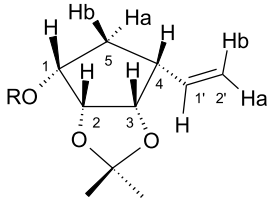
H_3 signals; separation of these signals was achieved, however, using benzene-d_6.

The ^{1}H NMR spectrum of **4b** in $CDCl_3$ was easier to analyze as, unlike **4a**, the H_2 and H_3 protons have different chemical shifts; the signals, of these two protons present as apparent triplets due to similar coupling between H_3 and either H_2 or H_4 as well as between H_2 and either H_3 or H_1. The vicinal coupling constants that we measured ($J_{3,2}$ and $J_{3,4}$ are both ca. 5 Hz) are consistent with the H_3 and H_4 protons *syn* to one another. We therefore assigned structure **4b** to the minor diastereoisomer isolated from the reaction of **2b** with SmI_2 in THF/MeOH (Table 1, entry b).

The NOE experiments that we ran support our structural assignments for compounds **4a** and **4b**. We saw a smaller NOE between the signals of H_4 and of H_2+H_3 in the case of isomer **4a** (where H_4 and H_3 are *anti* and the H_2 and H_3 signals overlap) than we saw in the case of isomer **4b** (where H_4 and H_3 are *syn*). Irradiation of **4a** in acetone-d_6 at 2.60 ppm (H_4) resulted in a total NOE of 1.3% for the overlapping H_2+H_3 signals. Irradiation of **4b** ($CDCl_3+D_2O$) at 2.28 ppm (H_4) resulted in a total NOE of 4.6% for the combined H_2+H_3 signals.



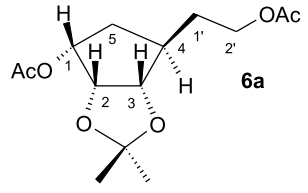
3a R = Ac
4a R = H



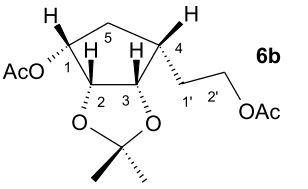
3b R = Ac
4b R = H

We determined the relative configuration of C_4 of compounds **3a** and **3b** in a similar fashion. The $J_{3,4}$ value of **3a** (1.3 Hz) was determined with the help of decoupling experiments and is consistent with H_3 and H_4 *anti* to one another. The COSY spectrum of **3a** showed only a weak correlation between H_4 and H_3. The $J_{3,4}$ coupling constant (4.8 Hz) of **3b** was determined with the help of ^{1}H–^{1}H decoupling and HOM2DJ experiments and was consistent with the H_3 and H_4 protons of **3b** *syn* to one another. Therefore, the relative configurations of compounds **3a** (*trans* isomer) and **3b** (*cis* isomer) are as shown. Our NOE experiments supported this stereochemical assignment. Upon irradiation of the H_3 signal of **3a** we observed a smaller NOE effect for H_4 (2.0%) than we did in the corresponding experiment for **3b** (i.e. 4.3% enhancement for H_4 upon irradiation at H_3). Irradiation of H_4 resulted in a smaller NOE effect for the H_3 proton of **3a** (1.6%) than for the H_3 proton of **3b** (5.7%).

The relative configurations of the simple cyclization products **6a** (*trans* isomer) and **6b** (*cis* isomer) were also determined by using the known configurations of C_1, C_2 and C_3 together with NOE experiments. Upon irradiation of the H_3 signal of compound **6a**, we observed a 8.4% enhancement for the H_2 signal but did not observe an effect for the H_4 signal. A 5.1% effect was also noted for the $H_{1'a}$ multiplet. Upon irradiation of the H_2 signal, we observed enhancements for the H_3 (7.4%) and H_1 (6.3%) signals. In the case of diastereoisomer **6b**, irradiation of the H_3 signal resulted in enhancements for the signals at 4.66 ppm (H_2 and H_1, 8.9%) and 1.78 ppm (H_4 and $H_{1'b}$, 4.8%). We therefore assigned structure **6a** to the major diastereoisomer isolated from the reaction of **1b** with Bu_3SnH and **6b** to the structure of the major isomer from the Bu_3SnH reaction of **1a**.

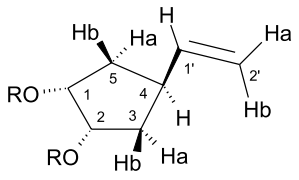


6a

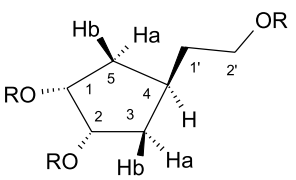


6b

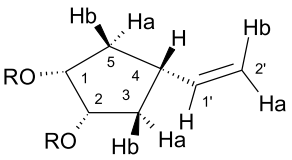
The NMR spectra of the tandem cyclization products **14–17** and the simple cyclization products **18–22** were simpler than those of the previously described compounds but the absence of a stereogenic center at C_3 or C_5 made assignment of the relative configurations at C_4 slightly more complicated. The C_3 and C_5 carbons are equivalent



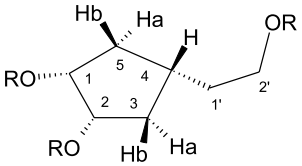
14a-17a



18a-22a



14b-17b



18b-22b

and each have 2 diastereotopic protons with distinct chemical shifts; assignments of the diastereotopic protons were made using the known configuration of C_1 and C_2 together with NMR data and NOE experiments. Once the identity of the Hb and Ha signals of each isomer was established, additional NOE experiments then allowed us to determine the configuration at C_4 for each of the diastereoisomers. Details for the NOE experiments are included in the Supplementary information.

3. Conclusions

The experiments described in this manuscript demonstrate that vinylcyclopentanes can be efficiently and stereoselectively synthesized by the reduction of carbohydrate derived ω-iodoallylic alcohols with an excess of Sm(II). In contrast, reductions of these same ω-iodoallylic alcohols with Bu_3SnH gave (2-hydroxyethyl)cyclopentanediol and -triol derivatives. The sequenced or tandem reactions, leading to vinylcyclopentane formation, are favored when the Sm(II) reaction mixtures are either irradiated with a xenon lamp or when HMPA is added. The quantity of HMPA used and the order of addition of HMPA and SmI_2 are important reaction parameters. Reactions can be run at either −78 °C or at room temperature. In general, the diastereomeric ratios of the *trans–cis* cyclization products for reactions run with HMPA were equal, or slightly higher, than those found for either the SmI_2–hν or Bu_3SnH reactions. The chemoselectivity of the Bu_3SnH reactions is different of course from the Sm(II) mediated reactions and we isolated only the simple reductive cyclization products from these reactions. For the substrates originating from 2-deoxy-D-ribose, reactions run under the SmI_2–hν conditions presented several advantages over those run with Sm(II)–HMPA. In addition to the obvious safety advantage of using visible light as a promoter, rather than HMPA, isolated yields of vinylcyclopentanediol derivatives were higher for substrates **11**–**13** due, in part, to a simpler workup procedure and because reactions run under the SmI_2–hν conditions gave exclusively (**11**–**13**), or nearly exclusively (**10a**, **10b**), the tandem cyclization products.

4. Experimental

4.1. General experimental

Unless otherwise noted, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Varian Gemini 300 BB instrument. The symbols s′, d′, t′, and q′, used for ^{13}C NMR data, represent carbons having zero, one, two and three attached hydrogens, respectively. HMQC and NOE NMR experiments were run on a Brüker AMX2 500 instrument. FTIR spectra were recorded on either a Bomem MB series instrument or a Perkin–Elmer Series 1600 instrument. Mass spectra were run on a Kratos 25 RFA instrument.[†] Melting points were recorded on a Fisher–Johns apparatus and are uncorrected. GC–MS analysis were run on a Hewlett–Packard GCD Plus instrument (HP-5 column, 30 m length, 0.25 mm diameter, 1 mL/min flow rate; electron ionization detector); oven ramp initial temperature 50 °C, final temperature 275 °C, rate = 22 °C/min. Optical rotations were measured at 589 nm in ethanol (100%) with a JASCO P-1010 Digital or a JASCO DIP-370 polarimeter. The reported concentrations are in g/100 mL. Radial chromatography was carried out with a Harrison Research Chromatotron and silica gel plates.

4.1.1. (2*E*)-2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (2a). A solution of **7a** (0.1511 g, 0.3794 mmol) in THF (9.1 mL) was prepared under a nitrogen atmosphere and cooled in a dry ice–acetone bath (−25 to −35 °C). To this solution was added, dropwise over 10 min, a solution of DIBAL (2.30 mL, 1.0 M solution in hexanes, 2.30 mmol).[16] The reaction mixture was stirred under these conditions for 1.5 h and then quenched with a saturated aqueous solution of NH_4Cl (5.0 mL). The mixture was stirred and the white cloudy solution was then filtered through a short pad of silica gel. The heterogeneous filtrate was transferred to a separatory funnel and the layers separated; the aqueous layer was extracted with EtOAc (20 mL × 3) and the combined organic phases were washed with H_2O (30 mL) and brine (30 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The residue was purified by radial chromatography [2 mm silica plate] to give 0.0934 g (75.7%) of **2a** (oil): R_f = 0.20 (1:1 EtOAc–hexanes). $[\alpha]_D$ = −5.4 (*c* 0.91, 15.7 °C). ^{1}H NMR δ: 6.00 (ddt, J = 15.5, 0.8, 4.9 Hz, 1H, H_2), 5.84 (ddt, J = 15.5, 6.9 Hz, 1.4 Hz, 1H, H_3), 4.74 (apparent t, J_{app} = 6.6 Hz, 1H, H_4), 4.20 (apparent d, J = 4.7 Hz, 2H, H_1), 3.98 (dd, J = 6.4, 8.0 Hz, 1H, H_5), 3.41–3.62 [m, 3H; H_6, H_{7a}, and OH. Upon D_2O exchange this region integrates for 2H and simplifies to a dd at 3.55 ppm (J = 2.4, 10.1 Hz, 1H, H_{7a}) and a partially resolved ddd at 3.47 ppm (J = 2.5, 8.7, 7.0 Hz, 1H, H_6), 3.35 (dd, J = 6.5, 10 Hz, 1H, H_{7b}), 2.83 (broad singlet, 1H, OH; D_2O exchangeable), 1.46 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C NMR δ: 132.7 (C_2), 126.4 (C_3), 108.9 ($C(CH_3)_2$), 80.0 (C_5), 77.6 (C_4), 68.9 (C_6), 62.5 (C_1), 27.8 (CH_3), 25.2 (CH_3), 14.2 (C_7). FTIR (cast): 3383 (s, br) cm^{-1}. GC–MS: t_R = 10.75 min; *m/z*: 313 (0.6%, M − CH_3), 157 (8.8%, M − ICH_2CHOH), 128 (9.5%), 125 (4.7%), 99 (24.1%), 59 [100%, $(CH_3)_2COH^+$]. HRMS: found 312.9934; calcd for M − CH_3 = $C_9H_{14}IO_4$: 312.9937.

4.1.2. (2*E*) 2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol diacetate (1a). A solution of **2a** (0.0935 g, 0.285 mmol) and DMAP (0.0017 g, 0.0139 mmol) in CH_2Cl_2 (1.5 mL) was prepared under anhydrous conditions and cooled at −78 °C. Acetic anhydride (0.12 mL, 1.27 mmol) and NEt_3 (0.17 mL, 1.22 mmol) were then simultaneously added dropwise (over 3 min) to this mixture.[17] The reaction mixture was stirred for 10 min, quenched with a mixture of H_2O–ether (5 mL, 1:1 v/v) and then warmed up to room temperature. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with aqueous citric acid (20 mL, 10%), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated. Purification of

[†] Most of our compounds do not give detectable molecular ions in EI mode but they do give an intense M − CH_3 fragment that is a well known characteristic of *O*-isopropylidene molecules;[23] we were able to obtain an accurate mass for these M − 15 fragments.

the residue by radial chromatography [(1 mm silica plate, eluant: 18% EtOAc–hexanes (100 mL) followed by 1:1 EtOAc–hexanes (50 mL)] gave **1a** (0.1094 g, 93.1%). R_f=0.24 (16% EtOAc–hexanes); mp 58–59 °C. $[\alpha]_D=-35$ (*c* 1.12, 25 °C). ^{1}H NMR δ: 5.92 (apparent ddt, J=15.5, 1.0, 5.7 Hz, 1H, H_2), 5.69 (apparent ddt, J=15.5, 6.8, 1.4 Hz, 1H, H_3), 4.70 (apparent t, J_{app}=6.3 Hz, 1H, H_4), 4.60–4.50 [2H, overlapping signals of H_{1a} (4.58 ppm, dd, J=5.5, 13.6 Hz) and H_{1b} (4.52 ppm, dd, J=5.9, 13.6 Hz)], 4.33 (apparent dt, J=8.6, 3.4 Hz, 1H, H_6), 4.25 (dd, J=5.9, 8.6 Hz, 1H, H_5), 3.51 [2H, overlapping signals of H_{7a} (3.54 ppm, dd, J=3.2, 11.1 Hz) and H_{7b} (3.49 ppm, dd, J=3.5, 11.0 Hz)], 2.08 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 1.48 (s, 3H, CH_3), 1.39 (s, 3H, CH_3). ^{13}C NMR δ: 170.5 (C=O), 169.3 (C=O), 127.9 (C_3 and C_2, confirmed by HMQC experiment), 109.3 ($C(CH_3)_2$), 77.8 (C_5), 76.9 (C_4), 68.9 (C_6), 63.6 (C_1), 27.7 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 20.9 (CH_3CO), 20.8 (CH_3CO), 7.5 (C_7). FTIR (solution in CH_2Cl_2) 1741 (s), 1736 (s) cm^{-1}. MS [EI] *m/z*: 397 (23.2%, M−CH_3), 235 (28%), 211 (51.6%), 170 (51.3%), 141 (40.3%), 43 (100%, CH_3CO^+). HRMS: found 397.0152; calcd for M−CH_3=$C_{13}H_{18}IO_6$: 397.0148. MS [CI, NH_3] *m/z*: 430 (20.6%, M+NH_4), 397 (19.7%), 355 (74.1%), 43 (100%).

4.1.3. (2*Z*)-2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (2b). A solution of DIBAL (6.2 mL, 1.0 M in hexanes, 6.2 mmol) was added, dropwise over 10 min, to a cooled (−25 to −35 °C) solution of **7b** (0.4097 g, 1.0288 mmol) in THF (23.3 mL) under a nitrogen atmosphere.[16] After an additional 55 min the reaction mixture was quenched with MeOH (8.5 mL). Ether (6.5 mL), NaF (0.18 g, 4.3 mmol) and H_2O (1 mL) were added and the cloudy solution was filtered. The filter cake was washed with EtOAc (3×5 mL) and the combined filtrates were concentrated. Purification by radial chromatography (1:1 EtOAc–hexanes, 4 mm silica plate) allowed for the separation of **7b** (0.0509 g, 12.4% recovery) from **2b** (0.2319 g, 68.7% yield of pure sample and 0.0162 g, 4.8% yield of a slightly impure sample as determined by ^{1}H NMR). Compound **2b**: mp 88–90 °C, R_f=0.27 (silica, 1:1 EtOAc–hexanes). $[\alpha]_D$=30.4 (*c* 1.5, 25 °C). ^{1}H NMR δ: 5.97 (partially resolved dddd, J=11.2, 1.1, 7.4, 6.4 Hz, 1H, H_2), 5.67 (partially resolved ddd, J=1.3, 9.5, 11.1 Hz, 1H, H_3), 5.15 (ddd, J=1.0, 6.1, 9.4 Hz, 1H, H_4), 4.29 (ddd, J=1.5, 7.4, 12.4 Hz, 1H, H_{1a}), 4.13 (dd, J=6.4, 12.3 Hz, 1H, H_{1b}), 4.04 (dd, J=6.2, 8.7 Hz, 1H, H_5), 3.58 (m, 1H, H_{7a}), 3.35–3.50 (m, 3H, H_6, H_{7b}, OH; upon D_2O exchange this region integrates for 2H), 2.40 (broad s, 1H, OH; D_2O exchangeable), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). ^{13}C NMR δ: 131.4 (d′), 130.8 (d′), 109.5 (s′), 80.4 (d′), 73.5 (d′), 68.3 (d′), 57.9 (t′), 28.1 (q′), 25.5 (q′), 13.7 (t′). FTIR (film): 3357 (s, br) cm^{-1}. MS [CI] *m/z*: 346 (1.0%, M+NH_4), 329 (2.3%, M+1), 253 (100%, loss of H_2O and CH=$CHCH_2OH$). MS [EI] *m/z*: 313 (4.7%, M−CH_3), 295 [6.7%, M−(CH_3 and H_2O)], 171 (12.4%, ICH_2CHOH^+), 157 (13.2%, M−ICH_2CHOH), 99 (81.0%), 59 [100%, $(CH_3)_2COH^+$]. HRMS: found 312.9934; calcd for M−CH_3=$C_9H_{14}IO_4$: 312.9937.

4.1.4. (2*Z*)-2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol diacetate (1b). A solution of **2b** (0.1697 g, 0.5173 mmol) and DMAP (0.0061 g, 0.0499 mmol) in CH_2CH_2 (2.7 mL) was prepared under anhydrous conditions and cooled to −78 °C. Ac_2O (0.21 mL, 2.226 mmol) and NEt_3(0.30 mL, 2.2 mmol) were then simultaneously added dropwise (over 3 min).[17] The reaction mixture was stirred for 1.5 h, quenched with a mixture of H_2O–ether (5 mL, 1:1 v/v) and then warmed up to room temperature. The mixture was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with aqueous citric acid (20 mL, 10%), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was then dried, filtered and concentrated. Purification by radial chromatography (20% EtOAc–hexanes, 2 mm silica plate) gave pure **1b** (0.2017 g, 95%) as a pale yellow oil. R_f=0.34 (TLC, 20% EtOAc–hexanes). $[\alpha]_D$=15.0 (*c* 1.69, 25 °C). ^{1}H NMR δ: 5.78 (m, 1H, H_2), 5.60 (m, 1H, H_3), 5.02 (ddd, J=1.1, 6.2, 8.6 Hz, 1H, H_4), 4.74 [ddd, J=1.1, 7.1, 13.3 Hz, 1H, H_{1a}), 4.61 (ddd, J=1.6, 6.2, 13.3 Hz, 1H, H_{1b}), 4.43 (m, 1H, H_6), 4.25 (dd, J=6.2, 8.3 Hz, 1H, H_5), 3.46–3.55 [2H, H_{7a}+H_{7b}; overlapping signals at 3.53 ppm (dd, J=3.4, 11.1 Hz) and 3.49 ppm (dd, J=3.9, 11.1 Hz)], 2.09 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 1.48 (s, 3H, CH_3), 1.40 (s, 3H, CH_3). ^{13}C NMR δ: 170.5 (s′, C=O), 169.4 (s′, C=O), 128.6 (d′, C_3), 128.1 (d′, C_2), 109.4 (s′, $C(CH_3)_2$), 77.8 (d′, C_5), 73.0 (d′, C_4), 68.8 (d′, C_6), 59.8 (t′, C_1), 27.6 (q′, $C(CH_3)_2$), 25.1 (q′, $C(CH_3)_2$), 20.91 (q′, $COCH_3$), 20.86 (q′, $COCH_3$), 7.3 (t′, C_7). FTIR (film) 1741 (s) cm^{-1}. MS [EI] *m/z*: 397 (6.6%, M−CH_3), 43 (100%, CH_3CO^+). HRMS: found 397.0153; calcd for M−CH_3=$C_{13}H_{18}IO_6$: 397.0148.

4.1.5. (2*E*) 2,3,4,7-Tetradeoxy-7-iodo-5,6-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (10a). The method used for the reduction of **8a** is based on a procedure described in the literature.[18] A solution of DIBAL (1.0 M in toluene, 1.05 mL, 1.05 mmol) was added dropwise over 10 min to a cooled (0 °C) solution of compound **8a** (0.200 g, 0.523 mmol) in anhydrous toluene (10 mL) under an argon atmosphere. The reaction mixture was stirred at 0 °C for 2 h and then quenched by the addition of *tert*-butanol (1.2 mL). The mixture was stirred for 30 min, water (0.10 mL) was added and stirring continued for another 30 min. To this mixture was added an aqueous solution of NaOH (2 M, 1.5 mL), CH_2Cl_2 (20) mL and H_2O (10 mL). The layers were separated and the aqueous phase was neutralized by the addition of dilute aqueous HCl (0.1 M) and re-extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were washed successively with saturated aqueous solutions of $NaHCO_3$ (25 mL) and NaCl (25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Radial chromatography of the crude residue gave 0.007 g (3.5% recovery) of starting material, 0.013 g (8% yield) of the corresponding conjugated aldehyde (GC purity 95%, contaminated with the saturated aldehyde) and 0.097 g (60% yield) of the allylic alcohol **10a** (GC purity 98%) as a colorless oil (R_f=0.35 silica, 4:1:1 CH_2Cl_2–Et_2O–hexanes). $[\alpha]_D$=87.7 (*c* 0.18, CH_2Cl_2, 20.7 °C). ^{1}H NMR δ: 5.77 (m, 2H, H_2 and H_3), 4.37 (partially resolved ddd,* J=5.5, 6, 8 Hz, 1H, H_6), 4.19 (ddd, J=5.5, 6, 7 Hz, 1H, H_5), 4.14 (m which simplifies after resolution enhancement to a partially resolved dd, J=1, 1 Hz, 1H, H_{1a}), 4.13 (m that simplifies to a dd after resolution enhancement, J=1, 2 Hz, 1H, H_{1b}), 3.20 (dd, J=8, 10 Hz, 1H, H_{7a}), 3.15 (dd, J=6, 10 Hz, 1H, H_{7b}), 2.35 (m, 2H, H_{4a} and H_{4b}), 1.63 (s

large, 1H, 1×OH), 1.48 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). $^*J$ values calculated after resolution enhancement. ^{13}C NMR δ: 132.1 (d, C_2/C_3), 127.7 (d, C_2/C_3), 108.7 (s, $C(CH_3)_2$), 78.2 (d′, C_5/C_6), 77.2 (d′, C_5/C_6), 63.5 (t′, C_1), 32.3 (t′, C_4), 28.4 (q′, CH_3), 25.7 (q′, CH_3), 3.4 (t′, C_7). FTIR (film): 3405 (broad, OH), 1675 (w) cm^{-1}. GC–MS: t_R=8.21 min, (EI) *m/z*: 297 (9.1%, M−CH_3), 241 (100%, M−CH_2CH=$CHCH_2OH$), 185 (38.5%, M−I), 183 (58%), 155 (24.6%), 59 (23.6%), 43(60.9%). HRMS (EI) found 296.9985; calcd for M−CH_3=$C_9H_{14}IO_3$: 296.9988.

4.1.6. (2*Z*) 2,3,4,7-Tetradeoxy-7-iodo-5,6-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (10b). A solution of DIBAL (1.0 M toluene, 1.57 mL, 1.57 mmol) was added dropwise over 15 min to a cooled solution (0 °C) of **8b** (0.272 g, 0.712 mmol) in anhydrous toluene (14 mL) under argon. The mixture was stirred at 0 °C for 5 h and then worked up as per compound **10a**. After radial chromatography we isolated 0.164 g (74%) of allylic alcohol **10b** (GC purity=98%) as a colorless oil. R_f=0.31 (silica, 4:1:1 CH_2Cl_2-Et_2O–hexanes). $[\alpha]_D$=12.9 (*c* 0.26, CH_2Cl_2, 20.7 °C). ^{1}H NMR δ: 5.86 (m, 1H, H_2; decoupling of H_4 protons transformed the signal to an apparent dt with *J*=11, 7 Hz), 5.65 (m, 1H, H_3; decoupling of H_4 protons simplifies this signal to an apparent dt, *J*=11, 1 Hz), 4.40 (apparent dt, *J*=6, 7 Hz, 1H, H_6), 4.29–4.09 [m, 3H, H_{1a}, H_{1b} and H_5; signal is simplified upon decoupling of H_4 protons to a ddd centered at 4.25 ppm (*J*=1, 7, 12.5 Hz, 1H, H_{1a}), a multiplet at 4.17 ppm (1H, H_5) and a ddd centered at 4.12 ppm (*J*=1, 6.5, 12.5 Hz, 1H, H_{1b})], 3.22 (dd, *J*=7,10 Hz, 1H, H_{7a}), 3.17 (dd, *J*=6.5, 10 Hz, 1H, H_{7b}), 2.42 (m, 2H, H_{4a} and H_{4b}), 1.71 (s large, 1H, OH), 1.49 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR δ: 131.4 (d′, C_2/C_3), 128.0 (d′, C_2/C_3), 108.7 (s′, $C(CH_3)_2$), 78.1 (d′, C_5/C_6), 76.8 (d′, C_5/C_6), 58.1 (t′, C_1), 28.1 (q′, CH_3), 27.7 (t′, C_4), 25.5 (q′, CH_3), 3.2 (t′, C_7). FTIR (film): 3410 (s, br), 1650 (w), 1040 (s) cm^{-1}. GC–MS: t_R=8.17 min, (EI) *m/z*: 297 (5.6%, M−CH_3), 241 (100%, M−$CH_2CHCHCH_2OH$), 185 (36.3%, M−I), 183 (71.7%), 155 (30.9%), 85 (20.6%), 59 (27.6%), 43 (61.3%). HRMS (EI) found 296.9990; calcd for M−CH_3=$C_9H_{14}IO_3$: 296.9987.

4.1.7. (2*E*) 2,3,4,7-Tetradeoxy-7-iodo-5,6-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol acetate (13). Pyridine (5.5 mmol, 0.44 mL) and Ac_2O (4.6 mmol, 0.43 mL) were added to a cooled (0 °C) solution of **10a** (0.2862 g, 0.9148 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere. The mixture was stirred 0 °C for 1 h and at room temperature for 12 h. Water (10 mL) was added, the phases separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed successively with aqueous HCl (0.1 M, 10 mL) and saturated aqueous solutions of $NaHCO_3$ (20 mL) and NaCl (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude was purified by radial chromatography to give 0.290 g (89%) of **13** as a colorless oil. R_f=0.91 silica, 4:1:1 CH_2Cl_2–Et_2O–hexanes. $[\alpha]_D$=12.5 (*c* 0.17, CH_2Cl_2, 20.4 °C). ^{1}H NMR δ: 5.76 (m, 2H, H_2 and H_3), 4.54 (apparent dd, 2H, *J*=6, 1 Hz, $2H_1$), 4.36 (partially resolved ddd, 1H, *J*=6, 6, 8 *Hz*, H_6), 4.18 (partially resolved ddd, 1H, *J*=6, 7, 5.5 Hz, H_5), 3.18 (dd, 1H, *J*=10, 8 Hz, H_{7b}), 3.13 (dd, 1H, *J*=10, 6 *Hz*, H_{7a}), 2.35 (m, 2H, H_{4a} and H_{4b}), 2.07 (s, 3H, C=OCH_3), 1.47 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR δ: 170.7 (s′, C=O), 130.9 (d′, C_2/C_3), 126.9 (d′, C_2/C_3), 108.7 (s′, $C(CH_3)_2$), 78.1 (d′, C_5/C_6), 76.98 (d′, C_5/C_6), 64.7 (t′, C_1), 32.4 (t′, C_4), 28.4 (q′, CH_3), 25.7 (q′, CH_3), 20.9 (q′, CH_3), 3.1 (t′, C_7). FTIR (film) 1738 (w), 1673 (w) cm^{-1}. GC–MS: t_R=8.75 min, (EI) *m/z*: 339 (6.1%, M−CH_3), 241 (100%, M−$CH_2CHCHCH_2OAc$), 185 (38.2%), 183 (57.7%, ICH_2CHCHO), 43 (78.8%, CH_3CO). HRMS (EI) found 339.0090; calcd for M−CH_3=$C_{11}H_{16}IO_4$: 339.0093.

4.1.8. (2*E*) 2,3,4,7-Tetradeoxy-7-iodo-5,6-O-(1-ethylpropylidene)-D-*ribo*-hept-2-enoic acid *tert*-butyl ester (9). A mixture of pentan-3-one (5.72 mL, 54.0 mmol), *tert*-butyl (*2E*) 2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-2-enoate[10] (0.500 g, 1.46 mmol), pTSA·H_2O (0.003 g, 0.2 mmol) and molecular sieves were stirred under an argon atmosphere at 70 °C for 24 h. The mixture was filtered and the filtrate diluted with ether (15 mL) and successively washed with saturated aqueous solutions of $NaHCO_3$ (15 mL) and NaCl (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by radial chromatography (4 mm silica plate) to give 0.253 g (51%) of starting material and 0.209 g (35%) of **9** (R_f=0.90, 2:2:3 CH_2Cl_2–EtOAc–hexanes) as a white solid, mp 44–45 °C. $[\alpha]_D$=−24 (*c* 0.18, CH_2Cl_2, 20.1 °C). ^{1}H NMR δ: 6.88 (dt, *J*=15.5, 7 Hz, 1H, H_3), 5.86 (dt, *J*=15.5, 1.5 Hz, 1H, H_2), 4.43 (partially resolved ddd, *J*=6, 6, 8 Hz, 1H, H_6), 4.27 (partially resolved ddd, *J*=5.5, 5.5, 8 Hz, 1H, H_5), 3.21 (dd, *J*=7.5, 10 Hz, 1H, H_{7a}), 3.10 (dd, *J*=6.5, 10 Hz, 1H, H_{7b}), 2.45 (m, 2H, H_{4a} and H_{4b}), 1.68 (q, *J*=7.5 Hz, 2H, $C(CH_2CH_3)_2$), 1.64 (q, *J*=7.5 Hz, 2H, $C(CH_2CH_3)_2$), 1.49 (s, 9H, $C(CH_3)_3$), 0.94 (t, *J*=7.5 Hz, 3H, $C(CH_2CH_3)_2$), 0.90 (t, *J*=7.5 Hz, 3H, $C(CH_2CH_3)_2$). ^{13}C NMR δ: 165.5 (s′, C_1), 142.8 (d′, C_3), 125.5 (d′, C_2), 112.8 (s′, $C(CH_2CH_3)_2$), 80.4 (s′, $C(CH_3)_3$), 77.9 (d′, C_5/C_6), 76.0 (d′, C_5/C_6), 32.4 (t′, C_4), 30.1 (t′, CH_2CH_3), 29.1 (t′, CH_2CH_3), 28.1 (q′, $C(CH_3)_3$), 8.6 (q′, CH_2CH_3), 8.0 (q′, CH_2CH_3), 3.1 (t′, C_7). FTIR (KBr) 1700 (s), 1650 (m), 1160 (s) cm^{-1}. GC–MS: t_R=10.04 min, (EI) *m/z*: 381 (24.6%, M−Et), 251 (26.8%), 213 [20.1%, M−(ICH_2 and C_4H_8)], 123 (17.2%), 57 (100%, *t*Bu). HRMS (EI) found 381.0559; mass calcd for M–Et=$C_{14}H_{22}IO_4$: 381.0563.

4.1.9. (2*E*) 2,3,4,7-Tetradeoxy-7-iodo-5,6-*O*-(1-ethylpropylidene)-D-*ribo*-hept-2-enitol (11). A solution of DIBAL (1.0 M toluene, 1.22 mL, 1.22 mmol) was added dropwise over 12 min to a cooled (0 °C) solution of **9** (0.227 g, 0.554 mmol) in anhydrous toluene (12 mL) under an argon atmosphere. The reaction mixture was stirred at 0 °C for 5 h and then worked up as previously described for compound **10a**. Radial chromatography (2 mm silica plate) of the crude products allowed for the separation of 0.118 g (63%) of allylic alcohol **11** from the minor reaction products. Compound **11** was isolated as a colorless oil (GC purity=96%). R_f=0.44 silica, 4:1:1 CH_2Cl_2–ether–hexanes. ^{1}H NMR δ: 5.77 (m, 2H, H_2 and H_3), 4.40 (partially resolved ddd, *J*=6, 6, 8 Hz, 1H, H_6), 4.21 (m, 1H, H_5; signal simplifies to a partially resolved ddd after resolution enhancement, *J*=8, 6, 6 Hz), 4.14 (m, 2H, H_{1a} and H_{1b}), 3.20 (dd, *J*=8, 10 Hz, 1H, H_{7a}), 3.15 (dd, *J*=6, 10 Hz, 1H, H_{7b}), 2.35 (m, 2H, H_{4a} and H_{4b}), 1.68 (m, 4H, 2×CH_2CH_3), 1.56 (s large, OH and H_2O), 0.95 (t, *J*=7.5 Hz, 3H, CH_2CH_3), 0.90 (t, *J*=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR δ:

131.9 (d′, C_2/C_3), 127.9 (d′, C_2/C_3), 112.5 (s′, $C(CH_2CH_3)_2$), 78.0 (d′, C_5/C_6), 77.0* (d′, C_5/C_6, *This signal is masked by the $CDCl_3$ signal and was detected by a DEPT experiment.), 63.5 (t′, C_1), 32.5 (t′, C_4), 30.2 (t′, CH_2CH_3), 29.1 (t′, CH_2CH_3), 8.6 (q′, CH_2CH_3), 8.0 (q′, CH_2CH_3), 3.8 (t′, C_7). FTIR (film) 3395 (l), 1677 (w) cm^{-1}. GC–MS: $t_R=9.11$ min, (EI) *m/z*: 311 (17.6%, M -Et), 269 (11.1%, M−$CH_2CH{=}CHCH_2OH$), 213 (14.6%, M−I), 81 (27.1%), 57 (100%, $CH{=}CHCH_2OH$). HRMS (EI) found 311.0141; mass calcd for M−Et=$C_{10}H_{16}IO_3$: 311.0144.

4.1.10. (2*E*) 2,3,4,7-Tetradeoxy-7-iodo-D-*ribo*-hept-2-enitol (12). Deprotection was accomplished using the protocol of Hillier et al.[19] A mixture of **10a** (0.151 g, 0.485 mmol), MeOH (1 mL) and an acidic resin (Amberlite IR-120) was stirred at room temperature for 24 h under an argon atmosphere. The mixture was filtered using Celite and the filtrate concentrated. Radial chromatography (2 mm silica plate) gave 0.112 g (85%) of pure **12**: solid, mp 78–79 °C. $R_f=0.30$ (silica, 19:1 CH_2Cl_2-MeOH). $[\alpha]_D=16.1$ (*c* 0.19, 21.4 °C). ^1H NMR (300 MHz, DMSO-d_6) δ: 5.58 (m, 2H, H_2 and H_3), 5.13 (d, 1H, $J=6$ Hz, C_5–OH), 4.69(d, 1H, $J=6$ Hz, C_6-OH), 4.56 (dd, 1H, $J=5$, 5.5 Hz, C_1–OH), 3.87 (apparent t, 2H, H_{1b} and H_{1a} that simplifies to a d with $J=4$ Hz after D_2O exchange), 3.46 (dd, $J=3$, 10 Hz, 1H, H_{7a}), 3.28 (dd, $J=6$, 10 Hz, 1H, H_{7b}), 3.21 (m, 1H, H_5), 3.04 (m, 1H, H_6; simplifies to a ddd after D_2O exchange and resolution enhancement, $J=3$, 6, 7.5 Hz), 2.35 (m, 1H, H_{4a}), 2.04 (m, 1H, H_{4b}). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 132.3 (d′, C_2/C_3), 127.2 (d′, C_2/C_3), 73.3 (d′, C_5/C_6), 72.8 (d′, C_5/C_6), 61.6 (t′, C_1), 36.0 (t′, C_4), 15.7 (t′, C_7). FTIR (KBr) 3304 (br, OH) cm^{-1}. FTIR (solution in CCl_4–MeOH) 1669 (very weak) cm^{-1}. GC–MS: $t_R=8.28$ min, (EI) *m/z*: 254 (1.6%, M−H_2O), 183 (11.2%), 84 [24.5%, M−(ICH_2CHOH and OH)], 83 (60.1%, M−(ICH_2CHOH and H_2O)], 57 (32.3%, $CH{=}CHCH_2OH$), 55 (100%), 54 (50.1%), 44 (19.7%), 43 (26.5%). MS (CI, NH_3) *m/z*: 290 [3.3%, M+18 (M=$C_7H_{13}IO_3$)], 255 [3.3%, (M+1)-H_2O], 254 (16.2%, M−H_2O), 83 [100%, M−(ICH_2CHOH and H_2O)]. HRMS (EI) found 253.9800; calcd for M−$H_2O{=}C_7H_{11}IO_2$: 253.9804.

4.2. General procedures for reactions with samarium(II) iodide

Method A1. A flask containing the substrate (0.15 mmol) and a magnetic stirring bar was closed with a septum and purged with argon using a Firestone valve. Distilled THF (2.5–5.5 mL) was added followed by HMPA and/or MeOH where appropriate; reaction flasks for experiments run at −78 °C were cooled in a dry ice–acetone bath. A commercial solution of SmI_2 in THF (0.1 M, 4.5–7.5 mL, 0.45–0.75 mmol) was transferred via cannula to the reaction mixture. The final concentration of the iodide substrate was 0.015 M. The solution was stirred at −78 °C for 2 h and then at 0 °C for 1.3–2 h under ambient lighting conditions. The reaction was quenched by addition of a dilute aqueous solution of HCl (0.1 M, 5 mL). The mixture was diluted with water (5 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed successively with water (20 mL or 3×20 mL when HMPA was used), saturated aqueous solutions $Na_2S_2O_3$ (20 mL) and NaCl (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude products were purified by radial chromatography (silica gel or Adsorbosil plates, with a mixture of EtOAc and hexanes).

Method A2. As per Method A1, except that reactions were run at room temperature.

Methods B1 and B2. A solution of the substrate (0.348 mmol) in THF (8 mL), HMPA (1.16 mL, 6.67 mmol), and MeOH (0.14 mL, 3.5 mmol) was prepared under an argon atmosphere and either cooled to −78 °C (Method B1) or kept at room temperature (Method B2). To this solution was added, dropwise (ca. 1.2 mL/min), a commercial solution of SmI_2 in THF (0.1 M, 13.9 mL, 1.39 mmol). The reaction was run under ambient lighting conditions and the final concentration of substrate= 0.015 M. The reaction mixture was stirred under an argon atmosphere for 1.75 h and then quenched by the addition of dilute aqueous HCl (0.1 M, 20 mL). The mixture was diluted with ether (20 mL), the phases separated and the aqueous layer re-extracted with ether (3×30 mL). The combined organic phases were washed successively with saturated aqueous solutions of $CuSO_4$ (3×30 mL), $Na_2S_2O_3$ (30 mL) and NaCl (30 mL), dried over $MgSO_4$, filtered. The filtrate was analyzed by GC–MS, concentrated and the crude residue purified by radial chromatography.

Method C. As per Method B1, with the following exceptions: a solution of the substrate (0.385 mmol) in THF (8.8 mL) and MeOH (0.16 mL, 3.9 mmol) was prepared under an argon atmosphere and cooled to −78 °C. In a second flask, a solution of HMPA (1.28 mL, 7.36 mmol) and SmI_2 in THF [0.1 M, 15.4 mL, 1.54 mmol] was stirred at room temperature under an argon atmosphere for 20 min and then transferred dropwise, by cannula (ca. 1.2 mL/min), to the flask containing the iodide substrate.

Method D. A solution of the substrate (0.340 mmol) in THF (8.9 mL) and MeOH (0.14 mL, 3.4 mmol) was prepared under an argon atmosphere in a pyrex flask at room temperature. To this mixture was transferred, via cannula, a solution of SmI_2 in THF [0.1 M, 13.6 mL, 1.36 mmol]. The resulting reaction mixture was irradiated for 4 h in the visible range with a xenon lamp and appropriate filters. A water filter [quartz cylinder dimensions=55 mm (length)× 28 mm (diameter)] and a Schott GG 375 nm filter were placed between the Sciencetech 150 W xenon lamp and the reaction flask at spacing intervals of ca. 0.7, 2.0 and 3.5 cm respectively. Workup as per Method B1 but without the aqueous $CuSO_4$ wash.

4.3. Characterization of the vinylcyclopentanetriol derivatives

Reaction of **2b** *with SmI_2 in THF/MeOH (Method A): preparation of* **4a**, **4b** and **5a**. A THF solution of SmI_2 (6.8 mL, 0.1 M, 0.68 mmol) was added to a solution of **2b** (0.0743 g, 0.2264 mmol), MeOH (0.085 mL, 2.1 mmol) and THF (8.5 mL). After 4 h at room temperature reaction was worked up and the crude residue purified by radial chromatography [using the following series of eluants: 6% EtOAc–CH_2Cl_2 (80 mL), 26% EtOAc–CH_2Cl_2 (100 mL),

50% EtOAc–CH_2Cl_2 (50 mL); 2 mm silica plate] in order to separate **2b** (0.0268 g, 36.1%, slightly impure by ^{1}H NMR) from two other fractions (A and B). Further purification of fraction A (20% EtOAc–hexenes, 1 mm plate) allowed for the separation of **4a** (0.0144 g, 34.5%) and **4b** (0.0055 g, 13.2%). Attempts to further purify fraction B (26% EtOAc–CH_2Cl_2, 1 mm plate) were only partially successful; we isolated **5** (0.0078 g, 18.7% yield) as a slightly impure sample. Although compounds **4a** and **4b** are separable by TLC, they are not separable using our GC method as both compounds have a t_R=6.5 min.

4.3.1. Compound 4a. Oil. R_f=0.26 (TLC, 20% EtOAc–hexanes). $[\alpha]_D$=16.6 (*c* 1.22). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.75 (ddd, J=6.5, 10.5, 17.2 Hz, 1H, $H_{1'}$), 5.09 [2H, overlapping ddd signals; $H_{2b'}$ (5.09 ppm, J=17.3, 1.4, 1.6 Hz) and $H_{2a'}$ (5.07 ppm, J=10.6, 1.4, 1.5 Hz)], 4.49 [2H, apparent d, H_2 and H_3. Upon decoupling at 4.08 ppm (H_1), this signal collapses to an apparent singlet but decoupling at 2.75 ppm (H_4) or at 1.90 (H_{5a} and H_{5b}) had no obvious effect on the H_2+H_3 signal.], 4.08 (broad m, 1H, H_1), 2.75 (m, 1H, H_4), 2.40 (broad, 1H, OH, D_2O exchangeable), 1.90 (m, 2H, $H_{5a}+H_{5b}$), 1.52 (s, 3H, CH_3), 1.36 (s, 3H, CH_3). ^{1}H NMR (benzene-d_6, 300 MHz) δ: 5.42 (ddd, J=10.2, 17.5, 6.7 Hz, 1H, $H_{1'}$), 4.86–4.79 (m, 2H, overlapping signals of $H_{2a'}$ and $H_{2b'}$), 4.13 [dd, 1H, $J_{3,2}$=5.9 Hz, $J_{3,4}$=1.8 Hz, H_3. Upon decoupling at 2.74 ppm (H_4), this H_3 dd collapses to a d (J=6 Hz)], 4.02 [apparent t (J_{app}=ca. 6 Hz) which is a partially resolved dd, 1H, H_2], 3.94 (broad m, 1H, H_1), 2.74 (broad m, 1H, H_4), 2.42 (broad, 1H, OH, D_2O exchangeable), 1.90 [m, 1H, H_5; upon decoupling at 2.74 ppm (H_4), this multiplet collapses to a dd, J=13, 8 Hz], 1.65 [m, 1H, H_5; upon decoupling at 2.74 ppm (H_4), this multiplet collapses to a dd, J=13, 5 Hz], 1.33 (s, 3H, CH_3), 1.12 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.0 (*C*H=CH_2), 115.3 (CH=*C*H_2), 111.6 (s′, *C*$(CH_3)_2$), 84.3 (d′, C_2 or C_3), 79.0 (d′, C_2 or C_3), 71.1 (C_1), 44.3 (C_4), 36.0 (C_5), 26.1 (CH_3), 24.3 (CH_3). FTIR (film): 3457 (s) cm^{-1}. MS [EI] *m*/*z*: 184 (0.5%, $M^{+\cdot}$), 169 (100%, M−CH_3). HRMS: found: 169.0862; calcd for M−CH_3=$C_9H_{13}O_3$: 169.0865.

4.3.2. Compound 4b. Oil. R_f=0.18 (TLC, 20% EtOAc–hexanes). ^{1}H NMR δ: 5.91 (m, 1H, $H_{1'}$), 5.08–5.16 (m, 2H, $H_{2a'}+H_{2b'}$), 4.54 [dd that presents as an apparent t, J_{app}=5 Hz, 1H, H_3. Decoupling at 2.28 ppm (H_4) simplifies the H_3 signal to a d ($J_{2,3}$=5 Hz).], 4.47 [dd that presents as an apparent t, J_{app}=5.5 Hz, 1H, H_2. Decoupling at 3.91 ppm (H_1) simplifies the H_2 signal to a d ($J_{2,3}$=5 Hz).], 3.91 (broad m, 1H, H_1), 2.41 (d, J=11 Hz, 1H, OH, D_2O exchangeable), 2.28 (m, 1H, H_4), 1.94 (m, 1H, H_{5b}), 1.63 (m, 1H, H_{5a}), 1.50 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR δ: 135.8 (*C*H=CH_2), 116.2 (CH=*C*H_2), 110.6 (s′, *C*$(CH_3)_2$), 81.6 (C_3), 78.8 (C_2), 72.2 (C_1), 42.8 (C_4), 35.5 (C_5), 25.6 (CH_3), 24.1 (CH_3). MS [EI] *m*/*z*: 183 (11.3%, M−1), 169 (100%, M−CH_3). HRMS: found: 169.0862; calcd for M−CH_3=$C_9H_{13}O_3$: 169.0865.

4.3.3. Compound 5. Compound **5** was isolated as a slightly impure pale yellow oil. R_f=0.39 (TLC, 26% EtOAc–CH_2Cl_2). ^{1}H NMR (acetone-d_6, 300 MHz) δ: 5.81–5.64 (m, 2H, H_2 and H_6), 5.36 (m, 1H, H_3), 5.23 (ddd, J=1, 2, 17 Hz, 1H, H_7), 5.11 (ddd, J=1, 2, 10 Hz, 1H, H_7), 5.03 (partially resolved ddd, J=1, 7, 9 Hz, 1H, H_4), 4.58 (m, 1H, H_5), 4.22 (m, 1H, H_{1a}), 4.05 (m, 1H, H_{1b}), 3.75 (apparent t, J_{app}=5.5 Hz, 1H, OH), 1.42 (s, 3H, CH_3), 1.32 (s, 3H, CH_3]. ^{13}C NMR ($CDCl_3$, 75 MHz): 134.2, 132.4, 128.3, 118.4, 109.0, 80.0, 74.4, 58.8, 28.0, 25.5. FTIR (film): 3421(s) cm^{-1}. GC–MS: t_R=7.09 min; [EI] *m*/*z*: 169 (5.8%, M−15), 109 (26.3%), 98 (100%).

4.3.4. Compound 3a. Compound **3a**: pale yellow oil. R_f=0.29 (TLC, 12% EtOAc–hexanes). $[\alpha]_D$=95.5 (*c* 1.49). ^{1}H NMR δ: 5.77 (ddd, J=6.4, 10.6, 17 Hz, 1H, $H_{1'}$), 5.07–5.16 [2H, overlapping signals for $H_{2b'}$ (δ 5.12, partially resolved ddd, J=17, 1.2, 1.7 Hz) and $H_{2a'}$ (δ 5.10, partially resolved ddd, J=10.6, 1.4, 1.3 Hz)], 4.91 (m, 1H, H_1), 4.67 (apparent t, J_{app}=5.5 Hz ($J_{2,3}\cong J_{2,1}$), 1H, H_2), 4.48 [apparent d ($J_{2,3}$=5.7 Hz), 1H, H_3; this signal is actually more complex. Decoupling at 1.95 ppm (H_{5b}) results in a change of the signal to a dd ($J_{2,3}$=5.7, $J_{3,4}$=1.3 Hz).], 2.77 (broad m, 1H, H_4), 2.09–2.22 (4H, s at δ 2.12 (OCO*C*H_3) and m for H_{5a}], 1.95 (m, 1H, H_{5b}), 1.50 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR δ: 170.7 (C=O); 137.7 (*C*H=CH_2), 115.5 (CH=*C*H_2), 111.4 (*C*$(CH_3)_2$), 84.1 (C_3), 77.9 (C_2), 73.3 (C_1), 43.8 (C_4), 31.7 (C_5), 26.1 (CH_3), 24.5 (CH_3), 20.9 (*C*H_3CO). FTIR (film): 1739 (s), 1637 (w) cm^{-1}. MS [EI] *m*/*z*: 226 (0.6%, $M^{+\cdot}$), 211 (72.3%, M−CH_3), 43 (100%, CH_3CO^+). HRMS: found 211.0973; calcd for M−CH_3=$C_{11}H_{15}O_4$: 211.0970.

4.3.5. Compound 3b. Compound **3b**: pale yellow oil. R_f=0.21 (TLC, 12% EtOAc–hexanes) ^{1}H NMR δ: 5.93 (m, 1H, $H_{1'}$), 5.10–5.17 (m, 2H, overlapping $H_{2a'}$ and $H_{2b'}$ signals), 4.70 [m, 2H, overlapping H_1 and H_2 signals.], 4.53 [1H, H_3. This signal appears to be a dd with line overlap ($J_{3,2}$=5.1, $J_{3,4}$=4.8 Hz) but is actually more complex. Decoupling at δ 2.35 (H_4) collapses the signal to an apparent d, $J_{3,2}$=5.2 Hz. Decoupling at δ 4.70 (H_1+H_2) changes this signal to a m.], 2.35 (m, 1H, H_4), 2.13 (s, 3H, *C*H_3CO), 1.95 (m, 2H, $H_{5a}+H_{5b}$), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR δ: 170.9 (C=O); 135.7 (*C*H=CH_2), 116.4 (CH=*C*H_2), 110.8 (*C*$(CH_3)_2$), 81.3 (C_3), 77.8 (C_1 or C_2), 73.7 (C_1 or C_2), 42.5 (C_4), 31.5 (C_5), 25.7 (CH_3), 24.2 (CH_3), 20.9 (*C*H_3CO). FTIR (film): 1738 (s) cm^{-1}. MS [EI] *m*/*z*: 226 (1.1%, $M^{+\cdot}$), 211 (100%, M−CH_3). HRMS: found 211.0968; calcd for M−CH_3=$C_{11}H_{15}O_4$: 211.0970.

4.4. Characterization of the vinylcyclopentanediol derivatives

In most instances *cis* and *trans* vinylcyclopentanediol diastereoisomers were isolated as an inseparable (by radial chromatography) mixture.

4.4.1. NMR and GC–MS analysis of mixtures of 14a (*trans*) and 14b (*cis*) isolated from reactions with 10a, 10b or 13. *Compounds* **14a** and **14b**. Colorless oil (mixture of *cis* and *trans*). R_f=0.91 (silica, 1:2:3 Et_2O–CH_2Cl_2–pentane). GC–MS: t_R=4.2 min, *trans* compound **14a**. [EI] *m*/*z*: 153 (100%, M−CH_3), 111 (19.5%), 93 (86.4%, M−$C_3H_7O_2$), 91 (35.5%), 77 (25%), 59 (16.4%, $(CH_3)_2COH$), 43 (60.4%). t_R=4.4 min, *cis* compound. [EI] *m*/*z*: 153 (98.9%, M−CH_3), 111 (17.6%), 93 (100%, M−$C_3H_7O_2$), 91 (39.5%), 77 (29.2%), 67 (21.2%), 59 (20.8%, $(CH_3)_2COH$), 43 (69.8%). ^{13}C NMR (125 MHz, $CDCl_3$)

chemical shifts assigned to the *trans* isomer **14a**: δ: 140.4 (d′, $C_{1'}$), 113.9 (t′, $C_{2'}$), 108.8 (s′, $C(CH_3)_2$), 80.4 (d′, C_1/C_2), 39.8 (d′, C_4), 39.5 (t′, C_3/C_5), 26.1 (q′, CH_3), 23.7 (q′, CH_3); chemical shifts assigned to the *cis* isomer **10b**: δ: 142.1 (d′, $C_{1'}$), 113.1 (t′, $C_{2'}$), 111.3 (s′, $C(CH_3)_2$), 81.0 (d′, C_1/C_2), 43.0 (d′, C_4), **38.7** (t′, C_3/C_5), 26.9 (q′, CH_3), 24.4 (q′, CH_3). ^{1}H NMR (300 MHz, $CDCl_3$) chemical shifts assigned to the *trans* isomer **14a**: δ 5.74 (partially resolved ddd, 1H, $J_{1'-4}=7$ Hz, $J_{1'-2a'}=10$ Hz and $J_{1'-2b'}=17$ Hz, $H_{1'}$), 5.04 (ddd, 1H, $J_{2b'-4}=1$ Hz, $J_{2b'-2a'}=2$ Hz and $J_{2b'-1'}=17$ Hz, $H_{2b'}$), 4.94 (ddd, 1H, $J_{2a'-4}=1$Hz, $J_{2a'-2b'}=2$ Hz and $J_{2a'-1'}=10$ Hz, $H_{2a'}$), 4.62 (m, 2H, H_1/H_2), 2.80 (m, 1H, H_4), 1.95 (apparent dd, 2H, $J_{4-3a/5a}=6$ Hz and $J_{gem}=14$ Hz, H_{3a}/H_{5a}), 1.44 (s, 3H, CH_3), 1.33 (m, 2H, H_{3b}/H_{5b}), 1.27 (s, 3H, CH_3); chemical shifts assigned to the *cis* isomer **14b**: δ 5.96 (partially resolved ddd, 1H, $J_{1'-4}=$ 8 Hz, $J_{1'-2a'}=10$ Hz and $J_{1'-2b'}=17$ Hz, $H_{1'}$), 4.97 (ddd, 1H, $J_{2b'-4}=1$ Hz, $J_{2b'-2a'}=2$ Hz and $J_{2b'-1'}=17$ Hz, $H_{2b'}$), 4.88 (ddd, 1H, $J_{2a'-4}=1$ Hz, $J_{2a'-2b'}=2$ Hz and $J_{2a'-1'}=$ 10 Hz, $H_{2a'}$), 4,62 (m, 2H, H_1/H_2), 2.59 (m, 1H, H_4), 2.03 (m, 2H, H_{3b}/H_{5b}), 1.69 (m, 2H, H_{3a}/H_{5a}), 1.48 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

4.4.2. NMR and GC–MS analysis of mixtures of 15a (*trans*) and 15b (*cis*) isolated from reactions with 11. *Compounds* **15a** *and* **15b**. Colorless oil (mixture of *cis* and *trans*). $R_f=0.46$ (silica, 2:5 CH_2Cl_2–pentane). GC–MS: $t_R=5.6$ min, *trans* compound **15a**. [EI] *m/z*: 167 (100%, M−Et), 93 (80.1%, M−$C_5H_{11}O_2$), 91 (33.7%), 77 (22.6%), 57 (76.3%). $t_R=5.7$ min, *cis* compound **15b**. [EI] *m/z*: 167 (76.3%, M−Et), 93 (86.4%, M−$C_5H_{11}O_2$), 91 (37.4%), 77 (26.1%), 57 (100%). ^{13}C NMR chemical shifts assigned to the *trans* isomer **15a**: δ 140.7 (d′, $C_{1'}$), 113.8 (t′, $C_{2'}$), 112.8 (s′, $C(CH_2CH_3)_2$), 80.4 (d′, C_1 and C_2), 40.1 (d′, C_4), 39.5 (t′, C_3 and C_5), 28.2 (t′, CH_2CH_3), 27.8 (t′, CH_2CH_3), 8.8 (q′, CH_2CH_3), 7.6 (q′, CH_2CH_3); chemical shifts assigned to the *cis* isomer **15b**: δ: 141.3 (d′, $C_{1'}$), 113.4 (t′, $C_{2'}$), 116.5 (s′, $C(CH_2CH_3)_2$), 80.8 (d′, C_1 and C_2), 43.0 (d′, C_4), 38.7 (t′, C_3 and C_5), 28.8 (t′, CH_2CH_3), 28.5 (t′, CH_2CH_3), 8.6 (q′, CH_2CH_3), 7.9 (q′, CH_2CH_3); ^{1}H NMR chemical shifts assigned to the *trans* isomer **15a**: δ 5.76 (partially resolved ddd, 1H, $J_{1'-4}=7$ Hz, $J_{1'-2a'}=10$ Hz and $J_{1'-2b'}=17$ Hz, $H_{1'}$), 5.06 (partially resolved ddd, 1H, $J_{2b'-4}=2$ Hz, $J_{2b'-2a'}=2$ Hz and $J_{2b'-1'}=17$ Hz, $H_{2b'}$), 4.96 (partially resolved ddd, 1H, $J_{2a'-4}=1$ Hz, $J_{2a'-2b'}=2$ Hz, $J_{2a'-1'}=10$ Hz, $H_{2a'}$), 4.63 (m, 2H, H_1 and H_2; same chemical shift for both **15a** and **15b**), 2.87 (m, 1H, H_4), 2.01 (partially resolved ddd, 2H, $J_{4-3a/5a}=6$ Hz, $J_{1/2-3a/5a}=$ 1 Hz, $J_{gem}=13$ Hz, H_{3a} and H_{5a}), 1.71 (q, 2H, $J=7$ Hz, CH_2CH_3), 1.58 (q, 2H, $J=7$ Hz, CH_2CH_3), 1.33 (m, 2H, H_{3b} and H_{5b}; this signal overlaps with the H_{3a}/H_{5a} multiplet of the *cis* isomer), 0.97 (t, 3H, CH_2CH_3), 0.88 (t, 3H, CH_2CH_3); the chemical shifts of **15b** overlap with those of **15a** with the exception of the following signals assigned to the *cis* isomer **15b**: δ 5.90 (partially resolved ddd, 1H, $J_{1'-4}=7$ Hz, $J_{1'-2a'}=10$ Hz, $J_{1'-2b'}=17$ Hz, $H_{1'}$), 2.11 (m, 1H, H_4), 1.72 (q, 2H, $J=7$ Hz, CH_2CH_3), 0.96 (t, 3H, CH_2CH_3), 0.87 (t, 3H, CH_2CH_3).

4.4.3. NMR and GC–MS analysis of mixtures of 16a(*trans*) and 16b(*cis*) isolated from reactions with 12. *Compounds* **16a** *and* **16b**. Solid (mixture of *cis* and *trans*). $R_f=0.39$ (silica, 1:19 MeOH–CH_2Cl_2). GC–MS: $t_R=4.62$ min, *trans* isomer **16a**. [EI] *m/z*: 110 (41.9%, M−H_2O), 95 (46.7%), 83 (100%, C_5H_7O), 82 (47.7%), 67 (30.2%), 56 (33.9%), 55 (89.9%), 43 (27.3%), 41 (32.9%), 29 (24.1%), 28 (22.6%), 27 (20.9%); $t_R=4.58$ min, *cis* isomer **16b**. [EI] *m/z*: 110 (37.5%, M−H_2O), 95 (42.4%), 83 (100%, C_5H_7O), 82 (42.4%), 81 (20%), 69 (21%), 67 (31.1%), 56 (37.5%), 55 (93.9%), 43 (28.2%), 41 (33.6%), 39 (27%). ^{13}C NMR chemical shifts assigned to the *trans* isomer **16a**: δ 142.6 (d′, $C_{1'}$), 112.8 (t′, $C_{2'}$), 73.5 (d′, C_1 and C_2), 38.6 (d′, C_4), 38.3* (t′, C_3 and C_5; *both isomers have the same chemical shift for their C_3/C_5 carbons); chemical shifts assigned to the *cis* isomer **16b**: δ 142.8 (d′, $C_{1'}$), 112.9 (t′, $C_{2'}$), 73.2 (d′, C_1 and C_2), 38.3* (t′, C_3 and C_5), 37.9 (d′, C_4). ^{1}H NMR chemical shifts assigned to the *trans* isomer **16a**: δ 5.76 (partially resolved ddd, 1H, $J_{1'-4}=8$ Hz, $J_{1'-2a'}=10$ Hz, $J_{1'-2b'}=17$ Hz, $H_{1'}$), 4.99* (ddd, 1H, $J_{gem}=1$ Hz, $J_{2b'-4}=3$ Hz, $J_{2b'-1'}=17$ Hz, $H_{2b'}$), 4.91* (ddd, 1H, $J_{gem}=1$ Hz, $J_{2a'-4}=2$ Hz, $J_{2a'-1'}=10$ Hz, $H_{2a'}$; *the *cis* and *trans* isomers have the same chemical shifts signals for the $H_{2a'}$ and $H_{2b'}$ protons.), 4.18 (m, 2H, H_1 and H_2), 2.98 (m, 1H, H_4), 2.18 [s large, 2H, 2×OH; the OH signals for the *cis* and *trans* isomers overlap to give a broad singlet centred at 2.18 ppm (exchanges with D_2O) that partially overlaps with the multiplet assigned to the H_{3b} and H_{5b} protons of the *cis* isomer], 1.93 (m, 2H, H_{3a} and H_{5a}), 1.68 (m, 2H, H_{3b} and H_{5b}); chemical shifts assigned to the *cis* isomer **16b**: δ 5.84 (partially resolved ddd, 1H, $J_{1'-4}=$ 7 Hz, $J_{1'-2a'}=17$ Hz, $J_{1'-2'b}=10$ Hz, $H_{1'}$), 4.99* (ddd, 1H, $J_{gem}=1$ Hz, $J_{2b'-4}=3$ Hz, $J_{2b'-1'}=17$ Hz, $H_{2b'}$), 4.91* (ddd, 1H, $J_{gem}=1$ Hz, $J_{2a'-4}=2$ Hz, $J_{2a'-1'}=10$ Hz, $H_{2a'}$; *the *cis* and *trans* isomers have the same chemical shifts signals for the $H_{2a'}$ and $H_{2b'}$ protons.), 4.05 (m, 2H, H_1 and H_2), 2.46 (m, 1H, H_4), 2.18 [broad s, 2H, 2×OH; the OH signals for the *cis* and *trans* isomers overlap to give a broad singlet centred at 2.18 ppm (exchanges with D_2O) that partially overlaps with the multiplet assigned to the H_{2b} and H_{5b} protons of the *cis* isomer], 2.16 (m, 2H, H_{3b} and H_{5b}), 1.55 (m, 2H, H_{3a} and H_{5a}).

4.4.4. NMR and GC–MS analysis of mixtures of 17a (*trans*) and 17b (*cis*) obtained by acetylation of mixtures of 16a and 16b. *Compounds* **17a** *and* **17b**. Oil (mixture of *cis* and *trans*), $R_f=0.87$ (silica, 4:1:1CH_2Cl_2–hexanes–ether). GC–MS: $t_R=6.3$ min, the *cis* and *trans* isomers were not separable using our method; [EI] *m/z*: 212 (2.9%, $M^{\cdot+}$]), 152 [3.5%, M−CH_3COOH (McLafferty)], 127 (10%), 110 (17.7%), 92 [38.8%, M−2×CH_3COOH (McLafferty)], 83 (13.8%), 43 (100%, CH_3CO). ^{13}C NMR chemical shifts assigned to the *trans* isomer: δ: 170.34 (s′, 2×CH_3C=O), 141.7 (d′, $C_{1'}$), 113.6* (t′, $C_{2'}$), 73.8 (d′, C_1 and C_2), 38.0 (d′, C_4), 35.1 (t′, C_3 and C_5), 20.9* (q′, 2×CH_3). *Same chemical shift for CH_3CO and C_2' for both isomers. Chemical shifts assigned to the *cis* isomer: δ 170.29 (s′, 2×CH_3C=O), 142.0 (d′, $C_{1'}$), 113.6* (t′, $C_{2'}$), 73.3 (d′, C_1 and C_2), 37.2 (d′, C_4), 35.2 (t′, C_3 and C_5), 20.9* (q′, 2×CH_3). *Same chemical shift for carbons $C_{2'}$ and CH_3CO for both isomers. ^{1}H NMR chemical shifts assigned to the *trans* isomer **17a**: δ 5.76 (partially resolved ddd, 1H, $J_{1'-4}=7.5$ Hz, $J_{1'-2a'}=10$ Hz and $J_{1'-2b'}=16.5$ Hz, $H_{1'}$], 5.25 (m, 2H, H_1 and H_2), 5.01 (m, 1H, $H_{2b'}$),* 4.94 (m, 1H, $H_{2a'}$),* 2.97 (m, 1H, H_4), 2.05 (s, 2×CH_3 of *trans* and *cis* isomers), 2.02 [m, 2H, H_{3a} and H_{5a} (overlaps with the CH_3 singlet of *cis* and *trans* isomers)], 1.79 (m, 2H, H_{3b} and H_{5b}).

*The signals for protons $H_{2a'}$ and $H_{2b'}$ of the *cis* and *trans* isomers overlap. Chemical shifts assigned to the *cis* isomer **17b**: δ 5.82 (partially resolved ddd, 1H, $J_{1'-4}=8$ Hz, $J_{1'-2a'}=17$ Hz and $J_{1'-2b'}=10$ Hz, $H_{1'}$), 5.13 (m, 2H, H_1 and H_2), 5.01 (m, 1H, $H_{2b'}$),* 4.94 (m, 1H, $H_{2a'}$),* 2.56 (m, 1H, H_4), 2.23 (m, 2H, H_{3b} and H_{5b}), 2.05 (s, $2\times CH_3$ for *trans* and *cis* isomers), 1.65 (m, 2H, H_{3a} and H_{5a}). *The signals of the $H_{2a'}$ and $H_{2b'}$ protons of the *cis* and *trans* isomers overlap.

4.5. Typical procedure for reactions with Bu_3SnH/AIBN (Bu_3SnH Method E)

A solution of **1b** (0.2275 g, 0.5519 mmol) in freshly distilled benzene (9 mL) was prepared under an argon atmosphere at room temperature. Solutions of AIBN (7.5 mg, 0.046 mmol in 2 mL benzene) and Bu_3SnH (0.613 mmol in 2 mL benzene) were then simultaneously added (dropwise over ca. 2 min) to this solution. The reaction mixture was heated at reflux for 4 h, cooled, and concentrated. The residue was diluted with ether (10 mL) and DBU (0.15 mL, 1.0 mmol) was added.[20] The mixture was titrated with a 1 M solution of iodine in ether (2 mL, ca. 2 mmol) and the yellow precipitate that formed was removed by filtration through a short column of silica gel (2×3 cm). The silica was washed with ether (3×10 mL) and the combined filtrates concentrated. The residue was dissolved in ether (10 mL) and the solution stirred with a 30% aqueous solution of KF (10 mL) for 3 h.[21] The heterogeneous mixture was filtered twice, the layers separated and the organic layer was then refiltered through a short pad of silica gel and concentrated. The crude products were purified by radial chromatography [2 mm plate with the following series of eluants: 10% EtOAc–hexanes (50 mL), 20% EtOAc–hexanes (50 mL), 30% EtOAc–hexanes (50 mL)] to give 0.0196 g of **6b** (12.4%), 0.0793 g of **6a** (50.2%) and 0.0150 g of a mixture of **6b** (0.0044 g, 2.8%) and **6a** (0.0106 g, 6.7%).

4.5.1. Compound 6a. Compound **6a** (*trans*): pale yellow oil, $R_f=0.26$ (30% EtOAc–hexanes). $[\alpha]_D=73.5$ (*c* 0.83, 25 °C). ^{1}H NMR δ: 4.92 (m, 1H, H_1), 4.66 [apparent t, $J_{app}=6$ Hz ($J_{1,2}\cong J_{2,3}$), 1H, H_2], 4.34 (d, $J_{2,3}=5.8$ Hz, $J_{4,3}\cong 0$ Hz, 1H, H_3), 4.11 (m, 2H, $H_{2a'}$ and $H_{2b'}$), 2.01–2.22 (m, 8H; H_4, $1\times H_5$, and both OCO*CH*$_3$ singlets at 2.10 and 2.04 ppm.), 1.44–1.81 [m, 6H; CH_3 (s,1.47 ppm) and multiplets for $H_5\times 1$, $H_{1'a}$ and $H_{1'b}$. The multiplets are better separated in the 500 MHz spectrum *i.e.* δ 1.76 ($1\times H_5$), 1.68 (m, $H_{1'a}$) and 1.55 (m, $H_{1'b}$).], 1.30 (s, 3H, CH_3). ^{13}C NMR δ: 170.9 (C=O), 170.7 (C=O), 111.8 ($C(CH_3)_2$), 84.5 (C_3), 78.1 (C_2), 73.1 (C_1), 62.6 ($C_{2'}$), 38.1 (C_4), 32.6 (C_5), 31.2 ($C_{1'}$), 26.1 (CH_3), 24.5 (CH_3), 20.92 (*C*H$_3$C=O), 20.90 (*C*H$_3$C=O). FTIR (film): 1732 (s), 1371 (s), 1238 (s, br), 1071 (s) 1044 (s) cm^{-1}. MS (EI) *m/z*: 271 (100%, M−CH_3), 229 (11.6%), 169 (15.7%), 151 (28.6%), 127 (11.6%), 109 (25.7%), 108 (11.3%), 91 (39.6%). HRMS (EI) found: 271.1180; calcd for M−15=$C_{13}H_{19}O_6$: 271.1182.

4.5.2. Compound 6a. Compound **6b** (*cis*): pale yellow oil. $R_f=0.29$ (30% EtOAc–hexanes). $[\alpha]_D=46.4$ (*c* 0.38, 25 °C). ^{1}H NMR δ: 4.66 (m, 2H, H_1 and H_2), 4.50 [apparent t, $J_{app}=4$ Hz ($J_{2,3}\cong J_{3,4}$), 1H, H_3], 4.05–4.24 (m, 2H, $H_{2'a}$ and $H_{2'b}$), 2.11 [s, 3H, $OCOCH_3$], 2.00 (s, 3H, $OCOCH_3$), 1.93 (m, 2H, $1\times H_5$ and $1\times H_{1'a}$), 1.78 (m, 2H, H_4 and $1\times H_{1'b}$), 1.63–1.70 (m, 1H, $1\times H_5$), 1.47 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR δ: 171.1 (C=O), 170.9 (C=O), 110.6 ($C(CH_3)_2$), 79.8 (C_3), 77.6 (C_2 or C_1), 73.6 (C_2 or C_1), 63.2 ($C_{2'}$), 35.2 (C_4), 31.8 (C_5), 27.6 ($C_{1'}$); 25.7 (CH_3), 24.2 (CH_3), 21.0 (*C*H$_3$CO), 20.9 (*C*H$_3$CO). FTIR (film): 1735 (s, br), 1260 (s), 1094 (s), 1023 (s) cm^{-1}. MS (EI) *m/z*: 271 (100%, M−CH_3), 169 (10.7%), 151 (61.6%), 109 (32.3%), 108 (18.3%), 91 (65.5%). HRMS (EI) *m/z*: found: 271.1183; calcd for M−15=$C_{13}H_{19}O_6$: 271.1182.

4.6. Typical procedure for reactions run with Bu_3SnH/Et_3B (Bu_3SnH Method F)

The method used is an adaptation of a literature procedure.[22] A solution of Et_3B in hexanes (1 M, 0.37 mL, 0.37 mmol, 1.1 equiv) was added to a solution of **10a** (0.106 g, 0.339 mmol) in anhydrous toluene (3 mL) under an argon atmosphere. A solution of Bu_3SnH in toluene was prepared and slowly added to the reaction mixture over 2 h (0.18 mL, 0.67 mmol, 2 equiv of Bu_3SnH in 0.72 mL toluene). After 4 h of stirring at room temperature, the mixture was diluted with hexanes (5 mL) and treated with TBAF (1.0 mL, 1.0 M in THF, 1.0 mmol). Stirring was continued at room temperature for 30 min before filtering the mixture through a short pad of silica gel. The silica was washed with ether (100 mL) and the combined filtrates concentrated. Tin compounds were still present and so the residue was next taken up in ether (10 mL) and treated with DBU (0.67 mmol, 0.10 mL) and an ether solution of I_2 (1 M, 1 mL). The mixture was filtered through a short pad of silica and the silica washed with ether (3×10 mL). The combined filtrates were treated with a 30% aqueous solution of KF (5 mL) and the mixture stirred for 3 h at room temperature. The layers were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated. Radial chromatography of the residue [1 mm plate, Et_2O–hexanes 1:3 gave 0.0475 g (75%) of compounds **18a** and **18b** in a 4.4:1 ratio determined by GC–MS. The mixture of **18a** and **18b** was rechromatographed and the collected fractions were first analyzed by GC–MS before being combined and concentrated. In this way we were able to isolate a pure sample of the *trans* isomer **18a** for characterization purposes; although we were not able to isolate a pure sample of the *cis* isomer **18b** we were able to obtain an enriched sample (*trans–cis*=1:6) for characterization purposes.

4.6.1. Compound 18a. Compound **18a** (*trans*): isolated as an oil; $R_f=0.38$ (silica, 3:1 Et_2O–hexanes). ^{1}H NMR δ: 4.63 (m, 2H, H_1 and H_2), 3.67 (t, 2H, $J_{2',1'}=7$ Hz, $H_{2'}$ protons), 2.24 (m, 1H, H_4), 1.99 (m, 2H, H_{3a} and H_{5a}; in the 500 MHz spectrum this signal appears as a dd with $J=6$ and 14 Hz), 1.61(apparent quadruplet, 2H, $J_{4,1'}=7$ Hz, $J_{2',1'}=7$ Hz, $H_{1'}$ protons), 1.57 (broad s, OH), 1.45 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.14 (m, 2H, H_{3b} and H_{5b}). ^{13}C NMR δ: 108.7 (s′, $C(CH_3)_2$), 80.4 (d′, C_1 and C_2), 62.1 (t′, $C_{2'}$), 39.8 (t′, C_3 and C_5), 37.1 (t′, $C_{1'}$), 32.8 (d′, C_4), 26.0 (q′, CH_3), 23.7 (q′, CH_3). GC–MS: $t_R=6.3$ min, (EI) *m/z*: 171 (79.6%, M−CH_3), 111 (53.5%), 93 (100%), 91 (24.3%), 83 (25.7%), 81 (23.7%), 67 (55.9%), 59 (18.7%), 55 (21.1%), 43 (54.2%).

4.6.2. GC–MS and NMR chemical shifts attributed to

18b (*cis*). R_f=0.38 (silica, 3:1 Et_2O–hexanes). GC–MS: t_R=6.4 min, (EI) *m/z*: 171 (76.3%, M−CH_3), 111 (22.9%), 93 (100%), 91 (21%), 83 (24.3%), 67 (56.8%), 59 (19.5%), 55 (20.7%), 43 (47.5%). Chemical shifts attributed to **18b**: ^{1}H NMR δ: 4.63 (m, 2H, H_1 and H_2), 3.68 (t, 2H, $J_{2',1'}$= 6 Hz, $H_{2'}$ protons), 2.12 (m, 1H, H_4), 1.99 (m, 2H, H_{3b}/H^*_{5b}), 1.79 (partially resolved dt, J=6.5, 7 Hz, 2H, $H_{1'}$ protons), 1.63 (m, 2H, H_{3a}/H^*_{5a}), 1.53 (broad s, OH), 1.50 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). *Tentative assignment of these two signals. ^{13}C NMR δ: 81.1 (d′, C_1 and C_2), 61.9 (t′, $C_{2'}$), 39.8 (t′, C_3 and C_5), 38.0 (t′, $C_{1'}$), 35.5 (d′, C_4), 26.9 (q′, CH_3), 24.2 (q′, CH_3). We were not able to detect a signal for the quaternary carbon ($C(CH_3)_2$) of **18b**.

4.6.3. Compounds 20a and 20b. Reaction of **13** with Bu_3SnH/Et_3B in toluene gave an inseparable mixture of compounds **20a** and **20b** [oil, R_f=0.76 (silica, 4:1:1 CH_2Cl_2–Et_2O–hexanes; 86% yield, **20a** (*trans*): **20b** (*cis*)=3.1:1.0 (GC ratio)]. GC–MS (**20a**) t_R=6.9 min, (EI) *m/z*: 213 (43.5%, M−CH_3), 111 (15.4%), 93 (100%), 43 (46.9%). GC–MS (**20b**): t_R=7.1 min, (EI) *m/z*: 213 (40.5%, M−CH_3), 111 (14%), 93 (100%), 43 (49.1%). NMR chemical shifts attributed to **20a** (*trans*) and **20b** (*cis*). ^{1}H NMR δ: 4.61 (m, 2H, H_1/H_2, *cis* and *trans*), 4.07 (t, 2H, $J_{2',1'}$=7 Hz, $H_{2'}$ protons, *cis* and *trans*), 2.21 (m, 1H, H_4, *trans*), 2.03 (s, 3H, OCOCH_3 of *cis* and *trans*), 1.98 (m, 2H, H_{3a}/H_{5a} signal of *trans* overlaps with the H_{3b}/H_{5b} signal of the *cis*), 1.83 (apparent q, 2H, $J_{4,1'}$=$J_{1',2'}$=6,5 Hz, $H_{1'}$, *cis*), 1.65 (apparent q, 2H, $J_{4,1'}$=$J_{2',1'}$=7 Hz, $H_{1'}$ protons *trans* isomer; partially overlaps with H_{3a}/H_{5a} signal of *cis* isomer), 1.63 (m, 2H, H_{3a} and H_{5a} partial overlap with $H_{1'}$ protons of *trans* isomer), 1.48 (s, 3H, CH_3, *cis*), 1.43 (s, 3H, CH_3, *trans*), 1.275–1.295 (m, 1H, H_4 overlaps with CH_3 singlets of *trans* and *cis* at 1.280 and 1.278 ppm respectively), 1.13 (m, 2H, H_{3b}/H_{5b}, *trans*). ^{13}C NMR (**20b**, *cis*) δ: 171.14 (s′, C=O, Ac), 111.0 (s′, $C(CH_3)_2$), 81.0 (d′, C_1/C_2), 63.6 (t′, $C_{2'}$), 38.0 (t′, C_3/C_5), 35.8 (d′, C_4), 33.9 (t′, $C_{1'}$), 26.9 (q′, CH_3), 24.1 (q′, CH_3), 21.0* (q′, OCOCH_3). ^{13}C NMR (**20a**, *trans*) δ: 171.08 (s′, C=O, Ac), 108.7 (s′, $C(CH_3)_2$), 80.3 (d′, C_1/C_2), 63.8 (t′, $C_{2'}$), 39.7 (t′, C_3/C_5), 33.2 (d′, C_4), 32.8 (t′, $C_{1'}$), 26.0 (q′, CH_3), 23.7 (q′, CH_3), 21.0* (q′, OCOCH_3). *A single signal was observed for both *cis* and *trans* isomers.

4.6.4. Compounds 19a (*trans*) and 19b (*cis*). Reaction of **11** with Bu_3SnH/Et_3B in toluene gave a mixture of compounds **19a** and **19b** [oil, R_f=0.38 (silica, 2:3:2 CH_2Cl_2–hexanes–EtOAc; 73% yield, **19a** (*trans*): **19b** (*cis*)=7.7:1.0 (GC ratio)]. The mixture of **19a** and **19b** was rechromatographed and the collected fractions were first analyzed by GC–MS before being combined and concentrated. In this way, we were able to isolate a pure sample of the *trans* isomer **19a** for characterization purposes; although we were not able to isolate a pure sample of the *cis* isomer **19b** we were able to obtain an enriched sample (*trans*–*cis*=2.8:1.0) for characterization purposes. Compound **19a** (*trans*): isolated as an oil, R_f= 0.38 (silica, 2:3:2 CH_2Cl_2–hexanes–EtOAc). ^{1}H NMR δ: 4.61 (m, 2H, H_1/H_2), 3.67 (t, 2H, $J_{2',1'}$=7 Hz, $H_{2'}$), 2.27 (m, 1H, H_4), 2.02 (apparent ddd, 2H, J=6, 1, 13 Hz, H_{3a}/H_{5a}), 1.69 (q, 2H, J=7.5 Hz, CH_2CH$_3$), 1.60 (apparent q, 2H, $J_{2',1'}$=$J_{4,\ 1'}$=7 Hz, $H_{1'}$), 1.57 (q, 2H, J=7.5 Hz, CH_2CH$_3$), 1.51 (s large, 1H, 1×OH), 1.15 (m, 2H, H_{3b}/H_{5b}), 0.94 (t, 3H, J=7.5 Hz, CH_2CH_3), 0.87 (t, 3H, J=7.5 Hz, CH_2CH_3). ^{13}C NMR δ: 112.8 (s′, $C(CH_2CH_3)_2$), 80.4 (d′, C_1/C_2), 62.2 (t′, $C_{2'}$), 39.9 (t′, C_3/C_5), 37.4 (t′, $C_{1'}$), 33.1 (d′, C_4), 28.2 (t′, CH_2CH_3), 27.7 (t′, CH_2CH_3), 8.8 (q′, CH_2CH_3), 7.6 (q′, CH_2CH_3). GC–MS: t_R=7.3 min, (EI) *m/z*: 185 (64.5%, M−Et), 111 (51.5%), 93 (100%), 91 (23.1%), 81 (26.7%), 67 (67.9%), 57 (90%).

GC–MS and NMR chemical shifts attributed to **19b** (*cis*). GC–MS: t_R=7.5 min, (EI) *m/z*: 185 (50.7%, M− Et), 111 (28.4%), 93 (100%), 91 (20.6%), 67 (65.6%), 57 (87.2%). ^{1}H NMR: The signals of the *cis* isomer **19b** overlap with those of the *trans* isomer **19a** with the following exceptions: δ: 3.66 (t, 2H, $J_{2',1'}$=6.5 Hz, $H_{2'}$), 2.10 (m, 3H, H_{3b}/H_{5b} and H_4), 0.95 (t, 3H, J=7.5 Hz, CH_2CH_3), 0.86 (t, 3H, J=7.5 Hz, CH_2CH_3). ^{13}C NMR δ: 116.2 (s′, $C(CH_2CH_3)_2$), 80.8 (d′, C_1/C_2), 61.8 (t′, $C_{2'}$), 38.4 (t′, C_3/C_5), 38.1 (t′, $C_{1'}$), 35.6 (d′, C_4), 28.8 (t′, CH_2CH_3), 28.23 (t′, CH_2CH_3), 8.6 (q′, CH_2CH_3), 8.0 (q′, CH_2CH_3).

Compounds **22a** and **22b** were prepared by first carrying out a reductive cyclization on compound **12** with Bu_3SnH/Et_3B in THF and by then adding, after 24 h, an excess of Ac_2O (15 equiv) and pyridine (10 equiv) directly to the reaction mixture. The resulting mixture was stirred at room temperature overnight before workup, under our usual conditions, and radial chromatography. Compounds **22a** and **22b** were isolated as a mixture [oil, R_f=0.68 (silica, 4:1:1 CH_2Cl_2–Et_2O–hexanes), 62% yield, NMR ratio of **22a**–**22b**=1.0:1.4]. GC–MS: t_R=8.4 min, the *cis* and *trans* isomers were not separable by our method. (EI) *m/z*: 229 (0.05%), 213 (0.14%), 212 (0.15%), 169 (16%), 152 (4%), 127 (23.1%), 110 (54.2%), 92 (11.6%), 83 (43.2%), 43 (100%). NMR chemical shifts attributed to **22a** (*trans*) and **22b** (*cis*): ^{1}H NMR δ: 5.23 (m, 2H, H_1/H_2, **22a**), 5.12 (m, 2H, H_1/H_2, **22b**), 4.074 (t, 2H, $J_{2',1'}$=7 Hz, $H_{2'}$, **22a**), 4.067 (t, 2H, $J_{2',1'}$=7 Hz, $H_{2'}$, **22b**), 2.39 (m, 1H, H_4, **22a**), 2.22 (m, 2H, H_{3b}/H_{5b}, **22b**), 2.11–1.95 (m, H_{3a}/H_{5a} signal of **22a** overlaps with the H_4 multiplet of **22b** and the CH_3 singlets of both isomers at 2.053 and 2.046 ppm), 1.77 (apparent q, 2H, $J_{4,1'}$=$J_{2',1'}$=7 Hz, $H_{1'}$ protons, **22b**), 1.64 [m, 4H, $H_{1'}$ and H_{3b}/H_{5b} protons, **22a**. After resolution enhancement the signal for the $H_{1'}$ protons appears as a quadruplet at 1.68 ppm ($J_{4,1'}$=$J_{2',1'}$=7 Hz)], 1.50 (m, 2H, H_{3a}/H_{5a}, **22b**). ^{13}C NMR δ: 171.1, 170.4 and 170.3 (s′, C=O, **22a** and **22b**), 73.9 (d′, C_1/C_2, **22a**), 73.3 (d′, C_1/C_2, **22b**), 63.2 (t′, $C_{2'}$, **22a**), 63.1 (t′, $C_{2'}$, **22b**), 35.7 (t′, $C_{1'}$, **22b**), 35.4 (t′, $C_{1'}$, **22a**), 35.1 (t′, C_3/C_5, **22a**), 35.0 (t′, C_3/C_5, **22b**), 31.3 (d′, C_4, **22a**), 30.0 (d′, C_4, **22b**), 20.98 and 20.94 (q′, CH_3 of **22a** and **22b**).

Acknowledgements

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Université du Québec à Montréal for financial support of our research. We thank Mr. Nadim Saade of McGill University for mass spectra results and Dr. Hoa Le Thanh of UQÀM for help with NMR experiments.

Supplementary data

Supplementary data associated with this article can be found at doi:10.1016/j.tet.2004.06.099.

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Tetrahedron 60 (2004) 8131–8135
Tetrahedron

Supercritical CO_2 as a superior solvent for the cyclization of diallylmalonate catalyzed by palladium-containing zeolites

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Received 4 February 2004; revised 25 May 2004; accepted 18 June 2004

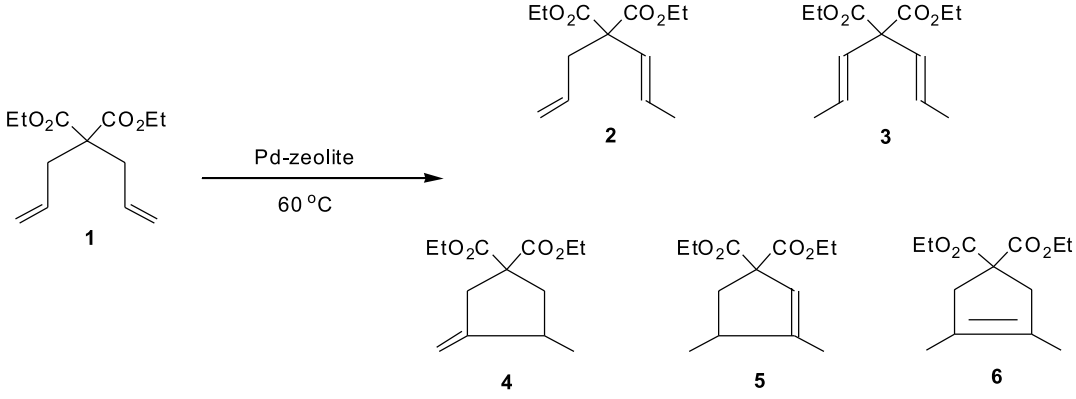
Available online 22 July 2004

Abstract—Palladium-containing zeolites catalyze the cycloisomerization of diethyl diallylmalonate to dimethylcyclopentenes. When the reaction is carried out in toluene, the performance of the palladium catalyst depends on the pore size of the zeolites. At 60 °C, palladium adsorbed on large pore size Beta zeolite (pore size ~7.4 Å) is more active than medium pore size ZSM-5 (pore size ~5.4 Å). This lower activity of ZSM-5 compared to Beta is attributable to the restricted diffusion of reagent and products through the ZSM-5 channels as compared to Beta zeolite. However, due to the gas-like diffusion characteristic of the supercritical state, the activity of ZSM-5 increases and becomes identical to that of Beta zeolite using supercritical CO_2 as medium.

1. Introduction

Palladium catalyzed C–C bond formation is among the most versatile reactions in modern organic synthesis due to the typical mild conditions and its compatibility with a large variety of functional groups.[1–3] While most of the work on palladium catalysis has been carried out in homogeneous phase using soluble palladium salts or complexes, there is a current interest in developing solid catalysts for heterogeneous catalysis.[4–8] Use of heterogeneous catalysts allows easy recovery and reuse of the palladium-containing catalyst without noble metal loss.[5]

One of the simplest palladium catalyzed reactions is the cyclization of diallyl-malonates to form cyclopentenes (Scheme 1).[9–17] Novel procedure for five member rings are always of interest given their widespread occurrence in natural products. Cycloisomerization of diallylmalonates to



Scheme 1. Cyclization of diallylmalonate to cyclic pentenes.

Keywords: Pd Catalysis; Cyclization; Supercritical carbon dioxide.
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doi:10.1016/j.tet.2004.06.118

Table 1. Some physico-chemical properties of the catalysts

Catalyst	Pore structure	Si/Al	A_{BET} (m^2/g)	Micro-pore area (m^2/g)	Pd (wt%)
ZSM-5	2D; 5.4×5.6 Å	—	—	—	—
Pd^{2+}ZSM-5	—	15	430	228	0.8
Beta	3D; 7.5×5.7 Å	—	—	—	—
Pd^{2+}Beta		12.5	730	383	0.6

cyclopentenes is a reaction specific of hard palladium sites, since these products are not formed under Brönsted acid catalysis.

Zeolites are crystalline aluminosilicates whose rigid framework defines channels and cavities of nano- and subnanometric dimensions called micropores.[18–20] These micropores allow mass transfer from the exterior to the interior of the particles provided that the molecular size of the diffusing molecules is smaller than the diameter of the pores. The accessibility of the internal voids determines that zeolites are ranking in the top of the list among the solids with larger specific surface area. Due to their microporosity, large surface area, thermal and chemical stability zeolites are paradigmatic reusable and regenerable solid catalysts for Green chemistry.[5] Recently, we and others have used zeolites as large area solids to support palladium species with activity as heterogeneous C–C bond forming catalysts.[6–8,21,22]

However, one of the problems typically encountered in the use of zeolites as catalysts in liquid phase reactions is the unfavourable intraparticle diffusion of reagents or products through the channels and cavities, thus, lowering and limiting the intrinsic catalytic activity of the internal sites.[23] When pore dimensions are considerably larger than those of the molecules involved in the reaction, then, diffusion limitations becomes less important. On the other extreme, if the size of the molecules is larger than that of the micropores, then internal diffusion becomes completely impeded and the micropores are not accessible to the reagents. It is in those cases in which the size of the reagents or products is similar to that of the zeolite micropores when the strategies to overcome diffusional limitations becomes a crucial issue in zeolite catalysis.

Normally diffusion enhancement is achieved by performing the reaction at higher temperatures to increase the kinetic energy of the molecules, overcoming the activation barrier to diffusion or by performing the reactions in the gas phase in the absence of solvent. In a related precedent we have shown that supercritical CO_2 is a suitable solvent to perform the hydroxyalkylation of anisole with formaldehyde.[24]

Herein, by using the palladium-catalyzed cycloisomerization of diallylmalonates we illustrate how the special properties of the supercritical state can be used to increase diffusion as compared to conventional organic solvents.

2. Results and discussions

For the present study we have used two palladium-containing zeolites, namely zeolites Beta and ZSM-5, differing in the void geometry and pore dimensions.[25] Zeolite Beta is a tridirectional, large-pore zeolite whose internal voids encompasses oval-shaped cages (11 Å longest axis) defined by the crossing of 12-oxygen channels of 7.4 Å of diameter. In contrast, the internal voids of bidirectional, medium-pore ZSM-5 contains two 10-oxygen perpendicular channel systems, one formed by straight ellipsoidal channels and other by circular zig-zag channels. Table 1

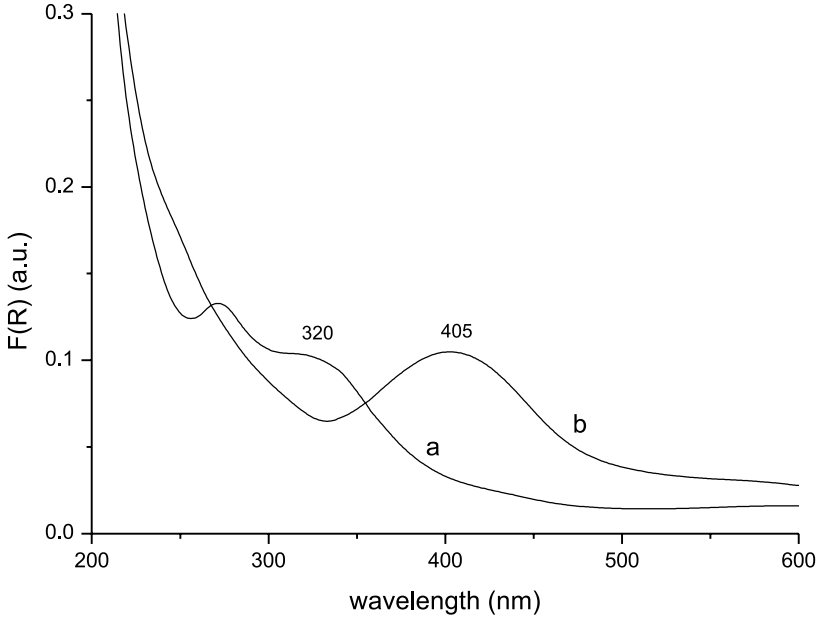

Figure 1. Diffuse reflectance UV–visible spectra of (a) $Pd(NH_3)_4^{2+}$-Beta and (b) Pd^{2+}-Beta.

Table 2. Conversion of diallylmalonate on Pd^{2+}-zeolites catalysts

Catalyst	Reactions in toluene at		Reactions in $SCCO_2$		
	60 °C	110 °C	60 °C	Reused	Regenerated
Pd^{2+}-ZSM-5	1% (1 h)		51% (1 h)		
	42% (4 h)		57% (4 h)		
	54% (12 h)	100% (1 h)	87% (12 h)	46% (12 h)	89% (12 h)
Pd^{2+}-Beta	72% (1 h)		97% (1 h)		
	92% (4 h)	100% (1 h)	97% (4 h)		

summarizes the most relevant textural and porosity parameters of the two zeolites.

Palladium was included in the zeolites by ion-exchange following a reported procedure[26–29] that is known to introduce Pd^{2+} ions. The procedure uses aqueous solutions of $Pd(NH_3)_4^{2+}$, followed by ammonia evacuation at mild temperatures. The process can be conveniently followed by monitoring the diffuse reflectance UV–Vis spectrum of the palladium containing zeolites. As reported, the solids containing $Pd(NH_3)_4^{2+}$ exhibit an absorption at 300 nm that is replaced by a band at about 450 nm upon NH_3 removal and formation of ammonia-free Pd^{2+}. Figure 1 shows the representative diffuse-reflectance UV–Vis spectra of Pd^{2+}-Beta samples to illustrate the changes accompanying the catalyst preparation step.

As it could be anticipated in view of the precedents existing in the literature[9–14] about the reaction of diallylmalonate with soluble palladium complexes, heating a solution of diallylmalonate in toluene in the presence of Pd^{2+}-Beta or Pd^{2+}-ZSM-5 leads to the formation of cyclopentenes. The results achieved for the cycloisomerization in toluene as solvent are indicated in Table 2. Control experiments in the absence of catalyst or in the presence of the corresponding zeolites lacking palladium showed that no cyclopentenes were formed. Therefore, in agreement with the chemical literature about cycloisomerization in homogeneous phase, the formation of cyclopentenes from diallylmalonate catalyzed by palladium-containing zeolites appears to be specific of palladium catalysis.

Conversion of diallylmalonate was found to depend on the reaction temperature. At toluene reflux temperature, the performance of Pd^{2+}-Beta and Pd^{2+}-ZSM-5 was quite similar and within 1 h complete conversion of diallylmalonate was obtained. In contrast, at 60 °C Pd^{2+}-Beta was found to be significantly more active than Pd^{2+}-ZSM-5. Figure 2 shows the time conversion plot at 60 °C for the cyclization of diallymalonate in the presence of both zeolite-supported catalysts. While with Pd^{2+}-Beta almost 100% conversion was achieved within 6 h, with Pd^{2+}-ZSM-5 conversion was much lower and after 24 h only 60% conversion of the diallylmalonate was observed. With Pd^{2+}-Beta 90% conversion of diallylmalonate was obtained within 4 h. However, it took about 72 h to reach similar level of conversion with Pd^{2+}-ZSM-5. Also in case of Pd^{2+}-ZSM-5 a short induction period was also observed presumably due to the restricted diffusion in the narrower pore channels.

The above findings about the influence of the reaction temperatures on the zeolite catalyst activity can be easily interpreted as the reflection of diffusion control for the reaction of diallylmalonate catalyzed by Pd^{2+}-ZSM-5 when the reaction was carried out at 60 °C. At higher temperatures the two zeolites either large or medium pore size behaves similarly since the activation barrier for diffusion in ZSM-5 was overcome. At lower temperatures, diffusion of reagents and products inside the pores of ZSM-5 becomes an important factor controlling the activity of the internal sites. Under such conditions the activity of large-pore Pd^{2+}-Beta zeolite was found to be significantly higher than that of Pd^{2+}-ZSM-5. The lower activity of Pd^{2+}-ZSM-5 is not an intrinsic property of the catalyst since at higher temperatures both catalysts exhibit similar activity.

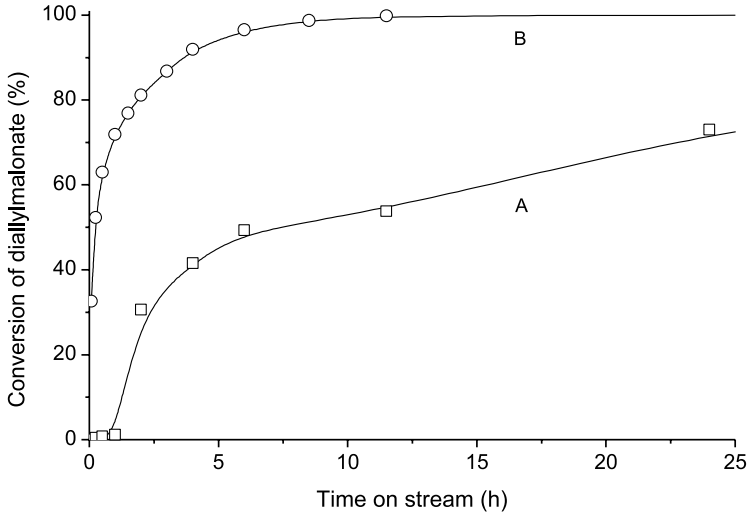

Figure 2. Conversion of diallylmalonate with reaction time at 60 °C on (A) Pd^{2+}ZSM-5 and (B) Pd^{2+}Beta catalysts.

Cyclization of diallylmalonate in the presence of palladium-containing zeolites was also carried out in supercritical CO_2. The results obtained are also indicated in Table 2. Under these conditions, it is assumed that the reaction occurs in a bi-phasic system defined by supercritical CO_2 and the solid catalyst, reagents and products being in both phases according to their adsorption coefficient in these media.

In contrast to what was observed in toluene, when the palladium-catalyzed diallylmalonate cyclization is carried out in supercritical CO_2 as solvent at 60 °C, the two zeolitic catalysts becomes again equally active. Moreover, while the activity of Pd^{2+}-Beta in toluene and supercritical CO_2 at the same temperature is similar, there is a remarkable increase in the activity of the medium-pore size ZSM-5 catalyst. These results point that diffusion inside the micropores of ZSM-5 in supercritical media is considerably favored as compared to toluene. Since for Beta zeolite the reaction is not diffusion controlled at 60 °C, this effect of activity enhancement in supercritical CO_2 is not observed. The influence observed for the Pd^{2+}-ZSM-5 catalyzed cyclization in supercritical CO_2 derives from the high diffusion coefficient characteristics of the supercritical state[30] that has liquid-like properties of in terms of solubility and density, but also gas-like properties in terms of diffusion.

The beneficial effect of supercritical CO_2 was also observed in the final product distribution of the cyclopentenes (Fig. 3). It was observed that at 60 °C and at around similar conversion level, reactions in supercritical CO_2 produced higher amounts of the cyclized pentenes and lesser diene isomers than the reaction in toluene. Also among the cyclized isomers the amount of product **4** obtained was almost 4-fold higher in $SCCO_2$.

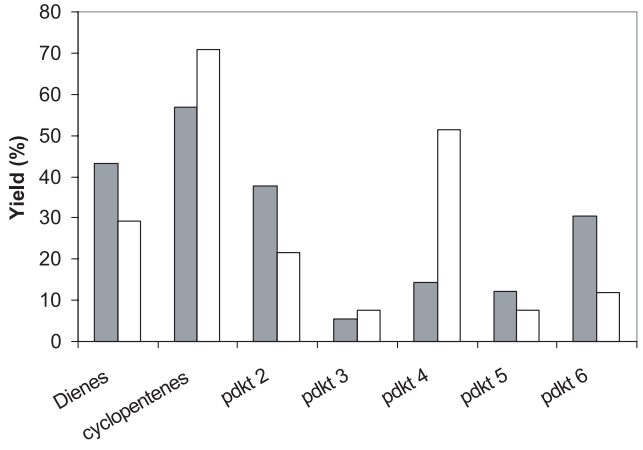

Figure 3. Selectivity to different isomers at 60 °C with Pd^{2+}ZSM-5 catalysts. Dienes and cyclopentenes correspond to the sum of compounds (2+3) and (4+5+6), respectively. For the compound numbers see Scheme 1.

The positive influence of supercritical media in zeolite catalysis has been already reported.[31] But in most of the precedents, the higher activity of zeolite catalysts arise from a less severe catalyst deactivation due to the higher solubility of the poisons in supercritical media compared to organic solvents.[32–34] Poisons are responsible for blocking the zeolite pores impeding access to the internal sites of the particles. The example reported here is conceptually different, since we are comparing initial reaction rates that correspond to the activity of the initial, fresh catalyst. Moreover, after the reaction the Pd^{2+}-ZSM-5 is largely deactivated. In fact, in a second use Pd^{2+}-ZSM-5 exhibits about 50% of the activity of the fresh Pd^{2+}-ZSM-5 (see Table 2) indicating that the effect of the supercritical medium is not due to its influence in catalyst activity decay. However, almost complete regeneration of the deactivated Pd^{2+}-ZSM-5 catalyst can be accomplished by calcination at 550 °C in air flow.

In summary, from the data present it can be concluded that the features of the supercritical state are particularly applicable to heterogeneous catalysis using microporous solids as catalysts. This effect is remarkable in those cases in which intracrystalline diffusion becomes the controlling factor of the catalysis.

3. Experimental

Ethyl 2,2-diallylmalonate (0.125 μL, 0.5 mmol) and toluene (10 ml) were added to previously dehydrated solid catalysts and the suspension was magnetically stirred in a preheated oil bath at a desired reaction temperature. The amount of the catalyst was adjusted to get 5 wt% Pd in each case. To monitor the progress of the reaction, stirring was stopped briefly and 0.1 mL samples of the supernatant solution were periodically taken and analysed by GC (HP 5890 GC equipped with a 25 m capillary column of 5% phenyl-methylsilicone) using nitrobenzene as an external standard. At the end of the reaction the suspension was filtered and the catalyst was submitted to exhaustive solid–liquid extraction with CH_2Cl_2 using a Soxhlet set-up. The extract was concentrated under reduced pressure and analysed by CG. Mass balances higher than 95% are achieved. The structures of the products obtained were characterized by GC (comparison with authentic sample), GC-MS (Varian Saturn II, same column and conditions as GC) and also by ^1H NMR spectroscopy (Varian Geminis, 300 MHz, $CDCl_3$ as solvent).

Reactions under supercritical conditions was carried out in a Büchi stainless steel reactor using same quantities of the reactant and catalysts as mentioned earlier. After sealing the reactor was charged with liquid CO_2 and then heated at 60 °C for desired reaction time. At the end, excess CO_2 was released slowly and the products were collected with small amounts of dichloromethane, filtered from the solid particles and was analysed by gas chromatography as mentioned earlier.

Acknowledgements

Financial support by the Spanish Ministry of Science and Technology (MAT-2003-1226) is gratefully acknowledged. D. D. thanks the Generalitat Valenciana for a postdoctoral fellowship. A L. is the recipient of a postgraduate research scholoarship from the Ministry of Science and Technology.

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Tetrahedron 60 (2004) 8137–8141
Tetrahedron

One-pot reactions: enantiomerically pure bicyclo[5.3.1]undecanes; synthesis of a taxoid compound

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Received 29 April 2004; revised 3 June 2004; accepted 17 June 2004

Available online 20 July 2004

Dedicated to Professor Armin de Meijere on the occasion of his 65th birthday

Abstract—Reaction of C-2 substituted cyclohexenone with an enantiomerically pure α-bromopentenoate leads to enantiopure tricyclooctane, which can be transformed into a taxoid like compound having the typical bicyclo[5.3.1]undecane skeleton.

1. Introduction

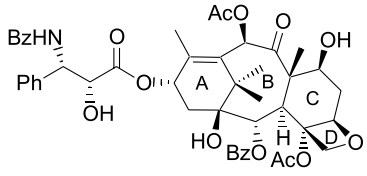
Search and synthesis of new microtubule stabilizing agents is still of high interest for cancer research.[1] Only a few natural products, possessing these exceptional molecular properties, have been identified so far.[2] By far the most widespread and extensively investigated class are taxoids.[3] The bicyclo[5.3.1]undecane skeleton is the key structural feature of taxoid compounds,[4] for example paclitaxel (= Taxol®) (**1**)[5,6] or aromatic C-ring analogous like **2**[7] (Fig. 1).

Retrosynthetic analysis (Fig. 2) of a taxoid skeleton **A** with an attached aromatic C-ring similar to **2** leads via the tricyclic fragment **B** to a bicyclo[3.2.1]octane[8,9] **C** and benzyl halide **D**. Synthon **C** is available by ring opening of the push–pull substituted cyclopropane moiety[10] of tricyclo[3.2.1.$0^{2,7}$]octane **E**, which can be synthesized in enantiopure form by using an anionically induced Domino reaction.[11,12]

'One pot' syntheses or domino reactions[13,14] have been used many times to increase the preparation efficiency of complex natural products.[15,16] Tricyclo[3.2.1.$0^{2,7}$]octanes are useful and flexible building blocks for a variety of carbon skeletons,[17,18] however, to the best of our knowledge, they have not been used until now for the synthesis of a bicyclo[5.3.1]undecane ring system. We will present in this paper a straightforward way to generate such a skeleton in enantiopure form.

2. Results and discussions

We first investigated the alkylation of the enantiomerically pure bicyclo[3.2.1]octane **4** (Scheme 1), which was obtained from tricyclo[3.2.1.$0^{2,7}$]octane **3** by hydrogenolytic cleavage of the benzyl ether function and consecutive ring-opening of the push–pull cyclopropane moiety.[11] Alkylation of bicyclo[3.2.1]octane **4** with 2-bromobenzyl bromide (**5**) occurred regioselectively at C-3 to give exclusively bicycle **7**, but not the desired C-7 alkylated



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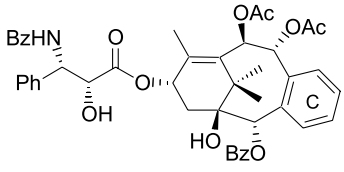

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Figure 1. Paclitaxel and analog.

Keywords: Domino reaction; Taxoids; Diastereoselective synthesis; Ring closure.

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doi:10.1016/j.tet.2004.06.094

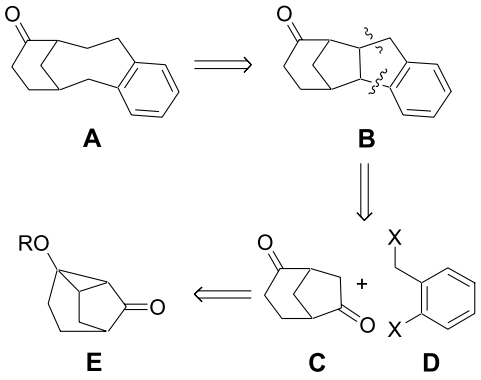


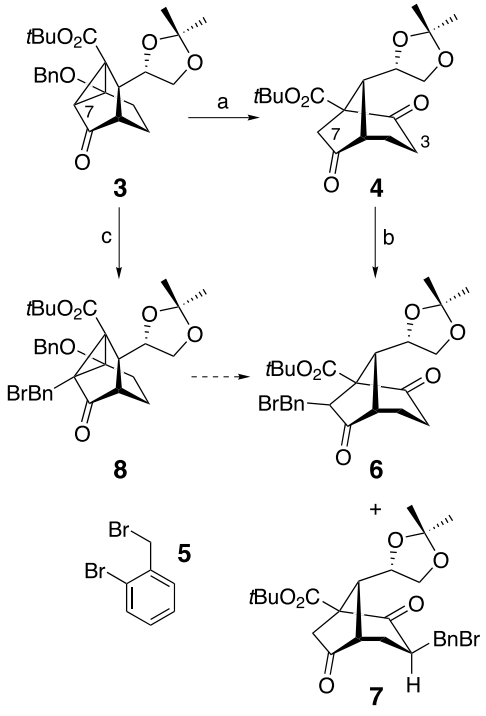
Figure 2. Retrosynthetic analysis.

product **6**. The structure of **7** was determined by NOESY (vicinity of 3-H and 7-H) and $^{1}H,^{1}H$-COSY. This structure is in agreement with the corresponding PC-MODEL calculation.[19] Obviously, the 6-membered ring ketone possesses a higher reactivity.

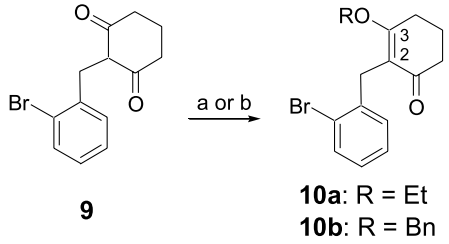
One could envision an alternative way to generate **6** by kinetically controlled alkylation at C-7[20,21] of tricycle **3** with bromide **5**. However, this transformation led to tricycle **8** in only poor yield ($\leq$8%). The kinetic acidity of such a strained carbocylic ketone is dramatically diminished both by an ethoxy and a benzyloxy group.[20]

We turned our interest to introduce the aromatic moiety at C-7 by a rather straightforward manner. Our synthesis commenced from the C-2 substituted enones **10**, which were prepared from dione **9** (Scheme 2).

The kinetically controlled generated lithium dienolate Li-**10a** reacted smoothly with the enantiomerically pure



Scheme 1. (a) Pd/C, H_2, EtOAc, 80%; (b) LDA, **5**, THF, **6**: 0%, **7**: 47% (d.e.>95%); (c) LDA, **5**, THF, ca. 8%; BrBn=2-bromobenzyl.



Scheme 2. (a) Et_3OBF_4, CH_2Cl_2, 79%; (b) BnOH, *p*-TsOH, toluene, 84%.

Michael acceptor **11**[11,22] to form diastereoselectively tricyclo[3.2.1.$0^{2,7}$]octane **12** (d.e.$\geq$95%) in 51% yield.

By using Li-**10b** as starting material only a minor amount ($\leq$9%) of the corresponding tricycle was obtained.

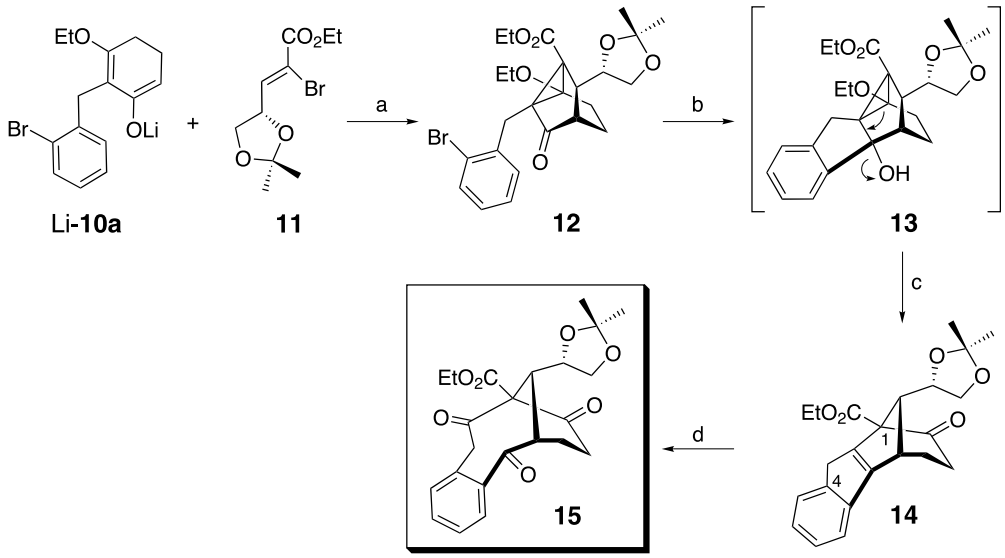
The characteristic bicyclo[5.3.1]undecane skeleton of taxoids can be synthesized in only three steps from tricycle **12** (Scheme 3). Formation of the carbon–carbon bond between the carbonyl and the aromatic ring could be performed either by using a radical reaction[23] or halogen–metal exchange. Lithiation with *tert*-butyllithium at −110 °C gave tertiary alcohol **13**, which was used as a crude product for the next step. Protonation of **13** followed by dehydration and ring opening of the push–pull substituted cyclopropane unit yielded olefin **14**. Under these conditions, the dioxolane moiety was not hydrolyzed. Both structure confirmation of **14** and determination of the absolute configuration were done by X-ray analysis.[24] Ozonolysis of the double bond of olefin **14** at −95 °C and work-up with dimethylsulfide yielded triketone **15**, which can be further transformed into different paclitaxel analogous. The oxidative cleavage of a double bond in a bicyclo[3.2.1]octane system to form a bicyclo[5.3.1]undecane has been applied previously[25,26] and it is a common tactic in the synthesis of medium and large ring systems.[27] In our case, the enantiopure taxoid skeleton **15** possessing the opposite absolute configuration of the naturally occurring taxanes was formed in only four steps in 24% overall yield starting from easily available precursors.

In summary, enantiopure tricyclo[3.2.1.$0^{2,7}$]octanes are flexible building blocks for a variety of carbon skeletons including bicyclo[5.3.1]undecanes. Moreover, we could show that the diastereoselectivity of the domino reaction with Michael acceptors of type **11** is not influenced by a C-2 substitution of enone **10**, however, the yield of this reaction strongly depends on the C-3 substituent of enone **10**.[28]

3. Experimental

3.1. General

All reagents were commercial products (Fluka, Aldrich or Lancaster) and used as received. THF and toluene were freshly distilled from sodium/benzophenone. All other solvents were distilled prior to use. Diisopropylamine was distilled from CaH_2. *n*-Butyl-lithium was obtained as solution in hexane from Chemetall, Frankfurt, Germany, and titrated prior to use. LDA was freshly prepared from diisopropylamine and *n*-butyllithium. Reactions involving



Scheme 3. (a) LDA, THF, 51%; (b) *tert*-BuLi, THF; (c) 15% HCl, CH_2Cl_2, 59% (over 2 steps); (d) O_3, MeOH, −95 °C, Me_2S, 81%.

air and/or moisture sensitive reagents were conducted under an atmosphere of argon, and the glassware was oven dried (140 °C) and purged with argon. All reactions were monitored by analytical TLC (silica gel 60 F_{254}), Merck, Darmstadt, Germany. Preparative column chromatography: silica gel 60 (63–200 μm), Macherey and Nagel, Düren, Germany. NMR: ^{Unity}INOVA Varian 300 spectrometer (^{1}H: 300 MHz; ^{13}C: 75.48 MHz) in $CDCl_3$ if not otherwise stated with TMS as internal standard; chemical shifts (δ) in ppm and coupling constants (J) in Hz. IR: Perkin–Elmer Paragon 1000 FT-IR spectrometer; wave number (ν) in cm^{-1}. MS: Finnigan MAT 8200 in EI mode (70 eV); data in m/z (%). Mp (uncorrected): Büchi melting-point apparatus. $[\alpha]_D$: Perkin–Elmer polarimeter 241 with concentrations (c) expressed in g/100 mL. Elemental analyses were obtained from Mikroanalytisches Laboratorium, Universität Stuttgart, Germany.

3.1.1. *tert*-Butyl (1*R*,3*R*,5*S*,8*R*,4′*S*)-3-(2-bromobenzyl)-8-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2,6-dioxobicyclo[3.2.1]octane-1-carboxylate (7). A solution of bicycle **4**[11] (0.47 g, 1.40 mmol) in THF (5 mL) was slowly added via syringe at −78 °C to LDA (3.08 mmol) in THF (15 mL). Stirring was continued for 30 min and then 2-bromobenzyl bromide (**5**) (0.35 g, 1.40 mmol) in THF (5 mL) was added. The reaction mixture was stirred at −78 °C for additional 30 min, slowly warmed to room temperature and quenched with sat. aqueous NH_4Cl (15 mL). The reaction mixture was extracted with Et_2O, the combined extracts dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, Et_2O/petroleum ether = 1 + 1) to give 0.33 g (47%) of bicycle **7** (d.e. ≥ 95%, determined by ^{1}H NMR of the crude reaction mixture). Colorless crystals, mp 102–104 °C (petroleum ether). ^{1}H: 1.32 and 1.38 [s, each 3H, $C(CH_3)_2$], 1.49 [s, 9H, $C(CH_3)_3$], 1.87 (dddd, J = 1.6, 3.6, 8.4, 13.4 Hz, 1H, 4-H), 2.13 (ddd, J = 3.4, 12.0, 13.4 Hz, 1H, 4-H), 2.69 (dd, J = 8.6, 13.9 Hz, 1H, $CH_2C_6H_4Br$), 2.71 (d, J = 19.5 Hz, 1H, 7-H), 2.77 (m, 1H, 8-H), 2.78 (d, J = 19.5 Hz, 1H, 7-H), 2.85–2.96 (m, 2H, 3-H and 5-H), 3.48 (dd, J = 4.7, 13.9 Hz, 1H, $CH_2C_6H_4Br$), 3.84 (dd, J = 7.3, 8.8 Hz, 1H, 5′-H), 4.07 (ddd, J = 5.7, 7.3, 9.0 Hz, 1H, 4′-H), 4.29 (dd, J = 5.7, 8.8 Hz, 1H, 5′-H), 7.08 (m, 1H), 7.20–7.23 (m, 2H), 7.52 (d, J = 7.8 Hz, 1H). ^{13}C: 25.54 and 26.62 [q, $C(CH_3)_2$], 27.98 [q, $C(CH_3)_3$], 28.98 (t, C-4), 35.47 (t, $CH_2C_6H_4Br$), 44.05 (d, C-3), 47.64 (t, C-7), 50.05 (d, C-5), 50.07 (d, C-8), 63.65 (s, C-1), 70.57 (t, C-5′), 73.37 (d, C-4′), 82.67 [s, $C(CH_3)_3$], 108.26 (s, C-2′), 124.69 (s, H_4C_5CBr), 127.45, 128.28, 131.57 and 133.00 (d, C_6H_4Br), 137.97 (s, C_6H_4Br), 168.79 (s, COO), 205.82 (s, C-2), 212.38 (s, C-6). IR (KBr): 3070, 2990, 2940, 2890, 1740, 1710 (C=O), 1565, 1475, 1305, 1285. MS: 506/508 (1) $[M]^+$, 491/493 (1) $[M-CH_3]^+$, 57 (100) $[C_4H_9]^+$. APCI-MS (neg.): 505/507 (100) $[M-H]^-$, 449/451 (84), 79/81 (86) $[Br]^-$. UV (MeOH): λ_{max} (log ε) = 212 nm (4.045), 266 nm (2.740). CD (MeOH): λ_{max} ($\Theta/\Delta\varepsilon$) = 295 nm (−7602/−2.30), 303.5 nm (−7421/−2.25). $[\alpha]_D^{23} = -13.1°$ (c = 1.23, $CHCl_3$). $C_{25}H_{31}O_6Br$ (507.42): calcd C 59.18, H 6.16, Br 15.75; found C 58.97, H 6.25, Br 15.62.

3.1.2. 2-(2-Bromobenzyl)-1,3-cyclohexandione (9). Bromide **5** (7.50 g, 30 mmol) was liquified in a water bath and a solution of 1,3-cyclohexandione (3.36 g, 30 mmol) and KOH (2.02 g, 36 mmol) in H_2O (9 mL) was added under vigorous stirring. The suspension was stirred for 5 days at room temperature in the dark and continuously adjusted to pH 12 with aqueous 20% KOH. Then 1 M NaOH (100 mL) was added and the reaction mixture extracted twice with Et_2O. The organic layer was discarded and the aqueous phase acidified under cooling with 2 M HCl to pH = 1. The precipitate was filtered off, rinsed with H_2O, dried under high vacuum and finally recrystallized from Et_2O to yield 5.42 g (64%)[29,30] of dione **9**. Colorless crystals, mp 189–191 °C (Et_2O). ^{1}H (CD_3OD): 1.92 (tt, $J_1 = J_2 = 6.4$ Hz, 2H, 5-H), 2.38 (t, J = 6.4 Hz, 4H, 4-H and 6-H), 3.52 (s, 2H, $CH_2C_6H_4Br$), 6.84 (dd, J = 1.7, 7.7 Hz, 1H, C_6H_4Br), 6.88 and 7.04 (ddd, J_1 = 1.7, $J_2 = J_3$ = 7.7 Hz, 2H, C_6H_4Br), 7.38 (dd, J = 1.7, 7.7 Hz, 1H, C_6H_4Br). IR (KBr): 3060, 2970, 2940, 2600 (C=COH), 1640 (C=O), 1565, 1470, 1455, 1415, 1370, 1280, 1230, 1195, 1155, 1105, 1080, 1025, 930, 865, 810, 755, 680, 670, 610.

3.1.3. 2-(2-Bromobenzyl)-3-ethoxy-cyclohex-2-en-1-one (10a). To a suspension of dione **9** (12.5 g, 44.5 mmol) in anhydrous CH_2Cl_2 (120 mL) was added triethyloxonium tetrafluoroborate (11.4 g, 60.0 mmol). The mixture was stirred for 3 days at room temperature and then slowly poured under vigorous stirring into sat. aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2, the combined extracts dried (Na_2SO_4) and concentrated. The product was suspended in Et_2O (250 mL) and the precipitate (dione **9**) filtered off and rinsed with Et_2O. The filtrate was concentrated under vacuum, precipitated in a refrigerator from petroleum ether/Et_2O (3+1), filtered off and dried under vacuum to obtain 10.8 g (79%) of enone **10a**. Colorless crystals, mp 79–81 °C. ^{1}H: 1.22 (t, J=7.0 Hz, 3H, CH_3), 2.05 (m, 2H, 5-H), 2.44 (t, J=7.0 Hz, 2H, 4-H/6-H), 2.63 (t, J=7.0 Hz, 2H, 6-H/4-H), 3.76 (s, 2H, CH_2Ph), 4.02 (q, J=7.0 Hz, 2H, OCH_2), 6.96–7.04 (m, 2H, Ph–H), 7.15–7.20 (m, 1H, Ph–H), 7.52 (m, 1H, Ph–H). ^{13}C: 15.05 (q, CH_3), 20.87 (t, C-5), 25.42 (t, C-4/C-6), 28.14 (t, C-6/C-4), 36.30 (t, CH_2Ph), 63.72 (t, OCH_2), 117.34 (s, C-2), 124.62 (s, Ph–C), 126.77, 126.85, 129.11, 132.13 (d, Ph–C), 140.40 (s, Ph–C), 173.27 (s, C-3), 197.81 (s, C-1). IR (KBr): 2960, 1630 (C=O), 1610 (C=C), 1380, 1240, 1200, 1050, 760. MS: 229 (94) $[M-Br]^+$, 201 (100), 171 (14), 115 (20), 54 (20). $C_{15}H_{17}BrO_2$ (309.2): calcd C 58.27, H 5.54; found C 58.14, H 5.58.

3.1.4. 3-Benzyloxy-2-(2-bromobenzyl)-cyclohex-2-en-1-one (10b). Benzyl alcohol (1.62 g, 15 mmol) and a catalytic amount of *p*-TsOH were added to a solution of dione **9** (3.37 g, 12 mmol) in toluene (100 mL). The mixture was heated to reflux at a Dean–Stark trap charged with 3Å molecular sieves until the disappearance of the starting material (TLC: Et_2O/petroleum ether=4+1). The reaction mixture was neutralized with sat. aqueous $NaHCO_3$, the organic phase separated and the aqueous phase extracted with Et_2O. The combined and dried ($MgSO_4$) organic phases were concentrated and the residue chromatographed (silica gel, Et_2O/petroleum ether=4+1) to yield 3.74 g (84%) of enone **10b**. Waxy yellow solid. ^{1}H: 2.00 (tt, J_1=J_2=6.2 Hz, 2H, 5-H), 2.40 (m, J=6.2 Hz, 2H, 6-H), 2.60 (t, J=6.2 Hz, 2H, 4-H), 3.79 (s, 2H, C$H_2C_6H_4$Br), 5.05 (s, 2H, OC$H_2C_6H_5$), 6.96–7.16 (m, 4H, C_6H_4Br and C_6H_5), 7.26–7.31 (m, 3H, C_6H_4Br and C_6H_5), 7.36 and 7.49 (m, 1H, C_6H_4Br, each). ^{13}C: 20.83 (t, C-5), 25.60 (t, C-4), 28.22 (t, C$H_2C_6H_4$Br), 36.22 (t, C-6), 69.34 (t, OC$H_2C_6H_5$), 117.99 (s, C-2), 124.78 (s, CBr), 126.63, 126.91, 126.97, 128.08, 128.58, 129.06, 132.25 (d, C_6H_4Br and C_6H_5), 136.14 (s, C_6H_5), 140.15 (s, C_6H_4Br), 172.80 (s, C-3), 197.81 (s, C-1). IR (film): 3060, 3040, 2950, 2890, 1645 (C=O), 1610 (C=C), 1500, 1470, 1455, 1440, 1370, 1240, 1190, 1115, 1085, 1045, 1035, 975, 930, 875, 845, 755, 710. MS: 326/328 (3), 291 (48) $[M-Br]^+$, 200 (19) $[M-C_7H_7]^+$, 199 (72), 108 (12), 92 (20), 91 (100) $[C_7H_7]^+$, 65 (16). APCI-MS: 371/373 (100) $[M+H]^+$, 91 (8) $[C_7H_7]^+$. $C_{20}H_{19}O_2Br$ (371.27): calcd C 64.70, H 5.16, Br 21.52; found C 64.99, H 5.37, Br 21.44.

3.1.5. Ethyl (1*S*,2*R*,5*S*,7*S*,8*R*,4′*S*)-7-(2-bromobenzyl)-8-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-ethoxy-6-oxotricyclo[3.2.1.0^{2,7}]octane-1-carboxylate (12). To LDA (5.8 mmol) in THF (100 mL) was added under stirring a solution of enone **10a** (1.67 g, 5.40 mmol) in THF (50 mL) within 20 min at −80 °C. After 30 min a solution of bromoester **11**[11,21] (1.62 g, 5.80 mmol) in THF (20 mL) was added via a syringe pump within 5 h at −80 °C. The reaction mixture was allowed to warm to room temperature overnight. Sat. aqueous NH_4Cl was added and the mixture extracted with Et_2O. The combined organic phases were washed with brine (2×20 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue was chromatographed (silica gel, ether/petroleum ether, 2+1) to yield 1.40 g (51%) of **12** (d.e.≥95%, determined by ^{1}H NMR of the crude reaction mixture). Colorless crystals, mp 96–98 °C. ^{1}H (C_6D_6): 0.71 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.01 (t, J=7.0 Hz, 3H, CH_2CH_3), 1.32 and 1.34 (s, each 3H, CH_3), 1.25–1.50 (m, 1H, 4-H), 1.73–1.86 (m, 1H, 4-H), 2.05–2.19 (m, 2H, 3-H), 2.55 (m, 1H, 5-H), 2.83 (dd, J=5.7, 9.0 Hz, 1H, 8-H), 3.21 (q, J=7.0 Hz, 2H, OCH_2), 3.49–3.71 (m, 2H, OCH_2), 3.65 and 3.77 (d, J=17.1 Hz, 1H, CH_2Ph), 3.89 (dd, J=7.5, 8.4 Hz, 1H, 5′-H), 4.21 (m, 1H, 4′-H), 4.32 (dd, J=5.7, 8.4 Hz, 1H, 5′-H), 6.60 (t, J=8.1 Hz, 1H, Ph–H), 6.98 (t, J=8.1 Hz, 1H, Ph–H), 7.17 (d, J=8.1 Hz, 1H, Ph–H), 7.40 (d, J=8.1 Hz, 1H, Ph–H). ^{13}C (C_6D_6): 13.65 and 15.41 (q, CH_2CH_3), 20.34 (t, C-4), 21.68 (t, C-3), 26.06 and 26.74 (q, CH_3), 27.87 (t, 7-CH_2), 43.48 (s, C-7), 43.89 (d, C-5/C-8), 44.50 (d, C-8/C-5), 50.54 (s, C-1), 60.91 (t, OCH_2), 63.92 and 70.43 (t, OCH_2), 75.46 (s, C-2), 76.12 (d, C-5′), 108.28 (s, C-2′), 125.56 (s, Ph–C), 127.31, 127.40, 128.73, 132.68 (d, Ph–C), 139.09 (s, Ph–C), 167.99 (s, CO_2Et), 207.07 (s, C-6). IR (KBr): 2990, 1720, 1700, 1520, 1490, 1380, 1270, 1250, 1070, 880, 760. MS: 508/506 (6) $[M]^+$, 493/491 (5) $[M-CH_3]^+$, 427 (8) $[M-Br]^+$, 369 (33), 169 (19), 101 (45), 43 (100). $C_{25}H_{31}BrO_6$ (507.4): calcd C 59.18, H 6.16; found C 59.19, H 6.21. $[\alpha]^{20}$=+46.94 (c=1.0, MeOH).

3.1.6. Ethyl (1*S*,2*S*,6*S*,7*S*,10*R*,11*R*,4′*S*)-benzo[4,5]-6-hydroxy-11-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-tetracyclo[5.3.1.0^{2,6}.0^{2,10}]undecane-1-carboxylate (13). To a solution of tricycle **12** (2.46 g, 4.85 mmol) in THF (120 mL) was added *tert*-butyllithium in pentane (6.7 mL, 10.0 mmol, 1.5 M) within 10 min at −115 °C. The reaction mixture was kept at this temperature for 2 h, warmed to −45 °C within 1 h and quenched with sat. aqueous NH_4Cl (30 mL). The reaction mixture was extracted with Et_2O, the combined organic phases dried (Na_2SO_4) and concentrated to yield alcohol **13** as a pale yellow oil, which was used directly without further purification.

3.1.7. Ethyl (1*S*,7*R*,11*R*,4′*S*)-benzo[4,5]-11-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-10-oxotricyclo[5.3.1.0^{2,6}]undec-2(6)-ene-1-carboxylate (14). Crude alcohol **13** was dissolved in CH_2Cl_2 (80 mL) and treated with 15% HCl (2 mL) for 1 h. The reaction mixture was alkalinized with sat. aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), concentrated and chromatographed (silica gel, petroleum ether/Et_2O=4+1) to give 1.09 g (59%) of ketone **14**. Colorless oil, that solidified upon standing at 0 °C, mp 82–85 °C. ^{1}H (C_6D_6): 0.99 (t, J=7.3 Hz, 3H, OCH_2CH_3), 1.35 and 1.42 (s, each 3H, CH_3), 1.38–1.60 (m, 1H, 8-H), 1.82 (dd, J=10.0, 17.5 Hz, 1H, 9-H), 2.03 (dd, J=7.5, 17.5 Hz, 1H, 9-H), 2.28–2.41 (m, 1H, 8-H), 3.14 (dd, J=4.1, 10.0 Hz, 1H, 11-H) 3.14 and 3.36 (d, J=23.2 Hz, each

1H, 3-H), 3.43 (s_{br}, 1H, 7-H), 4.03 (q, $J=7.3$ Hz, 2H, OCH_2), 4.04 (dd, $J=7.8$, 8.8 Hz, 1H, 5′-H), 4.34 (m, 1H, 4′-H), 4.53 (dd, $J=5.6$, 8.8 Hz, 1H, 5′-H), 7.07–7.28 (m, 4H, Ph–H). ^{13}C (C_6D_6): 14.14 (q, CH_2CH_3), 22.52 (t, C-8), 25.97 and 26.86 (q, CH_3), 35.68 (t, C-9), 38.03 (d, C-11), 60.13 (d, C-7), 61.05 (t, CH_2CH_3), 69.77 (s, C-1), 71.14 (t, C-5′), 74.23 (d, C-4′), 108.15 (s, C-2′), 119.97, 124.88, 125.56, 126.81 (d, Ph–C), 140.01 and 147.93 (s, Ph–C), 147.97 (s, C-6), 153.31 (s, C-2), 168.84 (s, CO_2Et), 202.27 (s, C-10). IR (KBr): 3000, 1740 (C=O), 1710 (C=O), 1470, 1380, 1260, 1070, 880, 740. MS: 382 (12) $[M]^+$, 367 (24) $[M-CH_3]^+$, 324 (77), 238 (24), 165 (25), 43 (100). $C_{23}H_{26}O_5$ (382.5): calcd C 72.23, H 6.85; found C 72.12, H 6.91.

3.1.8. Ethyl (1*S*,7*R*,11*R*,4′*S*)-benzo[4,5]-11-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2,6,10-trioxobicyclo[5.3.1]undecane-1-carboxylate (15). A solution of alkene **14** (0.35 g, 0.91 mmol) in MeOH (40 mL) was cooled to −95 °C and treated with ozone until the mixture remained blue. Dimethylsulfide (15 mL) was added immediately after completion of the reaction. The reaction mixture was allowed to warm to room temperature within 2 h. The solvents were evaporated under vacuum and the residue crystallized at −25 °C from Et_2O/petroleum ether (1+1, 5 mL) to yield 0.31 g (81%) of triketone **14**. Colorless crystals, mp 91–96 °C. ^1H (C_6D_6): 0.88 (t, $J=7.5$ Hz, 3H, OCH_2CH_3), 1.13 and 1.14 (s, each 3H, CH_3), 1.60–1.75 (m, 1H, 8-H), 2.16–2.30 (m, 1H, 8-H), 2.41–2.54 (m, 1H, 9-H), 2.97 (m, 1H, 9-H), 3.36 (d, $J=4.6$ Hz, 1H, 11-H), 3.43 (dt, $J=3.5$, 6.9 Hz, 1H, 7-H), 3.51 and 3.89 (d, $J=22.0$ Hz, each 1H, 3-H), 3.90 (q, $J=7.5$ Hz, 2H, OCH_2CH_3), 3.99 (dd, $J=5.0$, 9.6 Hz, 1H, 5′-H), 4.25 (dd, $J=6.1$, 9.6 Hz, 1H, 5′-H), 4.62 (dt, $J=4.8$, 6.3 Hz, 1H, 4′-H), 6.61–6.67 (m, 1H, Ph–C), 6.88–6.93 (m, 2H, Ph–H), 7.00–7.05 (m, 1H, Ph–H). ^{13}C (C_6D_6): 13.77 (q, OCH_2CH_3), 21.07 (t, C-8), 24.41 and 26.46 (q, CH_3), 36.65 (t, C-9), 44.78 (d, C-11), 46.47 (t, C-3), 48.40 (d, C-7), 62.32 (t, OCH_2CH_3), 70.65 (t, C-5′), 74.22 (d, C-4′), 77.10 (s, C-1), 109.36 (s, C-2′), 127.86, 128.15, 129.88, 130.05 (d, Ph–C), 131.47 (s, C-5), 139.99 (s, C-6), 166.63 (s, CO_2Et), 200.93 (s, C-6), 201.14 (s, C-10), 207.32 (s, C-2). IR (CCl_4): 2980, 1725, 1700, 1660, 1460, 1380, 1070, 880. MS: 414 (1) $[M]^+$, 399 (6) $[M-CH_3]^+$, 356 (5), 338 (6), 313 (44), 267 (84), 101 (95), 43 (100). $C_{23}H_{26}O_7$ (414.5): calcd C 66.65, H 6.32; found C 67.04, H 6.37.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (project: Sp 198/11-2), Bonn, and Chemetall GmbH, Frankfurt (Main), for generous gifts of chemicals. N. A. B. thanks the Landesgraduiertenförderung, Baden-Württemberg, for a scholarship.

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Resolution and chiroptical properties of the neurotoxin 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) and related compounds: quantum chemical CD calculations and X-ray diffraction analysis☆

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Received 26 April 2004; revised 14 June 2004; accepted 17 June 2004

Available online 20 July 2004

Abstract—Separation and stereochemical attribution of the two enantiomers of the neurotoxin 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) has been achieved by applying chromatography on a chiral phase HPLC column in hyphenation with circular dichroism (CD) spectroscopy (LC-CD coupling). Assignment of the absolute configuration of TaClo and its *N*-methyl analog has been achieved by quantum chemical CD calculations and has finally been confirmed by single-crystal X-ray diffraction analyses of the two enantiomers of *N*-formyl-TaClo as obtained in enantiomerically pure form by crystallization.

1. Introduction

The discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **4**) (Fig. 1) as a highly selective dopaminergic neurotoxin that irreversibly produces parkinsonism in humans, monkeys, and mice[1–3] has triggered an intensive search for structurally related compounds that may accumulate in the brain and induce Parkinson's disease during aging. The highly chlorinated harman derivative 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo, **3**)[4–7] (Fig. 1) has emerged as one of the candidates because of its ability to easily penetrate the blood-brain barrier,[5,8] to severely affect the striatal dopamine[9,10] and extracellular serotonin[11] metabolism, and to trigger a slowly-developing neurodegeneration in rats resulting in a parkinsonian-type diminished locomotion of the animals.[12,13] Moreover, TaClo strongly inhibits complex I (NADH dehydrogenase) and complex II (succinate dehydrogenase) of the mitochondrial respiratory chain,[6,14,15] thus leading to massive neuronal energy deficiencies that ultimately cause cell death.

While MPTP (**4**) is a merely unnatural agent arising as a by-product in the illicit preparation of meperidine ('synthetic heroin'),[1,16] TaClo (**3**) constitutes a mammalian alkaloid[5–7]

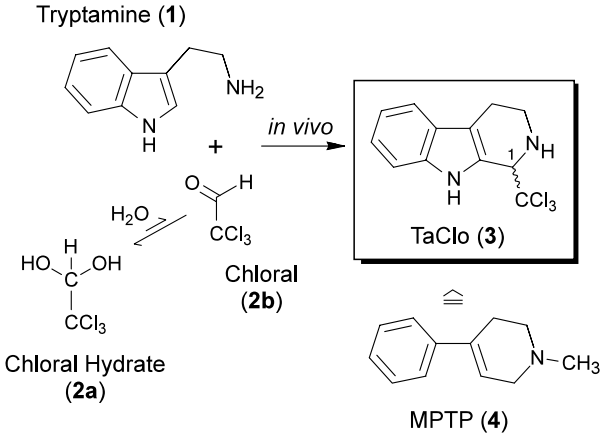

Figure 1. In vivo formation of 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo, **3**), structurally similar to the dopaminergic neurotoxin MPTP (**4**), from the biogenic amine tryptamine (Ta, **1**) and the hypnotic agent chloral (Clo, **2b**).

☆Part 40 in the series, Endogenous Alkaloids in Man; for part 39, see Ref. 35.

Keywords: Chloral-derived tetrahydro-β-carbolines; 1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo); Enantiomeric resolution; Absolute configuration; Circular dichroism; LC-CD coupling; Quantum chemical CD calculations; Crystal structures.

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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.093

that readily originates in the human organism from endogenously present tryptamine (Ta, **1**) and therapeutically administered chloral hydrate (Clo, **2a**).[17,18] Since chloral (**2b**) does not shorten or suppress the REM- and the non-REM-type sleep, its hydrate **2a** is still widely used as a hypnotic, applied even on a gram scale for the induction of sedation and sleep in children and adults.[19,20] In blood samples obtained from elderly patients who had been treated orally with **2a** for 3 days up to 6 months, TaClo (**3**) was unambiguously identified in trace amounts ranging from less than 1 ng up to 35 ng per mL.[17,18] An even enhanced TaClo concentration of ca. 70 ng/g of clot was detected in a young epileptic, obviously as a consequence of a long-term daily intake of 1 g of chloral hydrate (**2a**) over a period of nearly 5 years.[18]

In contrast to MPTP (**4**), TaClo (**3**) is a chiral compound that has as yet been prepared and analyzed as a racemic mixture. Although TaClo has been speculated to occur spontaneously in vivo by a merely chemical Pictet–Spengler cyclization of its precursors, **1** and **2b**, leading to a racemate,[5,6,18] studies on enantiomerically pure material of (*R*)-**3** and (*S*)-**3** were highly desirable, for example, for comprehensive neurotoxicological investigations, given the sometimes extremely different biological properties of enantiomers, cf., for example, the teratogenic versus sedative effects exhibited by the enantiomers of thalidomide[21,22] (Contergan®).

In extension to our earlier reports[6,18,23] on the chiroptical properties of TaClo (**3**), this paper deals with the stereochemical attribution of the two TaClo enantiomers, (*R*)-**3** and (*S*)-**3** (see Fig. 2), and their *N*-methyl analogs, (*R*)-**5** and (*S*)-**5** (see Fig. 3). This was achieved by quantum chemical calculation of their circular dichroism (CD) spectra and comparison with the experimental ones obtained directly, that is, by high-performance liquid chromatography (HPLC) on a chiral phase coupled to CD spectroscopy.

Furthermore, we report on the X-ray crystallographic determination of the absolute configuration of *N*-formyl-TaClo (**6**),[4] a most useful stock compound in TaClo synthesis on a 100-g scale.[6,23] Racemic **6** partially crystallizes in the form of stereochemically homogeneous material of (*R*)-**6** and (*S*)-**6**. These crystals were found to be well-suited for X-ray diffraction analysis (see Fig. 4). Hence, besides confirming the results from the quantum chemical CD calculations on TaClo and its derivatives, this approach finally gave rise to an attribution of the stereostructures of both TaClo enantiomers by conversion of enantiomerically pure material of (*R*)-**6** and (*S*)-**6** into (*R*)-**3** and (*S*)-**3**, respectively, by a smooth deformylation reaction without racemization at C-1.

2. Results and discussion

The elucidation of the absolute configuration of TaClo (**3**) was not trivial at all. A directed synthetic access to stereochemically homogeneous material of (*R*)-**3** and (*S*)-**3**, for example, by stereoselective total synthesis or by racemate resolution via diastereomeric products turned out to be difficult and has failed until now. Investigations on the circular dichroism (CD),[24–28] by contrast, should not be limited by these experimental restrictions, and thus promised to be an ideal and reliable approach for the attribution of the stereostructures of both TaClo enantiomers.

As outlined in Figure 2 (left), (*rac*)-**3** can easily be resolved by using a chiral HPLC OD-H column, showing a large difference of nearly 13 min (!) between the retention times of the two TaClo enantiomers, thus giving rise to the option of running this racemate resolution online in combination with CD spectroscopy without the necessity to isolate the pure enantiomers on a preparative scale. By applying the LC-CD coupling technique in the stop-flow mode it was possible to directly obtain high-quality full CD spectra of both TaClo enantiomers, in a single HPLC run. As presented in Figure 2 (center), the CD spectrum of the more rapidly eluting TaClo enantiomer shows a significant positive Cotton effect at 273 nm and a strong negative one at 234 nm, while the CD curve of the quite slowly eluting one is—as expected—opposite.

The assignment of the absolute configuration of each of the two TaClo enantiomers, however, cannot be deduced directly from the measured CD spectra, because **3** represents a novel type of chiral compounds, and structural analogs with comparable chiroptical properties and known absolute configurations are not available for an empirical CD comparison. Moreover, the molecular framework of **3** does not fit into conventional CD rules,[24–27] thus not allowing a configurative attribution based on the interpretation of the CD curves of both TaClo enantiomers nor, for example, by applying the widely used Exciton Chirality method,[24–26] due to the lack of a set of two similar chromophores.

The quantum chemical calculation of CD spectra, which has recently been improved by our group,[29–32] constitutes an efficient method for the elucidation of the absolute configuration, in particular for novel classes of chiral compounds.[28,33] Without being restricted in its applicability by the necessity of chemically introducing additional chromophores—which, for **3** would have been difficult, if not impossible, anyhow—computational simulation of CD spectra can be done directly, without derivatization. The quantum chemical calculations of the CD spectra were started arbitrarily with the (1*R*)-configured enantiomer. Semiempirical AM1[34] calculations in the gas phase revealed the presence of four conformers. The computed single CD spectra calculated for each of the structures thus obtained were added up according to the Boltzmann statistics, that is, according to the energies of these conformations, to give the theoretical overall CD spectrum for (1*R*)-**3**. To take into account systematic shifts of the calculated CD spectra, a UV correction was carried out for each calculated spectrum as introduced earlier.[28] By reflection of this curve to the zero line, the predicted spectrum was obtained for (1*S*)-**3**, too. As outlined in Figure 2, the agreement of the spectrum computed for (1*R*)-**3** with the experimental one of the more rapidly eluting enantiomer (peak 1) and of the one calculated for (1*S*)-**3** with the one measured for the slowly eluting enantiomer (peak 2) was excellent, especially in the diagnostically decisive short-wavelength part of the CD

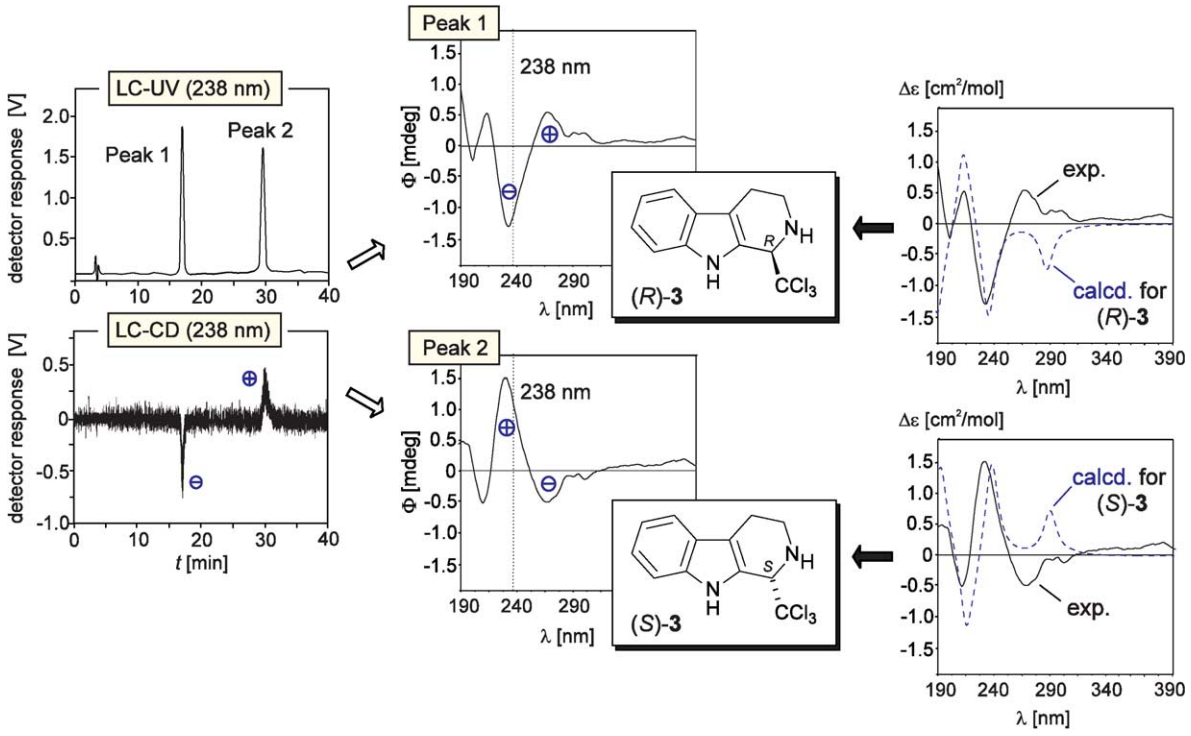


Figure 2. LC-UV and LC-CD chromatograms of the two TaClo enantiomers, (*R*)-**3** and (*S*)-**3**, at 238 nm after separation on a chiral reversed-phase (left); LC-CD spectra of (*R*)-TaClo and (*S*)-TaClo measured in the stop-flow mode exhibiting opposite curves (center); attribution of the absolute configuration, as established by comparision of the experimental CD spectra (shown as full lines, —) with the CD spectrum quantum chemically calculated for (*R*)-**3** (shown as dotted line, - - - -) (right).

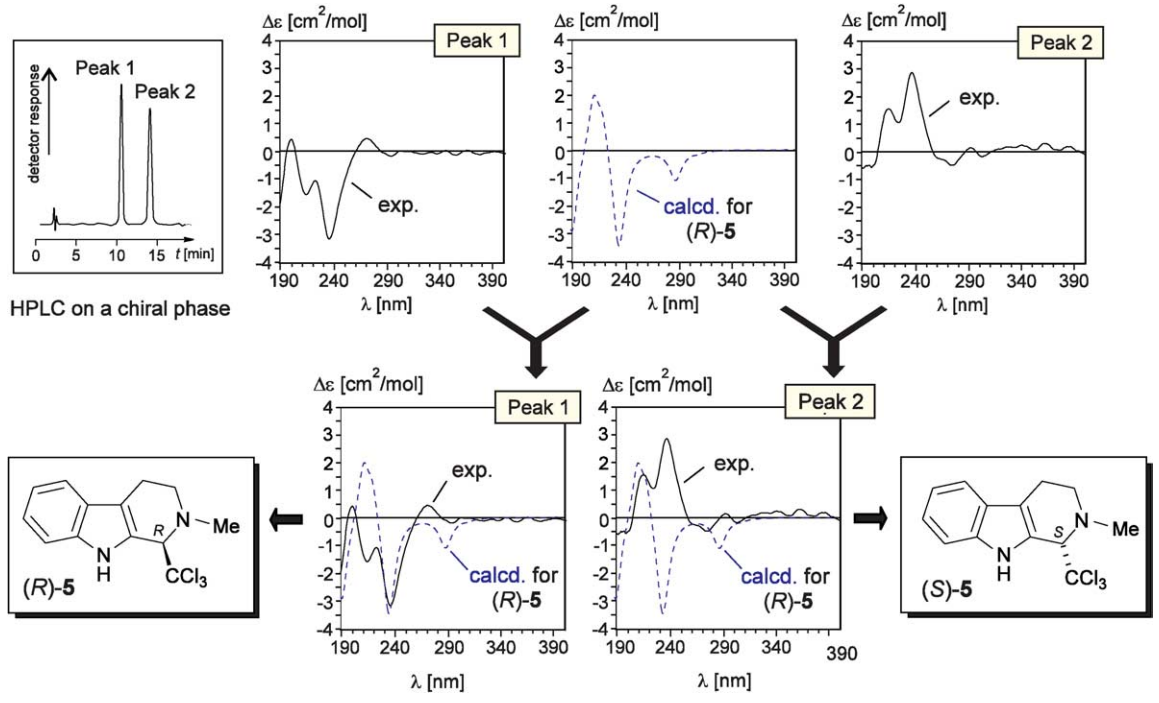


Figure 3. Enantiomeric resolution of *N*-methyl-TaClo (**5**) on a chiral HPLC phase, and assignment of the absolute configuration of the two enantiomers, (1*R*)-**5** and (1*S*)-**5** (represented by peaks 1 and 2 of the LC-UV chromatogram, respectively), by comparison of the CD spectrum theoretically predicted for (*R*)-**5** (center, shown as dotted line, - - - -) with the experimental LC-CD spectra (left and right, shown as full lines, —) of both enantiomers of **5** measured online in stop-flow mode.

spectra. This permitted to clearly attribute the *R*-configuration to peak 1, and the *S*-configuration to peak 2.

By its still closer structural analogy to MPTP (**4**), its strong neurotoxic potency,[6,7,15] and its presumable occurrence in man as a TaClo metabolite, the *N*-methylated TaClo derivative **5**[35] also warranted the availability of a sensitive stereoanalytical device for a rapid and reliable assignment

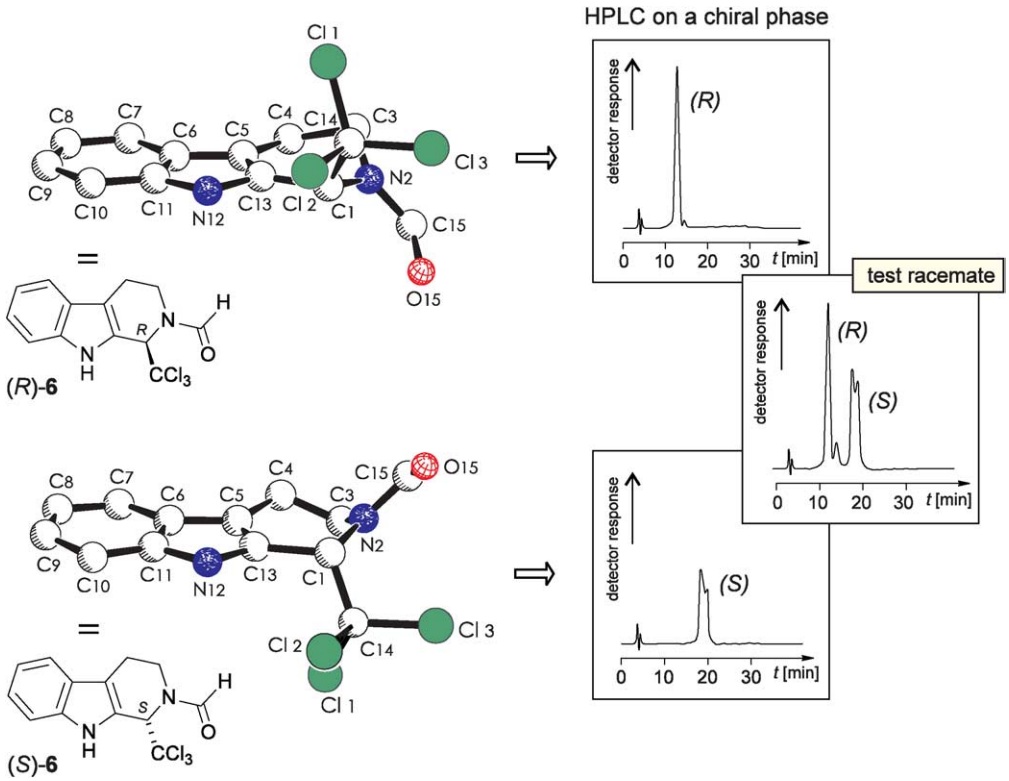


Figure 4. Stereoanalysis of the *N*-formyl-TaClo enantiomers, (*R*)-**6** and (*S*)-**6**, on a chiral HPLC phase, configurational assignment by X-ray crystallography. Note that there is an additional signal splitting for (*R*)-**6** and (*S*)-**6** due to the occurrence of amide rotamers. Schakal plot of the crystal structures with a guide of the atomic numbering system adopted in the X-ray investigation (hydrogen atoms omitted for reasons of clarity).

of its enantiomers, (1*R*)-**5** and (1*S*)-**5**. For this purpose, we again applied our HPLC-CD on-line coupling technique using the same analytical protocol (see Section 4) established for the enantiomeric resolution of TaClo (**3**). Similar to (*rac*)-**3**, it was also possible to analytically separate (*rac*)-**5** on a chiral HPLC phase, thus giving the option of directly measuring the CD spectra of the two resulting peaks. As can be clearly seen (Fig. 3, full line CD spectra), the CD curve of peak 1 (left) eluting at 10.1 min is dominated by a strong negative Cotton effect at 238 nm, while the CD spectrum obtained for peak 2 (right) eluting at 13.8 min expectedly is opposite showing a distinct positive Cotton effect at 237 nm. The CD behavior of **5** was calculated, again starting with the arbitrarily chosen (1*R*)-enantiomer. A semiempirical conformational analysis using the AM1[34] parameterization was performed and—similar to **3**—showed the existence of four conformers. The calculated individual CD spectra for these conformers were added up with Boltzmann-weighting, and were subsequently UV corrected[28] to give the computed overall CD spectrum for (1*R*)-**5**. Comparison of this theoretical CD curve with the experimental spectrum of the chromatographically more rapid enantiomer (peak 1) revealed a good agreement, whereas the calculated one for (1*R*)-**5** is nearly the mirror image of the spectrum measured for the more slowly eluting *N*-methyl-TaClo enantiomer (peak 2).

The discovery that racemic *N*-formyl-TaClo (**6**), a most useful intermediate in TaClo synthesis,[4,6,23] at least partially crystallized in an enantiomerically pure form, finally gave rise to an additional approach for the attribution of the absolute configuration of the enantiomers of TaClo (**3**) and *N*-methyl-TaClo (**5**). As illustrated in Figure 4, the absolute configuration of (*R*)-**6** and (*S*)-**6** has successfully been established for both enantiomers, independently by single-crystal X-ray crystallography. For both *N*-formyl-TaClo enantiomers, the huge trichloromethyl group at C(1)—due to its high steric demand—was found to be largely twisted out of the β-carboline ring 'plane', occupying a pseudo-axial position. The three chlorine atoms at C(14) adopt a perfectly staggerd orientation with respect to the C(1)–C(14) bond, leading to a minimization of their steric interactions with C(13) and the amide function. Again, for steric reasons, the tetrahydropyrido moiety is partially planarized with only C(3) and N(2) being located distinctly out of the ring 'plane'.

For a rapid correlation which of the *N*-formyl-TaClo crystals belonged to which stereochemical series and which of them were stereochemically homogeneous, an enantiomer-specific device based on chromatography on a chiral HPLC column was used. Applying the analytical protocol previously elaborated for the enantiomeric resolution of (*rac*)-**3** and (*rac*)-**5**, the enantiomers of (*rac*)-**6** were again efficiently separated giving the expected two peaks (Fig. 4, right, center). The signal splitting observed for these two peaks can be explained by the occurrence of a C–N bond rotation that is frozen on the time-scale of the HPLC experiment. Stereoanalyis of the authentic crystals used for the elucidation of the absolute configuration of (*R*)-**6** and (*S*)-**6** by X-ray measurements, unequivocally revealed the (*R*)-enantiomer to represent the more rapidly eluting peak (Fig. 4, top), while the (*S*)-configured enantiomer turned out to be the more slowly eluting peak (Fig. 4, bottom).

Finally, enantiomerically pure crystalline material, that is, exclusively showing either a peak for (*R*)-**6** or only for (*S*)-**6**, was collected on a milligram scale, and separately converted into the likewise stereochemically homogeneous TaClo enantiomers (*R*)-**3** and (*S*)-**3** by an acid catalyzed deformylation reaction, which proceeded without racemization at C-1. Comparison of the CD spectrum theoretically predicted for (*R*)-**3** with the respective experimental CD curves obtained for the pure isolated material of (*R*)-**3** and (*S*)-**3**, permitted full confirmation of the previously assigned absolute stereostructures of both TaClo enantiomers, thus providing independent corroboration of our results from the quantum chemical calculations of their chiroptical properties. Furthermore, by treatment of enantiomerically pure material of (*R*)-**3** and (*S*)-**3** with methyl iodide in the presence of sodium hydrogencarbonate the likewise stereochemically homogeneous *N*-methyl-TaClo enantiomers (*R*)-**5** and (*S*)-**5** were obtained. Besides the fact that the two experimental CD spectra showed a convincing agreement with the ones calculated for (*R*)-**5** and (*S*)-**5**, the CD curves monitored online were virtually identical as compared to those obtained offline (data not shown). Online and offline CD measurements on (*R*)-**3** and (*S*)-**3** provided nearly congruent CD spectra, too (data not shown).

These results emphasize the efficiency of our HPLC-CD online coupling technique[36–38] for a rapid and reliable stereoanalysis of chiral compounds, thus demonstrating that application of CD spectroscopy is not limited to isolated enantiomerically pure material, but also well-suited for chiroptical investigations, for example, from racemic mixtures.

3. Conclusion

Independent from empirical data or reference material, the absolute stereostructures of the two chiral neurotoxic agents TaClo (**3**) and its putative metabolite *N*-methyl-TaClo (**5**) have unambiguously been attributed by quantum chemical CD calculations in combination with racemate resolution on a chiral HPLC column and online CD measurements (LC-CD coupling). The fact that the absolute configurations of the enantiomers of these chloral-derived tetrahydro-β-carbolines **3** and **5** were independently attributed the same by X-ray crystallographic measurements on crystalline material of the two enantiomers of *N*-formyl-TaClo (**6**), which were finally converted into enantiomerically pure material of **3** and **5**, confirms the reliability of the results and the value of the applied computational methodology.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Jung Thermovar hot-stage apparatus and are uncorrected. Optical rotation measurements were performed on a Perkin–Elmer 241 MC polarimeter (25 °C, 10-cm cell). Circular dichroism spectra were recorded on a J-715 spectropolarimenter (JASCO Deutschland, Gross-Umstadt, Germany) at room temperature within the range of 200–350 nm using using a 0.1-cm standard cell and spectrophotometric grade EtOH, and are reported in $\Delta\varepsilon$ in cm^2/mol at the given wavelength λ (nm). Stereoanalytical separations were performed on a chiral stationary phase employing a Chiralcel OD-H HPLC column (dimensions: 4.6×250 mm; particle size: 5 μm) from Daicel Chemical Industries Ltd. (Tokyo, Japan). HPLC experiments were carried out on a modular system, consisting of two M 510 pumps, a U6K injection valve, and a Lambda-Max Model 481 spectrophotometer (Waters, Eschborn, Germany). The UV absorption wavelength was set at 254 nm and the flow-rate was 0.8 mL min^{-1}. For enantiomeric resolutions, an isocratic solvent system using PE and *i*PrOH (70:30) was used througout the study. For HPLC-CD coupling experiments, the J-715 CD spectrometer was equipped with an LG-980-025 ternary gradient unit, a PU1580 pump (JASCO), a Rheodyne 7725i injection valve, and the Borwin chromatographic software (JASCO Deutschland). Simultaneous UV and CD detection was performed with a standard flow cell at 238 nm. CD spectra were measured in the stop-flow mode. For TLC, precoated silica gel 60 F_{254} aluminum plates (5×10 cm) from Merck (Darmstadt, Germany) were used. Spots were detected under UV light. All reagents used were of commercial quality. Organic solvents were dried and distilled prior to use. Petroleum ether (PE) used refers to the fraction boiling at 30–70 °C. As described previously,[4,6,23] 1-trichloromethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (TaClo, **3**) was prepared on a 100-g scale in a two-step synthetic pathway by running the condensation reaction of tryptamine (**1**) and chloral (**2b**) in formic acid as the solvent, affording 2-formyl-1-trichloromethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**6**) as an intermediate. By a smooth deformylation of pure **6** in methanolic hydrochloric acid, the target molecule **3** was obtained as its hydrochloride salt. 2-Methyl-1-trichloromethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole hydrochloride (**5**·HCl) was synthesized by treatment of TaClo hydrochloride (**3**·HCl)[4] with methyl iodide as reported earlier.[35]

4.2. Preparation of enantiomerically pure material of *N*-formyl-TaClo (6), TaClo (3), and *N*-methyl-TaClo (5)

4.2.1. Enantiomerically pure material of 6 by recrystallization. A methanolic solution saturated with (*rac*)-**6**[4] was slowly cooled giving rise to the formation of clear crystalline colorless needles (weight: ca. 1.5 mg). According to HPLC analysis on a Chiralcel OD-H HPLC column, some of these crystals proved to consist of enantiomerically pure material. Elucidation of the absolute configuration of both of the enantiomers, (*R*)-**6** and (*S*)-**6**, was achieved by single-crystal X-ray diffraction analyses (see chapter 4.3), thus allowing an unequivocal stereochemical attribution of (*R*)-**6** and (*S*)-**6** in the order of their chromatographic elution on a Chiralcel OD-H HPLC column. Furthermore, both enantiomers were characterized by their sign of optical rotation as given as follows.

Compound (*R*)-**6**. Mp 95 °C (dec); $[\alpha]_D^{20} = +87.5$ ($c = 0.5$, MeOH); HPLC on Chiralcel OD-H: t_R: 12.9 and 14.9 min (due to the presence of amide rotamers). The spectroscopic data (^{1}H NMR, MS) are identical to those reported for (*rac*)-**6**.[4]

Compound (*S*)-**6**. Mp 95 °C (dec); $[\alpha]_D^{20} = -87.3$ ($c = 0.4$, MeOH); HPLC on Chiralcel OD-H: t_R: 17.1 and 19.1 min (due to the presence of amide rotamers). The spectroscopic data (^{1}H NMR, MS) are identical to those reported for (*rac*)-**6**.[4]

4.2.2. Enantiomerically pure 3·HCl. Stereochemically pure crystals of (*R*)-**6** (19.2 mg, 60.5 μmol) or (*S*)-**6** (18.3 mg, 57.6 μmol) obtained as described above (see Section 4.2.1) were dissolved in MeOH (10 mL) previously saturated with HCl, and heated at reflux for 90 min. Removal of the solvent under reduced pressure and recrystallization from MeOH gave (*R*)-**3**·HCl (18.7 mg, 57.5 μmol, 95% yield) and (*S*)-**3**·HCl (18.0 mg, 55.3 μmol, 96% yield), respectively, as amorphous colorless solids, their enantiomeric purites were determined by HPLC on a Chiralcel OD-H column.

Compound (*R*)-**3**·HCl. Mp >172 °C (dec); $[\alpha]_D^{20} = -66.4$ ($c = 0.3$, MeOH); UV (EtOH): λ_{max} 217 (log ε 2.16), 275 (log ε 1.41), 353 (log ε 0.88); CD (EtOH): $\Delta\varepsilon_{206}$ −20.8, $\Delta\varepsilon_{220}$ +15.3, $\Delta\varepsilon_{234}$ +23.6, $\Delta\varepsilon_{273}$ +8.0, $\Delta\varepsilon_{286}$ +0.5, $\Delta\varepsilon_{290}$ +1.9, $\Delta\varepsilon_{295}$ −3.9, $\Delta\varepsilon_{302}$ +3.6; HPLC on Chiralcel OD-H: t_R: 20.9 min. The spectroscopic data (^{1}H NMR, MS) are identical to those reported for (*rac*)-**3**·HCl. [4]

Compound (*S*)-**3**·HCl. Mp >171 °C (dec); $[\alpha]_D^{20} = +63.4$ ($c = 0.3$, MeOH); UV (EtOH): λ_{max} 218 (log ε 2.34), 275 (log ε 1.52), 355 (log ε 0.98); CD (EtOH): $\Delta\varepsilon_{220}$ −16.3, $\Delta\varepsilon_{234}$ +23.6, $\Delta\varepsilon_{275}$ −6.3, $\Delta\varepsilon_{287}$ −1.5, $\Delta\varepsilon_{290}$ −2.5, $\Delta\varepsilon_{295}$ +1.4, $\Delta\varepsilon_{301}$ −3.4; HPLC on Chiralcel OD-H: t_R: 38.6 min. The spectroscopic data (^{1}H NMR, MS) are identical to those reported for (*rac*)-**3**·HCl. [4]

4.2.3. Enantiomerically pure 5·HCl. Stereochemically pure material of (*R*)-**3**·HCl (16.4 mg, 50.4 μmol) or (*S*)-**3**·HCl (15.8 mg, 48.5 μmol) was reacted with a suspension of $NaHCO_3$ (60 mg, 0.72 mmol) and MeI (300 μL, 454 mg, 3.2 mmol) in MeOH (8 mL) at room temperature for 24 h. After evaporation of the solvent, the resulting crude materials were purified by semi-preparative TLC on silica gel (eluent: PE/MTB, 1:1). Spots containing the desired products were eluted with MeOH. Evaporation of the solvent and recrystallization from methanolic HCl afforded (*R*)-**5**·HCl (8.5 mg, 25.2 μmol, 50% yield) and (*S*)-**5**·HCl (7.9 mg, 23.3 μmol, 48% yield), respectively, as amorphous yellowish solids, the enantiomeric purities of which were determined by HPLC on a Chiralcel OD-H HPLC column.

Compound (*R*)-**5**·HCl. Mp 95 °C (dec); $[\alpha]_D^{20} = +38.6$ ($c = 0.1$, MeOH); UV (EtOH): λ_{max} 223 (log ε 1.89), 284 (log ε 1.22), 293 (log ε 1.15); CD (EtOH): $\Delta\varepsilon_{205}$ +23.5, $\Delta\varepsilon_{217}$ −54.2, $\Delta\varepsilon_{225}$ −26.1, $\Delta\varepsilon_{238}$ −74.0, $\Delta\varepsilon_{264}$ +5.7, $\Delta\varepsilon_{271}$ −9.1, $\Delta\varepsilon_{278}$ +1.6, $\Delta\varepsilon_{286}$ −18.4, $\Delta\varepsilon_{291}$ −12.3, $\Delta\varepsilon_{296}$ −17.8, $\Delta\varepsilon_{303}$ −6.5; HPLC on Chiralcel OD-H: t_R: 10.1 min. The spectroscopic data (^{1}H NMR, MS) were identical to those reported for (*rac*)-**5**·HCl.[35]

Compound (*S*)-**5**·HCl. Mp 96 °C (dec); $[\alpha]_D^{20} = -34.9$ ($c = 0.15$, MeOH); UV (EtOH): λ_{max} 224 (log ε 2.21), 284 (log ε 1.43), 295 (log ε 1.34); CD (EtOH): $\Delta\varepsilon_{211}$ +34.3, $\Delta\varepsilon_{223}$ +8.2, $\Delta\varepsilon_{237}$ +72.6, $\Delta\varepsilon_{275}$ −13.8, $\Delta\varepsilon_{287}$ +4.5, $\Delta\varepsilon_{291}$ −1.1, $\Delta\varepsilon_{296}$ +4.9, $\Delta\varepsilon_{301}$ −8.2; HPLC on Chiralcel OD-H: t_R: 13.8 min. The spectroscopic data (^{1}H NMR, MS) were identical to those reported for (*rac*)-**5**·HCl.[35]

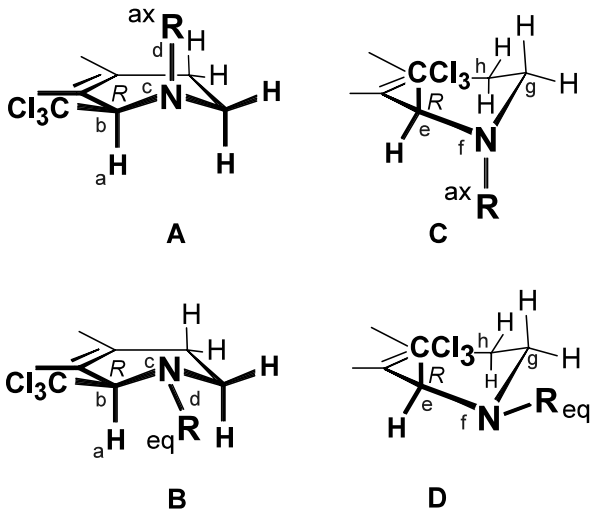
4.3. X-ray crystallographic data

The single crystals of (*R*)-**6** and (*S*)-**6** chosen for X-ray investigations were clear colorless needles obtained from MeOH. All measurements of diffraction intensities were performed at room temperature on a BRUKER AXS P4 four-circle diffractometer with an incident beam graphite monochromator (Mo K_α radiation, $\lambda = 0.71073$ Å) in ω-scan mode and $2\theta_{max} = 55°$.[39] The unit cell parameters were determined by least-squares refinement using 60 centered reflections. The structures were solved by direct phase determination and refined by full-matrix anisotropic least-squares with the aid of the program package Shelxtl-Plus.[40] In refinements, weights were used according to the scheme $w = 1/[\sigma^2(F_o^2) + (0.0657P)^2 + 0.3946P]$ for (*R*)-**6** and $w = 1/[\sigma^2(F_o^2) + (0.01P)^2 + 0P]$ for (*S*)-**6**, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined anisotropically. The position of the hydrogen atom H(1) was established by difference synthesis and refined. All other hydrogen positions were calculated using a riding model with a common isotropic thermal parameter of 0.08 Å^2. To establish the absolute configuration,[41] 1393 Friedel pairs were employed for (*R*)-**6**, and 1345 Friedel pairs for (*S*)-**6**. The corresponding Flack parameter for (*R*)-**6** was found to be 0.05(7), and for (*S*)-**6** it was determined to be 0.02(7). In the crystals of (*R*)-**6** and (*S*)-**6**, the molecules are connected

Table 1. Crystallographic data for (*R*)-**6** and (*S*)-**6**

Compound	(*R*)-**6**	(*S*)-**6**
Empirical formula	$C_{13}H_{11}Cl_3N_2O$	$C_{13}H_{11}Cl_3N_2O$
Molecular mass	317.60	317.60
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions		
a (Å)	6.2667 (6)	6.2744 (4)
b (Å)	12.8750 (9)	12.8884 (8)
c (Å)	17.2140 (2)	17.2273 (9)
Volume (Å^3)	1388.8 (2)	1393.1 (1)
Formula units per cell	$Z = 4$	$Z = 4$
D_{calcd} (g cm^{-3})	1.519	1.514
Crystal size (mm)	0.15×0.75×0.85	0.45×0.55×0.60
Scan mode	ω-Scan	ω-Scan
θ range (°)	1.75–27.5	1.75–27.5
Range in *hkl*	*h*: −1→8	*h*: −8→1
	k: −1→16	*k*: −16→1
	l: −22→22	*l*: −22→22
Reflections collected	4590	4597
Unique reflections	3197	3200
Reflections with $F > 3\sigma(F)$	3106	3009
Lin. absorption coeff. (mm^{-1})	0.65	0.65
Absorption correction	ψ-Scan	ψ-Scan
Data/restraints/parameters	3149/0/172	3200/0/172
Data-to-parameter ratio	17.95	17.39
Final agreement factors	$R = 0.041$, $R_w = 0.044$	$R = 0.047$, $R_w = 0.045$
Weighting scheme for R_w	$w = 1/\sigma^2(F)$	$w = 1/\sigma^2(F)$
Largest difference peak (e Å^{-3})	0.38	0.86
Largest difference hole (e Å^{-3})	0.49	0.54

Table 2. Conformational analysis of (*R*)-**3** and (*R*)-**5**: relative energies, position of the substituent at N(2) with respect to the tetrahydropyrido ring system, and the characteristic dihedral angles [abcd] and [efgh] of the four conformers **A**-**D**



Conformational analysis of (*R*)-**3**				
Conformer	Δ*E* (kcal/mol)	N–H	∢ [abcd] (°)	∢ [efgh] (°)
A	0	Axial	−164	59
B	3.7	Equatorial	−28	49
C	0.8	Axial	−28	−53
D	1.5	Equatorial	−74	−55
Conformational analysis of (*R*)-**5**				
Conformer	Δ*E* (kcal/mol)	N–Me	∢ [abcd] (°)	∢ [efgh] (°)
A	2.5	Axial	−169	61
B	2.8	Equatorial	−7	29
C	0	Axial	−19	−53
D	3.6	Equatorial	−44	−56

by intermolecular hydrogen bonds H(12)···O(15) [2.11 Å for (*R*)-**6** and 2.12 Å for (*S*)-**6**] to form a zigzag chain parallel to [010] in both compounds. Software used to prepare material for publication: Schakal 88.[42]

The details of the crystal structure determination and refinement for the compounds (*R*)-**6** and (*S*)-**6** are given in Table 1. The crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-234567 [for (*R*)-**6**] and no. CCDC-234566 [for (*S*)-**6**]. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

5. Computational section

5.1. Conformational analyses

The conformational analyses (see Table 2) of the TaClo enantiomer (*R*)-**3** and its *N*-methyl derivative (*R*)-**5** were performed on Silicon Graphics OCTANE (R10000) workstations by means of the AM1[34] parameterization as implemented in the program package VAMP,[43] starting from pre-optimized geometries generated by the TRIPOS[44] force field as implemented in the modeling package SYBYL.[44]

5.2. CD calculations

The wavefunctions required for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/2S-CI[45,46] calculations with a CI expansion including 400 singly occupied configurations and the ground state determinant. These calculations were carried out with LinuX PentiumIII workstations by the use of the BDZDO/MCDSPD[45] program package. All single CD spectra obtained in this way were added up by the Boltzmann statistics using appropriate heats of formation, to give the calculated overall CD spectrum. For a better visualization, the rotational strengths were transformed into $\Delta\varepsilon$ values and superimposed with a Gaussian band shape function.

Acknowledgements

This investigation was supported by the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie

(Förderkennzeichen 01 KL 9405; 'Neurotoxine und Neuroprotektion: Hydrophile radikalische Schäden und Chloralabgeleitete endogene Neurotoxine bei Morbus Parkinson'), by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 690: 'Electron Density: Theory and Experiment'), and by the Fonds der Chemischen Industrie. Two of us (R. G. and K. M.) thank the Freistaat Bayern and the Deutsche Forschungsgemeinschaft, respectively, for graduate research fellowships. Our special thanks are due to Prof. J. Fleischhauer (RWTH Aachen, Germany), Prof. J. Michl, and Dr. J. W. Downing (University of Colorado, USA) for providing the program package BDZDO/MCDSPD, and to Jasco Deutschland for generous technical help. Moreover, we are indebted to S. Bender and M. Michel for valuable technical assistance.

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SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 8153–8160

Nitrite increases the enantioselectivity of sulfoxidation catalyzed by myoglobin derivatives in the presence of hydrogen peroxide

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Received 20 April 2004; revised 25 May 2004; accepted 17 June 2004

Available online 21 July 2004

Abstract—The effect of nitrite in the sulfoxidation of organic sulfides catalyzed by myoglobin (Mb) in the presence of hydrogen peroxide has been investigated. A general improvement in enantioselectivity was found for the reaction catalyzed by horse heart metMb and a series of sperm whale metMb derivatives including the wild type protein, the active site mutants T67K Mb, T67R Mb, T67R/S92D Mb, and the T67K Mb derivative reconstituted with the modified prosthetic group protohemin-L- histidine methyl ester.

1. Introduction

Recent studies show that many proteins can provide low levels of activity in reactions different from those involved in their normal biological function.[1] Activity can be improved by engineering the proteins, particularly in the active site features. Such a strategy has become popular in the case of metalloproteins, where the metal-binding sites have been redesigned in different ways, to introduce structural features which are specific to other proteins or enzymes.[2] Among these proteins is myoglobin (Mb), the protein of storage and intracellular transfer of molecular oxygen,[3] which is widely used as a catalyst in peroxide-dependent one-electron oxidation, such as oxidation[4] and nitration[5] of phenolic substrates, and in reactions involving formal two-electron oxidation, such as sulfoxidation of organic sulfides and epoxidation of alkenes.[6] The latter type of reactions, termed peroxygenations, can proceed with a certain degree of stereoselectivity. Both enantioselective sulfoxidation[7] and epoxidation[8] are catalyzed much more efficiently by chloroperoxidase, but in general, commercial applications of peroxidases are limited by the high cost and the low stability of the enzyme, due to the rapid inactivation by the oxidant.[9] For this reason, other proteins such as Mb and its derivatives are explored as potential biocatalysts to perform asymmetric transformations. Single or double mutations can provide substantial contributions to the optimization of the new activity: by engineering the active site of Mb, the group of Watanabe obtained mutants that exhibit significant catalytic turnover with high stereoselectivity in the sulfoxidation and epoxidation of substituted aromatic substrates.[4a,6,10] A different strategy of Mb modification involves replacement of the natural prosthetic group with a synthetic hemin.[4b,11]

We have recently found that during the catalytic cycle of peroxidase-type reactions by Mb, nitrite, in the presence of hydrogen peroxide, produces two powerful nitrating and oxidizing species, nitrogen dioxide ($NO_2^{\cdot}$) and peroxynitrite ($ONOO^-$), depending on nitrite concentration.[5] Herein we report on the effect of nitrite in the oxidation of aromatic sulfides catalyzed by horse heart Mb (hh Mb), sperm whale Mb (WT Mb), the three active site mutants of the latter protein T67R Mb,[12] T67K Mb[13] and T67R/S92D Mb,[14] and the mutant T67K Mb reconstituted with the modified hemin obtained by covalently linking an L-histidine methyl ester residue to one of the propionate side chains of protohemin IX, T67K-His Mb.[4b,13] All the proteins are utilized in their met (Fe^{3+}) form. The aim of this investigation is to assess whether the highly reactive species generated in the presence of nitrite could participate in the sulfoxidation catalytic cycle of Mb and increase the efficiency and/or stereoselectivity of the reaction. Indeed, a general improvement in enantioselectivity was obtained both for horse heart Mb and sperm whale Mb mutants. In addition, we performed NMR studies on Mb-substrate complexes with the aim of gaining a picture of the interaction between the sulfides and the protein.

Keywords: Asymmetric oxidation; Myoglobin; Nitrite; NMR; Sulfoxidation.
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doi:10.1016/j.tet.2004.06.097

2. Results and discussion

2.1. Effect of nitrite in the sulfoxidation reaction

The sulfoxidation of thioanisole (**1**) catalyzed by hh Mb in the presence of hydrogen peroxide was chosen as a standard reaction to optimize reaction conditions. The effects of reaction time, temperature, amount of hydrogen peroxide, and concentration of Mb on the enantioselectivity and conversion of sulfoxide were taken into consideration in these preliminary experiments. It was also established that the non-catalyzed reaction, that is, the reaction carried out in the absence of Mb by simply mixing the sulfide with hydrogen peroxide (and nitrite when required) was negligible in the optimized conditions (see Section 4). The effect of nitrite concentration on sulfoxide yield and enantiomeric excess was then studied in order to investigate the eventual involvement of the two different active species derived from nitrite in the mechanism of sulfoxidation. Indeed, an improvement in enantioselectivity by nitrite was observed and the concentration of nitrite that maximizes the enantioselectivity was found to be 50 mM (Table 1). At this relatively low [NO_2^-] the only active species derived from nitrite which may be involved in the sulfoxidation is nitrogen dioxide.[5] On the other hand, the yield of sulfoxide decreased in the presence of nitrite, indicating that part of the hydrogen peroxide was consumed in the parallel, unproductive oxidation of nitrite to nitrate.

The increase of enantioselectivity in the sulfoxidation carried out in the presence of nitrite was confirmed with the other substrates (Table 2). We chose sulfides carrying a para substituent, methyl *p*-tolylsulfide (**2**), the *iso*-propyl *p*-tolylsulfide (**3**), and methyl 2-pyridylsulfide (**4**). Different reactions conditions were needed for compound **4** (see Section 4), because this substrate is more difficult to oxidize than the others, due to the electron withdrawing effect of the heteroatom. For this reason, it was necessary to increase the reaction time and add the oxidizing agent and nitrite in small aliquots in order to protect the Mbs from degradation.

In order to exclude the possibility that nitrite acted in the reaction through a simple salt effect, that is, by an electrostatic interaction with the protein, the sulfoxidation of **1** catalyzed by hh Mb was carried out in the presence of sodium nitrate. These experiments were made at different concentrations of nitrate and in every case the enantiomeric excess did not change with respect to the reactions carried out in the absence of nitrate.

2.2. Asymmetric sulfoxidation catalyzed by Mb mutants

In our previous studies, we prepared Mb mutants containing

Table 1. Effect of addition of nitrite in the sulfoxidation of thioanisole catalyzed by hh Mb in the presence of hydrogen peroxide (the *R* enantiomer is always the major sulfoxide product)

Conversion (%)	ee (%)	[NO_2^-] (M)
39±4	10±2	—
15±2	21±2	0.01
24±1	29±3	0.05
20±1	22±1	0.10
28±1	5±1	0.20

Table 2. Enhancement of the ee in the sulfoxidation of **2**–**4** catalyzed by hh Mb and hydrogen peroxide in the presence of nitrite (the *R* enantiomer is always the major sulfoxide product)

Substrates	[NO_2^-]=0 M		[NO_2^-]=0.05 M		Method
	Conversion (%)	ee (%)	Conversion (%)	ee (%)	
2	15±2	10±1	10±1	16±1	A
3	5±0.5	5±1	11±3	10±1	A
4	3±0.5	0	3±0.5	0	A
4	14±1	20±2	12±1	24±2	B

a basic residue in the heme distal pocket, by replacement of Thr67 with either Arg (T67R Mb)[12] or the more flexible Lys residue (T67K Mb),[13] and a double mutant where, in addition to the Thr67Arg mutation, the proximal Ser92 was substituted with an Asp residue (T67R/S92D Mb).[14] These modifications aimed at introducing into the Mb active site those amino acid residues which are critical for the activation of hydrogen peroxide in peroxidases.[4b] In addition, we prepared a derivative of T67K Mb reconstituted with protohemin-L-histidine methyl ester (T67K-His Mb).[13] The latter hemin contains only one free carboxylate group and therefore, reconstitution of Mb with the modified cofactor involves the loss of the interaction with one of the propionate groups which stabilize heme binding to the protein. This causes a relaxation of the protein fragment around the heme which was found to increase the accessibility of donor molecules and phenolic substrates to the active site.[4b]

All Mb mutants shared with hh Mb the positive effect of nitrite in the sulfoxidation of thioanisole (Table 3). Among the Mb mutants studied here, the best enantioselective catalyst was found to be T67R Mb, since it afforded the highest increase of enantiomeric excess with respect to WT Mb in the presence of nitrite (from 15 to 51%). The yield of sulfoxide was also significantly improved. The highest conversion to sulfoxide was actually obtained with the mutant T67K Mb, but in this case the enantiomeric excess did not increase with respect to WT Mb. The low asymmetric induction is possibly due to the fact that the lysine residue at position 67 is not rigid enough to control the preferential formation of one sulfoxide enantiomer. Apparently, the guanidinium group in the arginine side chain exerts stronger steric control on the binding of the sulfide to the protein, that leads to a better stereodifferentiation in the oxygenation process.

The T67R Mb derivative gives higher enantioselectivity and yield also in the oxidation of substrate **4** (Table 4). In this case, the reactions were only carried out in the presence of nitrite, since the enhancement of enantioselectivity by nitrite in the oxidation of **4** was already observed for the reaction catalyzed by hh Mb (Table 2). With both the substrates, the T67K-His Mb derivative produced racemic sulfoxides: the increased protein mobility around the heme is clearly not advantageous for the immobilization of the substrate and results in the formation of achiral sulfoxides.

2.3. Mechanism of sulfoxidation

Mechanistic investigations of oxygen transfer reactions by heme peroxidases resulted in a 'hydrogen abstraction oxygen-rebound' mechanism; the actual oxygen transfer reagent could be one of the high-valent oxoferryl intermediates known as compound I ($P^{\cdot+}$ Fe^{IV}=O, where $P^{\cdot+}$ indicates a porphyrin cation radical) and compound II (Fe^{IV}=O), depending on the nature of the enzyme used.[15] For Mbs, unlike peroxidases, the high-valent oxoferryl species resulting from oxidation of Fe^{3+} by hydrogen peroxide cannot be differentiated, because instead of a porphyrin cation radical the initial species contains the radical localized on protein residues.[16] However, the possibility to stabilize a 'compound I-like' species for the Mb mutants obtained upon replacement of the distal His64 residue, allowed Watanabe and co-workers to investigate the direct sulfide-induced reduction of different compound I species and compare the mechanism of sulfoxidation of these proteins with that of horseradish peroxidase (HRP).[17] Two distinct pathways were found: the reduction of HRP compound I by thioanisoles proceeds via electron transfer in the protein cage (followed by oxygen rebound from compound II), whereas the reduction of H64S Mb compound I proceeds via direct oxygen transfer (the intermediate compound II being not involved). Compound I was observed as the catalytic species for the peroxygenase activity of all His64 Mb mutants, whereas only compound II was observed with WT Mb.[18]

Considering that all the proteins investigated here contain the His64 residue, both the oxoferryl intermediates produced in the catalytic cycle, that we indicate as. $MbFe^{IV}$=O and $MbFe^{IV}$=O, are involved in the sulfoxidation. The catalytic scheme can be summarized as follows:

$$MbFe^{3+} + H_2O_2 \rightarrow^{\cdot} MbFe^{IV}{=}O + H_2O \quad (1)$$

$$^{\cdot}MbFe^{IV}{=}O + S \rightarrow MbFe^{3+} + SO \quad (2)$$

$$^{\cdot}MbFe^{IV}{=}O + S \rightarrow [MbFe^{IV}{=}O + S^{\cdot+}] \quad (3)$$

$$[MbFe^{IV}{=}O + S^{\cdot+}] \rightarrow MbFe^{3+} + SO \quad (4)$$

Table 4. Sulfoxidation of methyl 2-pyridyl sulfide catalyzed by Mb mutants and hydrogen peroxide in the presence of 50 mM nitrite (the *R* enantiomer is always the major sulfoxide product)

Mb	Conversion (%)	ee (%)
Horse heart	12±1	24±2
WT	39±4	19±3
T67R	76±5	33±3
T67K-His	40±4	0

Table 3. Sulfoxidation of thioanisole catalyzed by Mb mutants and hydrogen peroxide in the presence of 50 mM nitrite (the *R* enantiomer is always the major sulfoxide product)

	$[NO_2^-]$=0 M		$[NO_2^-]$=0.05 M	
Mbs	Conversion (%)	ee (%)	Conversion (%)	ee (%)
Horse heart	39±4	10±2	24±1	29±1
WT	30±4	13±2	22±2	15±1
T67R	61±4	20±2	54±4	51±2
T67K	27±3	10±2	75±5	15±3
T67R/S92D	1±0.5	[a]	25±2	9
T67K-His	12±1	0	40±3	0

[a] The low conversion does not allow a reliable estimate of the enantiomeric excess.

$$[MbFe^{IV}{=}O + S^{\cdot+}] \rightarrow MbFe^{IV}{=}O + S^{\cdot+} \quad (5)$$

$$MbFe^{IV}{=}O + S \rightarrow MbFe^{3+} + S^{\cdot+} \text{ (slow)} \quad (6)$$

$$2S^{\cdot+} + H_2O \rightarrow S + SO + 2H^+ \quad (7)$$

where $MbFe^{3+}$ is the initial metMb form, S indicates the sulfide, SO the sulfoxide and $S^{\cdot+}$ the sulfur cation radical, respectively.

The first protein intermediate, $^{\cdot}MbFe^{IV}{=}O$, can convert sulfide to sulfoxide with a certain degree of stereoselectivity by a direct O-transfer reaction (formally a two-electron process), reaction (2). $^{\cdot}MbFe^{IV}{=}O$ may also form a sulfur cation radical by one-electron oxidation in the protein cage (indicated with square brackets) according to reaction (3). The latter reaction converts the protein into the second intermediate, $MbFe^{IV}{=}O$, containing a $S^{\cdot+}$ cation radical in the active site. This species can evolve according to two competitive pathways: it can give the oxygen rebound to afford the sulfoxide with a certain degree of stereoselectivity according to reaction (4), or the sulfenium radical can diffuse from the protein cage according to reaction (5). The following reduction of $MbFe^{IV}{=}O$ by another molecule of sulfide produces with low efficiency (see below) a sulfur cation radical, reaction (6). Finally, the dismutation of sulfur cation radicals in the bulk of the solution by reaction (7) gives the racemic product. Therefore, the stereoselectivity in the sulfoxidation depends on the fraction of Mb that reacts *via* $^{\cdot}MbFe^{IV}{=}O$ (reaction (2)) or *via* oxygen rebound from $MbFe^{IV}{=}O$ in the protein cage (reaction (4)).

Reaction (6) is a slow, low efficiency, process. In fact, treating the $MbFe^{IV}{=}O$ intermediate of hh Mb with different amount of thioanisole did not significantly affect the rate of disappearance of the $MbFe^{IV}{=}O$ bands; that is, the formation of metMb and Mb dimers through self oxidation of the active species is faster than reaction with the sulfide.

In contrast, nitrite efficiently reduces the $MbFe^{IV}{=}O$ intermediate to the native state with a second order rate constant $k=(18.6\pm0.6)\ M^{-1}\ s^{-1}$ according to the reaction:[5]

$$MbFe^{IV}{=}O + NO_2^- \rightarrow MbFe^{3+} + NO_2^{\cdot} \quad (8)$$

This process is faster than reaction (6). Furthermore, the reduction rate of $MbFe^{IV}{=}O$ by nitrite is not affected by the presence of thioanisole in the reaction mixture (see Section 4), indicating that the sulfide does not inhibit reaction (8) to a significant extent.

According to this mechanism, nitrite efficiently competes with sulfide for reduction of $MbFe^{IV}{=}O$. As a result, in the presence of this anion the importance of reaction (6) is reduced and, along with this, the contribution of the pathway that produces the sulfoxide through the stereochemically unproductive coupling of sulfur cation radicals. The protein returning to its native form can be involved in another catalytic cycle. Therefore, the effect of nitrite is to increase the fraction of protein that proceeds via two-electron oxidation of the substrate and thereby increase also the stereoselectivity of sulfoxidation.

Nitrite could participate in the sulfoxidation reaction also through the oxidant species $NO_2^{\cdot}$ produced by reaction (8). Nevertheless, by reacting thioanisole with nitrogen dioxide gas, we did not observe appreciable formation of the sulfoxide during the reaction time of the catalytic experiments. As a result, nitrite acts only as a quencher of the intermediate $MbFe^{IV}{=}O$ in the present system. It is worth nothing that increasing the nitrite concentration above 50 mM, where the Mbs can generate peroxynitrite,[5] the enantiomeric excess in the sulfoxidation reaction drops (Table 1). Probably, the formation of $ONOO^-$ implies a decreased reactivity of $^{\cdot}MbFe^{IV}{=}O$ with the sulfide and, at the same time, the highly reactive $ONOO^-$ readily diffuses into the bulk solution, where its reaction with the sulfide produces racemic sulfoxide.

The formation of racemic sulfoxide in the reaction catalyzed by the T67K-His Mb both in the absence and in the presence of nitrite (see Table 3) confirms the effect of nitrite according to the proposed mechanism. In fact, if the oxygen transfer from $^{\cdot}MbFe^{IV}{=}O$ (or from $MbFe^{IV}{=}O$ in the protein cage) is not stereoselective, then quenching of $MbFe^{IV}{=}O$ by nitrite according to reaction (8) cannot increase the enantiomeric excess in the sulfoxidation.

Considering the fast reaction of nitrite with the intermediate $MbFe^{IV}{=}O$, also the rate of the sulfoxidation, and consequently the conversion into product, should increase in the presence of nitrite. However, a fraction of hydrogen peroxide is involved in the unproductive oxidation of nitrite to nitrate according to the reaction:

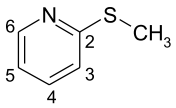
$$NO_2^- + H_2O_2 \rightarrow NO_3^- + H_2O \quad (9)$$

which is also catalyzed by Mb. As a result, the yields of sulfoxide in the presence of nitrite are smaller than those obtained without nitrite.

2.4. NMR relaxation measurements and ^{1}H NMR spectroscopy

To gain an understanding of the protein–substrate interaction, as this is the basis for the stereoselective effects in the sulfoxidation reaction, we performed ^{1}H NMR relaxation time measurements on substrate **4** in the presence of a representative set of proteins, including the best enantioselective catalyst (T67R Mb), the catalyst that produces racemic sulfoxide (T67K-His Mb), and WT Mb, for comparison purposes. In these experiments, the paramagnetic contribution to relaxation by the high spin Fe^{3+} center of the protein can be exploited to get an estimate of the distances of the protons of the bound substrate from the iron atom. The study had to be restricted to substrate **4**, because it is the only sulfide sufficiently soluble in aqueous buffer; attempts to obtain NMR relaxation data with other substrates gave unreliable data due to the very limited range of concentrations attainable. As shown by the data collected in Table 5, the iron-proton distances for protein bound **4** were in the range of 6.9–7.3 Å for WT Mb, 5.8–6.2 Å for T67R Mb, and 6.5–7.0 Å for T67K-His Mb. The similarity in the iron-proton distances for the substrate protons in each protein complex clearly indicates that the sulfide maintains a certain degree of mobility even when

Table 5. Substrate proton relaxation times and iron–proton distances for protein–substrate **4** complexes of Mb derivatives, in deuterated 0.2 M phosphate buffer pD 7.5, 25 °C



Proton (ppm)	WT Mb		T67R Mb		T67K-His Mb	
	T_{1M} (s)	r (Å)	T_{1M} (s)	r (Å)	T_{1M} (s)	r (Å)
H-3 7.29	$(2.6\pm0.1)\times10^{-3}$	6.9	$(9.3\pm0.9)\times10^{-4}$	5.8	$(1.9\pm0.1)\times10^{-3}$	6.6
H-4 7.66	$(3.2\pm0.2)\times10^{-3}$	7.2	$(9.8\pm0.4)\times10^{-4}$	5.9	$(1.8\pm0.2)\times10^{-3}$	6.5
H-5 7.10	$(3.5\pm0.2)\times10^{-3}$	7.3	$(1.16\pm0.06)\times10^{-3}$	6.1	$(2.1\pm0.1)\times10^{-3}$	6.7
H-6 8.27	$(3.1\pm0.1)\times10^{-3}$	7.1	$(1.09\pm0.05)\times10^{-3}$	6.0	$(2.3\pm0.1)\times10^{-3}$	6.8
CH_3 2.47	$(2.7\pm0.1)\times10^{-3}$	7.0	$(1.33\pm0.06)\times10^{-3}$	6.2	$(2.8\pm0.2)\times10^{-3}$	7.0

bound to the protein active site. The distance values agree with a disposition of methyl 2-pyridyl sulfide partially inside the distal cavity of the Mbs, as previously found for the binding to Mb of *p*-cresol, which has comparable size.[12] The sulfide can approach the heme in T67R Mb more closely than in WT Mb, suggesting that this can be a key feature for the enhancement of the enantioselectivity of the sulfoxidation reaction (see Table 4). In the complex between substrate **4** and T67K-His Mb, the iron-proton distances are larger than those observed for T67R Mb. Moreover, the data account for a different orientation of the substrate inside the cavity of T67R Mb and T67K-His with respect to WT Mb, the aromatic protons being more inside the heme cavity and the methyl group more outside in the former cases. We can speculate that the basic residue (Arg or Lys) present in the two mutants contributes to the binding by hydrogen bonding to the sulfur atom or the pyridyl nitrogen atom of the substrate. The interaction with the sulfur atom, however, would be the only polar interaction established by T67R Mb with thioanisole, which gives the best enantioselectivity in the sulfoxidation. The larger mobility of the polypeptide chain of T67K-His Mb around the heme would prevent the relative immobilization of the sulfides, which results in racemic products (Tables 3 and 4).

In order to complete the analysis of the interaction between the Mb derivatives and the sulfides, the paramagnetic ^{1}H NMR spectra of the proteins were studied in the presence of excess sulfide. The downfield region of the NMR spectrum of horse heart Mb is compared in Figure 1 with the spectrum obtained after the addition of substrate **1** to the protein. The assignment of the resonances of hh Mb are made on the basis of the data previously reported.[19] The most notable differences can be found in the chemical shifts of the signals of the heme propionate-7 protons, H_α and $H_{\alpha'}$: while the former undergoes an upfield shift of 1.7 ppm, the latter shifts 0.5 ppm downfield. Actually, this propionate group is localized in the solvent accessible side of the heme moiety. A slight shift of 0.3 ppm upfield can be detected also for the methyl group in position 1 of the porphyrin, probing the ability of thioanisole to deeply enter into the heme distal cavity.

The addition of substrate **4** to a solution of hh Mb produces appreciable changes in several of the downfield paramagnetic signals (Fig. 2); this is probably due to polar effects established by methyl 2-pyridyl sulfide within the protein active site. The largest shifts are again observed for the resonances of the propionate-7 protons H_α (from 72.7 to 71.0 ppm) and $H_{\alpha'}$ (from 31.0 to 31.9 ppm), and for methyl-1 (from 51.3 to 52.0 ppm), but here also methyl-5 is affected (from 83.8 to 84.5 ppm). The selective perturbation of the NMR signals accounts for a disposition of both the sulfides at least partially into the heme distal cavity, spanning the space above the substituents at positions 1, 7 and 8 of the porphyrin, and is in agreement with the range of distances of the substrate protons from the iron center obtained in the relaxation rate measurements.

3. Conclusion

We have shown that nitrite can be used as a reagent to improve the enantioselectivity of the sulfoxidation of organic sulfides catalyzed by several Mb derivatives in the presence of hydrogen peroxide. A model for the interaction between the substrates and the proteins has been obtained through NMR experiments. Although the sulfoxidation of thioanisole catalyzed by the double mutants H64D/V68A and H64D/V68S of Mb[6b,10c] has been reported to occur with enantioselectivities higher than those found here, the effect of nitrite is significant and may find other applications in catalytic oxidation reactions.

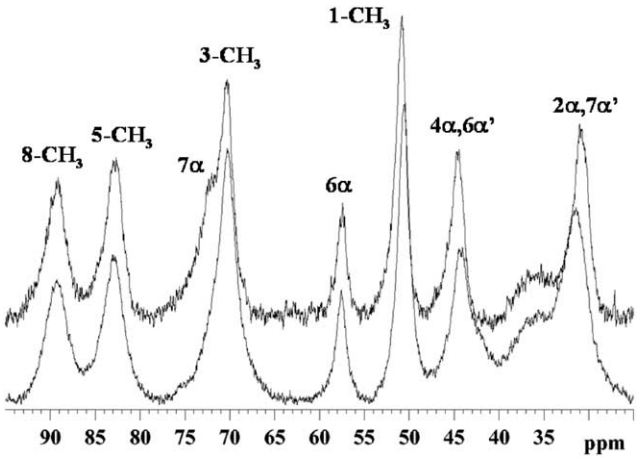


Figure 1. Downfield region of 400 MHz ^{1}H NMR spectrum of hh Mb (~0.1 mM) in deuterated 0.2 M phosphate buffer pD 7.5 in the presence of substrate **1** (0.5 mM) at 25 °C (lower trace), compared with the protein spectrum in the absence of substrate (upper trace). The assignment of the peaks, according to Ref. 19, is shown.

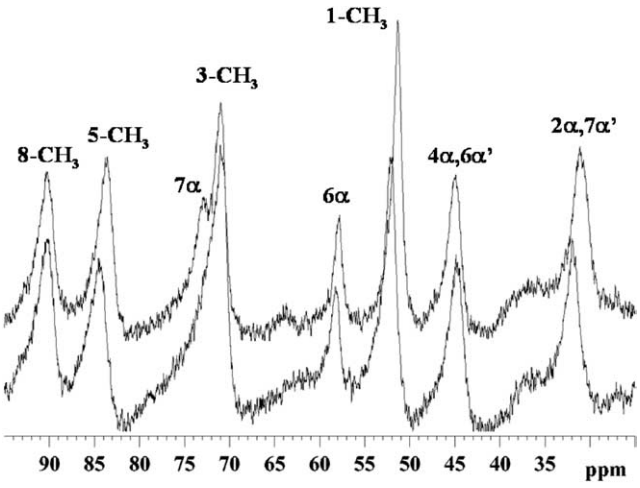


Figure 2. Downfield region of 400 MHz ^{1}H NMR spectrum of hh Mb (~0.1 mM) in deuterated 0.2 M phosphate buffer pD 7.5 in the presence of substrate **4** (12 mM) at 25 °C (lower trace), compared with the protein spectrum in the absence of substrate (upper trace). The assignment of the peaks, according to Ref. 19, is shown.

4. Experimental

4.1. Materials

The substrates **1** and **2** were from Aldrich, while **3** and **4** were synthesized as previously reported.[20] The sulfoxides were synthesized from the corresponding sulfide by oxidation with sodium metaperiodate. Horse heart Mb was obtained from Sigma as a lyophilized sample. The protein derivatives WT Mb, T67R Mb, T67K Mb and T67R/S92D Mb were produced, expressed and purified as previously reported.[12–14] The synthesis of hemin-L-histidine methyl ester and the reconstitution of T67K Mb with the modified hemin were performed as previously reported.[13]

The concentration of Mb solutions was determined from the extinction coefficients of the met forms in 100 mM phosphate buffer, pH 6.0, as follows: hh Mb, 1.88×10^5 M^{-1} cm^{-1} at 408 nm;[3] WT Mb, 1.57×10^5 M^{-1} cm^{-1} at 410 nm;[12] T67K Mb, 1.52×10^5 M^{-1} cm^{-1} at 408 nm;[13] T67R Mb, 1.49×10^5 M^{-1} cm^{-1} at 410 nm;[12] T67R/S92D Mb, 1.61×10^5 M^{-1} cm^{-1} at 408 nm;[14] T67K-His Mb, 1.33×10^5 M^{-1} cm^{-1} at 410 nm.[13] The other reagents were obtained from commercial sources at the best grade available.

4.2. Enzymatic sulfoxidation

Method A—The sulfides (**1–3**) (0.50 mM) were reacted, at 25 °C, under stirring, in 4 ml of 10 mM phosphate buffer, pH 7.5, containing hh Mb or the Mb mutants (5.0 μM) and H_2O_2 (0.50 mM). When required, $NaNO_2$ (0.010–0.20 M) in the usual phosphate buffer was added. After 5 min the reaction mixtures were extracted with dichloromethane (3× 10 ml) and the combined organic phase dried with Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was then analyzed by HPLC.

Method B—Sulfide **4** (0.50 mM) was reacted, at 25 °C, under stirring in 4 ml of 10 mM phosphate buffer, pH 7.5, containing hh Mb or the Mb mutants (5.0 μM). H_2O_2 (0.50 mM) and $NaNO_2$ (0.05 M), when required, were added in 100 min in 10 aliquots at 10 min intervals. After 5 min additional time the reaction mixture was extracted with dichloromethane (3×10 ml) and the organic phase dried with Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was then analyzed by HPLC.

The HPLC analyses were performed with a Merck–Hitachi L-7100 pump and a DAD 1050 HP detector on Daicel chiral columns OD and OB, at a flow rate of 0.8 ml/min. Elution conditions were as follows: column OD, 20% isopropanol, 80% hexane for **1**; column OB, 20% isopropanol, 80% hexane for **2**; column OB, 15% isopropanol, 85% hexane for **3** and **4**. Readings were made at 230 nm for **1–3** and at 210 nm for **4**. On Chiralcel OB the (*S*)-sulfoxides eluted first, whereas on Chiralcel OD the elution order was the opposite.[21] Standard curves prepared using synthetic sulfoxides were used for quantitative analysis and the value of % conversion and enantiomeric excess were determined on the basis of the peak areas of HPLC traces.

4.3. Reactions of $MbFe^{IV}$=O with thioanisole and with nitrite

The hh $MbFe^{IV}$=O intermediate was prepared by incubating metMb (4 μM) in 0.2 M phosphate buffer, pH 7.5 with 2 equiv. H_2O_2 for about 15 min, until the Soret band shifted from 410 to 420 nm and stabilized at this wavelength. The reaction with **1** was monitored observing the return of the Soret band from 420 to 410 nm with time, after the addition of the substrate at different concentrations (up to 0.5 mM). The spontaneous evolution of $MbFe^{IV}$=O to metMb was a slow process and was not influenced by thioanisole, since an appreciable increment in the rate of this process in the presence of the sulfide was not observed.

Moreover, the observed first-order rate constants for reduction of $MbFe^{IV}$=O by nitrite (followed spectrophotometrically under pseudo-first order conditions as previously reported)[5] were not affected by the presence of thioanisole (0.5 mM) in the reaction mixture.

4.4. Reaction of $NO_2^{\cdot}$ with thioanisole

$NO_2^{\cdot}$ was obtained by air oxidation of $NO^{\cdot}$. 200 μl of 1 atm gaseous $NO_2^{\cdot}$ (a slight excess with respect to the amount that gives a final concentration of 1 mM) were bubbled through a gas-tight syringe into a solution of substrate **1** (0.50 mM) in 4 ml of 0.2 M phosphate buffer, pH 7.5. After 5 min, the solution was extracted with CH_2Cl_2, the organic phase was dried under vacuum and then analyzed by HPLC as reported above (see Section 4.2).

4.5. NMR relaxation measurements and ^{1}H NMR spectroscopy

The T_1 relaxation time for the protons of substrate **4** in the presence of variable amounts of WT Mb, T67R Mb, or T67K-His Mb were determined at 25 °C with a Bruker AVANCE 400 NMR spectrometer operating at 400.13 MHz, using the standard inversion recovery

method.[22] The solutions of **4** were prepared in deuterated 0.2 M sodium phosphate buffer pD 7.5 and contained different amount of the proteins. In order to eliminate interferences by metal impurities, a small amount of EDTA was added to the solutions. The concentrations employed were the following: [**4**] = 12.0 mM and [WT Mb] = 0–6 μM; [**4**] = 14.0 mM and [T67R Mb] = 0–2 μM; [**4**] = 14.5 mM and [T67K-His Mb] = 0–4 μM. The relaxation rate of the protons of the substrate molecules interacting with the Mbs, T_{1b}, was calculated from experimental relaxation rate, T_{1obs}, through the equation:[23]

$$\frac{1}{T_{1obs}} = \left[\frac{1}{T_{1b}} - \frac{1}{T_{1f}}\right]\frac{E_0}{K_D + S_0} + \frac{1}{T_{1f}} \quad (10)$$

where T_{1f} is the T_1 value for free substrate, E_0 and S_0 are the initial protein and substrate concentrations, respectively, and K_D is the dissociation constant for the Mb-substrate complex. The major contribution to the T_{1b} value is the paramagnetic contribution (T_{1M}), which is correlated to the distance (r) of the nucleus from the Fe^{3+} center according to the Solomon–Bloembergen equation (assuming an electron relaxation time τ_s of 5×10^{-11} s).[12,24,25] The K_D values are not known and were neglected in the present calculations; however, the magnitude of the error associated with this approximation is identical for all the substrate protons. It is possible to estimate for r a maximum error of 10% assuming a dissociation constant equal to the substrate concentration.

The paramagnetic proton NMR spectra of hh Mb were recorded at 25 °C on solutions of the protein (~0.1 mM) in deuterated 0.2 M sodium phosphate buffer, pD 7.5. The interaction of hh Mb with the sulfides was studied by recording NMR spectra of the Mb solution containing substrate **1** (~0.5 mM) or **4** (12 mM). Spectra were recorded acquiring 5K scans, with a 80000 Hz spectral window, and suppressing the water signal by presaturation for 0.3 s.

Acknowledgements

This work was supported by a PRIN Project of the Italian MIUR. We thank Giuseppe Celentano for HPLC analyses.

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Reactive species from aromatics and oxa-di-π-methane rearrangement: a stereoselective synthesis of (±)-hirsutene from salicyl alcohol

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Received 9 April 2004; revised 25 May 2004; accepted 17 June 2004

Available online 20 July 2004

Abstract—A total synthesis of hirsutene, a triquinane sesquiterpene, from salicyl alcohol is reported. Oxidation of salicyl alcohol in the presence of cyclopentadiene gave 9-spiroepoxy-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one which was elaborated to the 3-hydroxy-2-methyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-10-en-8-one containing major structural and functional features of hirsutene. Photochemical sigmatropic 1,2-acyl shift in 3-hydroxy-2-methyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-10-en-8-one followed by radical induced cleavage of peripheral cyclopropane bond, olefination and Simmon–Smith reaction furnished 11-hydroxy-1-methyl-4-spirocyclopropanetricyclo[6.3.0.0^{2,6}]undecane that upon treatment with hydrogen on PtO_2 and PCC oxidation gave 1,4,4-trimethyltricyclo[6.3.0.0^{2,6}]undecan-11-one, a known precursor. Wittig methylenation on this precursor gave hirsutene.

1. Introduction

Recently, reactive species such as cyclohexadienone ketals, quinols, *o*-imido quinones and congeners generated from aromatic compounds have received increasingly greater attention for the development of new methods.[1–5] These methods provide efficient and stereoselective avenues for the creation of complex molecular structures that are not readily available otherwise, and also led to synthesis of various types of natural products.[1–5] Polyquinane sesquiterpenoids have stimulated a longstanding interest on account of their novel molecular architecture and interesting biological profiles. This led to the development of a plethora of methodologies involving a number of ways to create the triquinane ring systems.[6] However, except for a few, the majority of routes generate tricyclic framework iteratively often in a non stereoselective fashion, although the search for new and efficient methods is continuing.[7] Hirsutene **1**, a polyquinane sesquiterpenoid isolated from *Coriolus consors*,[8] is believed to be the biogenetic precursor of other oxygenated and biologically active members of hirsutane family.[8] Recently, new hirsutane based sesquiterpenes such as **2a**,**b** were isolated from salt water cultures of a marine sponge derived fungus and some of its members were found to be anti-microbial (Fig. 1).[9] Hirsutene has served as a popular target for synthesis because of its molecular structure and role in biogenesis, and considered as a test case for new methods of cyclopentanoid synthesis.[6,10] In view of the above and to demonstrate the potential of 6,6-spiroepoxycyclohexa-2,4-dienone **4**, and photochemical reactions of β,γ-enones in organic synthesis,[2] we developed a synthesis of hirsutene **1** from salicyl alcohol **3**, and wish to report the details herein.[11] The key features of our approach are the cycloaddition of spiroepoxycyclohexadienone **4**, a reactive species generated from salicyl alcohol **3**, a photochemical 1,2-acyl shift and an unusual alkylation at ring junction of a bridged carbocyclic framework.

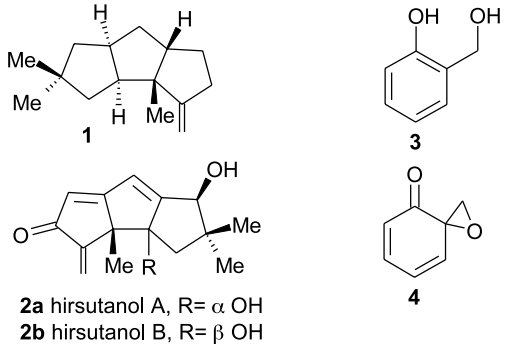

Figure 1.

Keywords: Spiroepoxycyclohexa-2,4-dienone; Cycloaddition; Oxa-di-π-methane rearrangement.

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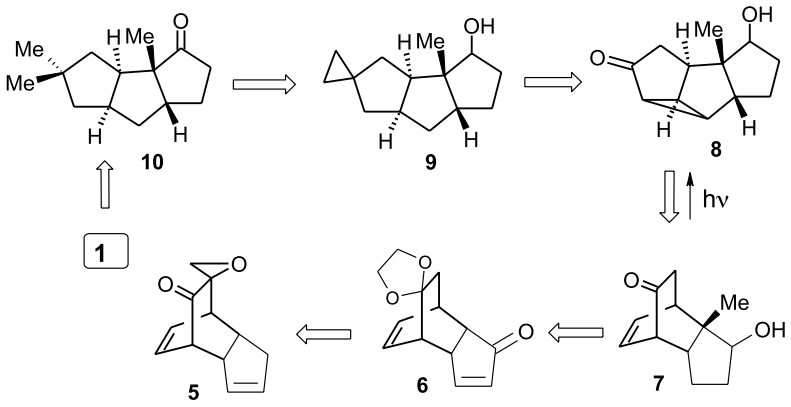
doi:10.1016/j.tet.2004.06.096



Scheme 1.

2. Strategy

Our strategy for the synthesis of hirsutene **1** is depicted in Scheme 1. We envisaged that major structural, functional and stereochemical elements of hirsutene are present in the bridged tricyclic compound **7** in latent fashion. It was thought that the bridged structure of **7** may be transformed into the ring fused triquinane framework **8** via a photochemical sigmatropic 1,2-acyl shift,[12,13] and that the triquinane **8** could be readily elaborated to hirsutene via the intermediates **9** and **10**. We further contemplated that the tricyclic compound **7** might be obtained by alkylation in **6** followed by reduction and removal of the ketal group. The dienone **6** in turn, was thought to be derived from the keto-epoxide **5** which is readily available via oxidation of salicyl alcohol followed by interception of the resulting spiroepoxycyclohexa-2,4-dienone **4** with cyclopentadiene.

Some of the salient features of our strategy are as follows. The eleven carbons of hirsutene, which make its *cis*:*anti*:*cis* triquinane frame, are present in the *endo* adduct **5** in a latent form, and were assembled in the first step itself with appropriate connectivity and correct stereochemical orientation. A photochemical reaction in the key precursor **7** would generate the *cis*:*anti*:*cis* triquinane framework in a single stereoselective step. Further, the β,γ-enone chromophore which is required for the key step (**7**→**8**) is also generated in the very first step. However, the introduction of the methyl group at the ring junction in compound **6** appeared to be crucial for the synthesis of hirsutene especially since such type of alkylations are generally not observed.

3. Results and discussion

3.1. Synthesis of the tricyclic system 7 and congeners

In principle, the key tricyclic precursor **7** may be derived from the dienone **11** by selective manipulation, and the dienone **11** may be obtained by the cycloaddition of cyclohexa-2,4-dienone **12** and 1-methyl cyclopentadiene **13** (Fig. 2).

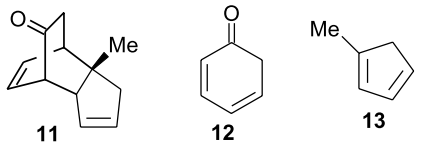
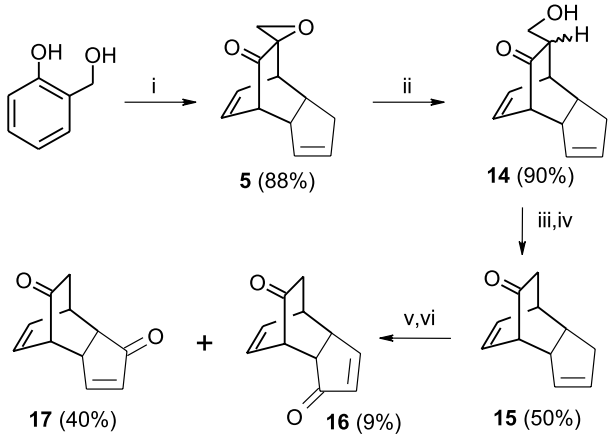


Figure 2.

However, this approach appeared to be difficult in practice since there are no methods for the generation of **12** (a keto tautomer of phenol). Moreover, the preparation of 1-methyl cyclopentadiene in pure form is difficult due to its tendency to undergo 1,5-sigmatropic shifts. Therefore, we devised an indirect sequence to the tricyclic intermediate **7** from the keto epoxide **5** which is readily prepared in a single step from salicyl alcohol by modification of a method developed earlier in our laboratory.[13b]

Thus, a solution of salicyl alcohol in acetonitrile was oxidized with aqueous sodium *meta*periodate[13b,14] and the resulting spiroepoxycyclohexa-2,4-dienone **4** was intercepted with freshly cracked cyclopentadiene to give the keto-epoxide **5** in excellent yield (88%) (Scheme 2). The structure of the adduct was deduced from its spectral data and comparison.[13b] The stereochemical orientation of the oxirane ring was suggested on the basis of the general tendency of cyclohexa-2,4-dienones during cycloaddition.



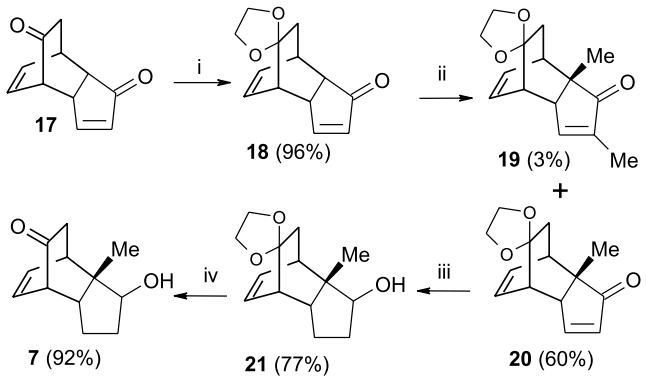
Scheme 2. Reagents/conditions: (i) CH_3CN, aq. $NaIO_4$, cyclopentadiene; (ii) Zn, NH_4Cl, aq. MeOH, rt; (iii) Jones reagent, acetone, 0–5 °C; (iv) THF–H_2O, Δ; (v) SeO_2, aq. dioxane, KH_2PO_4; (vi) PDC, CH_2Cl_2.

The presence of the epoxy ketone group in the ethano bridge and the double bond in the five membered ring of the adduct **5** provided a unique opportunity for its elaboration to the desired chromophoric system **7**. Thus, the reduction of **5** with activated zinc and ammonium chloride in a protic solvent (MeOH–H_2O) gave the β-keto-alcohol **14** as a major product in excellent yield (90%). The β-keto alcohol **14** was oxidized with Jones' reagent and the resulting keto-acid was decarboxylated to give the known[13b] tricyclic compound **15**. Allylic oxidation of **15** with SeO_2 in a buffered solution of aqueous dioxane gave an inseparable mixture of regio-isomeric alcohols that was further oxidized with PDC[15] to give the enones **16** and **17** from which the desired enone **17** was isolated in the major amount (Scheme 2). The structures of both the enones were deduced from their spectroscopic data, and COSY spectra which were confirmed through further transformations (vide infra).

Towards the synthesis of the precursor **7**, the diene–dione **17** was first converted into the ketal–enone **18** in quantitative yield. After having prepared the ketal **18**, introduction of the methyl group in **18** at the ring junction α' to the carbonyl group was required. In general, the alkylation of α,β-enones having a γ-methine or methylene results in α-alkylation via the extended thermodynamic dienolate.[16] We considered it possible to generate the kinetic enolate by abstraction of the proton at the α' carbon and alkylate the ring junction.

In view of the above, the enone **18** was treated with excess LDA at −78 °C followed by addition of methyl iodide in THF. However, the desired alkylated product was not obtained. Moreover, attempts to alkylate the enone–ketal with a variety of bases under different reaction conditions also proved to be futile. After considerable experimentation, it was observed that simultaneous addition of enone **18** and methyl iodide to a solution of LDA at −78 °C led to the desired alkylation and furnished the alkylated product **20** as the major product (60%), in addition to a small amount of dialkylated product **19** (3%) (Scheme 3). The structure of the alkylated product **20** was deduced from the spectroscopic data, comparison with spectral features of its precursor, and COSY spectrum.

Towards the synthesis of the key chromophoric system **7**, the alkylated enone **20** was reduced with sodium borohydride to give the alcohol **21** as a single diastereoisomer



Scheme 3. Reagents/conditions: (i) ethylene glycol, *p*-TsOH, benzene, (ii) LDA, −40 to −78 °C, MeI; (iii) $NaBH_4$, MeOH, 25 °C; (iv) aq. HCl(50%), acetone, 25 °C.

(^{1}H NMR (300 MHz), ^{13}C NMR). However, no attempts were made to ascertain the orientation of the hydroxyl group since it would be later converted to a carbonyl group (vide infra). Acid catalyzed hydrolysis of the ketal group in **21** readily furnished the chromophoric system **7** (Scheme 3) with the necessary functionalities required for further elaboration to hirsutene.

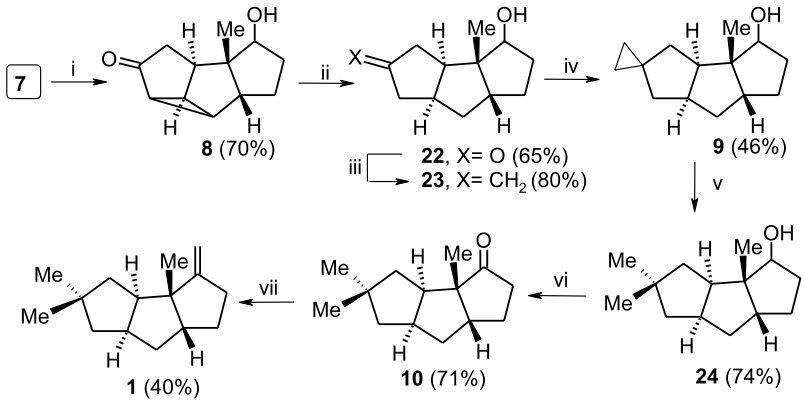
3.2. Photochemical reaction of the tricyclic compound 7 and further transformations: synthesis of the intermediates 9, 10 and hirsutene

Photochemical reaction of β,γ-enones have stimulated interest in the past two decades[17] which has been further enhanced recently because of their synthetic potential.[12,13] Rigid β,γ-enones undergo two unique reactions that are characteristic of their excited states. In general, the triplet sensitized irradiation leads to a 1,2-acyl shift (or oxa-di-π methane rearrangement) and the direct excitation (1*S*) induces a 1,3-acyl shift. Though the scope of oxa-di-π-methane rearrangement is fairly wide, it is quite sensitive to the structure of the chromophoric system, functional groups and substituents.[13,17] Moreover, appropriate sensitizers are required to generate lowest triplet excited state otherwise a mixture of products are obtained due to indiscriminate populations of excited states.

In view of the above, a solution of **7** in acetone (both as solvent and triplet sensitizer) was irradiated with a mercury vapour lamp (125 W, Applied Photophysics) in a Pyrex immersion well for 1 h, upon which a clean reaction occurred. Removal of solvent followed by column chromatography of the photolysate furnished the tetracyclic intermediate **8** as a crystalline solid in excellent yield (70%) (Scheme 4). It may be interesting to note that the triplet sensitised 1,2-acyl migration in **7** rendered the transformation of a bridged structure into a ring fused carbocyclic system that is otherwise very difficult via ground state reactions.

In order to synthesize the triquinane intermediate **9**, a selective cleavage of the peripheral cyclopropane bond in the photoproduct **8** was required. The reductive cleavage of carbonyl conjugated cyclopropane rings with various reagents has been well studied and the stereoelectronic requirements of the process have been found to control the rupture of the cyclopropane bonds. Though there are various reagents for the cleavage of the peripheral cyclopropane sigma bond,[18,19] we opted for radical induced reduction.[18a] Therefore, a solution of the tetracyclic compound **7** in benzene containing Bu_3SnH-AIBN was refluxed for 12 h. Removal of the solvent followed by chromatography furnished the triquinane **22** whose structure was clearly revealed from its spectral data and comparison with the spectral features of its progenitor.

Further elaboration of **22** into hirsutene required conversion of carbonyl group into a geminal methyl group, oxidation and Wittig reaction. There are various methods reported in the literature for the conversion of a carbonyl to a geminal methyl group.[20,21] Functional group constraints and mildness of the reaction prompted us to adopt a Wittig olefination, cyclopropanation and reductive cleavage



Scheme 4. Reagents/conditions: (i) *hν*, acetone, pyrex, 1 h; (ii) Bu_3SnH, AIBN, benzene, Δ; (iii) $Ph_3P{=}CH_2$, toluene, 0–5 °C; (iv) CH_2I_2, Et_2Zn, benzene; (v) H_2, PtO_2, AcOH; (vi) PCC, CH_2Cl_2, molecular sieve; (vii) $Ph_3P{=}CH_2$, toluene, Δ.

sequence. In general, Wittig reactions of five membered ring ketones are difficult due to enolisation. Interestingly, the treatment of the ketone **22** with excess of triphenyphoshonium methylide at 0 °C furnished the olefin **23** in excellent yield (Scheme 4). The presence of remote oxygen functionality perhaps facilitated the olefination.[10b] Towards cyclopropanation of the olefin **23** to the spiro alcohol **9**, LeGoff's method employing the Zn–Cu couple procedure was first attempted.[22] However, it gave a complex mixture of products and the desired product could not be isolated. Consequently, cyclopropanation was attempted with diiodomethane in the presence of diethyl zinc,[23] which furnished the desired compound **9** in moderate yield (46%). The ^{1}H NMR spectrum (300 MHz) of **9** was devoid of signals due to olefinic protons and exhibited characteristic signals at δ 0.52–0.41 (m, 2H) and 0.37–0.28 (m, 2H) for the methylene protons of the cyclopropane ring in addition to other signals. The ^{13}C NMR (75 MHz) spectrum also showed characteristic signal at δ 13.48 and 10.41 for the methylene cyclopropane ring carbons in addition to other signals for the methylene, methine, methyl and quaternary carbons.

The reductive cleavage of the cyclopropane ring in **9** with Adams' catalyst gave the triquinane **24**. Oxidation of the alcohol **24** with PCC[24] furnished the known norketone **10** whose spectral features were found to in good agreement with those literature.[25] The triquinane intermediate **10** has already been converted to hirsutene hence the formal synthesis of hirsutene was complete. Wittig reaction of ketone **10** with triphenylphosphoniummethylide furnished hirsutene **1** whose spectral features compared well with those reported in literature.[26]

4. Conclusion

In summary, a novel synthesis of hirsutene, a fungal metabolite of *Coriolus consors*, from salicyl alcohol and cyclopentadiene is described. Cycloaddition of a reactive spiroepoxycyclohexadienone with cyclopentadiene, oxa-di-π-methane rearrangement and an unusual alkylation at ring junction of annulated bicyclo[2.2.2]octenone framework are the key features of our approach. In the present route, the six carbons of the aromatic ring are combined with five carbons of cyclopentadiene so as to give a tricyclic system that contains the tricyclopentanoidal framework of hirsutene in latent fashion and is also endowed with appropriate functionalities for the introduction of angular methyl group, geminal methyls and exocyclic olefin present in the hirsutene.

5. Experimental

5.1. General remarks

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. UV spectra were recorded on Shimadzu UV 160 or Shimadzu U 260 instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker Avance-400 NMR spectrometer, Varian NMR and Varian VXR 300 instruments. The samples were dissolved in $CDCl_3$ as solvent and $SiMe_4$ as internal standard. The standard abbreviations s, d, t, m and dd, td refers to singlet, doublet, triplet, multiplet, doublet of doublet and triplet of doublet respectively. In some cases to conserve $CDCl_3$, CCl_4 was used to record NMR. Mass spectra were recorded on HP GCD 1800A GS-MS, Q Tof micro and Bruker Daltonics APEX 3 Tesla Fourier Transform, Mass Spectrometers. Microanalyses were done on a CEST 1106 instrument. Melting points were determined on a veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulphate. Reactions were monitored with thin layer chromatography and spots were visualized with iodine vapour. Column chromatography was done on Acme/SRL silica gel (60–120 or 100–200 mesh). The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixtures or low boiling petroleum ether (40–60 °C) ether mixtures. The fractions eluted from column were concentrated at reduced pressure on a Buchi-RE 111 rotary evaporator. The solvents used for all reactions were purified/ dried by using standard procedures.

5.1.1. 9-Spiroepoxy-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (5). To a solution of salicyl alcohol **3** (5 g, 40.3 mmol) in acetonitrile (100 mL) cooled at ~0 °C was added freshly cracked cyclopentadiene (5 mL, excess) followed by the addition of a saturated solution of sodium *meta*periodate (25 g, 117 mmol in 135 mL water) drop wise over a period of 2 h. After stirring the reaction mixture in ice-bath for an additional hour, more cyclopentadiene

(5 mL) was added. The reaction mixture was further stirred overnight at ambient temperature (~28 °C). The reaction mixture was saturated with sodium chloride and the organic layer was separated and the aqueous layer was extracted with ethyl acetate (4×25 mL). The combined extract was washed with brine and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel. Elution with petroleum ether gave the dimer of cyclopentadiene and other hydrocarbon impurities. Further elution with petroleum ether–ethyl acetate (90:10) gave the compound **5** (6.15 g, 88%) as a colourless liquid. IR (neat) ν_{max}: 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.42–6.40 (superimposed dd, $J=7.5$ Hz, 1H, γ-H of β,γ-enone group), 6.16–6.09 (superimposed dd, $J=7.5$ Hz, 1H, β-H of β,γ-enone group), 5.75–5.70 (m of d, $J=6$ Hz, 1H, olefinic H), 5.50–5.44 (m of d, $J=6$ Hz, 1H, olefinic H), 3.42–3.34 (m, 2H, methine H), 3.12 (part of an AB system, $J_{AB}=6$ Hz, 1H, OCH_2), 3.09–3.00 (m, 1H, methine H), 2.84 (part of an AB system, $J_{AB}=6$ Hz, 1H, OCH_2), 2.68–2.56 (merged m, 2H), 2.08–1.97 (m of d, $J=18$ Hz, 1H, allylic methylene). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.54 (CO), 133.36, 132.04, 129.37, 128.97 (four olefin carbons), 57.92, 52.71, 52.03, 50.25, 43.67, 38.29, 35.91. HRMS (EI): *m/z* calculated for $C_{12}H_{12}O_2$ 211.0735 [M^++Na]; found 211.0741.

5.1.2. *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-8-one (15). To a solution of the adduct **5** (5 g, 26.3 mmol) in MeOH–H_2O (5:1, 175 mL) was added activated zinc (30 g, excess) and NH_4Cl (5.5 g, 101.8 mmol). The reaction mixture was stirred at ambient temperature (~30 °C). After completion of reaction (tlc, 8 h) the reaction mixture was filtered through a celite bed and washed with ethyl acetate (5×3 mL). The filtrate was concentrated under vacuum; the residue was diluted with water (15 mL) and extracted with ethyl acetate (4×20 mL). The combined extract was washed with brine and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed. Elution with petroleum ether–EtOAc (80:20) gave the β-ketoalcohol **14** as a liquid (*syn*:*anti* mixture, 1:4, 4.45 g, 90%). IR (neat) ν_{max}: 3635, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.46–6.41 (superimposed dd $J=7.3$ Hz, 1H, γ-H of β,γ-enone group), 6.10–6.03 (m, 1H, β-H of β,γ-enone group), 5.69–5.65 (m, 1H, olefinic H), 5.46–5.42 (m, 1H, olefinic H), 3.92–3.85 (m, 1H, OCH_2), 3.74–3.57 (m, 1H, OCH_2), 3.20–3.04 (m, 2H, methine H), 2.79–2.47 (cluster of multiplets, 3H) 2.27–2.21 (m, 1H, allylic methylene), 2.06–1.93 (m of d, $J=9$ Hz, 1H, allylic methylene). Mass (*m/z*): 190 (M^+). The keto-alcohol **14** was subjected to oxidation and decarboxylation as given below.

To a solution of the β-keto-alcohol **14** (5 g, 26.3 mmol) in acetone (150 mL) at ~5 °C, was added freshly prepared Jones' reagent drop wise. After completion of reaction (tlc, 1 h), acetone was removed under vacuum. The residue was diluted with water (20 mL) and extracted with ethyl acetate (6×25 mL). The extract was combined, dried over anhydrous sodium sulphate and the solvent was removed under vacuum to give the β-keto-acid which was dissolved in THF–H_2O mixture (1:1, 150 mL) and refluxed for 12 h. The aqueous layer was saturated with sodium chloride, extracted with ether (6×30 mL) and dried. Removal of solvent followed by chromatography of the residue [petroleum ether–EtOAc (97:3)] gave the title compound **15** as a colourless liquid (2.1 g, 50%). IR (neat) ν_{max}: 1727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.35 (superimposed dd, $J=7.2$ Hz, 1H, γ-H of β,γ-enone group), 6.05 (superimposed dd, $J=7.2$ Hz, 1H, β-H of β,γ-enone group), 5.68–5.63 (m of d, $J=6$ Hz, 1H, olefinic H), 5.48–5.21 (m of d, $J=6$ Hz 1H, olefinic H), 3.25–3.13 (m, 2H, methine H), 3.04–2.98 (m, 1H, methine H), 2.72–2.50 (cluster of m, 2H), 2.08 (d, $J=2.5$ Hz, 2H, $COCH_2$), 2.03–1.93 (m of d, $J=18$ Hz, 1H, allylic CH_2). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 211.55 (CO), 134.24, 132.58, 130.32, 128.52 (four olefinic carbons), 52.61(methine), 49.50 (methine), 40.15 (methylene) 39.99 (methine), 39.00 (methylene), 37.69 (methine). These assignments were made on the basis of spectrum recorded in DEPT mode. HRMS (EI): *m/z* calculated for $C_{11}H_{12}O$ 183.0786 [M^++Na]; found 183.0792.

5.1.3. *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-4,10-dien-3,8-dione (17) and *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,10-dien-5,8-dione (16). To a solution of **15** (3 g, 18.8 mmol) in dioxane–water (5:1, 180 mL) was added selenium dioxide (4.16 g, 37.6 mmol) and potassium dihydrogen phosphate (2.55 g, 18.7 mmol), and the reaction mixture was refluxed for 6 h. After which more selenium dioxide (2.08 g, 18.8 mmol) and potassium dihydrogen phosphate (2.55 g, 18.7 mmol) were added at intervals of six hours over a period of additional 12 h. After near completion of reaction (tlc, 18 h), the reaction mixture was filtered on a celite bed and washed with ethyl acetate (3×5 mL). The filtrate was concentrated under vacuum; the residue was diluted with water (25 mL) and extracted with ethyl acetate (4×20 mL). The combined extract was washed with saturated sodium bicarbonate (2×20 mL) and dried. Removal of solvent followed by chromatography of the residue [petroleum ether–EtOAc (40:60)] furnished an inseparable mixture of the hydroxy ketones (1.7 g, 53%). The mixture of hydroxyketones was dissolved in dichloromethane (60 mL) and PDC (7.26 g, 19.3 mmol) was added to it and the reaction mixture was stirred at ambient temperature for 4 h. The reaction mixture was filtered on a celite pad and washed with ethyl acetate (3×5 mL). The filtrate was concentrated under vacuum and the residue was purified by column chromatography to give a mixture of the diene–diones **17** and **16**. Fractional crystallization from petroleum ether–ethylacetate (90:10) gave the enone **17** as a colourless solid (1.3 g, 40%) in major amount and the enone **16** as a colourless solid (0.3 g, 9%) in the minor amount.

Data for **17**. Colourless solid, mp 120–121 °C. IR (neat) ν_{max}: 1724 and 1692 cm^{-1}. UV (MeOH) λ_{max}: 217.8 nm ($\varepsilon=4785$ L mol^{-1} cm^{-1}). ^1H NMR (300 MHz, $CDCl_3+CCl_4$) δ: 7.37 (dd, $J_1=5.4$ Hz, $J_2=2.4$ Hz, 1H, β-H of α,β-enone moiety), 6.27 (m, 1H, γ-H of β,γ-enone moiety), 6.23 (m, 1H, α-H of α,β-enone moiety), 5.87 (superimposed dd, $J=7.2$ Hz, 1H, β-H of β,γ-enone moiety), 3.40 (m, 1H, methine H) 3.33–3.32 (m, 1H, methine H), 3.28 (m of d, $J=6.3$ Hz, 1H, methine H), 2.60 (dd, $J_1=6.4$ Hz, $J_2=3.1$ Hz, 1H, methine H), 2.1 (d of partly merged AB system, $J_{AB}=17$ Hz, $J_2=3.5$ Hz, 1H, $COCH_2$), 1.91 (d of merged AB system, $J_{AB}=17$ Hz, $J_2=3.6$ Hz, 1H, $COCH_2$). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 209.18, 207.93 (two carbonyls),

162.04, 137.8, 134.34, 125.61 (four olefinic carbons), 51.65 (methine), 48.65 (methine), 42.99 (methine), 37.84 (methylene), 34.42 (methine). Mass (*m/z*): 174 (M^+). Analysis: found: C, 76.17; H, 5.36%; Calcd for $C_{11}H_{10}O_2$: C, 75.86; H, 5.74%.

Data for **16**. Colourless solid, mp 101–102 °C. IR (film) ν_{max}: 1718, 1697 cm^{-1}. UV (MeOH) λ_{max}: 233.8 nm (ε= 7955 L mol^{-1} cm^{-1}). ^1H NMR (300 MHz, $CDCl_3+CCl_4$) δ: 7.52 (dd, $J_1=5.5$ Hz, $J_2=2$ Hz, 1H, β-H of α,β-enone moiety), 6.25–6.22 (m, 1H, α-H of α,β-enone moiety), 6.19–6.15 (m, 1H, γ-H of β,γ-enone moiety), 6.07–6.02 (m, 1H, β-H of β,γ-enone moiety), 3.55–3.53 (m, 1H, methine H), 3.29–3.27 (m, 1H, methine H), 3.16–3.13 (m, 1H, methine H), 2.71–2.67 (m, 1H, methine H), 2.22–2.1 (m, 2H, $COCH_2$). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 208.08, 206.97 (two carbonyls), 164.41, 137.99, 133.35, 126.51 (four olefinic carbons), 51.04 (methine), 46.62 (methane), 44.80 (methine), 38.95 (methylene), 35.27 (methine). Mass (*m/z*): 174 (M^+). Analysis: found: C, 75.91; H, 5.83%; Calcd for $C_{11}H_{10}O_2$: C, 75.86; H, 5.74%.

5.1.4. *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-8-(1,3-dioxolan)-4,10-dien-3-one (18). To a mixture of ethylene glycol (0.8 mL, excess), *p*-toluenesulphonic acid (catalytic amount) and dry benzene in a Dean–Stark apparatus was added a solution of the diene–dione, **17** (1.0 g, 5.7 mmol) in dry benzene. The reaction mixture was heated at 80 °C for 4 h. The reaction mixture was washed with saturated sodium bicarbonate (2x20 mL) and the benzene layer was dried. The solvent was removed under vacuum. Purification of the crude product by flash chromatography (petroleum ether–EtOAc, 80:20) gave the ketal–enone **18** (1.2 g, 96%) which was recrystallized from petroleum ether to give a colourless solid, mp 127–129 °C. IR (KBr) ν_{max}: 1694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42 (dd, $J_1=6.0$ Hz, $J_2=3.0$ Hz, 1H, β-H of α,β-enone moiety), 6.16 (dd with structure, 1H, $J_1=$ 6.0 Hz, $J_2=2.0$ Hz, α-H of α,β-enone moiety), 6.12 (superimposed dd with structure, 1H, $J=7$ Hz, 1H, olefinic H), 5.89 (superimposed dd with structure, $J=7$ Hz, 1H, olefinic H), 3.98–3.92 (m, 4H, $-OCH_2CH_2O-$), 3.48–3.43 (m, 1H, methine H), 3.16–3.09 (m, 1H, methine H), 2.76 (m of d, $J=6$ Hz, 1H, methine H), 2.49 (dd, $J_1=6$ Hz, $J_2=$ 3 Hz, 1H, methine H), 1.82 (d of part of an AB system, $J_{AB}=13.5$, $J_2=3$ Hz, 1H, [$CH_2C(OCH_2)_2$], 1.78 (d of part of an AB system, $J_{AB}=13.5$, $J_2=3$ Hz, 1H, [CH_2-$C(OCH_2)_2$]. ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 209.77 (CO), 164.62, 136.88, 131.81, 128.31, (four olefinic carbons), 112.96 [$C(OCH_2)_2$], 64.23, 64.10 (methylene carbons of ketal group), 48.12 (methine), 42.46 (methine), 41.95 (methine), 39.61 (methylene), 34.22 (methine). HRMS (EI): *m/z* calculated for $C_{13}H_{14}O_3$: 219.1021 [M^++H]; found 219.1020.

5.1.5. 2-Methyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-8-(1,3-dioxolan)-4,10-dien-3-one (20) and 2,4-dimethyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-8-(1,3-dioxolan)-4,10-dien-3-one (19). To a flame dried three necked round bottom flask fitted with two dropping funnels and N_2 inlet was added dry THF (35 mL). The reaction flask was cooled to −40 °C and diisoproplyamine (5 mL, 35.7 mmol) was added to it. *n*-Butyl lithium (1.6 M in hexane, 22 mL, 35.2 mmol) was added dropwise to the solution of diisopropylamine. The resulting solution of lithium diisopropylamide was stirred over a period of 1 h and then cooled to −78 °C. A solution of the ketal enone **18** (0.5 g, 2.3 mmol) in THF (20 mL) and methyl iodide (8 mL, excess) in THF (15 mL) were added simultaneously over a period of 1.5 and 0.5 h, respectively. After consumption of starting material (tlc, ~50 min) the reaction mixture was quenched with cold water, saturated with sodium chloride and extracted with EtOAc (4× 25 mL). The combined extract was washed with saturated sodium thiosulfate (1×25 mL) and dried. The solvent was evaporated and the residue was purified by flash chromatography. Elution with petroleum ether–EtOAc 90:10 first gave the minor product **19** (17 mg, 3%) as a colourless liquid. Further elution with the same solvent gave the title compound **20** (0.32 g, 60%) as a colourless liquid (which crystallized after cooling in refrigerator).

Data for **20**. Colourless solid, mp 83–84 °C. IR (film) ν_{max}: 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) : 7.36 (dd, $J_1=$ 5.7 Hz, $J_2=2.7$ Hz, 1H, β-H of α-β enone moiety), 6.21 (superimposed dd, $J=7$ Hz, 1H, olefinic H), 6.11 (dd with str, $J_1=5.7$ Hz, $J_2=1.5$ Hz, 1H, α-H of α-β enone moiety), 5.8 (superimposed dd, $J=7$ Hz, 1H, olefinic H), 3.98–3.89 (m, 4H, $-OCH_2CH_2O-$), 3.06 (m, 1H, methine H), 2.75–2.71 (m, 1H, methine H), 2.70–2.67 (m, 1H, methine H), 2.11 (d of part of an AB system, $J_{AB}=14.0$ Hz, $J_2=2.4$ Hz, 1H, $COCH_2$), 1.62 (d of part of an AB system, $J_{AB}=$ 14.0 Hz, $J_2=3.1$ Hz, 1H, $COCH_2$), 1.20 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 213.23 (CO), 163.24, 135.07, 134.52, 127.91 (four olefinic carbons), 113.60 [$C(OCH_2)_2$], 64.39, 64.09 (methylene carbons of ketal group), 50.19 (methine), 48.64 (quaternary C, *C*Me), 43.20 (methine), 38.83 (methine), 35.51 (methylene), 18.95 (methyl carbon). Mass (*m/z*): 232 (M^+). Analysis: found C, 72.54; H, 7.05%; Calcd for $C_{14}H_{16}O_3$: C, 72.43; H, 6.89%.

Data for **19**. Liquid, IR (neat) ν_{max}: 1702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.95 (broad dd, $J_1=2.6$ Hz, $J_2=$ 1.3 Hz, 1H, β-H of α,β-enone moiety), 6.20–6.13 (superimposed dd with structure, $J_1=7.2$ Hz, 1H, olefinic H), 5.82–5.75 (superimposed dd $J_1=7.2$ Hz, 1H, olefinic H), 3.99–3.90 (m, 4H, $-OCH_2CH_2O-$), 2.91 (d with structure, $J=2.0$ Hz, 1H, methine H), 2.72–2.62 (m, 2H, methine H), 2.10 (d of part of an AB system, $J_1=14.2$ Hz, $J_2=2.41$ Hz, 1H, methylene H-α to carbonyl), 1.71 (t, $J=1.6$ Hz, 3H, C=CCH_3), 1.60 (d of part of an AB system, $J_1=14.2$ Hz, $J_2=3.29$ Hz, 1H, methylene H-α to carbonyl, partly merged with signal due to H_2O in $CDCl_3$), 1.15 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 207.58 (CO) 157.7, 142.86, 134.41, 128.18 (olefinic carbons), 113.26 [$C(OCH_2)_2$], 64.42, 64.07 (methylene carbons of ketal group), 48.90 (quaternary C, *C*Me), 47.82, 43.57, 39.05 (three methine carbons), 35.61 (methylene carbons), 19.16, 10.36 (two methyl carbons). HRMS (EI): *m/z* calculated for $C_{15}H_{18}O_3$: 247.1334 [M^++H]; found 247.1345.

5.1.6. 3-Hydroxy-2-methyl-*endo*-tricyclo[5.2.2.0^{2,6}] undeca-8-(1,3-dioxolan)-10-ene (21). To a stirred solution of **20** (0.27 g, 1.16 mmol) in methanol (30 mL) was added $NaBH_4$ (0.132 g, 3.47 mmol) in small portions and the reaction mixture was stirred at ambient temperature for 2 h. After which methanol was removed under vacuum and the

residue was diluted with water (15 mL) and extracted with ethyl acetate (2×25 mL). The combined extract was washed with brine (1×25 mL) and dried. Removal of solvent followed by chromatography of the residue [petroleum ether–EtOAc (80:20)] gave the title compound **21** as a colourless liquid (0.213 g, 77%). IR (neat) ν_{max}: 3466 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.59 (superimposed dd with structure, $J_1=7$ Hz, $J_2=1$ Hz, 1H, olefinic H), 6.2–6.12 (broad superimposed dd, $J=7$ Hz, 1H, olefinic H), 3.98–3.85 (m, 4H, $-OCH_2CH_2O-$), 3.76 (broad s, 1H, *H*–C–OH), 2.60–2.50 (m, 2H), 2.16–2.03 (m, 2H), 1.86–1.68 (m, 2H), 1.58–1.46 (m merged with signal due to H_2O present in $CDCl_3$, 2H), 1.42–1.34 (m, 1H), 1.28–1.16 (m, 1H), 1.11 (s, 3H, CH_3). ^{13}C NMR (75 MHz $CDCl_3+CCl_4$) δ: 137.56, 129.63 (two olefinic carbons), 113.24 [*C*$(OCH_2)_2$], 83.69 (H*C*OH), 64.26, 63.65 (methylene carbons of ketal group), 50.38 (*C*Me), 48.23, 44.41, 38.95 (three methine carbons), 36.99, 34.49, 28.95 (three methylene carbons), 27.74 (methyl carbon). HRMS (EI): *m/z* calculated for $C_{14}H_{20}O_3$: 237.1485 [M^++H]; found 237.1477.

5.1.7. 3-Hydroxy-2-methyl-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-10-en-8-one (7). To a stirred solution of **21** (0.2 g, 0.8 mmol) in acetone (20 mL) was added a few drops of HCl (25%). After completion of reaction (2 h, tlc), the reaction mixture was diluted with water (10 mL), cooled, and neutralized (pH=7) by addition of solid $NaHCO_3$. The reaction mixture was concentrated; the residue was diluted with water (15 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layer was washed with saturated sodium bicarbonate (1×25 mL), brine (1×25 mL) and dried. Removal of solvent gave the crude product that was purified by flash chromatography [petroleum ether–EtOAc (85:15)] to give the title compound **7**, as a sticky solid (0.16 g, 92%), mp 166–168 °C. IR (film) ν_{max}: 3439, 1721 cm^{-1}. UV (MeOH) λ_{max} (nm): 296.0 (ε=140 L mol^{-1} cm^{-1}), 210.4 (ε=1729 L mol^{-1} cm^{-1}). ^1H NMR (300 MHz, $CDCl_3+CCl_4$) δ: 6.73 (superimposed dd with structure, $J=7$ Hz, 1H, γ-H of β,γ-enone group), 6.10 (superimposed dd, $J=7$ Hz, 1H, β-H of β,γ-enone group), 3.83 (superimposed dd, $J=4.5$ Hz, 1H, *H*–C–OH), 3.07–3.05 (m of d, $J=4.8$ Hz, 1H, bridgehead methine H), 2.82 (broad m, 1H, bridgehead methine H), 2.31–2.25 (dd of part of an AB system, $J_1=18.6$ Hz, $J_2=2.6$ Hz, 1H, COC*H*$_2$), 1.99–1.39 (cluster of m, 7H), 1.07 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 212.46 (CO), 139.98, 125.40 (two olefinic carbons), 82.93 (H–*C*–OH), 54.55 (methine), 51.82 (methine), 51.66 (quaternary C, *C*Me), 39.56 (methine) 36.7, 35.37, 28.97 (three methylene carbons), 28.18 (methyl carbon). HRMS (EI): *m/z* calculated for $C_{12}H_{16}O_2$: 193.1223 [M^++H]; found 193.1229.

5.1.8. 9-Hydroxy-8-methyltetracyclo[6.3.0.0^{2,4}.0^{3,7}]undecan-5-one (8). A solution of **7** (0.1 g, 0.5 mmol) in degassed acetone (solvent as well as sensitizer) was irradiated with a mercury vapour lamp (125 W, Applied Photophysics) in a Pyrex immersion well under nitrogen. After near completion of reaction, (tlc, 1 h) acetone was evaporated under vacuum and the residue was flash chromatographed. Elution with petroleum ether–EtOAc (80:20) afforded the product **8** (70 mg, 70%) as a crystalline solid, which was recrystallized from petroleum ether, mp 111–112 °C. IR (film) ν_{max}: 3362, 1716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.86 (superimposed dd, $J=5.4$ Hz, 1H, *H*–C–OH), 3.0–2.95 (dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz, 1H), 2.77–2.72 (dd, $J_1=11.0$ Hz, $J_2=5.3$ Hz, 1H), 2.50–2.40 (m, 1H), 2.28–2.18 (m, 2H), 2.09–2.07 (broad d, $J=7.1$ Hz, 1H), 1.90–1.60 (cluster of m, 6H, partly overlapped with signal due to H_2O in $CDCl_3$), 0.84 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$) δ: 214.69 (CO), 82.54 (H–*C*–OH), 61.99 (quaternary C), 50.55, 42.95, 38.26, 37.39, 36.24 (five methine carbons), 44.72, 36.12, 29.84 (three methylene carbons), 22.93 (methyl carbon). Mass (*m/z*): 192 (M^+). Analysis: found C, 75.06; H, 8.68%; Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33%.

5.1.9. 11-Hydroxy-1-methyltricyclo[6.3.0.0^{2,6}]undecan-4-one (22). To a solution of **8** (0.15 g, 0.80 mmol) in dry benzene (12 mL) was added tri-*n* butyltin hydride (0.9 mL, 1.25 mmol) and AIBN (0.130 g, 0.79 mmol) under N_2 atmosphere and the reaction mixture was refluxed. After 6 h, more AIBN (70 mg, 0.43 mmol) was added and the reaction mixture was further refluxed for 6 h. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with petroleum ether first gave some tin impurities. Continued elution with petroleum ether–EtOAc (80:20) furnished the tricyclic compound **22** as a colorless liquid (0.1 g, 65%). IR (neat) ν_{max}: 3436, 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.85 (superimposed dd, $J=$ 5.5 Hz, 1H, *H*–C–OH), 2.90–2.78 (m, 2H), 2.44–2.08 (m, 4H), 2.0–1.8 (m, 2H), 1.71–1.58 (m, 5H, merged with signal due to H_2O in $CDCl_3$), 1.5–1.4 (m, 1H), 1.02 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 220.87 (CO), 82.58 (H–*C*–OH), 55.28, 51.45, 44.53, 43.83, 41.98, 40.39, 38.96, 34.83, 29.88, 24.75. HRMS (EI): *m/z* calculated for $C_{12}H_{18}O_2$: 195.1380 [M^++H], found 195.1376.

5.1.10. 4-Methylene-1-methyltricyclo[6.3.0.0^{2,6}]undecan-11-ol (23). To a stirred suspension of methyltriphenylphosphonium iodide (1.45 g, 3.58 mmol) in dry toluene (4.5 mL) was added freshly sublimed *t*-BuOK (0.36 g, 2.83 mmol) and the reaction mixture was stirred at ambient temperature for 0.5 h. The resulting ylide suspension was cooled to ~0 to −5 °C and a solution of the ketone **22** (0.1 g, 0.5 mmol) in dry toluene (2.5 mL) was added drop wise and the stirring was continued. After consumption of starting material, (tlc, 20 min), the reaction mixture was quenched with cold water and extracted with ether (4×15 mL). The combined extract was dried and the solvent was evaporated under reduced pressure to give the crude product, which was purified by flash chromatography. Elution with low boiling petroleum ether (40–60 °C)–ether (80:20) furnished the olefin **23** as a colourless liquid (79 mg, 80%). IR (neat) ν_{max}: 3374 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.83–4.81 (doublet with structure, $J=1.6$ Hz, 1H, =CH), 4.77–4.75 (doublet with structure, $J=1.6$ Hz, 1H, =CH), 3.81–3.75 (m, 1H, *H*–C–OH), 2.60–2.45 (m, 3H), 2.28 (s, 1H), 2.25 (s, 1H), 2.07 (broad s, 1H), 1.92–1.71 (complex m, 2H), 1.65–1.51 (complex m, merged with signal due to H_2O present in $CDCl_3$, 4H), 1.43–1.39 (m, 2H), 1.02 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.81, 105.13 (two olefinic carbons), 82.98 (H–*C*–OH), 55.10, 51.31, 47.62, 45.09, 39.13, 38.29, 35.25, 34.24, 29.20, 23.90.. HRMS (EI): *m/z* calculated for $C_{13}H_{20}O$: 192.1509 [M^+]; found 192.1516.

5.1.11. 11-Hydroxy-1-methyl-4-spirocyclopropanetricyclo[6.3.0.0^{2,6}]undecane (9). To a stirred solution of the olefin **23** (25 mg, 0.13 mmol) and freshly distilled diiodomethane (0.083 mL, 1.3 mmol) in dry benzene (1 mL) was added Et_2Zn (1 mL, 1 mmol, 1.0 M in hexane) and the reaction mixture was stirred at ambient temperature. After completion of reaction (tlc, 2 h), the reaction mixture was diluted with ether (20 mL) followed by the addition of saturated NH_4Cl solution (5 mL) and extracted with ether (3×10 mL). The combined extract was washed with saturated sodium thiosulfate (2×20 mL), dried and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography. Elution with low boiling petroleum ether (40–60 °C)–ether (80:12) furnished the compound **9** as a colourless liquid (12 mg, 46%). IR (neat) ν_{max}: 3373 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.78 (superimposed dd, J=6.9 Hz, 1H, *H*–C–OH), 2.72–2.56 (m, 2H), 2.13–2.05 (m, 1H) 1.96–1.22 (m, 11H merged with signal due to H_2O present in $CDCl_3$) 1.03 (s, 3H, CH_3) 0.52–0.41 (m, 2H, methylene of spirocyclopropane ring) 0.37–0.28 (m, 2H, methylene of spirocyclopropane ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 82.90, 54.47, 51.26, 48.07, 45.74, 41.59, 39.92, 37.66, 33.65, 29.59, 28.3, 23.50, 13.48, 10.41. HRMS (EI): *m*/*z* calculated for $C_{14}H_{22}O$: 206.1655 [M$^+$]; found 206.1655.

5.1.12. 11-Hydroxy-1,4,4-trimethyltricyclo[6.3.0.0^{2,6}]undecane (24). A mixture of the alcohol **9** (20 mg, 0.1 mmol), PtO_2 (45 mg, 0.2 mmol) and acetic acid (4 mL) were kept under H_2 atmosphere (10 kg pressure) in an autoclave for 48 h. The catalyst was removed by filtration and the filtrate was diluted with water (10 mL) and ether (20 mL), and aq. sodium carbonate was added to it (pH 8). The two layers were separated and the aqueous layer was extracted with ether (3×10 mL). The combined extract was dried and the solvent was evaporated under vacuum to give a residue, which was purified by flash chromatography. Elution with low boiling petroleum ether (40–60 °C)–ether (97:3) furnished the title compound **24** as a colourless liquid (15 mg, 74%). IR (neat) ν_{max}: 3412 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.78 (superimposed dd, J=6.6 Hz, 1H, *H*–C–OH), 2.68–2.50 (m, 2H), 2.14–2.02 (m, 1H), 2.0–1.9 (m, 1H), 1.80–1.2 (m, 9H, merged with signal due to H_2O present in $CDCl_3$), 1.16–1.04 (m, 4H, mulitplet merged with singlet due to angular methyl), 0.97 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 83.01 (H–*C*–OH), 51.50, 48.28, 47.34, 44.68, 43.38, 42.24, 40.65, 33.60, 30.17, 29.81, 28.09, 27.98, 23.05. HRMS (EI): *m*/*z* calculated for $C_{14}H_{24}O$: 208.1822 [M$^+$]; found 208.1815.

5.1.13. 1,4,4-Trimethyltricyclo[6.3.0.0^{2,6}]undecan-11-one (10). To a stirred solution of the alcohol **24** (17 mg, 0.08 mmol) in dichloromethane (6 mL) was added PCC (37 mg, 0.18 mmol) and molecular sieves (3 Å, previously dried) and the reaction mixture was stirred for 3 h at ambient temperature. The reaction mixture was filtered on a celite bed and washed with ether (4×5 mL). The filtrate was evaporated under reduced pressure and the crude product was purified by flash chromatography to furnish the known[25] norketone **10** as a low melting solid (12 mg, 74%, lit.[25b] mp 46 °C). IR (neat) ν_{max}: 1738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.8 (dd with structure, J_1=19 Hz, J_2=8.8 Hz, 1H), 2.5 (m, 1H), 2.44–2.2 (m, 3H), 2.06–1.93 (m, 1H), 1.76–1.62 (m, 3H partly merged with signal due to H_2O present in $CDCl_3$), 1.48–1.37 (m, 2H), 1.18 (superimposed dd, J=12 Hz, 1H), 1.04 (s, 3H, CH_3), 1.01–0.96 (m, 1H), 0.94 (s, 3H, CH_3), 0.90 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 229.68 (CO), 59.44, 48.97, 46.82, 43.41, 41.94, 41.22, 37.68, 34.33, 29.80, 29.32, 26.63, 22.48, 17.39. Mass (*m*/*z*): 206 (M$^+$). These spectral features were in good agreement with the literature.[25]

5.1.14. Hirsutene (1). To a stirred suspension of methyltriphenylphosphonium iodide (0.215 g, 0.5 mmol) in dry toluene (0.5 mL) was added freshly sublimed *t*-BuOK (54 mg, 0.5 mmol) and the reaction mixture was stirred at ambient temperature for 0.5 h. To the resulting yellow ylide solution, a solution of the ketone **10** (10 mg, 0.05 mmol) in dry toluene (1 mL) was added drop wise and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched with cold saturated NH_4Cl and extracted with ether (4×15 mL). The combined extract was dried and concentrated under vacuum to give a residue, which was purified by column chromatography. Elution with low boiling petroleum ether (40–60 °C) furnished the natural product **1** as a liquid (4 mg, ~44%). The volatility of this hydrocarbon hampered its isolation and determination of yield. IR (neat) ν_{max}: 2921, 2853, 1462 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.81 (br s, 1H, C=CH), 4.77 (br s, 1H, C=CH), 2.65–2.42 (m, 4H), 2.16–2.10 (m, 1H), 1.79–1.59 (m, 2H merged with H_2O in $CDCl_3$) 1.49–1.38 (m, 4H) 1.20–1.12 (m, 1H), 1.0 (m, 1H) 1.04 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 103.3 (olefinic carbons), 55.96, 53.41, 49.91, 48.97, 44.27, 41.85, 40.88, 38.61, 30.89, 29.71, 27.22, 26.80, 23.19. Mass (*m*/*z*): 204 (M$^+$). These spectral features were found in agreement with those reported earlier.[26]

Acknowledgements

We thank BRNS, Mumbai for continued financial support. Thanks are also due to RSIC, IIT Bombay for spectral facilities.

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Sulfoxide-controlled S_N2' displacements between cuprates and vinyl and alkynyl epoxy sulfoxides

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Received 31 March 2004; revised 15 June 2004; accepted 17 June 2004

Available online 21 July 2004

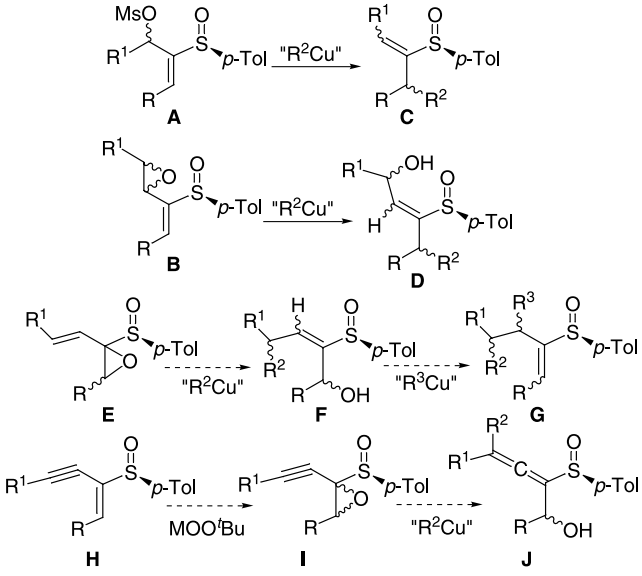
Dedicated to the memory of Dr. Juan Carlos del Amo deceased in Madrid (11 March 2004)

Abstract—The S_N2' displacement of readily available vinyl epoxy sulfoxides with organocopper reagents takes place in good yields with high *anti* selectivity and a good degree of *E*/*Z* stereocontrol to produce enantiopure α-hydroxy vinyl sulfoxides. A second allylic displacement on the related mesyloxy vinyl sulfoxides allows for the asymmetric construction of two adjacent chiral centers. In addition, cuprate mediated S_N2' addition to alkynyl epoxy sulfoxides affords α-hydroxy allenyl sulfoxides in good yields.

1. Introduction

Notwithstanding the advances in the past years, the asymmetric construction of carbon–carbon bonds remains a crucial challenge for the development of organic synthesis. Among the existing methodology, allylic substitution, namely S_N2' displacement of acetates, epoxides and other leaving groups, has been recognized as a powerful tool in the asymmetric synthesis of a number of complex molecules.[1] Within this field and in connection with our interest in the development of sulfur-directed methodology,[2] previous research from our group has been focused on the sulfoxide-controlled S_N2' displacements between cyanocuprates and mesyloxy and epoxy vinyl sulfoxides **A** and **B**. Indeed, we have demonstrated that allylic mesylates **A**, activated with a chiral sulfoxide, undergo copper mediated S_N2' displacements with high asymmetric induction and *Z*/*E* selectivity to produce enantiomerically pure trisubstituted vinyl sulfoxides **C**.[3] Additionally, we have extended the scope of this methodology to enantiopure epoxy vinyl sulfoxides **B** that produce densely functionalised allylic alcohols **D** through a highly regio- and stereoselective S_N2' process.[4] Moreover, further applications of these products could be envisioned due to the presence of the vinyl sulfoxide that should allow for subsequent synthetic manipulations of the molecules (Scheme 1).[5]

To extend this study, vinyl epoxy sulfoxides **E**, now available through nucleophilic epoxidation of vinyl and dienyl sulfoxides,[6] were considered. At the inception of this research, we were aware of previous studies on the somewhat anomalous behavior of simple sulfinyl oxiranes



Scheme 1.

Keywords: Sulfoxide; Epoxide; Cuprate; Asymmetric S_N2'; Allenes.
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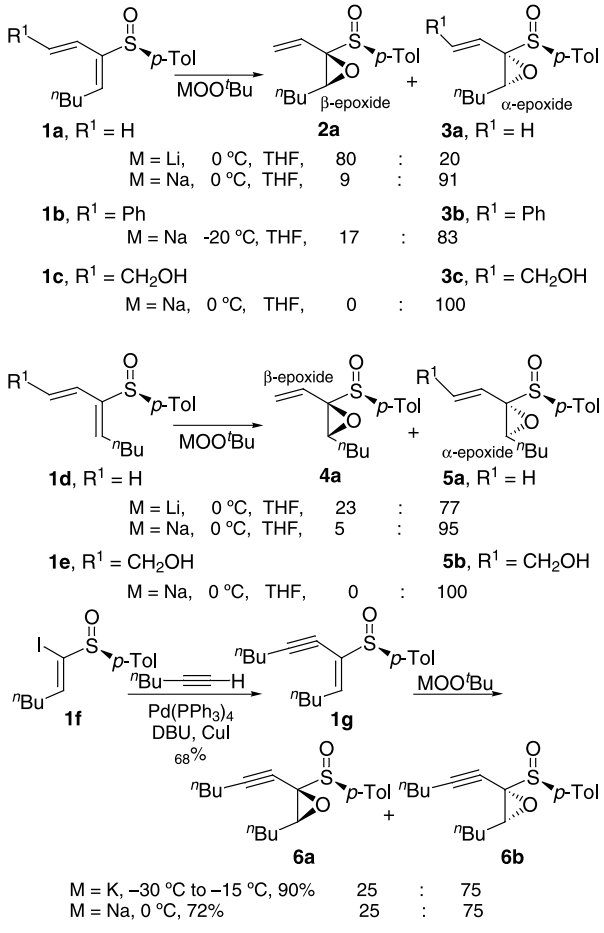
doi:10.1016/j.tet.2004.06.092

with organocuprates that rendered enolates in good yield without incorporation of the alkyl residue on copper. At any rate we chose to pursue this chemistry with the expectation that an alternative reaction pathway would be operative for our unsaturated oxiranes.[7] In fact, this new class of epoxides could undergo two consecutive asymmetric S_N2' reactions. First, allylic displacement on epoxides **E** would lead to allylic alcohols **F** that maintain the vinyl sulfoxide group and second, S_N2' substitution on a mesylate of **F** would render trisubstituted vinyl sulfoxides **G** with two adjacent newly created chiral centers. In addition, we planned the study of the nucleophilic epoxidation of sulfinyl enynes **H** to produce epoxides **I** that incorporate an alkyne at the electrophilic terminus[8] and could lead to the asymmetric synthesis of hydroxy sulfinyl allenes **J**.[9] In this paper, we present a full account of our results.

2. Synthesis of starting materials

The synthesis of the enantiopure starting oxiranes was performed through the nucleophilic epoxidation of readily available dienyl sulfoxides with LiOO^{t}Bu and NaOO^{t}Bu.[10] We have previously observed that the process takes place in good yields, with complete regiocontrol and preservation of the double bond geometry. Additionally, the diastereofacial selectivity varies from moderate to excellent, depending on the nature of the dienyl sulfoxide **1a-e** and the metalated peroxide (Li or Na).[10c] On the other hand, as an extension of the above methodology, alkynyl vinyl sulfoxide **1g**, available from Sonogashira coupling of *Z* iodovinyl sulfoxide **1f** and 1-hexyne, was submitted to epoxidation with KOO^{t}Bu and NaOO^{t}Bu. Both reagents rendered alkynyl epoxy sulfoxides **6a** and **6b** with good yield, complete regiocontrol and moderate stereoselectivity (25:75) (Scheme 2).[11–13]



Scheme 2.

3. Results and discussion

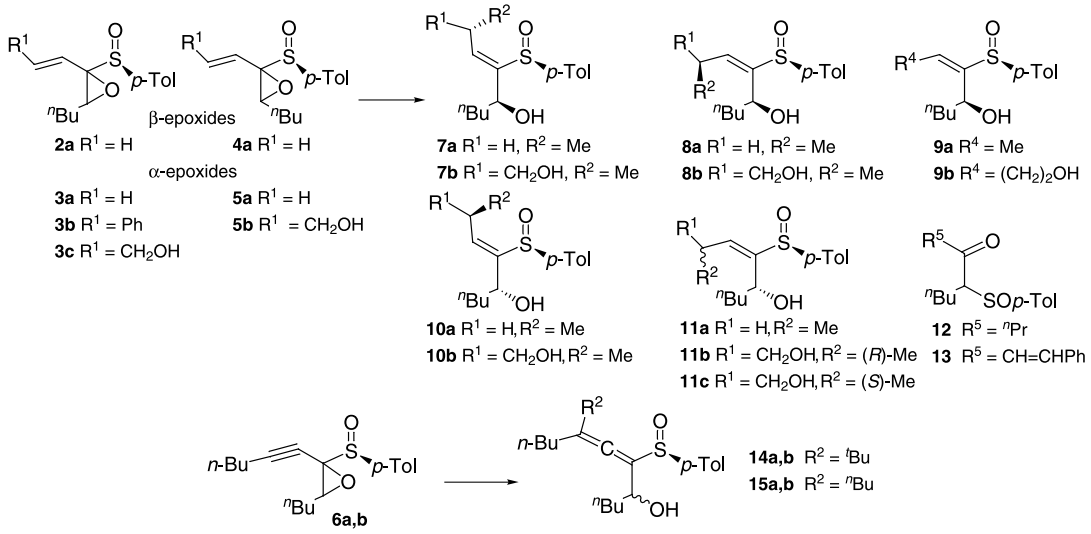
To establish the experimental conditions for the allylic displacement, we initially focused our efforts on β,trans-oxirane **2a** (Table 1). The lack of substituents at the double bond would preclude creation of new chiral centers but also simplify the analysis of the results. Treatment of **2a** with an excess of MeCuCNLi in Et_2O rendered a highly selective mixture of *Z* and *E* S_N2' displacement products **7a** and **8a** (95:2) along with a minor amount (3%) of **9a**. The structure of **9a** indicated that upon quenching, protonation instead of the slower reductive elimination was taking place at the S_N2'–Cu (III) intermediate. Indeed, shortening the reaction time [from 2 h 30 min (0 °C to rt) to 5 min (0 °C)] led to isolation of **9a** as the only product (entries 1 and 2).

The influence of the stereochemistry of the epoxide ring regarding the sulfoxide moiety was examined next.[13] However, we observed that upon treatment with MeCuCNLi α-oxirane **3a** gave a non-selective mixture of displacement products **10a** and **11a** along with 47% of ketone **12** presumably derived from S_N2 attack to the epoxide (see below). The presence of a phenyl group on the double bond, **3b** (R^1=Ph) increased the regioselectivity towards S_N2 attack affording exclusively ketone **13** upon using MeCuCNLi or BuCuCNLi as nucleophiles (entries 3–5). The formation of ketones **12** and **13** (Scheme 3) can be tentatively rationalized as an oxidative S_N2 addition of the cyanocopper reagent to give **K**. Rearrangement to a ketone, followed by migration of the sulfinyl group to the adjacent carbon and simultaneous loss of copper would lead to enone **L**. Then, in situ conjugate addition of excess of MeCuCNLi to **L**, followed by protonation of the enolate upon quenching would produce **12**. Alternatively, the presence of a phenyl ring attached to the enone would prevent the second conjugate addition affording **13**.

Interestingly, the low S_N2' reactivity of these α-epoxides can be partially overcome by placing a hydroxymethyl group at the double bond. Thus, the treatment of **3c** with MeCuCNLi afforded a moderately selective mixture of *Z* and *E* S_N2' compounds **10b**, **11b** and **11c** (70:26:4) (entry 6) although with a low conversion (50%).

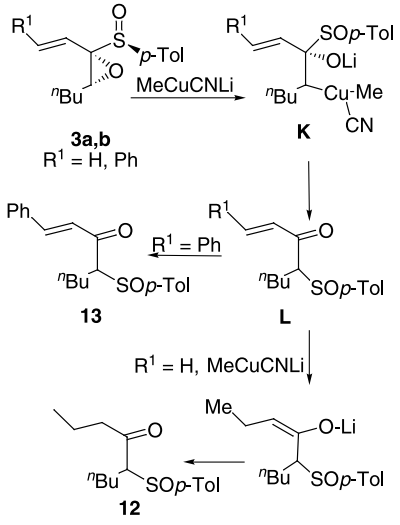
In contrast, *cis* epoxides **4** and **5** display a more selective behavior towards the S_N2' addition of cyanocuprates (entries 7–9) and we have obtained fairly selective mixtures of S_N2' products with high yields. In fact, β-epoxide **4a** underwent allylic displacement with MeCuCNLi affording a 14:86 mixture of **10a** and **11a**. Additionally, treatment of α-oxirane **5a** with MeCuCNLi afforded a remarkably selective mixture of *E* (**8a**) and *Z* (**7a**) displacement products (94:6), along with a small amount of reduction product **9a** (16%). However, sulfinyl epoxide **5b** did not

Table 1. S_N2' displacements between cyanocuprates and vinyl and alkynyl epoxy sulfoxides



Entry	Subs	Cuprate	Z-S_N2'[a]	E-S_N2'[a]	Reduction product[a]	S_N2[a]	Allene	Yield (%)[b]
1	**2a**	MeCuCNLi[c]	**7a** (95)	**8a** (2)	**9a** (3)	—	—	79
2[d]	**2a**	MeCuCNLi	—	—	**9a**	—		45
3	**3a**	MeCuCNLi	**10a** (29)	**11a** (24)	—	**12** (47)[e]		75
4	**3b**	MeCuCNLi	—	—	—	**13**[e]		76
5	**3b**	BuCuCNLi	—	—	—	**13**[e]		57
6[f]	**3c**	MeCuCNLi	**10b** (70)	**11b** (26) **11c** (4)	—	—		31
7	**5a**	MeCuCNLi	**7a** (5)	**8a** (79)	**9a** (16)	—		38
8[g]	**5b**	Me_2CuLi	**7b** (7)	**8b** (81)	**9b** (12)	—		52
9[h]	**4a**	MeCuCNLi	**10a** (14)	**11a** (86)				55
10[i]	**6a**,**b**	^{t}BuCuCNLi					**14a**,**b**	87
11[j]	**6a**,**b**	^{n}Bu$_2$CuLi					**15a**,**b**	64

[a] Ratios from ^{1}H NMR spectra of the crude mixtures shown in parentheses.
[b] Isolated yields for the major compound except for entries 3, 6, 10 and 11 where combined yields are given.
[c] All experiments were conducted in Et_2O.
[d] The mixture was quenched 5 min after addition of **2a**.
[e] As a 60:40 mixture of diastereomers.
[f] 50% of starting material was recovered.
[g] THF was used as solvent.
[h] 8% of starting material was recovered.
[i] **14** was obtained as a 39:61 mixture of diastereoisomers from a 59:41 mixture of **6a** and **6b**.
[j] **15** was obtained as a 37:63 mixture of diastereoisomers from a 34:66 mixture of **6a** and **6b**.

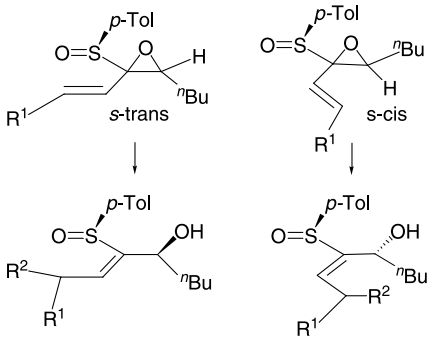


Scheme 3.

react with MeCuCNLi leading to starting material exclusively. At this point we explored different reaction conditions and found that **5b** behaved similarly to **5a** upon treatment with Gilman's cuprate (Me_2CuLi) affording a good selectivity of S_N2' products (**8b/7b**, 92:8) and a 12% of **9b**.

Finally, we briefly explored the reactivity of alkynyl epoxy sulfoxides **6a** and **6b** towards organocopper reagents (Table 1, entries 10 and 11). Addition of ^{t}BuCNCuLi to a 59:41 mixture of epoxides led to a diasteromeric mixture (39:61) of hydroxy allenyl sulfoxides **14a**,**b** with good yield (87%). Seeking to improve this result the addition of homocuprate, ^{n}Bu$_2$CuLi, was also carried out and a 37:63 mixture of allenes **15a**,**b** was obtained. These initial results outline the potential versatility of our methodology to produce highly functionalized enantiopure allenes.[14]

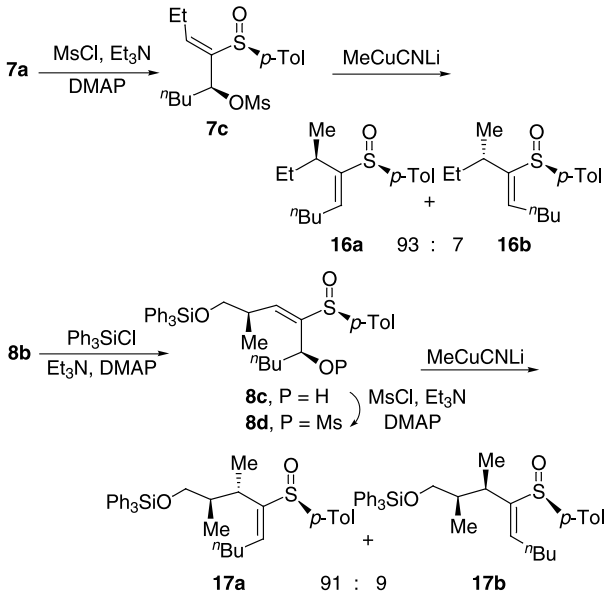
To understand the stereochemical outcome of the S_N2'



Scheme 4.

process we have considered that the major product from *cis* epoxides, [α-(**5a**,**b**) and β-(**4a**)], has an *E* stereochemistry (**8a**, **8b** and **11a**) and from *trans* epoxide [β-(**2a**) and α-(**3c**)] a *Z* vinyl sulfoxide was obtained (**7a**, **10b**). These results indicate that for *cis* and *trans* epoxides a different reactive conformation, *s-cis* or *s-trans*, is operative in these processes (Scheme 4). Indeed, for *trans* epoxides the arrangement of the butyl group would preclude the *s-cis* conformation leading to *Z* stereochemistry in the displacement products.[15] On the other hand, through an inspection of the NMR data of related vinyl sulfoxides, we have tentatively determined that addition of the cyanocuprate to vinyl epoxy sulfoxide **5b** occurs with *anti* stereochemistry for the major product **8b**.[16]

To extend the scope of our methodology we undertook the study of the second S_N2' displacement on allylic mesylates derived from **7a** and **8b**. This process would allow for the asymmetric construction of two adjacent chiral centers through two consecutive copper-mediated S_N2' displacements (Scheme 5). Therefore, α-hydroxy vinyl sulfoxide **7a** was reacted with mesyl chloride and Et_3N affording a good yield of **7c**, that upon treatment with MeCuCNLi gave a mixture of displacement products **16a**[17] and **16b** with high diastereoselectivity (93:7). Although the absence of substitution at the double bond of the precursor epoxy sulfoxide



Scheme 5.

(**2a**, R^1 = H, see scheme of Table 1) excluded the formation of two consecutive chiral centers, a high degree of diastereocontrol was observed for (*Z*)-α-mesyloxy vinyl sulfoxides **7a**. Thus, this result complements our previous studies of the S_N2' displacements of (*E*)-α-mesyloxy vinyl sulfoxides.

Subsequently, compound **8b** was selectively protected at the primary alcohol to give **8c** and then was mesylated at the secondary alcohol under standard conditions to render **8d**. The S_N2' addition of MeCuCNLi to allylic mesylate **8c** proceeds with high regio- and stereocontrol affording a 91:9 mixture of displacement products **17a** and **17b**. Tentative structural assignment of the products was based on an *anti* attack of the cuprate to the mesylate. Additionally, the comparison with the ^1H NMR data of related S_N2' compounds allowed to establish tentatively the structure of the new trisubstituted vinyl sulfoxides.[16,18]

In summary, we have demonstrated that S_N2' displacements of readily available vinyl epoxy sulfoxides using organocopper reagents as nucleophiles occur with high *anti* selectivity and a good degree of *E*/*Z* stereocontrol to produce enantiopure α-hydroxy vinyl sulfoxides in good yields. A subsequent allylic displacement on the related mesyloxy vinyl sulfoxides allows for the asymmetric construction of two adjacent chiral centers in the molecules. In addition, we have briefly explored the cuprate mediated S_N2' addition to alkynyl epoxy sulfoxides that leads to α-hydroxy allenyl sulfoxides in good yield. However, the future studies and applications of this methodology would require the development of alternative routes to alkynyl oxiranes.

4. Experimental

4.1. General

Reagents and solvents were handled by using standard syringe techniques. All reactions were carried out under an argon atmosphere. Hexane, toluene and CH_2Cl_2 were distilled from CaH_2, and THF and Et_2O from sodium. $(MeO)_2P(O)Me$, Et_3N, *i*-Pr_2NH, *i*-Pr_2EtN, *t*-$BuMe_2SiOTf$ were distilled from CaH_2. Crude products were purified by flash chromatography on Merck 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel plates with detection by UV light, iodine, acidic vanillin solution, 10% phosphomolybdic acid solution in ethanol. All reagents were commercial products purchased from Aldrich, Acros, Fluka or Merck. Organolithium reagents were titrated prior to use by reacting with 3,4-dimethoxybenzaldehyde. NaH and KH (60% in mineral oil) were washed repeatedly with dry hexane and dried prior to use. Through this section, the volume of solvents is reported in mL/mmol of starting material. Infrared spectra (IR) were obtained on a Perkin–Elmer 681 and on a Perkin–Elmer Spectrum one. ^1H and ^{13}C NMR spectra were recorded on a Brüker AM-200 (200 MHz), Varian Gemini-200 (200 MHz), Varian INOVA-300 (300 MHz) and Varian INOVA-400 (400 MHz) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and

77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Melting points were determined on a Reichert Kofler microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C using a sodium lamp and in $CHCl_3$ solution. Low resolution mass spectra were recorded by direct injection on a Hewlett–Packard 5973 MSD instrument using the electronic impact technique with an ionizacion energy of 70 eV or on a Hewlett–Packard 1100 MSD instrument using the atmospheric pressure chemical ionizacion (APCI) or electrospray (ES) chemical ionizacion techniques in its positive or negative modes. High resolution mass spectra (HRMS) were obtained on a VG-250-S spectrometer or on a Finnigan-4201 spectrometer. Elemental analyses were carried out on a Perkin–Elmer 240C and on a Heraus CHN-O-Rapid instruments at Instituto de Química Orgánica, CSIC (Madrid).

4.2. Preparation of starting materials

Vinyl epoxy sulfoxides **2a**, **3a-c**, **4a** and **5a**,**b** were prepared according to procedures previously reported by us.[10]

4.2.1. Synthesis of (±)-6-(*p*-tolylsulfinyl)-dodec-5-en-7-yne, 1g. To a solution of **1f**[17] (642 mg, 1.84 mmol) in benzene (18 mL) at room temperature was added CuI (105 mg, 0.552 mmol), DBU (1,8-diazabicyclo[5.4.0.]-undec-7-ene) (0.55 mL, 561 mg, 3.68 mmol), 1-hexyne (0.63 mL, 450 mg, 5.48 mmol) and $Pd(Ph_3P)_4$ (106 mg, 0.092 mmol). After 45 min the mixture was quenched with a saturated solution of NH_4Cl (5 mL/mmol) and H_2O (5 mL/mmol), and extracted with EtOAc (3×3 mL/mmol). The organic layer was washed with brine (2×4 mL/mmol) dried over anhydrous $MgSO_4$ and evaporated to afford a crude product that was purified by chromatography on silica gel (0–30% EtOAc–hexane). Pure **1g** was obtained (377 mg, 68%) as a yellow oil and was stored in benzene at −17 °C due to unstability of the samples

Data for **1g**. R_f=0.22 (20% EtOAc–hexane). ^{1}H NMR (200 MHz) δ 0.80 (t, 3H, J=7.1 Hz, Me *n*-Bu), 0.92 (t, 3H, J=7.1 Hz, Me *n*-Bu), 1.11–1.49 (m, 8H), 2.21 (t, 2H, J=6.8 Hz, H-9), 2.37 (s, 3H, Me *p*-Tol), 2.45–2.80 (m, 2H, H-4), 6.32 (dd, 1H, J=8.4, 7.7 Hz, H-5), 7.26 (d, 2H, J=7.9 Hz, ArH), 7.47 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.5 (Me *n*-Bu), 13.8 (Me *n*-Bu), 19.0, 21.4 (Me *p*-Tol), 21.7, 22.2, 28.7, 30.3, 31.2, 72.1 (C-7), 96.1 (C-8), 124.5 (2C *p*-Tol), 129.4 (2C *p*-Tol), 132.9, 139.9, 141.0, 145.2 (C-5). IR (film): 2965, 2940, 2300, 1595, 1485, 1460, 1445, 1075, 1050, 795 cm^{-1}. MS (APCI): 303 $[M+1]^+$ (100%).

4.2.2. Synthesis of (±)-(2*S*,3*R*,S_S)-3-*n*-butyl-2-(1′-hexynyl)-2-(*p*-tolylsulfinyl)oxirane, 6a and (±)-(2*R*,3*S*,S_S)-3-*n*-butyl-2-(1′-hexynyl)-2-(*p*-tolylsulfinyl)oxirane, 6b. From KH (24 mg, 0.60 mmol), *t*-BuOOH (75 μL, 54 mg, 0.60 mmol) in THF (3.0 mL) and a solution of **1g** (45 mg, 0.15 mmol) in 1.1 mL of THF, from −30 to −15 °C (35 min) following the method reported by us[10] was obtained a 25:75 mixture of **6a** and **6b**. Purification by chromatography on silica gel (0–60% EtOAc–CH_2Cl_2) yielded 43 mg (90%) of the mixture of epoxides as a yellow oil. Due to unstability of the samples rapid manipulation of the products and storage in benzene at −17 °C was necessary. A similar result was obtained from NaH (33 mg, 1.36 mmol) in 7.0 mL of THF, *t*-BuOOH (0.17 mL, 122 mg, 1.35 mmol) and a solution of **1g** (103 mg, 0.34 mmol) in 2.5 mL of THF at 0 °C (1 h 10 min). After chromatography (0–5% Et_2O–CH_2Cl_2) was isolated **6a** (14 mg, 13%), **6b** (31 mg, 29%) and a mixture of both epoxides (32 mg, 30%).

Data for **6a**. R_f=0.26 ($CHCl_3$). ^{1}H NMR (200 MHz) δ 0.82 (t, 3H, J=7.1 Hz, Me *n*-Bu), 0.94 (t, 3H, J=7.1 Hz, Me *n*-Bu), 1.17–1.65 (m, 8H), 1.95–2.19 (m, 4H), 2.40 (s, 3H, Me *p*-Tol), 3.48 (dd, 1H, J=6.8, 5.7 Hz, H-3), 7.30 (d, 2H, J=7.9 Hz, ArH), 7.57 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.5 (Me *n*-Bu), 13.9 (Me *n*-Bu), 18.6, 21.5 (Me *p*-Tol), 21.7, 22.4, 27.7, 28.3, 30.0, 67.5 (C-3), 70.1, 70.2, 92.0 (C-2′ alkyne), 125.2 (2C *p*-Tol), 129.3 (2C *p*-Tol), 136.8, 142.0. IR ($CHCl_3$): 3010, 2980, 2920, 2380, 1620, 1515, 1490, 1400, 1115, 830 cm^{-1}. MS (APCI): 319 $[M+1]^+$.

Data for **6b**. R_f=0.19 ($CHCl_3$). ^{1}H NMR (200 MHz) δ 0.82 (t, 3H, J=7.2 Hz, Me *n*-Bu), 0.93 (t, 3H, J=7.2 Hz, Me *n*-Bu), 1.15–1.59 (m, 8H), 1.90–2.02 (m, 2H), 2.13 (t, 2H, J=6.8 Hz, 2H-1′ *n*-Bu), 2.41 (s, 3H, Me *p*-Tol), 3.34 (m, 1H-3), 7.31 (d, 2H, J=7.9 Hz, ArH), 7.59 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.5 (Me *n*-Bu), 13.9 (Me *n*-Bu), 18.5, 21.5 (Me *p*-Tol), 21.7, 22.2, 27.7, 28.9, 29.9, 66.8 (C-3), 71.0, 71.8, 92.0 (C-2′ alkyne), 125.5 (2C *p*-Tol), 129.5 (2C *p*-Tol), 138.0, 142.3. MS (APCI): 319 $[M+1]^+$.

4.3. General procedure for the S_N2' displacement with cuprates

Argon was bubbled to a suspension of 3–6 equiv. of CuCN or CuI in Et_2O (10 mL×mmol) during 10 min (occasionally THF was employed as solvent). Then, the mixture was cooled to 0 °C and 3–6 equiv. of MeLi or *n*-BuLi was added. After 10 min stirring, 1 equiv. of sulfinyl oxirane in Et_2O (10 mL×mmol) was added dropwise and the yellow solution turned colorless. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature (2–18 h) approximately turning from colorless to black. Then the reaction was quenched with a saturated solution of $Na_2S_2O_4$ (4 mL×mmol) and diluted with EtOAc (8 mL×mmol). The aqueous layer was extracted with EtOAc (3×10 mL×mmol) and the organic extracts were washed with brine (4 mL×mmol), dried over anhydrous $MgSO_4$ and evaporated under vacuum. Chromatography on silica gel using mixtures of EtOAc–hexane as eluent afforded pure displacement products. The ratio of isomers was measured by integration of well resolved peaks of the crude ^{1}H NMR spectra.

4.3.1. Synthesis of (−)-(5*S*,S_S)-(3*Z*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 7a, (−)-(5*S*,S_S)-(3*E*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 8a and (−)-(4*S*,S_S)-(2*E*)-3-(*p*-tolylsulfinyl)-oct-2-en-4-ol, 9a. From CuCN (60.5 mg, 0.675 mmol) in 6.7 mL of Et_2O, MeLi (0.42 mL, 1.6 M, 0.675 mmol) and **2a** (59.5 mg, 0.225 mmol) in 2.2 mL of Et_2O following the above procedure (2 h) was obtained a mixture of **7a**, **8a** and

9a (95:2:3). After chromatography (20–50% EtOAc–hexane) 50 mg (79%) of **7a** was isolated as a pale yellow oil. When the reaction was quenched after 5 min at 0 °C [CuCN (19 mg, 0.21 mmol), MeLi (0.15 mL, 1.4 M, 0.21 mmol), **2a** (11 mg, 0.04 mmol)] was obtained **9a** as a single product (4.9 mg, 45%).

Data for **7a**. R_f=0.14 (30% EtOAc–hexane). $[\alpha]_D^{20}$=−181.1 (c=1.03). ^{1}H NMR (300 MHz) δ 0.72 (t, 3H, J=6.6 Hz, Me), 0.95–1.20 (m, 4H, H-7, H-8), 1.14 (t, 3H, J=7.4 Hz, Me), 1.23–1.32 (m, 1H, H-6), 1.50–1.60 (m, 1H, H-6), 2.38 (s, 3H, Me *p*-Tol), 2.48 (m, 1H, H-2), 2.71 (m, 1H, H-2), 3.53 (d, 1H, J=2.3 Hz, OH), 4.28 (ap td, 1H, J=7.8, 2.2 Hz, H-5), 6.17 (dd, 1H, J=8.2, 7.0 Hz, H-3), 7.28 (d, 2H, J=8.2 Hz, ArH), 7.41 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.7 (Me), 13.8 (Me), 21.2 (Me *p*-Tol), 22.1, 22.3, 27.5, 34.1 (C-2), 67.2 (C-5), 124.1 (2C *p*-Tol), 129.8 (2C *p*-Tol), 138.9 (2C), 140.9, 144.9. IR (film): 3400 (br), 2960, 2940, 2880, 1650, 1600, 1500, 1460, 1380, 1120, 1090, 1050, 1020, 810 cm^{-1}. MS (CI/CH_4): 282 $[M+2]^+$, 281 $[M+1]^+$ (100%), 263, 247, 139, 123. HRMS calcd for $C_{16}H_{25}O_2S$ $[M+1]^+$: 281.1575. Found: 281.1570.

Data for **9a**. R_f=0.10 (30% EtOAc–hexane). $[\alpha]_D^{20}$=−16.9 (c=0.80). ^{1}H NMR (500 MHz) δ 0.85 (t, 3H, J=6.7 Hz, Me *n*-Bu), 1.18–1.28 (m, 4H, H-6, H-7), 1.53–1.59 (m, 2H, H-5), 1.92 (d, 3H, J=7.2 Hz, H-1), 2.36 (s, 3H, Me *p*-Tol), 2.36–2.38 (m, 1H, OH), 4.42–4.45 (m, 1H, H-4), 6.37 (q, 1H, J=7.2 Hz, H-2), 7.25 (d, 2H, J=7.9 Hz, ArH), 7.47 (d, 2H, J=8.3 Hz, ArH). DNOE between Me vinyl/H-2: 9%; between Me vinyl/H-4: 3%; between H-2/Me vinyl: 3.3%; between H-2/ArH: 1.2%; between H-4/Me vinyl: 1.7%; between H-4/ArH: 1.1%. ^{13}C NMR (50 MHz) δ 13.8 (Me *n*-Bu), 14.5, 21.3, 22.2, 28.0, 36.6 (C-1), 68.8 (C-4), 125.3 (2C *p*-Tol), 129.8 (2C *p*-Tol), 131.9 (2C), 141.4, 147.6. IR (film): 3400 (br), 2980, 2970, 2940, 2870, 1600, 1500, 1460, 1380, 1120, 1090, 1050, 1020, 810 cm^{-1}. MS (CI/CH_4): 268, 267 $[M+1]^+$ (100%), 249, 233, 109. HRMS calcd for $C_{15}H_{23}O_2S$ $[M+1]^+$: 267.1419. Found: 267.1417. Anal. calcd for $C_{15}H_{22}O_2S$: C, 67.39;H, 8.20; S, 11.96. Found: C, 67.52;H, 8.05; S, 11.87.

4.3.2. Synthesis of (−)-(5*S*,*S*$_S$)-(3*E*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 8a. From CuCN (17.3 mg, 0.20 mmol) in 2 mL of Et_2O, MeLi (0.14 mL, 1.4 M, 0.20 mmol) and **5a** (17 mg, 0.064 mmol) in 0.6 mL of Et_2O following the above procedure (2 h) was obtained a mixture of **7a**, **8a** and **9a** (5:79:16). After chromatography (20–50% EtOAc–hexane) 7 mg (38%) of pure **8a** was isolated as a colorless oil.

Data for **8a**. R_f=0.13 (30% EtOAc–hexane). $[\alpha]_D^{20}$=−25.5 (c=0.64). ^{1}H NMR (200 MHz) δ 0.74 (t, 3H, J=7.0 Hz, Me), 1.08 (t, 3H, J=7.5 Hz, Me), 1.09–1.33 (m, 5H), 1.47–1.63 (m, 1H), 2.25–2.42 (m, 2H), 2.38 (s, 3H, Me *p*-Tol), 2.47 (d, 1H, J=5.3 Hz, OH), 4.42 (m, 1H, H-5), 6.28 (t, 1H, J=7.6 Hz, H-3), 7.27 (d, 2H, J=8.1 Hz, ArH), 7.49 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.5 (Me), 13.8 (Me), 21.3 (Me *p*-Tol), 22.1 (2C), 28.1, 37.0 (C-2), 68.9 (C-5), 125.3 (2C *p*-Tol), 129.8 (2C *p*-Tol), 138.6, 140.3, 141.4, 146.3. IR (film): 3400, 2980, 2960, 2940, 1600, 1490, 1460, 1380, 1090, 1040, 1010, 810 cm^{-1}. MS (CI/NH_3): 281 $[M+1]^+$, 265 (100%), 247, 233, 224, 195, 158, 141, 123, 108, 91, 81. HRMS calcd for $C_{16}H_{25}O_2S$ $[M+1]^+$: 281.1575. Found: 281.1562. Anal. calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63; S, 11.43. Found: C, 68.74; H, 8.78; S, 11.18.

4.3.3. Synthesis of (+)-(5*R*,*S*$_S$)-(3*E*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 11a. From CuCN (20 mg, 0.22 mmol) in 2.2 mL of Et_2O, MeLi (0.16 mL, 1.4 M, 0.22 mmol) and **4a** (19.7 mg, 0.074 mmol) in 0.7 mL of Et_2O following the above procedure (2 h) was obtained a mixture of **4a**, **11a** and **10a** (8:79:13). After chromatography (20–50% EtOAc–hexane) 11.4 mg (55%) of pure **11a** was isolated as a colorless oil.

Data for **11a**. R_f=0.15 (30% EtOAc–hexane). $[\alpha]_D^{20}$=+23.2 (c=1.09). ^{1}H NMR (200 MHz) δ 0.77 (t, 3H, J=7.3 Hz, Me), 1.10 (t, 3H, J=7.5 Hz, Me), 1.11–1.64 (m, 6H, H-6, H-7, H-8), 2.33 (m, 2H, H-2), 2.38 (s, 3H, Me *p*-Tol), 2.53 (br s, 1H, OH), 4.53 (m, 1H, H-5), 6.43 (t, 1H, J=7.6 Hz, H-3), 7.28 (d, 2H, J=8.9 Hz, ArH), 7.52 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.5 (Me), 13.8 (Me), 21.3 (Me *p*-Tol), 21.9, 22.3, 27.9, 36.6 (C-2), 70.2 (C-5), 125.0 (2C *p*-Tol), 129.8 (2C *p*-Tol), 139.3, 140.7, 141.2, 144.8. IR (film): 3400 (br), 2980, 2960, 2880, 1650, 1600, 1500, 1460, 1380, 1090, 1040, 810 cm^{-1}. MS (CI/NH_3): 292 $[M+NH_4]^+$, 281 $[M+1]^+$ (100%), 263, 247, 223, 195, 165, 140, 123. HRMS calcd for $C_{16}H_{25}O_2S$ $[M+1]^+$: 281.1575. Found: 282.1566.

Partial data for **10a** *from the mixture*. ^{1}H NMR (200 MHz): δ 4.35 (m, 1H, H-5), 6.21 (dd, 1H, J=8.2, 7.0 Hz, H-3).

4.3.4. Synthesis of (−)-(5*R*,*S*$_S$)-(3*Z*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 10a, and (+)-(5*R*,*S*$_S$)-(3*E*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 11a, and 5-(*p*-tolylsulfinyl)-non-4-one, 12. From CuCN (25 mg, 0.28 mmol) in 20.75 mL of Et_2O, MeLi (0.17 mL, 0.27 mmol) and **3a** (17 mg, 0.064 mmol) in 0.50 mL of Et_2O following the above procedure (2 h) was obtained a mixture of **10a**, **11a** and **12** (29:24:47). After chromatography (5–40% EtOAc–hexane) 3 mg (23%) of pure **10a**, 2 mg (16%) of pure **11a** and 9 mg (36%) of **12** as a 60:40 mixture of diastereoisomers was isolated. Data for isolated **11a** are the same as above.

Data for **10a**. R_f=0.18 (30% EtOAc–hexane). $[\alpha]_D^{20}$=−108.8 (c=1.25). ^{1}H NMR (300 MHz) δ 0.81 (t, 3H, J=7.1 Hz, Me *n*-Bu), 1.12 (t, 3H, J=7.4 Hz, Me Et), 1.10–1-38 (m, 4H, H-7, H-8), 1.52–1.61 (m, 2H, H-6), 2.24 (d, 1H, J=5.1 Hz, OH), 2.34–2.48 (m, 1H, H-2), 2.38 (s, 3H, Me *p*-Tol), 2.58–2.71 (m, 1H, H-2), 4.36 (ap q, 1H, J=6.5 Hz, H-5), 6.22 (dd, 1H, J=8.6, 6.8 Hz, H-3), 7.29 (d, 2H, J=8.1 Hz, ArH), 7.48 (d, 2H, J=8.3 Hz, ArH). IR (CCl_4): 3400 (br), 2960, 2930, 2860, 1740, 1640, 1600, 1495, 1460, 1380, 1260, 1080, 1030, 1015, 810 cm^{-1}. MS (EI): 281 (M+1), 263, 245, 223, 193, 149, 140 (100%), 139, 123, 111, 95, 92, 91, 81, 69, 57, 43, 41.

Partial data for **12** (*major isomer, from the mixture*). R_f=0.26 (30% EtOAc–hexane). ^{1}H NMR (300 MHz) δ 2.39 (s, 3H, Me *p*-Tol), 3.54 (dd, J=9.9, 4.9 Hz, H-5).

Partial data for **12** (*minor isomer, from the mixture*). R_f=0.26 (30% EtOAc–hexane). ^{1}H NMR (300 MHz) δ 2.40 (s, 3H, Me *p*-Tol), 3.67 (dd, J=9.6, 4.6 Hz, H-5).

4.3.5. Synthesis of (*E*)-1-phenyl-4-(*p*-tolylsulfinyl)-1-en-3-octanone, 13. From CuCN (16 mg, 0.18 mmol) in 0.4 mL of Et_2O, MeLi (0.11 mL, 0.18 mmol) and **3b** (10 mg, 0.03 mmol) in 0.3 mL of Et_2O following the above procedure (18 h) was obtained after chromatography (5–30% EtOAc–hexane) 8 mg (76%) of **13** as a 60:40 inseparable mixture of diastereomers. Alternatively, using *n*-BuLi (0.16 mL, 0.18 mmol) instead of MeLi and following the same procedure (5 h) was obtained after chromatography (5–30% EtOAc–hexane) 6 mg (57%) of **13** as a 60:40 mixture of diastereomers.

Data for **13** (*major, from the mixture*). R_f=0.37 (30% EtOAc–hexane). ^{1}H NMR (300 MHz) δ 0.86 (m, 3H, Me *n*-Bu), 1.31 (m, 2H), 1.52–1.60 (m, 2H), 2.05–2.13 (m, 2H), 2.26 (s, 3H, Me *p*-Tol), 3.97 (dd, 1H, J=9.9, 4.5 Hz, H-4), 6.49 (d, 1H, J=16.9 Hz, H-2), 7.16–7.49 (m, 10H, Ph, *p*-Tol and H-1). IR (CCl_4, mixture of isomers): 2960, 2930, 2860, 1680, 1650, 1610, 1580, 1495, 1450, 1345, 1080, 1050, 990, 975 cm^{-1}.

Data for **13** (*minor, from the mixture*). R_f=0.37 (30% EtOAc–hexane). ^{1}H NMR (300 MHz) δ 0.86 (m, 3H, Me *n*-Bu), 1.31 (m, 2H), 1.93–1.96 (m, 2H), 2.28–2.40 (m, 2H), 2.32 (s, 3H, Me *p*-Tol), 3.81 (dd, 1H, J=8.3, 6.2 Hz, H-4), 6.73 (d, 1H, J=16.0 Hz, H-2), 7.16–7.49 (m, 10H, Ph, *p*-Tol and H-1).

4.3.6. Synthesis of (−)-(2*S*,5*R*,S_S)-(3*Z*)-2-methyl-4-(*p*-tolylsulfinyl)-non-3-en-1,5-diol, 10b and (2*S*,5*R*,S_S)-(3*E*)-2-methyl-4-(*p*-tolylsulfinyl)-non-3-en-1,5-diol, 11b. From CuCN (27 mg, 0.30 mmol) in 0.75 mL of Et_2O, MeLi (0.18 mL, 0.29 mmol) and **3b** (14 mg, 0.05 mmol) in 0.5 mL of Et_2O following the above procedure (4 h) was obtained a mixture of **10b**, **11b**, and **11c** (70:26:4). After chromatography (20–100% EtOAc–hexane) was isolated 16 mg (22%) of **10b** and 7 mg (9%) of **11b** as colorless oils.

Data for **10b**. R_f=0.27 (75% EtOAc–hexane). $[\alpha]_D^{20}$=−23.6 (c=0.36). ^{1}H NMR (300 MHz) δ 0.84 (t, 3H, J=7.0 Hz, Me *n*-Bu), 1.03 (d, 3H, J=6.4 Hz, Me), 1.15–1.39 (m, 4H), 1.56–1.67 (m, 2H), 2.03 (br s, 1H, OH), 2.16 (br s, 1H, OH), 2.38 (s, 3H, Me *p*-Tol), 3.37–3.48 (m, 2H, H-1), 3.69 (m, 1H, H-2), 4.30 (t, 1H, J=6.6 Hz, H-5), 6.07 (d, 1H, J=10.3 Hz, H-3), 7.28 (d, 2H, J=8.0 Hz, ArH), 7.64 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.9 (Me), 16.7 (Me), 21.2 (Me *p*-Tol), 22.4, 27.8, 35.8, 37.3, 67.1, 69.8, 124.9, 126.6 (2C *p*-Tol), 129.9 (2C *p*-Tol), 142.1, 147.5, 147.9. MS (EI): 293, 259, 253, 223, 205, 177, 169, 153, 140, 139, 97, 95, 92, 69, 57, 43 (100%).

Data for **11b**. R_f=0.24 (75% EtOAc–hexane). ^{1}H NMR (300 MHz) δ 0.79 (t, 3H, J=6.6 Hz Me *n*-Bu), 0.90 (d, 3H, J=6.8 Hz, Me), 1.09–1.36 (m, 4H), 1.61–1.80 (m, 2H), 2.07 (br s, 1H, OH), 2.33 (br s, 1H, OH), 2.40 (s, 3H, Me *p*-Tol), 3.16–3.37 (m, 2H, H-1), 3.40–3.69 (m, 1H, H-2), 4.19 (dd, 1H, J=9.3, 3.5 Hz, H-5), 6.24 (d, 1H, J=10.7 Hz, H-3), 7.26–7.57 (m, 4H, ArH).

Partial data of **11c** (*from the mixture*). R_f=0.24 (75% EtOAc–hexane). ^{1}H NMR (300 MHz) δ 4.58 (m, 1H, H-5), 6.36 (d, 1H, J=10.5 Hz, H-5).

4.3.7. Synthesis of (+)-(2*R*,5*S*,S_S)-(3*E*)-2-methyl-4-(*p*-tolylsulfinyl)-non-3-en-1,5-diol, 8b, (2*S*,5*S*,S_S)-(3*Z*)-2-methyl-4-(*p*-tolylsulfinyl)-non-3-en-1,5-diol, 7b and (5*S*,S_S)-(3*E*)-4-(*p*-tolylsulfinyl)-non-3-en-1,5-diol, 9b. From CuI (288 mg, 1.51 mmol) in 3.75 mL of THF, MeLi (1.86 mL, 2.98 mmol) and **5b** (73 mg, 0.25 mmol) in 2.5 mL of THF following the above procedure (18 h) was obtained a mixture of **8b**, **7b**, and **9b** (81:7:12). After chromatography (20–100% EtOAc–hexane) was isolated 40 mg (52%) of **8b**, 3 mg (4%) of **7b** and 6 mg (8%) of **9b** as colorless oils.

Data for **8b**. R_f=0.09 (EtOAc). $[\alpha]_D^{20}$=+84.6 (c=2.0). ^{1}H NMR (300 MHz) δ 0.73 (t, 3H, J=7.0 Hz, Me *n*-Bu), 1.03 (d, 3H, J=6.7 Hz, Me), 1.05–1.66 (m, 6H, H-6, H-7, H-8), 2.38 (s, 3H, Me *p*-Tol), 2.93–3.00 (m, 1H, H-2), 3.22 (br s, 1H, OH), 3.45 (dd, 1H, J=10.4, 8.8 Hz, H-1), 3.62 (dd, 1H, J=10.6, 5.0 Hz, H-1), 4.56 (dd, 1H, J=8.9, 4.7 Hz, H-5), 6.15 (d, 1H, J=10.6 Hz, H-3), 7.26 (d, 2H, J=8.1 Hz, ArH), 7.52 (d, 2H, J=8.2 Hz, ArH). DNOE between H-2/Me: 3.5%; between H-2/H-5: 5.9%; between Me/H-2: 1.7%; between Me/H-3: 1.3%; between H-5/H-2: 8.0%; between H-5/Me: 2.7%. ^{13}C NMR (50 MHz) δ 13.7 (Me), 16.3 (Me), 21.4 (Me *p*-Tol), 22.2, 27.9, 35.6, 36.0, 66.8, 68.5, 126.1, 128.3 (2C *p*-Tol), 129.8 (2C *p*-Tol), 141.9, 147.9, 148.6. IR ($CHCl_3$): 3400 (br), 2960, 2930, 2870, 1600, 1395, 1460, 1380, 1305, 1215, 1080, 1030, 1010, 790, 760 cm^{-1}. MS (EI): 293, 253, 171, 153, 140, 139, 97, 95, 92, 71, 57, 55, 41 (100%).

Partial data for **7b**. R_f=0.12 (EtOAc). ^{1}H NMR (300 MHz) δ 1.11 (d, 3H, J=6.5 Hz, Me), 2.38 (s, 3H, Me *p*-Tol), 3.52 (m, 1H, H-2), 3.71 (dd, 1H, J=10.1, 5.1 Hz, H-1), 4.01 (dd, 1H, J=12.3, 4.8 Hz, H-1), 4.26 (dd, 1H, J=8.0, 5.7 Hz, H-5), 6.05 (d, 1H, J=10.1 Hz, H-3), 7.22–7.60 (m, 4H, ArH).

Partial data for **9b**. R_f=0.05 (EtOAc). ^{1}H NMR (200 MHz) δ 0.66 (t, 3H, J=7.0 Hz, Me *n*-Bu), 2.37 (s, 3H, Me *p*-Tol), 3.81 (t, 2H, J=5.6 Hz, H-1), 4.41 (dd, 1H, J=8.9, 4.4 Hz, H-5), 6.51 (t, 1H, J=7.4 Hz, H-3), 7.26 (d, 2H, J=8.0 Hz, ArH), 7.48 (d, 2H, J=8.2 Hz, ArH).

4.3.8. Synthesis of (±)-(5*R*,7*R*,S_S)-8-*tert*-butyl-6-(*p*-tolylsulfinyl)-dodeca-6,7-dien-5-ol, 14a and (±)-(5*S*,7*S*,S_S)-8-*tert*-butyl-6-(*p*-tolylsulfinyl)-dodeca-6,7-dien-5-ol, 14b. From CuCN (29 mg, 0.32 mmol) in 2.6 mL of THF, *t*-BuLi (1.5 M, 0.21 mL, 0.31 mmol) and a mixture of sulfinyl oxiranes **6a** and **6b** 41:59 (25 mg, 0.79 mmol) in 0.4 mL of THF following the above procedure (5 min at −78 °C and 30 min at rt) was obtained a mixture of **14a** and **14b** (39:61). After chromatography (0–30% EtOAc–CH_2Cl_2) was isolated 26 mg (87%) of the mixture of allenes as a colorless oil. Pure compounds were isolated by preparative TLC (3% MeOH–toluene).

Data for **14a**. R_f=0.13 (3% MeOH–toluene). ^{1}H NMR (300 MHz) δ 0.77 (t, 3H, J=6.9 Hz, Me *n*-Bu), 0.88 (t, 3H, J=7.2 Hz, Me *n*-Bu), 1.14 (s, 9H, 3Me *t*-Bu), 1.05–1.47 (m, 10H), 2.03 (t, 2H, J=7.9 Hz), 2.40 (s, 3H, Me *p*-Tol), 3.75 (br s, 1H, OH), 4.30 (dd, 1H, J=7.3, 5.9 Hz, H-5), 7.30 (d, 2H, J=7.9 Hz, ArH), 7.53 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.9 (Me *n*-Bu), 14.0 (Me *n*-Bu), 21.4

(Me *p*-Tol), 22.4, 22.7, 27.4, 27.6, 29.2 (3Me *t*-Bu), 30.8, 34.9, 35.0, 68.6 (C-5), 124.4, 124.6 (2C *p*-Tol), 125.4, 129.7 (2C *p*-Tol), 139.6, 141.4, 197.9 (C-7). IR ($CHCl_3$): 3370, 2960, 2884, 1930, 1585, 1483, 1460, 1230, 1021, 799 cm^{-1}. MS (ES): 775 $[2M+Na]^+$, 399 $[M+Na]^+$ (100%), 377 $[M+1]^+$.

Data for **14b**. R_f=0.09 (3% MeOH–toluene). ^1H NMR (300 MHz) δ 0.89 (s, 9H, 3Me *t*-Bu), 0.84–0.92 (m, 6H, 2Me *n*-Bu), 1.22–1.39 (m, 8H), 1.46–1.66 (m, 2H), 1.88–2.15 (m, 2H), 2.40 (s, 3H, Me *p*-Tol), 2.75 (br s, 1H, OH), 4.52 (br t, 1H, J=6.4 Hz, H-5), 7.28 (d, 2H, J=7.8 Hz, ArH), 7.55 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.9 (Me *n*-Bu), 14.0 (Me *n*-Bu), 21.4 (Me *p*-Tol), 22.5, 22.7, 27.5, 27.8, 28.9 (3Me *t*-Bu), 30.4, 34.7, 35.9, 69.1 (C-5), 117.9, 125.4 (2C *p*-Tol), 125.8, 129.6 (2C *p*-Tol), 140.4, 141.6, 195.7 (C-7). IR ($CHCl_3$): 3380, 2998, 2977, 2890, 1935, 1594, 1496, 1472, 1240, 1087, 1038, 812 cm^{-1}.

4.3.9. Synthesis of (±)-(5*R*,S_S)-8-*n*-butyl-6-(*p*-tolylsulfinyl)-dodeca-6,7-dien-5-ol, 15a and (±)-(5*S*,S_S)-8-*n*-butyl-6-(*p*-tolylsulfinyl)-dodeca-6,7-dien-5-ol, 15b. From CuI (57 mg, 0.30 mmol) in 3.0 mL of THF, *n*-BuLi (1.6 M, 0.37 mL, 0.59 mmol) and a mixture of sulfinyl oxiranes **6a** and **6b** 34:66 (19 mg, 0.060 mmol) in 0.6 mL of THF following the above procedure (2 h from −30 °C to rt) was obtained a mixture of **15a** and **15b** (37:63). After chromatography (0–25% EtOAc–CH_2Cl_2) was isolated 14 mg (64%) of the mixture of allenes as a colorless oil.

Data for **15a** (*from the mixture*). ^1H NMR (200 MHz) δ 0.75–0.95 (m, 9H), 1.09–1.70 (m, 12H), 1.83–2.30 (m, 6H), 2.40 (s, 3H, Me *p*-Tol), 3.79 (br s, 1H, OH), 4.27 (t, 1H, J=6.1 Hz, H-5), 7.29 (d, 2H, J=7.9 Hz, ArH), 7.49 (d, 2H, J=8.4 Hz, ArH).

Data for **15b** (*from the mixture*). ^1H NMR (200 MHz) δ 0.75–0.95 (m, 9H), 1.09–1.70 (m, 12H), 1.83–2.30 (m, 6H), 2.38 (s, 3H, Me *p*-Tol), 2.75 (br s, 1H, OH), 4.48 (t, 1H, J=6.1 Hz, H-5), 7.27 (d, 2H, J=7.9 Hz, ArH), 7.53 (d, 2H, J=8.4 Hz, ArH).

4.3.10. Synthesis of the mesylate of (−)-(5*S*,S_S)-(3*Z*)-4-(*p*-tolylsulfinyl)-non-3-en-5-ol, 7c. To a cold solution (0 °C) of **7a** (55 mg, 0.17 mmol) in 3.5 mL of THF was added 3 equiv. of Et_3N (73.3 mL, 53 mg, 0.52 mmol), 3 equiv. of MsCl (40 mL, 59.5 mg, 0.52 mmol) and the mixture was stirred for 1 h. After that time, a saturated solution of $NaHCO_3$ (5 mL) and EtOAc (5 mL) was added to the reaction mixture. The organic layer was washed with a saturated solution of NH_4Cl, dried over $MgSO_4$ and evaporated under vacuum. After chromatography on deactivated silica gel (washed with a 5% solution of $NaHCO_3$ in MeOH and dried) and using as solvent 20–50% EtOAc–hexane was obtained 67.0 mg (95%) of **7c** as a yellow oil.

Data for **7c**. R_f=0.32 (30% EtOAc–hexane). ^1H NMR (200 MHz) δ 0.58 (t, 3H, J=6.5 Hz, Me), 0.70–1.50 (m, 6H), 1.16 (t, 3H, J=7.4 Hz, Me), 2.37 (s, 3H, Me *p*-Tol), 2.58 (m, 1H), 2.76 (m, 1H), 3.07 (s, 3H, Me Ms), 5.07 (dd, 1H, J=9.2, 4.3 Hz, H-5), 6.41 (dd, 1H, J=8.6, 7.1 Hz, H-3), 7.28 (d, 2H, J=8.4 Hz, ArH), 7.38 (d, 2H, J=8.3 Hz, ArH).

4.3.11. Synthesis of (+)-(3*R*,S_S)-(4*E*)-3-methyl-4-(*p*-tolylsulfinyl)-non-4-ene, 16a. From CuCN (52 mg, 0.58 mmol) in 5.8 mL of THF, MeLi (0.36 mL, 1.6 M, 0.58 mmol) and mesylate **7c** (67 mg, 0.19 mmol) in 2 mL of THF following the above procedure (1 h at −78 °C) was obtained a mixture of **16a** and **16b** (93:7). After chromatography (20–50% EtOAc–hexane) was isolated 35 mg (71% from **7a**) of **16a** as a colorless oil.

Data for **16a**. R_f=0.39 (30% EtOAc–hexane). $[\alpha]_D^{20}$=+29.8 (c=3.12). ^1H NMR (200 MHz) δ 0.71 (d, 3H, J=7.3 Hz, Me), 0.73 (t, 3H, J=7.0 Hz, Me), 0.90 (t, 3H, J=6.9 Hz, Me), 1.22–1.50 (m, 6H), 2.20–2.32 (m, 3H), 2.36 (s, 3H, Me *p*-Tol), 6.35 (t, 1H, J=7.6 Hz, H-5), 7.22 (d, 2H, J=8.8 Hz, ArH), 7.46 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 12.3 (Me), 13.9 (Me), 19.8 (Me), 21.4 (Me *p*-Tol), 22.5, 28.5, 29.7, 31.3, 33.0, 125.5 (2C, *p*-Tol), 129.5 (2C, *p*-Tol), 135.0, 140.6, 141.1, 148.4. IR (film): 3060, 2980, 2940, 2880, 1600, 1490, 1460, 1400, 1380, 1305, 1290, 1180, 1150, 1090, 1050, 1020, 920, 910, 810 cm^{-1}. MS (CI/CH_4): 282, 281 $[M+1]^+$ (100%), 263, 247, 139, 123. HRMS calcd for $C_{17}H_{27}OS$ $[M+1]^+$: 281.1575. Found: 281.1570. Anal Calcd for $C_{17}H_{26}OS$: C, 72.60; H, 9.21; S, 11.34. Found: C, 72.89; H, 9.15; S, 11.24.

4.3.12. Synthesis of (2*R*,5*S*,S_S)-(3*E*)-2-methyl-4-(*p*-tolylsulfinyl)-1-triphenylsilyloxy-non-3-en-5-ol, 8c. To a cold (0 °C) solution of **8b** (25 mg, 0.08 mmol) in 1 mL of anhydrous CH_2Cl_2 was added 3.0 equiv. of Et_3N (34 μL, 24 mg, 0.24 mmol), a catalytic amount of DMAP and 1.2 equiv. of Ph_3SiCl (28.5 mg, 0.10 mmol). The mixture was stirred at rt until starting material disappearance (1H, TLC) and then was quenched with 5% solution of $NaHCO_3$ (4 mL/mmol) and diluted with EtOAc (10 mL/mmol). The aqueous layer was washed with EtOAc (3×10 mL/mmol) and the organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under vacuum. Chromatography of the crude (10–50% EtOAc–hexane) afforded 26 mg (57%) of **8c** as a colorless oil.

Data for **8c**. R_f=0.18 (30% EtOAc–hexane). ^1H NMR (300 MHz) δ 0.69 (t, 3H, J=7.0 Hz, Me *n*-Bu), 1.00–1.06 (m, 4H), 1.05 (d, 3H, J=6.7 Hz, Me), 1.20–1.60 (m, 2H, H-6), 2.31 (s, 3H, Me *p*-Tol), 2.41 (br s, 1H, OH), 3.01–3.11 (m, 1H, H-2), 3.66 (dd, 1H, J=9.8, 7.7 Hz, H-1), 3.75 (dd, 1H, J=9.8, 5.4 Hz, H-1), 4.39 (m, 1H, H-5), 6.20 (d, 1H, J=10.6 Hz, H-3), 7.08 (d, 2H, J=8.1 Hz, ArH), 7.34–7.57 (m, 17H, ArH).

4.3.13. Synthesis of the mesylate of (2*R*,5*S*,S_S)-(3*E*)-2-methyl-4-(*p*-tolylsulfinyl)-1-triphenylsilyloxy-non-3-en-5-ol, 8d. From **8c** (22 mg, 0.04 mmol), Et_3N (22 μL, 16 mg, 0.15 mmol), MsCl (9 μL, 13 mg, 0.12 mmol) and DMAP in THF following the procedured described for **7c** was obtained after chromatography (5–40% EtOAc–hexane) 16 mg (64%) of **8d** as a colorless oil.

Data for **8d**. R_f=0.20 (30% EtOAc–hexane). ^1H NMR (300 MHz) δ 0.59 (t, 3H, J=7.1 Hz, Me *n*-Bu), 0.72–0.97 (m, 4H), 1.05 (d, 3H, J=6.6 Hz, Me), 1.15–1.30 (m, 1H,

H-6), 1.66–1.80 (m, 1H, H-6), 2.35 (s, 3H, Me *p*-Tol), 2.95 (s, 3H, Me Ms), 3.08–3.18 (m, 1H, H-2), 3.68 (dd, 1H, $J=$ 9.8, 8.2 Hz, H-1), 3.80 (dd, 1H, $J=9.8$, 4.8 Hz, H-1), 5.06 (dd, 1H, $J=10.4$, 3.4 Hz, H-5), 6.50 (d, 1H, $J=11.1$ Hz, H-3), 7.11 (d, 2H, $J=8.1$ Hz, ArH), 7.35–7.58 (m, 17H, ArH).

4.3.14. Synthesis of (2*R*,3*S*,S_S)-(4*E*)-2,3-dimethyl-4-(*p*-tolylsulfinyl)-1-triphenylsilyloxy-non-4-ene, 17a. From CuCN (13.6 mg, 0.15 mmol) in 0.5 mL of THF, MeLi (93 mL, 0.15 mmol) and mesylate **8d** (12 mg, 0.02 mmol) in 0.5 mL of THF following the above procedure (40 h at rt) was obtained a mixture of **17a** and **17b** (91:9) along with a 45% of starting material. After chromatography (5–40% EtOAc–hexane) was isolated 8 mg (76%) of **17a** as a colorless oil.

Data for **17a**. $R_f=0.27$ (30% EtOAc–hexane). $[\alpha]_D^{20}=+56.1$ ($c=0.18$). ^{1}H NMR (400 MHz) δ 0.66 (d, 3H, $J=$ 6.9 Hz, Me-2), 0.79 (d, 3H, $J=7.2$ Hz, Me-3), 0.90 (t, 3H, $J=7.2$ Hz, Me *n*-Bu), 1.22–2.24 (m, 8H, H-2, H-3, H-6, H-7, H-8), 2.36 (s, 3H, Me *p*-Tol), 3.61 (dd, 1H, $J=10.1$, 5.1 Hz, H-1), 3.71 (dd, 1H, $J=10.1$, 3.2 Hz, H-1), 6.36 (t, 1H, $J=7.6$ Hz, H-5), 7.17 (d, 2H, $J=8.0$ Hz, ArH), 7.34–7.57 (m, 17H, ArH). IR (film): 3065, 2961, 2920, 2855, 1454, 1428, 1261, 1216, 1116, 807, 758, 700 cm^{-1}. MS (ES): 1155 $[2M+Na]^+$, 589 $[M+Na]^+$ (100%), 567 $[M+1]^+$.

Acknowledgements

This research was supported by CAM (Grant 08.5/0028/2003) and DGI MCYT (Grants BQU2001-0582 and BQU2003-02921). We thank JANSSEN-CILAG for additional support and MEC for a doctoral fellowship to M. T.

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11. The stereochemical assignment of diastereomers **6a** and **6b** is tentative since extensive decomposition upon storage at room temperature along with the low stereoselectivity found, could indicate a favourable [2,3]-sigmatropic rearrangement of the propargylic sulfoxides with loss of the stereochemical integrity at sulfur.

12. Sonogashira coupling followed by nucleophilic epoxidation of related (*E*)-1-iodo styryl sulfoxide led to an equimolecular

mixture of unstable alkynyl epoxides therefore we did not examine the S_N2' reactivity of these substrates.

13. Arbitrarily, we termed epoxides β (up) or α (down) regarding the plane of paper.
14. These results seems to indicate a higly stereocontrolled pathway of the allylic displacement. The structural assignment of **14a**,**b** was made on the basis of an *anti* attack, however, we cannot accurately establish the stereochemical outcome since the structural assignment for **6a**,**b** is tentative, see Ref. 11.
15. Structural assignments of the products are based in the comparison of NMR data with that of related hydroxy vinyl sulfoxides from our group previously characterized by X-ray diffraction analysis. The *Z*–*E* stereochemistry is easily established through the chemical shifts of vinyl protons. For example **7a** (H-3): 6.17 ppm; **11a** (H-3): 6.43 ppm. Significant differences are also found for H-2 protons in these compounds.
16. Additional data (i.e., X-ray) will be needed for unequivocal structural assignment of this compound.
17. Spectral data (^{1}H and ^{13}C NMR) of **16a** are almost identical to that encountered for (*E*)-5(*R*)-methyl-4(R_s)-(*p*-tolylsulfinyl) non-3-ene (compd. **8b** in Ref. 3a). As we have previously observed the newly introduced methyl group appears more shielded (0.71 ppm) for that relative stereochemistry.
18. The chemical shifts of vinylic protons usually appear downfield for the *E* double bond (6.35–6.36). Some similarities can be observed for the newly introduced methyl group with the same relative stereochemistry regarding the sulfoxide.
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Tributyltin hydride-mediated cyclisations of cinnamic enamides to piperidin-2-ones or pyrrolidin-2-ones. Indolizidinone ring formation by tandem radical cyclisation

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Received 12 March 2004; revised 24 May 2004; accepted 17 June 2004

Available online 24 July 2004

Abstract—Efficient 6-*endo-trig* free radical cyclisations of various 3-phenyl-acryl enamides to piperidin-2-ones, by using Bu_3SnH and AIBN in boiling toluene, are reported. A different result has been observed for related enamide system without phenyl substituent at the 3-position of an acrylic moiety, as such a reaction of 3-methyl-butenoic acid cyclohex-1-enyl-methyl-amide afforded only the 5-*exo-trig* product. The difference in the cyclisation mode has been explained in terms of a reversible process leading to the thermodynamically more stable product. An application of this method for the tandem cyclisation permits to obtain idolizidine derivatives.

1. Introduction

Considerable attention has been recently directed towards the synthesis of nitrogen-containing heterocycles using the tin hydride-mediated radical cyclisation.[1] Although over 15 years ago Enholm and co-workers[2] have shown that *O*-stannyl ketyls, prepared in reaction of tributyltin hydride with aldehydes, can undergo the cyclisation, only several papers exploring this strategy can be found in the literature.[3] Previously, we described a new and efficient method of preparing hexahydro-thiazolo[3,2-*a*]pyridin-5-ones and hexahydro-pyrido[2,1-*b*]thiazin-6-ones, by application of the tributyltin hydride-mediated radical cyclisation of 3-alkenoyl-2-methylene-1,3-thiazolidines and -tetrahydro-1,3-thiazines, respectively.[4]

As a logical extension of our study, we have examined the mode of cyclisation reactions of *N*-vinyl-cinnamic amides. In this paper, we describe in detail syntheses of six-membered lactams by free radical 6-*endo-trig* cyclisations of a large variety of enamides, and also demonstrate the feasibility of this method for a 6-*endo-trig*/5-*exo-trig* tandem process. The latter reaction provides a novel direct route to the indolizine skeleton. Radical cyclisation of acrylamides containing the 6-oxo-cyclohex-1-enyl substituent at the nitrogen atom had previously been studied by Parsons and Williams.[5] However, in those reactions intermediate allylic *O*-stannyl ketyl radicals were generated from the cyclohexenone carbonyl group, whereas in our case - from the amide carbonyl group.

2. Results and discussion

We began our investigations by examining the cyclisation of *N*-methyl-3-phenyl-*N*-(1-phenyl-vinyl)-acrylamide (**1a**), which was prepared by condensation of acetophenone and methylamine followed by *N*-acylation of the resultant imine with cinnamoyl chloride. When a boiling solution of **1a** in toluene was treated with 1.1 equiv. of Bu_3SnH in the presence of catalytic amount of AIBN, a mixture (1:6) of *cis* and *trans* 1-methyl-4,6-diphenyl-piperidin-2-one (**2a**) was obtained in 79% yield. The formation of piperidin-2-one **2a** from enamide **1a** most likely involves the 6-*endo-trig* cyclisation of the carbon-centred radical **B** to give a thermodynamically controlled radical **C** (Scheme 1). This reaction step is then followed by an attack of Bu_3SnH from the less hindered site of the latter radical centre to give predominantly *trans* (4*S*,6*R* and 4*R*,6*S*) δ-lactam **2a**, after final SiO_2-column hydrolysis of the tin(IV) enolates **C′**.[4] An observed exclusive 6-*endo-trig* cyclisation is noteworthy.

Similarly, when enamides **1b–d** were treated with Bu_3SnH under conditions described above, the corresponding piperidin-2-ones **2b–c** or octahydro-quinolin-2-one **2d**

Keywords: Tributyltin hydride; Enamides; Tandem radical cyclisation; Lactams; Indolizine.
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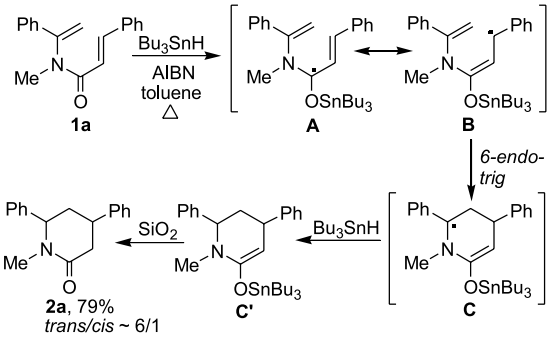
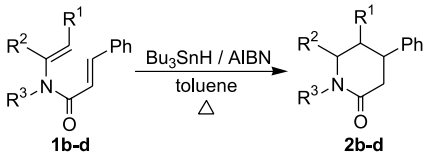
doi:10.1016/j.tet.2004.06.095

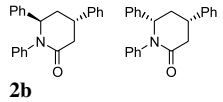
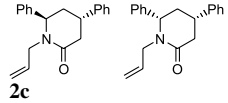
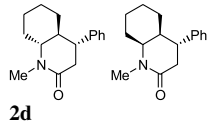


Scheme 1.

were obtained (Table 1). All these reactions proceed as 6-*endo-trig* cyclisations; products of a competitive 5-*exo-trig* process were not detected. Such a predominant formation of the 6-*endo-trig* cyclisation product has been observed previously.[4]

Table 1. Cyclisations of enamides **1b–d**

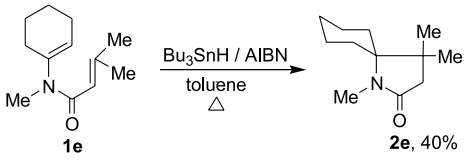


Starting compound	Product[a]	Yield (%)	Diastereomer ratio[a]
1b: R^1=H, R^2=R^3=Ph	 **2b**	57	4*S*,6*R*/4*S*,6*S* 6:1
1c: R^1=H, R^2=Ph, R^3=allyl	 **2c**	76	4*S*,6*R*/4*S*,6*S* 5:1
1d: R^1, R^2=–$(CH_2)_4$–, R^3=Me	 **2d**	75	4*R*,4a*S*,8a*R*/4*R*, 4a*S*,8a*S* 4:1

[a] Only one series of enantiomers is considered.

The structures of diastereomers **2a–d** were determined unambiguously on the basis of ^{1}H NMR spectra of their mixtures (except single products **2d**) and full analysis will be published independently.[6] Good agreement of experimental coupling constants, $^2J_{HH}$, with those calculated using an empirically generalised Karplus-type relation[7] for the HF/6-31G**-optimised geometries (achieved by an ab initio molecular modelling with GAMESS),[8] allowed determining the solution conformations and, at the same time, configurations of chiral centres in these δ-lactams. It was found that all their major isomers have protons at C(4) and C(6) [or C(8a)] in the 1,3-*trans* configuration.[9]

In sharp contrast to cases of **1a–d** giving rise only to the formation of the 6-*endo-trig* products **2a–d**, enamide **1e** was found to provide γ-lactam **2e** in 40% yield (Scheme 2). The five-membered-ring moiety in the latter compound was revealed spectroscopically ($\nu_{C=O}$ 1686 cm^{-1}; δ_C 173.61).



Scheme 2.

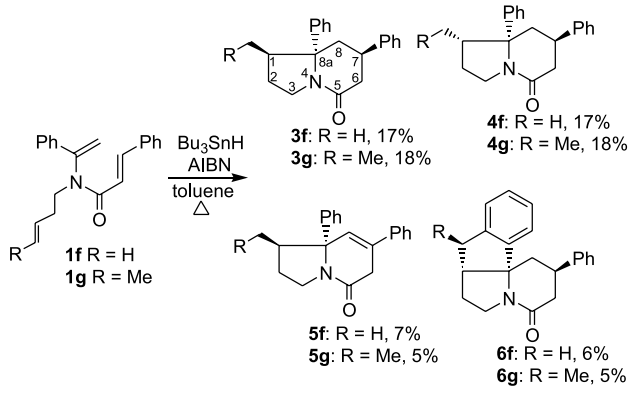
Very similar ^{13}C NMR data were determined also for the other unambiguously synthesised γ-lactams.[10] It was shown that **1e** undergoes solely the 5-*exo-trig* cyclisation to spirosystem **2e**, as even traces of related 6-*endo-trig* products were not observed in the NMR spectra. However, it should be noted that more severe experimental conditions were required for this reaction (Section 4.4).

The latter result reflects a crucial difference in the cyclisation mode among substrates **1a–d** and **1e**. Thus, it was shown above that phenyl group incorporated into the α,β-conjugated acid system is an essential factor for effecting the 6-*endo-trig* cyclisation. Such a preference for forming the six-membered-ring lactams can be explained if the cyclisation process is reversible and is governed mainly by a thermodynamic control. This mode of control has previously been postulated for the cyclisation of allylic *O*-stannyl ketyl radicals.[2c] The phenyl group occurring at a secondary C-radical centre of type **B** (Scheme 1) considerably increases its resonance stabilisation and so strongly favours, in addition, a thermodynamic outcome of the reaction that is usually manifested in the formation of six-membered rings. Moreover, a sterical hindrance around an α-carbon in vinyl system prefers an attack on the β-C atom and the formation of the 6-*endo-trig* product, as a result.

Enamide **1e** does not react under reaction conditions applied by us for a successful cyclisation of **1a–d**. In addition, its 5-*exo-trig* cyclisation (proceeded only with a poor yield) required a large excess of Bu_3SnH and 10 times longer reaction time. These severe conditions strongly suggest that **2e** was in fact the kinetic product, and that this mode of the control should be mainly taken into account in this case. Indeed, a tertiary C-centred radical formed from **1e** is most likely the radical centre less stabilised (more reactive) with respect to such sites discussed above. Consequently, it is able to attack on the sterically crowded α-position of vinyl system to give the 5-*exo-trig* product **2e**.

As noted before, the 6-*endo-trig* cyclisation of the radical **B** resulted in the formation of species **C**. Our interest then focused on the use of the latter type intermediates for performing related tandem radical processes. (A tandem cyclisation of enamides mediated by Bu_3SnH was used previously for the preparation of indolizidinones and pyrrolizidinones[11] as well as the erythrinane skeleton.[12]). For this aim we studied this type of cyclisations for enamides of α,β-conjugated acids **1f–g** bearing the but-3-enyl or pent-3-enyl substituent at a nitrogen atom. These substrates were prepared, as before, by initial condensation of acetophenone and but-3-enylamine (pent-3-enylamine) followed by *N*-acylation of the resultant imines with cinnamoyl chloride (Section 4.2).

The reaction of enamides **1f–g** with Bu_3SnH in the presence

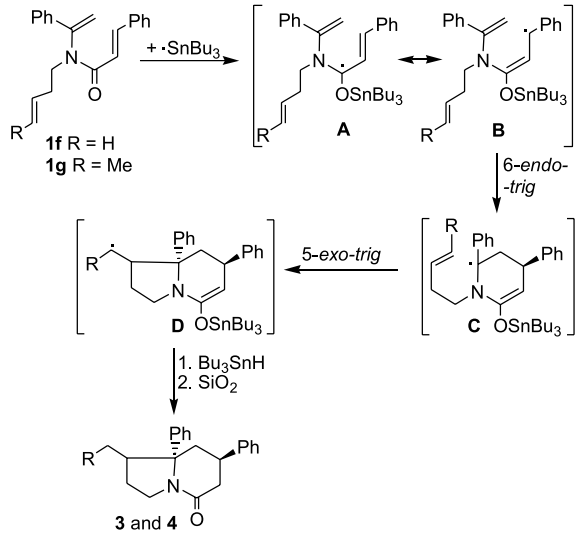


Scheme 3. Tandem cyclisations of enamides **1f–g**.

of a catalytic amount of AIBN in boiling toluene gave the expected products **3** and **4** of the tandem radical cyclisation as pairs of their isomers in a ratio of ca. 1:1 (i.e., in 34 and 36%, yield, respectively) together with very interesting by-products **5** and **6** (Scheme 3, here and thereafter only one series of enantiomers is shown).

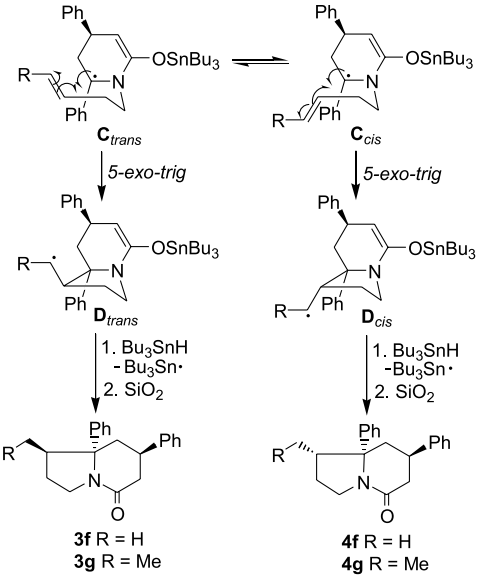
All indolizidinones **3f–g** and **4f–g** and the tetracyclic system **6f** were separated chromatographically, purified by recrystallization and fully characterised. Several attempts to isolate the minor unsaturated by-products **5** in pure state were unsuccessful. Their yields were determined by inspection of NMR spectra of the corresponding mixtures with lactams **3** (for the product ratios, see Section 4.5). Similarly, the complex lactam **6g** was obtained only as an inseparable mixture with **4g**. In the latter case, a work-up of the mother solution from an isolation of **4g** afforded ca. 2:1 mixture **6g** and **4g**. Therefore, structures of compounds **5** and **6g** were assigned based mainly on the ^{13}C NMR spectra of the foregoing mixtures (vide infra).

The formation of indolizidinones **3** and **4** showed that the tandem reaction proceeded by 6-*endo-trig*/5-*exo-trig* cyclisation as predicted (Scheme 4). It is highly remarkable that the configuration of substituents at atoms C(7) and C(8a) is the same in all obtained diastereomers **3f–g** and **4f–g**.



Scheme 4.

Hence, a stereochemical outcome of the final products formation is consistent with the 5-*exo* cyclisation for the *s-transoid* or *s-cisoid* arrangement of the C(2)–C(3) single bond in the alk-3-enyl side chain, respectively, at the moment of a key attack of the radical-carbon atom; for two important rotameric forms of the radical intermediates **C**, see Scheme 5.



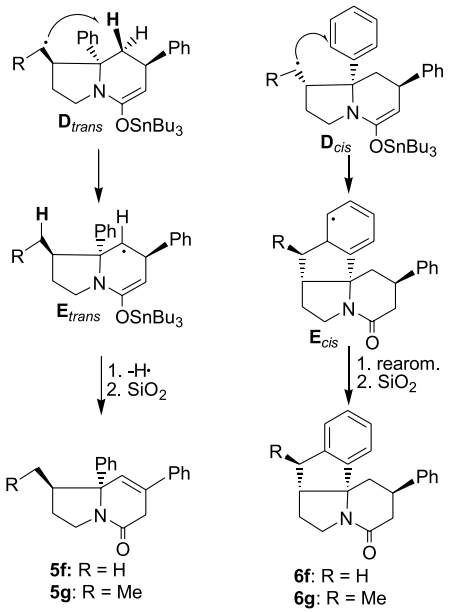
Scheme 5.

Indeed, an attack on the C(3)–C(4) alkenic bond in the *s-transoid* chair-like transition state $\mathbf{C}_{trans}$ gives a subsequent radical intermediate **D** in which the configuration of substituent at C(1) and C(8a) is *trans*, whereas a competitive attack on *s-cisoid* rotamer in the boat-like transition state $\mathbf{C}_{cis}$ leads to the radical $\mathbf{D}_{cis}$. (A negligible difference in the energy of chair- and boat-like transition states was postulated.[13]) This reaction step is then followed by the H-atom abstraction from Bu_3SnH to give desired lactams **3** and **4**.

Interestingly, the 1,3-*trans* configuration of both phenyl groups was found for products **3f–g** and **4f–g**. Such a structural information and analogous data concerning the other chiral centres in lactams **3–6** were unambiguously determined based on their NMR spectra. In this case, the experimentally measured chemical shift values δ_H and, especially, δ_C were correlated with the corresponding magnetic shieldings σ_X (X=H, C), computed by the GIAO method[14] at the DFT level of theory using the Gaussian 98W package.[15] The B3LYP/6-31G**-optimised geometries of different diastereomers of molecules **3–6** were examined. Full conformational investigation on all these heterocyclic systems will be published soon.[6]

The formation of compounds **5** and **6** can be explained in the terms of competition reactions involving the common radical intermediates **D** (Schemes 5 and 6).

The reaction of both radicals $\mathbf{D}_{cis}$ and $\mathbf{D}_{trans}$ with Bu_3SnH gave corresponding isomers **3** and **4**. On the other hand, radicals $\mathbf{D}_{trans}$ can undergo a 1,4-H atom transfer to form



Scheme 6.

new radical species $\mathbf{E}_{trans}$ which, in turn, give rise to the formation of products **5**, after the formal hydrogen-radical elimination. Inspection of the aforementioned DFT-level molecular models indicates that an intramolecular abstraction of the hydrogen from C(8) is a sterically more favoured process, compared with H-abstraction occurring at C(2) or other carbon atoms. In the case of radical $\mathbf{D}_{cis}$, an attack on a phenyl substituent gives the tetracyclic system **6**. An addition of C-centred radicals to aromatic rings followed by rearomatisation of such formed radical intermediates of the type $\mathbf{E}_{cis}$ is well known.[16]

The competition of formation of δ-lactams **3** and **4** or **5** and **6** is most presumably due to a slower rate of the Bu_3SnH addition (over 5 h). In fact, low concentration of tributyltin hydride has been found as a necessary condition for performing these tandem radical processes and to avoid the monocyclisation product formation.

3. Conclusion

This work has clearly demonstrated that enamides of α,β-conjugated acids can easily undergo radical cyclisation to form corresponding piperidin-, quinolin- or pyrrolidin-2-ones. Reactions of the variously substituted enamide precursors have shown that the substitution nature has an effect on both the efficiency and regioselectivity of the cyclisation reactions under study. Conclusively, utility of this method of tandem radical cyclisations providing a quick and mild entry to the new indolizidinone systems was presented.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded at ca. 21 °C with a Varian Gemini 200 BB VT instrument, operating at 200.11 and 50.33 MHz for ^1H and ^{13}C nuclei, respectively. Chloroform-*d* was used as solvent. Chemical shifts are δ-values reported in ppm downfield from internal TMS. Coupling constants (*J*) are given to the nearest 0.5 Hz. A vast majority of spectra were assigned with the aid of ATP, DEPT, COSY and/or HETCOR experiments. IR spectra were recorded for KBr pellets or neat films on a Thermo-Nicolet Nexus FT-IR spectrometer. Low- and high-resolution EI mass spectra (MS and HRMS) were taken on a Finnigan MAT 95 spectrometer at 70 eV; peaks ≥10% rel. intensity are only given (MS). Melting points (uncorrected) were determined on a Boëtius apparatus.

Column chromatography was carried out under gravity using silica gel (Merck 60, 63–200 μm). Thin layer chromatography (TLC) was performed on Merck 5554 aluminium-backed SiO_2 plates; products were visualised by UV light. Tributyltin hydride was purchased from Merck-Schuchardt. Toluene was distilled from the blue solution of sodium benzophenone ketyl. All reactions with *n*-Bu_3SnH were run under an inert atmosphere of Ar and were monitored by TLC. Starting imines were prepared following the literature procedure: methyl-(1-phenyl-ethylidene)-amine,[17] allyl-(1-phenyl-ethylidene)-amine,[18] phenyl-(1-phenyl-ethylidene)-amine,[17] cyclohexylidene-methyl-amine.[19]

4.2. Preparation of but-3-enyl-(1-phenyl-ethylidene)-amine and pent-3-enyl-(1-phenyl-ethylidene)-amine

A mixture of acetophenone (0.1 mol) and but-3-enylamine or pent-3-enylamine (0.1 mol) in 100 mL of benzene was refluxed through a Dean–Stark moisture trap for 24 h. At this time the theoretical quantity of water (1.8 mL) had been collected in the trap, and the water separation had apparently ceased. The solvent was removed in vacuo and the residual oil was distilled under reduced pressure.

4.2.1. But-3-enyl-(1-phenyl-ethylidene)-amine. Yield 12.46 g (72%). Colourless liquid, bp 76–77 °C/0.2 mm Hg. ^1H NMR: δ 2.18 (s, 3H), 2.22–2.68 (m, 2H), 3.51 (t, 2H, $J=$ 7 Hz), 4.88–5.28 (m, 2H), 5.60–6.22 (m, 1H), 7.18–7.40 (m, 3H), 7.60–7.90 (m, 2H). IR (neat, cm^{-1}): $\nu_{C=N}$ 1633.

4.2.2. Pent-3-enyl-(1-phenyl-ethylidene)-amine. Yield 14.09 g (75%). Colourless liquid, bp 77–80 °C/0.2 mm Hg. ^1H NMR: δ 1.53–1.73 (m, 3H), 2.20 (s, 3H), 2.22–2.60 (m, 2H), 3.50 (t, 2H, $J=7$ Hz), 5.21–5.75 (m, 2H), 7.18–7.40 (m, 3H), 7.60–7.90 (m, 2H). IR (neat, cm^{-1}): $\nu_{C=N}$ 1633.

4.3. General procedure for the preparation of enamides 1a–h

To a solution of imine (10 mmol) and triethylamine (or *N*,*N*-diethylaniline, for **1g** and **1h**) (12 mmol) in benzene (15 mL) a solution of appropriate acid chloride (10 mmol) in benzene (10 mL) was added at 0 °C and the mixture was stirred at room temperature for 2 h. The solution was filtered and solvent was removed in vacuo. A residue was dissolved in diethyl ether (50 mL), washed with water, 0.5 M aqueous hydrochloric acid, brine, and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was

chromatographed on the Al_2O_3 column (hexane/AcOEt). The following compounds were thus obtained.

4.3.1. *N*-Methyl-3-phenyl-*N*-(1-phenyl-vinyl)-acrylamide (1a). Purified by chromatography (hexane/AcOEt 8:2 v/v) and recrystallization. Yield 1.75 g (67%). Colourless crystals, mp 73–75 °C (hexane). [Found: C, 82.0; H, 6.6; N, 5.3. $C_{18}H_{17}NO$ (263.33) requires C, 82.10; H, 6.51; N, 5.32%]. ^{1}H NMR: δ 3.15 (s, 3H), 5.23 (s, 1H), 5.72 (s, 1H), 6.81 (d, 1H, $J=15$ Hz), 7.12–7.62 (m, 5H), 7.76 (d, 1H, $J=15$ Hz). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1670, $\nu_{C=C}$ 1628.

4.3.2. 3,*N*-Diphenyl-*N*-(1-phenyl-vinyl)-acrylamide (1b). Purified by chromatography (hexane/AcOEt 95:5). Yield 2.13 g (66%). Light yellow oil. [Found: C, 84.6; H, 6.0; N, 4.2. $C_{23}H_{19}NO$ (325.40) requires C, 84.89; H, 5.89; N, 4.30%]. ^{1}H NMR: δ 5.25 (s, 1H), 5.80 (s, 1H), 6.75 (d, 1H, $J=15$ Hz), 7.05–7.80 (m, 15H), 7.78 (d, 1H, $J=15$ Hz). IR (neat, cm^{-1}): $\nu_{C=O}$ 1668, $\nu_{C=C}$ 1624.

4.3.3. *N*-Allyl-3-phenyl-*N*-(1-phenyl-vinyl)-acrylamide (1c). Purified by chromatography (hexane/AcOEt 95:5) and recrystallization. Yield 1.84 g (64%). Colourless crystals, mp 69–71 °C (hexane). [Found: C, 83.0; H, 6.7; N, 4.8. $C_{20}H_{19}NO$ (289.37) requires C, 83.01; H, 6.62; N, 4.84%]. ^{1}H NMR: δ 4.10–4.28 (m, 2H), 4.85–5.20 (m, 2H), 5.17 (s, 1H), 5.60–6.33 (m, 1H), 5.73 (s, 1H), 6.79 (d, 1H, $J=15$ Hz), 7.10–7.58 (m, 10H), 7.80 (d, 1H, $J=15$ Hz). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1660, $\nu_{C=C}$ 1621.

4.3.4. *N*-Cyclohex-1-enyl-*N*-methyl-3-phenyl-acrylamide (1d). Purified by chromatography (hexane/AcOEt 95:5) and recrystallization. Yield 2.29 g (95%). Colourless crystals, mp 52–53 °C (hexane). [Found: C, 79.6; H, 7.95; N, 5.8. $C_{16}H_{19}NO$ (241.33) requires C, 79.63; H, 7.94; N, 5.80%]. ^{1}H NMR: δ 1.41–2.50 (m, 8H), 3.10 (s, 3H), 5.58–5.83 (m, 1H), 6.78 (d, 1H, $J=15$ Hz), 7.16–7.50 (m, 5H), 7.70 (d, 1H, $J=15$ Hz). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1665, $\nu_{C=C}$ 1635.

4.3.5. 3-Methyl-but-2-enoic acid cyclohex-1-enyl-methyl-amide (1e). Purified by chromatography (hexane/AcOEt 95:5). Yield 1.69 g (88%). Colourless oil. [Found: C, 74.7; H, 9.95; N, 7.0. $C_{12}H_{19}NO$ (193.29) requires C, 74.57; H, 9.91; N, 7.25%]. ^{1}H NMR: δ 1.38–1.88 (m, 4H), 1.78 (d, 3H, $J=1.5$ Hz), 1.92–2.33 (m, 4H), 2.05 (d, 3H, $J=1.5$ Hz), 2.97 (s, 3H), 5.43–5.67 (m, 1H), 5.72–5.90 (m, 1H). IR (neat, cm^{-1}): $\nu_{C=O}$ 1653.

4.3.6. *N*-But-3-enyl-3-phenyl-*N*-(1-phenyl-vinyl)-acrylamide (1f). Purified by chromatography (hexane/AcOEt 8:2). Yield 1.61 g (53%). Light yellow oil. [Found: C, 83.1; H, 7.2; N, 4.3. $C_{21}H_{21}NO$ (303.40) requires C, 83.13; H, 6.98; N, 4.62%]. ^{1}H NMR: δ 2.25–2.55 (m, 2H), 3.68 (t, 2H, $J=7$ Hz), 4.90–5.32 (m, 2H), 5.27 (s, 1H), 5.58–6.15 (m, 1H), 5.81 (s, 1H) 6.88 (d, 1H, $J=16$ Hz), 7.15–7.62 (m, 10H), 7.85 (d, 1H, $J=16$ Hz). IR (neat, cm^{-1}): $\nu_{C=O}$ 1651, $\nu_{C=C}$ 1622.

4.3.7. *N*-Pent-3-enyl-3-phenyl-*N*-(1-phenyl-vinyl)-acrylamide (1g). Purified by chromatography (hexane/AcOEt 8:2). Yield 1.62 g (51%). Light yellow oil. [Found: C, 83.1; H, 7.5; N, 4.1. $C_{22}H_{23}NO$ (317.42) requires C, 83.24; H, 7.30; N, 4.41%]. ^{1}H NMR: δ 1.55–1.65 (m, 3H), 2.10–2.53 (m, 2H), 3.55 (t, 2H, $J=7$ Hz), 5.20 (s, 1H), 5.26–5.65 (m, 2H), 5.75 (s, 1H), 6.81 (d, 1H, $J=16$ Hz), 7.11–7.70 (m, 10H), 7.75 (d, 1H, $J=16$ Hz). IR (neat, cm^{-1}): $\nu_{C=O}$ 1655, $\nu_{C=C}$ 1616.

4.4. General procedure for radical cyclisation of enamides 1a–e

To a previously degassed boiling solution of enamides **1a–e** (1 mmol) in toluene (15 mL) a solution of Bu_3SnH (350 mg, 1.2 mmol for **1a–d**; 436 mg, 1.5 mmol for **1e**) and AIBN (20 mg, 0.12 mmol for **1a–d**; 25 mg, 0.15 mmol for **1e**) in toluene (5 mL) was added. The mixture was heated under reflux for 2.5 h [for **1e** 10 h and then, only in this case, the solution of Bu_3SnH (291 mg, 1 mmol) and AIBN (16 mg, 1 mmol) in toluene (5 mL) was added and refluxed for a further 15 h]. Toluene was removed in vacuo and the residue was separated by chromatography on silica gel. The products were eluted with the hexane/AcOEt mixture.

4.4.1. 1-Methyl-4,6-diphenyl-piperidin-2-one (2a). Yield 210 mg (79%). Light yellow oil eluted with hexane/AcOEt 1:1 (v/v) as ca. 6:1 isomeric mixture (from integrals of NCH_3 singlets, δ 2.92 and 2.75). The major 4*S*,6*R* (and 4*R*,6*S*) diastereomer was separated and purified by recrystallization. Colourless needles, mp 103–105 °C (hexane). ^{1}H NMR: δ 2.05–2.20 (m, 1H), 2.30–2.50 (m, 1H), 2.50–2.65 (m, 1H), 2.80–2.85 (m, 1H), 2.92 (s, 3H, NCH_3), 3.00–3.15 (m, 1H), 4.60–4.70 (m, 1H), 7.05–7.45 (m, 10H). ^{13}C NMR: δ 33.30 (C-4), 34.23 (NCH_3), 38.20, 39.30 (C-3 and C-5), 62.62 (C-6), 126.35, 126.52, 126.76, 127.64, 128.67, 128.84 ($6\times C_{ar}$), 140.86, 143.11 ($2\times C_{q\ ar}$), 170.42 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1640. MS *m*/*z* (%): 266 (18), 265 ($M^{+\cdot}$, 100), 264 (58), 189 (10), 188 (75), 187 (89), 186 (44), 174 (10), 160 (13), 133 (17), 132 (42), 131 (95), 120 (28), 119 (35), 118 (97), 115 (14), 105 (17), 104 (53), 103 (44) 91 (31), 78 (17), 77 (27). HRMS (EI): calcd for $C_{18}H_{19}NO$ M 265.1467, found $M^{+\cdot}$ 265.1462.

A presence of the minor 4*S*,6*R* (and 4*R*,6*S*) diastereomer was also indicated by the ^{13}C NMR spectrum: δ 32.74 (C-4), 37.67 (NCH_3), 40.50, 42.80 (C-3 and C-5), 64.81 (C-6), 171.01 (C=O).

4.4.2. 1,4,6-triphenyl-piperidin-2-one (2b). Yield 186 mg (57%). Light yellow oil eluted with hexane/AcOEt 1:1 as ca. 6:1 isomeric mixture (by ^{13}C NMR). The major 4*S*,6*R* (and 4*R*,6*S*) diastereomer was separated and purified by recrystallization. Colourless solid, mp 151–153 °C (hexane). ^{1}H NMR: δ 2.20–2.35 (m, 1H), 2.50–2.65 (m, 1H), 2.70–2.90 (m, 1H), 3.00–3.15 (m, 1H), 3.20–3.40 (m, 1H), 5.05–5.15 (m, 1H), 7.00–7.40 (m, 15H). ^{13}C NMR: δ 33.58 (C-4), 38.83, 39.62 (C-3 and C-5), 63.99 (C-6), 126.43, 126.65, 126.80, 127.01, 127.35, 128.03, 128.61, 128.75, 128.92 ($9\times C_{ar}$), 141.14, 142.25, 143.15, ($3\times C_{q\ ar}$), 170.30 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1647. MS *m*/*z* (%): 328 (25), 327 ($M^{+\cdot}$, 100), 326 (18), 195 (16), 193 (10), 182 (18), 181 (21), 180 (17), 131 (10), 104 (18), HRMS (EI): calcd for $C_{23}H_{21}NO$ M 327.1623, found $M^{+\cdot}$ 327.1610.

A presence of the minor 4*S*,6*R* (and 4*R*,6*S*) diastereomer was indicated by the ^{13}C NMR spectrum: δ 38.35 (C-4), 41.03, 41.23 (C-3 and C-5), 65.61 (C-6), 126.81, 126.87,

127.59, 128.45, 128.63, 128.84 (6×C_{ar}), 140.83, 141.14, 142.95, (3×$C_{q\ ar}$) 170.46 (C=O).

4.4.3. 1-Allyl-4,6-diphenyl-piperidin-2-one (2c). Yield 220 mg (76%). Light yellow oil eluted with hexane/AcOEt 8:2 as ca. 5:1 isomeric mixture. The major diastereomer was separated and purified by recrystallization. Colourless solid, mp 73–75 °C (hexane). ^{1}H NMR: δ 2.10–2.20 (m, 1H), 2.30–2.45 (m, 1H), 2.50–2.70 (m, 1H), 2.80–3.20 (m, 3H), 4.70–4.80 (m, 1H), 4.85–5.20 (m, 3H), 5.70–5.90 (m, 1H), 7.00–7.50 (m, 10H). ^{13}C NMR: δ 33.10 (C-4), 38.03, 39.41 (C-3 and C-5), 47.58 (NCH_2), 58.91 (C-6), 117.39 (=CH_2), 126.48, 126.48, 126.69, 127.57, 128.59, 128.75 (6×C_{ar}), 132.59 (=CH), 140.86, 143.12 (2×$C_{q\ ar}$), 169.75 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1636. MS *m/z* (%): 292 (21), 291 ($M^{+\cdot}$, 100), 290 (25), 276 (45), 193 (13), 144 (11), 131 (37), 118 (12), 117 (12), 115 (11), 105 (14), 104 (38), 103 (21), 91 (25), 77 (10). HRMS (EI): calcd for $C_{20}H_{21}NO$ M 291.1623, found $M^{+\cdot}$ 291.1615.

A presence of the minor diastereomer was indicated by the ^{13}C NMR spectrum: δ 37.91 (C-4), 40.59, 41.41 (C-3 and C-5), 46.07 (NCH_2), 61.54 (C-6), 117.60 (=CH_2), 126.33, 126.77, 126.82, 127.90, 128.67, 128.90 (6×C_{ar}) 132.59 (=CH), 141.60, 142.89 (2×$C_{q\ ar}$), 170.31 (C=O).

4.4.4. 1-Methyl-4-phenyl-octahydro-quinolin-2-one (2d). Both diastereomers were separated by chromatography (hexane/AcOEt 1:1) and purified by recrystallization from hexane.

Major isomer [(4*R*,4a*S*,8a*R*)- and (4*S*,4a*R*,8a*S*)-**2d**]. Yield 146 mg (60%). Colourless needles, mp 94–96 °C. ^{1}H NMR: δ 0.85–0.95 (m, 1H), 1.00–1.50 (m, 4H), 1.50–1.70 (m, 2H), 1.75–1.95 (m, 1H), 2.25–2.40 (m, 1H), 2.55–2.80 (m, 3H), 2.95–3.10 (m, 1H), 2.99 (s, 3H, NCH_3), 7.10–7.40 (m, 5H). ^{13}C NMR: δ 25.10, 25.37, 29.22 (3×CH_2), 30.09 (CH_3), 31.65, 40.91 (2×CH_2), 44.17, 46.13, 63.91 (3×CH), 126.69, 127.35, 128.61 (3×C_{ar}), 142.02 ($C_{q\ ar}$), 169.87 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1641. MS *m/z* (%): 244 (15), 243 ($M^{+\cdot}$, 90), 201 (14), 200 (100), 186 (31), HRMS (EI): calcd for $C_{16}H_{21}NO$ M 243.1623, found $M^{+\cdot}$ 243.1623.

Minor isomer [(4*R*,4a*S*,8a*S*)- and (4*S*,4a*R*,8a*R*)-**2d**]. Yield 36 mg (15%). Colourless solid, mp 87–90 °C. ^{1}H NMR: δ 1.10–1.70 (m, 6H), 1.75–1.90 (m, 1H), 2.00–2.15 (m, 1H), 2.25–2.40 (m, 1H), 2.40–2.80 (m, 2H), 3.00 (s, 3H, NCH_3), 3.20–3.40 (m, 2H), 7.10–7.40 (m, 5H). ^{13}C NMR: δ 20.06, 24.86, 26.82, 27.74 (4×CH_2), 33.37 (CH_3), 37.62, 39.15 (2×CH), 40.11 (CH_2), 61.02 (CH), 126.79, 127.42, 128.82 (3×C_{ar}), 142.33 ($C_{q\ ar}$), 169.26 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1636. MS *m/z* (%): 244 (14), 243 ($M^{+\cdot}$, 79), 201 (14), 200 (100), 186 (32), HRMS (EI): calcd for $C_{16}H_{21}NO$ M 243.1623, found $M^{+\cdot}$ 243.1631.

4.4.5. 1,4,4-Trimethyl-1-aza-spiro[4.5]decan-2-one (2e). Yield 77 mg (40%). Light yellow oil eluted with hexane/AcOEt 1:1. ^{1}H NMR: δ 1.13 (s, 6H), 1.50–1.85 (m, 10H), 2.20 (s, 2H), 2.81 (s, 3H). ^{13}C NMR: δ 22.73 (2×CH_2), 25.35 (CH_2), 25.75 (2×CH_3), 25.97 (NCH_3), 30.09 (2×CH_2), 40.56 (C_q), 46.25 (CH_2), 65.74 (C_q), 173.61 (C=O). IR (neat, cm^{-1}): $\nu_{C=O}$ 1686. MS *m/z* (%): 195 ($M^{+\cdot}$, 26), 153 (10), 152 (100). HRMS (EI): calcd for $C_{12}H_{21}NO$ M 195.1623, found $M^{+\cdot}$ 195.1631.

4.5. General procedure for tandem radical cyclisation of enamides 1f–g

A solution of Bu_3SnH (786 mg, 2.7 mmol) and AIBN (44 mg, 0.27 mmol) in degassed toluene (195 mL) was added dropwise over 5 h via a syringe pump to the stirred and refluxed solution of enamide **1f** or **1g** (2.4 mmol) in degassed toluene (100 mL). The reaction mixture was stirred at reflux temperature under N_2 for 3 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel using the hexane/AcOEt 1:1 mixture.

4.5.1. (1*S*,7*S*,8a*S* and 1*R*,7*R*,8a*R*)-1-Methyl-7,8a-diphenyl-hexahydro-indolizin-5-one (3f). Yield 175 mg as ca. 5:2 mixture with **5f**, which corresponds to 17% yield of **3f**. The ratio of both products was determined from the ^{1}H NMR spectrum, by comparison of integrals for the methyl-group doublets (δ 1.11 and 1.23). Repeated chromatography followed by recrystallization from hexane gave analytically pure sample of **3f**. Colourless crystalline solid, mp 145–147 °C. ^{1}H NMR: δ 1.11 (d, 3H, J=7 Hz), 1.40–1.75 (m, 2H), 2.00–2.15 (m, 1H), 2.25–2.35 (m, 1H), 2.35–2.80 (m, 4H), 3.50–3.65 (m, 1H), 3.70–3.90 (m, 1H), 7.00–7.40 (m, 10H). ^{13}C NMR: δ 15.89 (CH_3), 27.78 (CH_2), 35.17 (CH), 38.51, 39.52, 43.46 (3×CH_2), 44.00 (CH), 71.85 (C_q), 125.30, 126.55, 126.70, 127.13, 128.60, 128.65 (6×C_{ar}), 143.83, 145.84 (2×$C_{q\ ar}$), 170.27 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1635. MS *m/z* (%): 306 (22), 305 ($M^{+\cdot}$, 95), 263 (29), 262 (100), 228 (53), 201 (14), 200 (21), 160 (10), 131 (43), 117 (10), 104 (16), 103 (23), 91 (11), HRMS (EI): calcd for $C_{21}H_{23}NO$ M 305.1780, found $M^{+\cdot}$ 305.1783.

4.5.2. (1*S*,8a*R* and 1*R*,8a*S*)-1-Methyl-7,8a-diphenyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one (5f). Yield 175 mg as ca. 2:5 mixture with **3f** (7% yield of **5f**). Colourless oil. ^{1}H NMR: δ 1.23 (d, 3H, J=7 Hz), 6.22 (s, br, 1H) in mixture with **3f**, all remaining signals were unidentifiable. ^{13}C NMR: δ 16.39 (CH_3), 28.93, 36.12, 42.98 (3×CH_2), 44.81 (CH), 70.15 (C_q), 120.52 (=CH), 125.31, 126.09, 127.12, 128.43, 129.30 (5×C_{ar}), 138.26 (C_q), 145.14, 148.01 (2×$C_{q\ ar}$), remaining signals unidentifiable.

4.5.3. (1*R*,7*S*,8a*S* and 1*S*,7*R*,8a*R*)-1-Methyl-7,8a-diphenyl-hexahydro-indolizin-5-one (4f). Yield 124 mg (17%). Recrystallization from hexane gave analytically pure sample. Colourless crystalline solid, mp 148–150 °C. ^{1}H NMR: δ 0.92 (d, 3H, J=7 Hz), 1.20–1.40 (m, 1H), 1.75–2.00 (m, 2H), 2.05–2.25 (m, 1H), 2.40–2.60 (m, 1H), 2.60–2.90 (m, 3H), 3.70–3.85 (m, 2H), 7.05–7.45 (m, 10H). ^{13}C NMR: δ 14.80 (CH_3), 28.59 (CH_2), 35.95 (CH), 38.58, 42.69, 45.29 (3×CH_2), 46.56 (CH), 70.55 (C_q), 126.69, 126.83, 127.15, 127.43, 128.40, 128.83 (6×C_{ar}), 140.34, 144.33 (2×$C_{q\ ar}$), 169.86 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1625. MS *m/z* (%): 306 (22), 305 ($M^{+\cdot}$, 95), 263 (29), 262 (100), 228 (37), 201 (19), 200 (35), 160 (12), 131 (35), 117 (12), 104 (17), 103 (22), 91 (11), HRMS (EI): calcd for $C_{21}H_{23}NO$ M 305.1780, found $M^{+\cdot}$ 305.1778.

4.5.4. (3a*R*,8*S*,9a*S* and 3a*S*,8*R*,9a*R*) 8-Phenyl-1,2-benzo-3,3a,4,5,8,9-hexahydro-7*H*-5a-aza-cyclopenta[c]inden-6-one (6f). Yield 44 mg (6%). Repeated chromatography gave analytically pure sample. Colourless oil. ^{1}H NMR: δ 1.10–1.50 (m, 2H), 1.95–2.30 (m, 2H), 2.50–2.80 (m, 3H), 2.95–3.30 (m, 3H), 3.40–3.60 (m, 1H), 3.75–4.00 (m, 1H), 7.15–7.40 (m, 9H). ^{13}C NMR: δ 28.42 (CH_2), 34.94 (CH), 35.13, 38.67, 40.10, 44.86 (4×CH_2), 51.27 (CH), 75.06 (C_q), 124.51, 126.31, 126.71, 126.73, 126.76, 128.48, 128.71 (7×C_{ar}), 140.69 143.66, 144.80 (3×$C_{q\ ar}$), 168.76 (C=O). IR (neat, cm^{-1}): $\nu_{C=O}$ 1635. MS *m*/*z* (%): 304 (24), 303 ($M^{+\cdot}$, 100), 302 (14), 275 (26), 274 (12), 262 (18), 212 (28), 211 (16), 200 (11), 199 (29), 171 (22), 158 (10), 157 (15), 156 (14), 143 (10), 131 (30), 130 (10), 129 (15), 128 (17), 115 (15), 104 (12), 103 (20), 91 (18), 77 (11). HRMS (EI): calcd for $C_{21}H_{21}NO$ M 303.1623, found $M^{+\cdot}$ 303.1615.

4.5.5. (1*S*,7*S*,8a*S* and 1*R*,7*R*,8a*R*)-1-Ethyl-7,8a-diphenyl-hexahydro-indolizin-5-one (3g). Yield 177 mg as ca. 7:2 mixture with **5g**, which corresponds to 18% yield of **3g**. The ratio of both products was estimated from the ^{13}C NMR spectrum. Repeated chromatography and recrystallization from hexane gave analytically pure sample of **3g**. Colourless crystalline solid mp 141–143 °C. ^{1}H NMR: δ 1.00 (t, 3H, J=7 Hz), 1.10–1.40 (m, 2H), 1.40–1.95 (m, 3H), 2.05–2.60 (m, 3H), 2.60–2.80 (m, 2H) 3.50–3.65 (m, 1H), 3.70–3.85 (m, 1H), 7.00–7.40 (m, 10H). ^{13}C NMR: δ 12.18 (CH_3), 21.55, 23.66 (2×CH_2), 35.24 (CH), 38.58, 39.44, 43.57 (3×CH_2), 51.54 (CH), 71.93 (C_q), 125.27, 126.56, 126.69, 127.05, 128.58, 128.65 (6×C_{ar}), 143.97, 146.28 (2×$C_{q\ ar}$), 169.85 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1633. MS *m*/*z* (%): 320 (20), 319 ($M^{+\cdot}$, 81), 263 (29), 262 (100), 242 (47), 214 (15), 131 (46), 117 (10), 104 (23), 103 (32), 91 (15), 77 (15). HRMS (EI): calcd for $C_{21}H_{23}NO$ M 319.1936, found $M^{+\cdot}$ 319.1936.

4.5.6. (1*S*,8a*R* and 1*R*,8a*S*)-1-Ethyl-7,8a-diphenyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one (5g). Yield 177 mg as ca. 2:7 mixture with **3g** (5% yield of **5g**). Colourless oil. ^{1}H NMR: δ 6.19 (s, 1H) in mixture with **3g**, remaining signals unidentifiable. ^{13}C NMR: δ 12.45 (CH_3), 22.28, 25.52, 35.80, 43.27 (4×CH_2), 52.42 (CH), 70.04 (C_q), 120.45 (=CH), 125.06, 125.96, 126.92, 128.31, 129.15 (5×C_{ar}), 138.24 (C_q), 145.41, 147.98 (2×$C_{q\ ar}$), remaining signals unidentifiable.

4.5.7. (1*R*,7*S*,8a*S* and 1*S*,7*R*,8a*R*)-1-Ethyl-7,8a-diphenyl-hexahydro-indolizin-5-one (4g). Yield 176 mg as ca. 7:2 mixture (by the ^{13}C NMR control) with **6g**, which corresponds to 18% yield of **4g**. Repeated chromatography and recrystallization from pentane gave analytically pure sample of **4g**. Colourless crystalline solid, mp 90–92 °C. ^{1}H NMR: δ 0.92 (t, 3H, J=7 Hz), 1.15–1.40 (m, 2H), 1.55–1.75 (m, 1H), 1.75–2.20 (m, 2H), 2.35–2.95 (m, 5H), 3.75–3.80 (m, 1H), 3.80–3.85 (m, 1H), 7.05–7.40 (m, 10H). ^{13}C NMR: δ 12.77 (CH_3), 23.13, 25.98 (2×CH_2), 35.90 (CH), 38.66, 42.84, 45.30 (3×CH_2), 54.12 (CH), 70.39 (C_q), 126.58, 126.70, 126.89, 127.28, 128.30, 128.70 (6×C_{ar}), 140.84, 144.22 (2×$C_{q\ ar}$), 169.63 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ 1636. MS *m*/*z* (%): 320 (20), 319 ($M^{+\cdot}$, 83), 263 (30), 262 (100), 242 (30), 215 (14), 214 (29), 131 (38), 117 (12), 104 (25), 103 (30), 91 (15), 77 (13). HRMS (EI): calcd for $C_{21}H_{23}NO$ M 319.1936, found $M^{+\cdot}$ 319.1936.

4.5.8. (3*S*,3a*S*,8*S*,9a*S* and 3*R*,3a*R*,8*R*,9a*R*)3-Methyl-8-phenyl-1,2-benzo-3,3a,4,5,8,9-hexahydro-7*H*-5a-aza-cyclopenta[c]inden-6-one (6g). Yield 176 mg as ca. 2:7 mixture with **4g** (5% yield of **6g**). The mother solution obtained after separation of **4g** gave an inseparable mixture of **6g** and **4g** (ca. 2:1, by ^{13}C NMR). Colourless oil. ^{1}H NMR: δ 1.35 (d, 3H, J=7 Hz) in the mixture with **4g**, remaining signals were unidentifiable. ^{13}C NMR: δ 21.93 (CH_3), 29.82 (CH_2), 35.23 (CH), 38.56, 43.29, 44.37, 44.56 (4×CH_2), 58.33 (CH), 74.93 (C_q), 124.54, 125.66, 126.77, 126.85, 127.13, 128.75, 128.83 (7×C_{ar}), 143.79 144.08, 146.54 (3×$C_{q\ ar}$), 168.36 (C=O).

Acknowledgements

This research project was supported by the grant No 505/681/2003 from University of Łódź.

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Reaction between quinone and thiazolidine. A study on the formation mechanism of new antiproliferative quinolindiones

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Received 24 January 2004; revised 20 May 2004; accepted 17 June 2004

Available online 21 July 2004

Abstract—Reaction between quinolinquinone and thiazolidine in basic medium was investigated. 2-Arylthiazolidine-4-carboxylic acid ethyl esters undergo two different cleavages in basic medium, yielding the 1-aryl-2-azadiene and a thiolic species. In the presence of quinolinquinone, the isomeric 1-aryl-3-ethoxycarbonyl-pyridoisoquinolin-5,10-diones and 3-amino-3-ethoxycarbonyl-dihydrothienoquinolin-4,9-diones are formed by a hetero-Diels–Alder reaction and 1,4-Michael addition reaction, respectively. A mechanism for the formation of the reaction products is presented.

1. Introduction

The quinone planar structure is common to numerous antitumor drugs and plays an important role in the DNA intercalating process, which is associated with antiproliferative activity.[1] The ability of quinones to accept electrons which form the corresponding semiquinone radicals is the first step of a redox chain which generates reactive species involved in enzymatic blocking and reading errors during the replication process.[2] Numerous studies on the activity of heterocyclic quinones containing nitrogen have shown that the number and position of nitrogens are considerably important for cytotoxicity,[3] while the optimum number of the rings in the polyannulated system ranges between 3 and 4. Significant examples of these DNA damaging agents are actinomycin D, doxorubicin, mitomycin, streptonigrin, and pyridophenoxazinones.[4] Therefore, it was of interest to study the activity of novel quinones related to 5*H*-pyrido[3,2-*a*]phenoxazin-5-one (PPH, Fig. 1), a potent anticancer agent previously described.[4] It is of note that the benzo-fused ring A of PPH seems to play an important role for π–π stacking interactions with the DNA base pairs and that the pyridine nitrogen is crucial for its antiproliferative activity.[4,5]

In pursuing our research in this field, we have designed a series of substituted pyridoquinolin-5,10-diones (PQDs),[6] which fulfill the requirements for intercalative binding between adjacent DNA base pairs and exhibit an anticancer activity at submicromolar concentrations on a large panel of limphoblastoid and solid-tumor derived cells. A topoisomerase I superhelix unwinding assay demonstrated the ability of PQDs to intercalate into double stranded DNA. UV–vis and ^{1}H NMR spectroscopic investigation on the complex PIQD/[d(GAAGCTTC)]$_2$ also provided evidence that intercalation occurs and alters the base sequence GC.

In this paper, we report the synthesis and formation mechanism of the 1-phenyl-3-ethoxycarbonyl-pyrido [3,2-*g*]isoquinolin-9,10-dione (**1a**), the lead compound of PQD series. Compound **1a** was prepared by a cycloaddition reaction, using quinolinquinone (**QQ**)

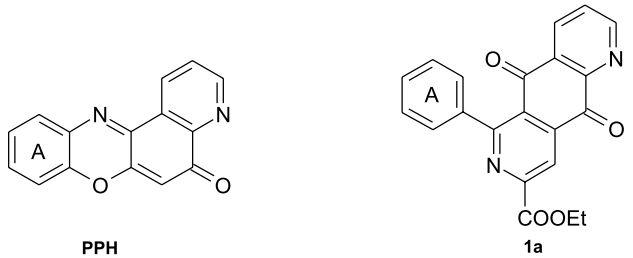

Figure 1.

Keywords: Quinone; Thiazolidine; Azadiene.
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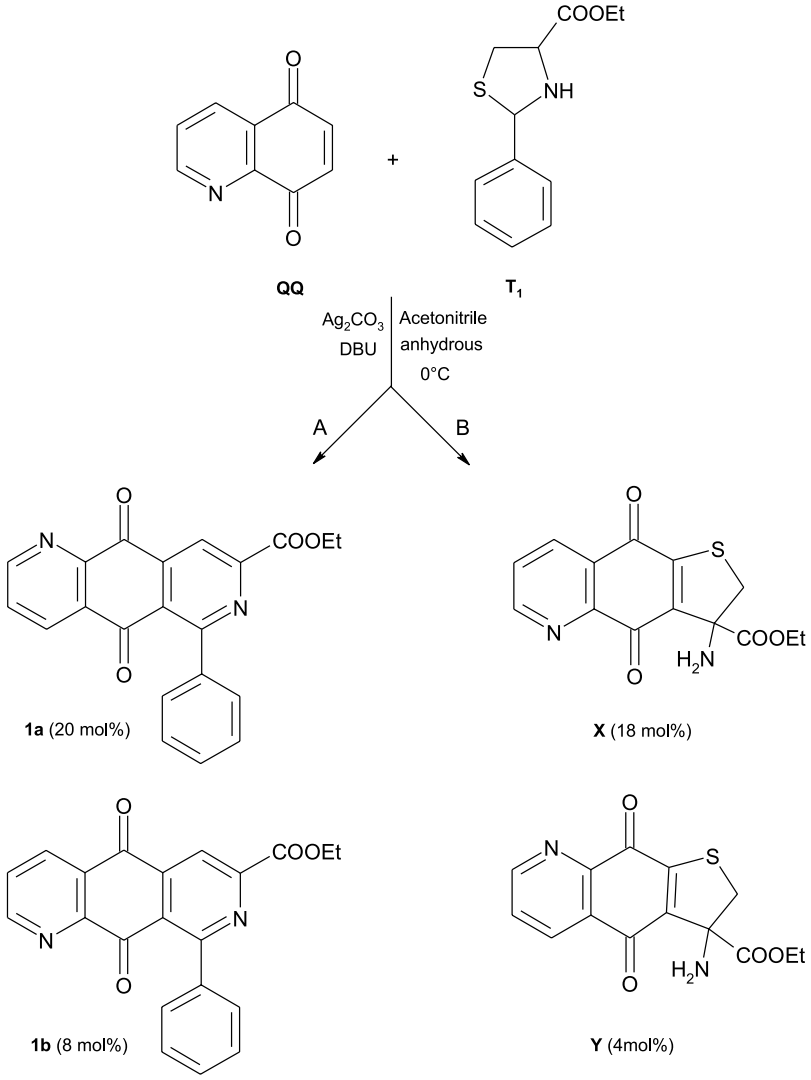
doi:10.1016/j.tet.2004.06.098

and 2-phenylthiazolidine-4-carboxylic acid ethyl ester ($\mathbf{T_1}$) in basic medium (Scheme 1) according to the general procedure reported in Section 2. It was previously reported that thiazolidines in basic medium yield the corresponding azadienes by cleavage of the heterocyclic ring.[7] $\mathbf{T_1}$ was prepared according to the reported procedures from L-cysteine ethyl ester and benzaldheyde.[8,9] **QQ** was prepared by hydroxylation followed by oxidation of 5-hydroxyquinoline.[10]

Together with **1a**, the products 1-phenyl-3-ethoxycarbonyl-pyrido[2,3-*g*]isoquinolin-5,10-dione (**1b**), 3-amino-3-ethoxy-carbonyl-2,3-dihydrothieno[2,3-*g*]quinolin-4,9-dione (**X**) and 3-amino-3-ethoxycarbonyl-2,3-dihydrothieno[3,2-*g*]quino-lin-4,9-dione (**Y**) were recovered from the reaction mixture.

Section 2 reports the general synthetic procedures and the characterization of all new compounds on the basis of the spectral data and the elemental analysis. Structural assign-ment of series **a** and **b** and of **X** and **Y** was accomplished through extensive 2D NMR spectroscopy, HMQC and HMBC. Figure 2 summarizes the HMBC correlations for compounds **1a**, **1b** (prototypes of series **a** and **b**), **X**, **Y** and **X′**. In the HMBC spectrum of **1a**, the double–doublet assigned to the H9 proton at δ_H 8.64 shows a very significant strong correlation $^3J_{C-H}$ with the singlet at δ_C 180.9 (C10, carbonyl group) and the H4 singlet at δ_H 8.82 with the singlet at δ_C 181.7 (C5, carbonyl group). The HMBC spectrum of **1b**, shows a very significant strong correlation $^3J_{C-H}$ of the singlet at δ_C 180.5 (C5, carbonyl group) with the double–doublet assigned to the H6 proton at δ_H 8.52 and the singlet at δ_H 8.92 assigned to the H4 proton. In the HMBC spectrum of **X**, the double–doublet assigned to the H8 proton at δ_H 8.40 shows a very significant, strong correlation $^3J_{C-H}$ with the singlet at δ_C 180.7 (C9, carbonyl group) and two weak interactions $^4J_{C-H}$ with the signals at δ_C 179.9 (C4, carbonyl group) and δ_C 154.9 (C9a). In the corresponding spectrum of **Y**, the double–doublet assigned to the H5 proton at δ_H 8.38 shows a very significant, strong correlation with the singlet at δ_C 180.0 (C4, carbonyl group) and two weak interactions $^4J_{C-H}$ with the signals at δ_C 180.1 (C9, carbonyl group) and δ_C 142.2 (C3a). The $^4J_{C-H}$ coupling of H8 proton with C9a, which is deshielded by the endocyclic sulfur effect, determinates the structure of **X**. Conversely, the $^4J_{C-H}$ coupling of H5 proton with the higher field C3a, determinates the structure of **Y**. To further



Scheme 1.

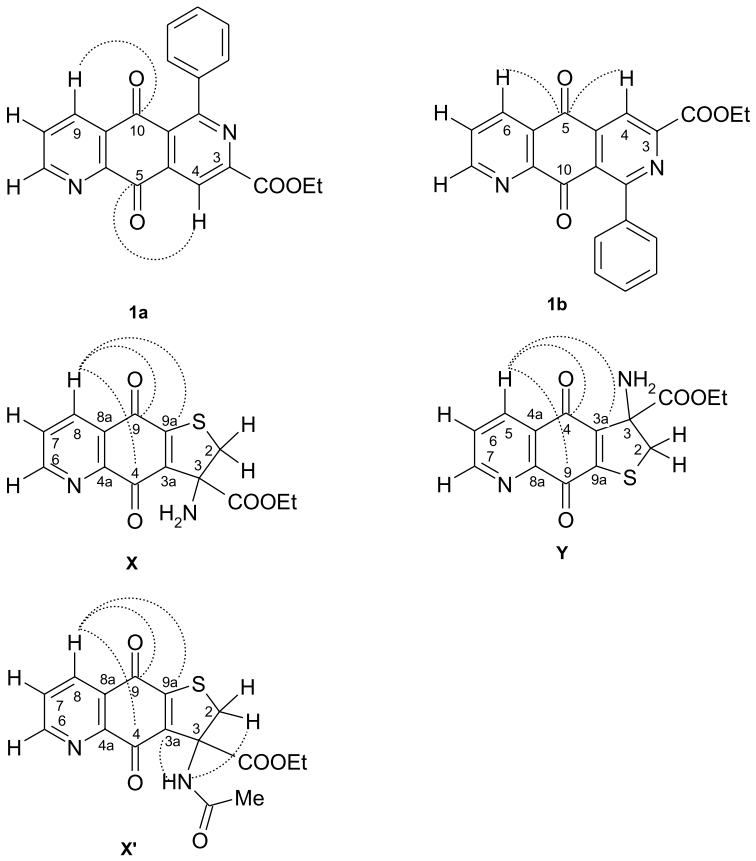


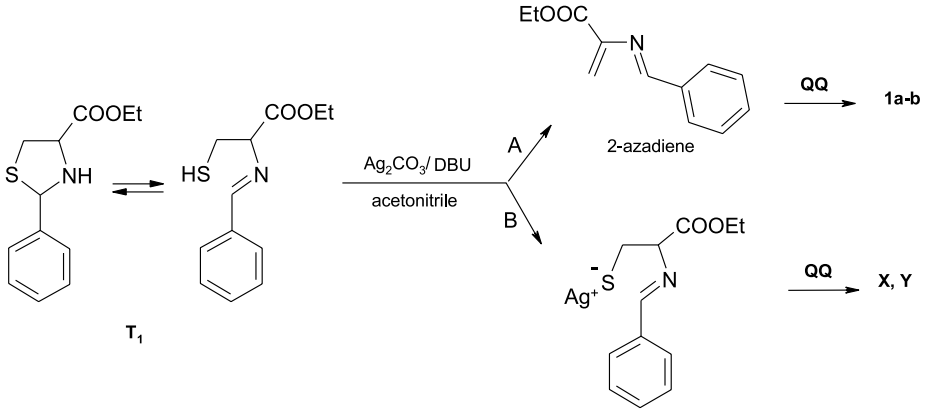
Figure 2. HMBC correlations for compounds **1a**, **1b**, **X**, **Y** and **X′**.

support the reported assignments, the N-acetyl derivative of **X** was prepared and analyzed by HMBC. The singlet assigned to the NH proton at δ_H 7.58 shows a strong $^3J_{C-H}$ correlation with the singlet at δ_C 142.0 (C3a) and with the triplet at δ_C 41.6 (C2), supporting the previous structure assignment.

In accordance with the widely reported reactivity of the quinone system toward the enophiles in the Diels–Alder reaction and toward the nucleophiles in the 1,4-Michael addition, the compounds **1a**-**b**, **X** and **Y** seem to be formed by the competitive attack of different species arising from the thiazolidine demolition[8,9] on **QQ** through the two different pathways A and B (Scheme 1). Scheme 2 depicts the species arising from the thiazolidine ring cleavage, according to the current literature.

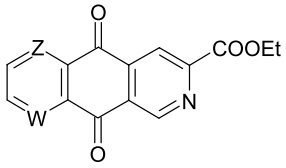
As a specific example, **1a**-**b** both seem to arise from a Diels–Alder reaction between the quinone acting as dienophile, and the enophile phenyl-2-aza-3-ethoxycarbonyl-1,3-butadiene, an azadiene which may be formed in situ by basic breakdown of $\mathbf{T_1}$[8,9] as described in Scheme 2. The total reaction yield was 50%, and the ratios **1a/1b**, **X/Y** were 20/8 and 18/4, respectively (Table 1). This result suggests that a preferential bond takes place between the 6,7 position of **QQ** and the 1,4 position of azadiene.

To further investigate this occurrence, the effect of



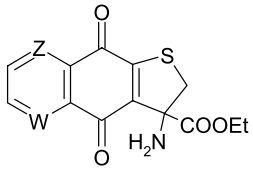
Scheme 2. Thiazolidine cleavage in basic medium (path A and B).

Table 1. Yields of products arising from the reaction between **QQ** and thiazolidines $\mathbf{T_1}$–$\mathbf{T_5}$



a W=CH, Z=N

b W=N, Z=CH



X W=N, Z=CH

Y W=CH, Z=N

Compound	R	Yield (%)	Yield **a/b**	Yield **X/Y**
1	C_6H_5	50	20/8	18/4
2	4-Me–C_6H_4	33	8/8	10/7
3	4-Cl–C_6H_4	40	21/11	6/2
4	4-NO_2–C_6H_4	51	22/12	9/8
5	H	20	—	14/6

thiazolidine substituents on the reaction yields was examined. 2-(4-Methylphenyl)-thiazolidin-4-carboxylic acid ethyl ester ($\mathbf{T_2}$), 2-(4-chlorophenyl)-thiazolidin-4-carboxylic acid ethyl ester ($\mathbf{T_3}$), 2-(4-nitrophenyl)-thiazolidin-4-carboxylic acid ethyl ester ($\mathbf{T_4}$) and thiazolidin-4-carboxylic acid ethyl ester ($\mathbf{T_5}$) were synthesized and used to produce the corresponding azadienes.

On the basis of the results reported in Table 1, the 4-electron-withdrawing substituents on the phenyl group of the thiazolidine increase the yields of compounds **a**-**b** to the detriment of **X**, **Y**. Every attempt to synthesize 3-ethoxycarbonyl-pyrido[*g*]isoquinolin-5,10-diones under the reported conditions by using unsubstituted thiazolidine as a starting compound was unsuccessful and only **X**, **Y** were obtained.

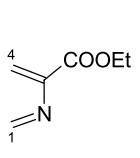
The bonds which develop between dienophile and enophile determining the product distribution in a Diels–Alder reaction can be predicted on the basis of the energy and orbital coefficients of the frontier orbitals (HOMO and LUMO).[11] Table 2 reports the corresponding data of the substituted 2-azadienes (diene) and of the quinolin-5,8-dione (dienophile) involved in the formation of the examined compounds. All the computations have been performed using the PBE0 hybrid density functional theory[12] implemented by one of the authors in the Gaussian03 package[13] with the 6-31G(d) (energies) and STO-3G (coefficients)[14] basis sets. The reliability of this computational level has been corroborated in several studies.[15]

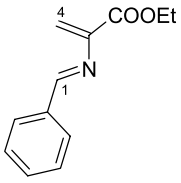
In agreement with our experimental results, the HOMO–LUMO gap between **QQ** and 2-phenylazadiene favours the formation of **1a**. Furthermore, the experimental trends (Table 1) are reproduced by the computations. In particular, the aromatic substituent reduces the gap between the azadiene HOMO and the **QQ** LUMO, thus favouring the Diels–Alder compounds and pushing the reaction to form **1a**-**b**, rather than **X**,**Y**. Unsubstituted thiazolidine, which gives rise to a higher energy gap, does not produce Diels–Alder adducts under our conditions, according to our experimental results.

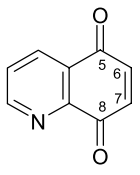
As regards compounds **X** and **Y**, (Scheme 1), they seem to be formed by a 1,4-Michael nucleophilic attack of the thiol group, arising from the opening of thiazolidines $\mathbf{T_{1-5}}$, on the 6 and 7 positions of the α–β unsaturated system of **QQ**.

Schemes 3 and 4, reporting a possible formation mechanism of the compounds **X** and **Y**, show that the silver ions play a determinant role in their formation. The thiazolidine ring, opened in basic medium (DBU), attacks the quinolin-5,8-dione through the thiolate group. A carbanion, arising from

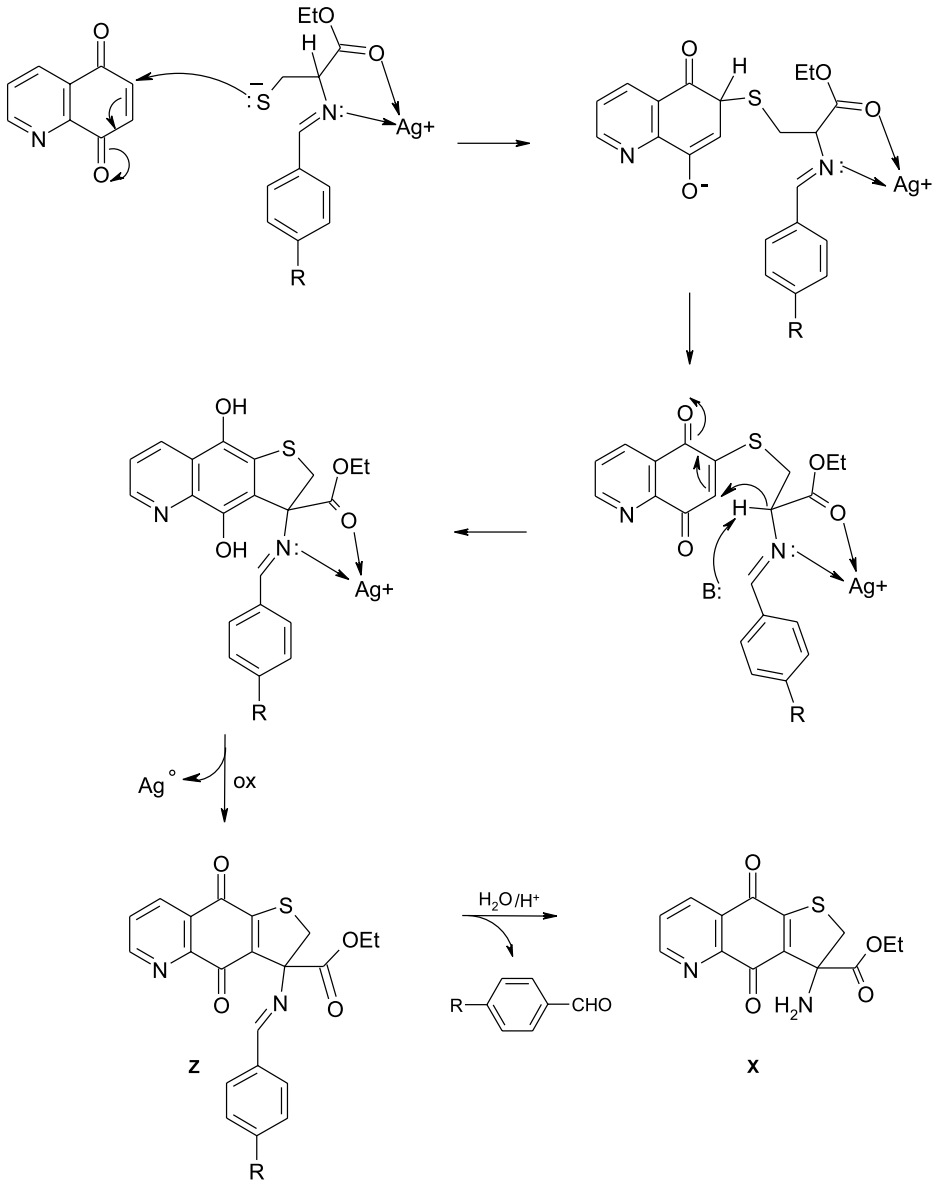
Table 2. Energies (eV) and orbital coefficients of the frontier orbitals of 2-aza-3-carbethoxybutadiene, phenyl-2-aza-3-carbethoxy-1,3-butadiene and quinolin-5,8-dione obtained by PBE0 computations (see text for details)







E (eV)	HOMO	LUMO	HOMO	LUMO		HOMO	LUMO
	−0.2674	−0.0629	−0.2406	−0.0708		−0.2816	−0.1241
			Coefficients				
C_1	−0.3922	0.5193	−0.2899	0.4757	C_5	−0.15153	−0.30222
N	−0.2823	−0.3299	−0.3812	−0.4119	C_8	−0.15438	0.27806
C_3	0.4385	−0.4491	0.2376	−0−3047	C_6	0.21778	−0.45891
C_4	0.5316	0.6735	0.3770	0.5262	C_7	0.21501	0.32492



Scheme 3. Formation mechanism of **X** involving 1,4-Michael addition (path B).

an acid–base reaction of a complex of silver–azomethine nitrogen–carbonyl oxygen, can attack the α,β-unsaturated system. Reduction, followed by re-oxidation, re-forms the quinone system. The unstable azomethine intermediates **Z** and **Z′** by acid treatment furnish **X** and **Y**, respectively. In accordance with the proposed mechanism, Ag° and benzaldehyde were recovered from the reaction mixture.

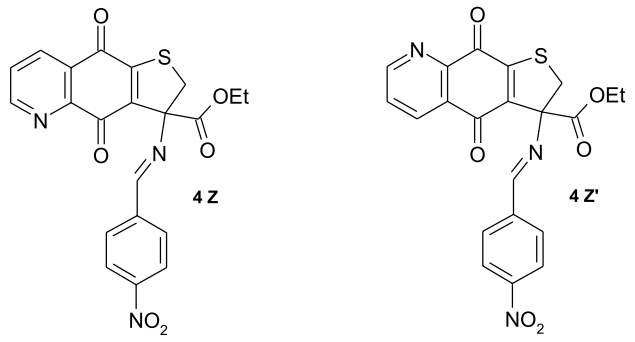
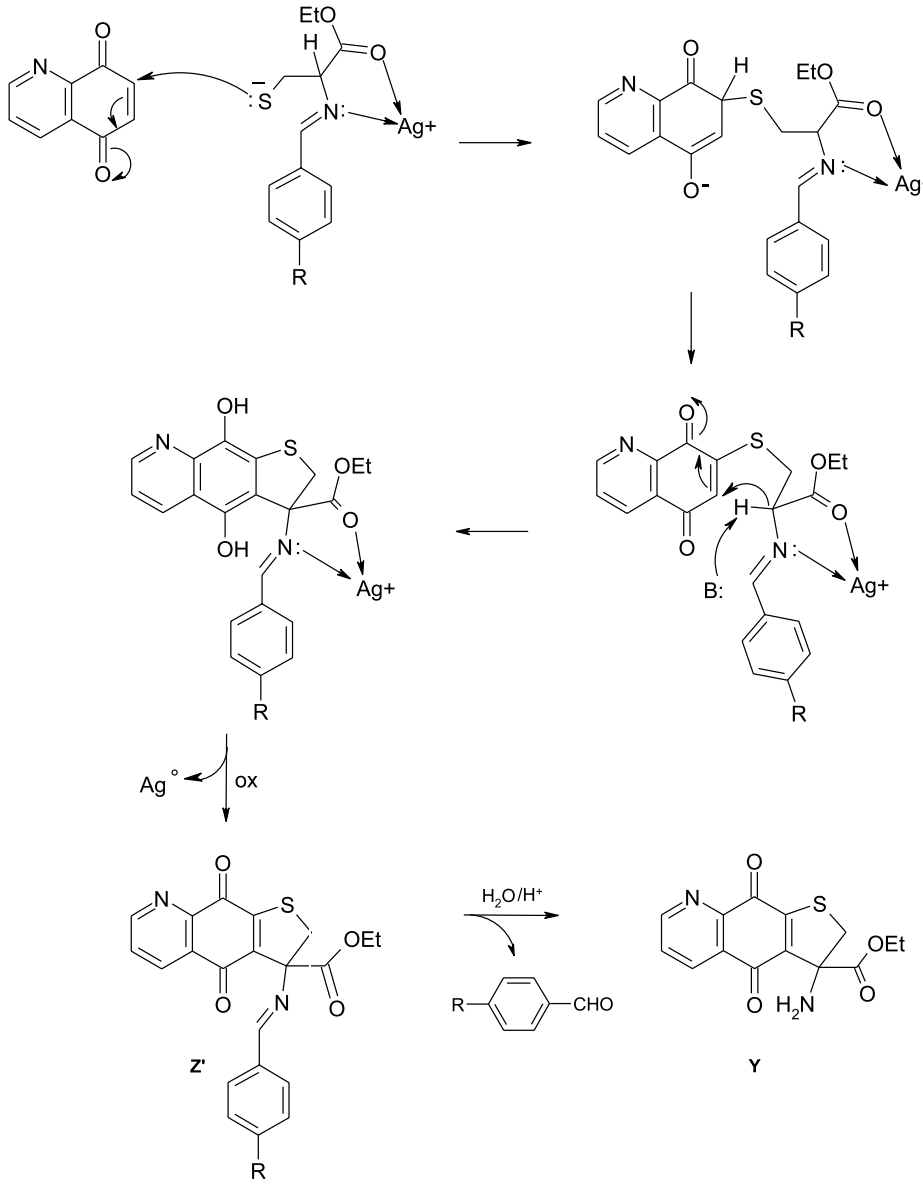


Figure 3. Azomethine intermediates **4Z** and **4Z′** isolated in the reaction mixture of **QQ** and $\mathbf{T_4}$.

In the exclusive case of the reaction performed with **QQ** and thiazolidine $\mathbf{T_4}$, the intermediates **4Z** and **4Z′** were isolated and characterized (Fig. 3). These compounds, present in small amount, support the formation mechanism of **X** and **Y**.

Summing up, 2-arylthiazolidine-4-carboxylic acid ethyl ester in basic medium seems to undergo two different cleavages: the first one produces an aryl-azadiene, the second one a thiolic species. In the presence of quinolinquinone, Diels–Alder product PQDs are formed together with those arising from an 1,4-addition reaction. No Diels–Alder compound is observed by using unsubstituted thiazolidine, which shows that the aryl substituents play a role in that reaction.



Scheme 4. Formation mechanism of **Y** involving 1,4-Michael addition (path B).

2. Experimental

2.1. General procedure

Melting points were determined by a Kofler apparatus and are uncorrected. Electron impact (EI) mass spectra were obtained at 70 eV on a ZAB 2F spectrometer. The purity of compounds was checked by ascending TLC on Merck's silica gel plates (0.25 mm) with fluorescent baking. UV spectra were recorded with Perkin–Elmer 550 S spectrophotometer. IR spectra were taken on Perkin–Elmer 399 spectrophotometer in KBr. NMR measurements (data reported in δ) were performed on a Bruker AMX-500 spectrometer equipped with a Bruker X-32 computer, using the UXNMR software package. NMR spectra were measured at 500 MHz (^{1}H) and 125 MHz (^{13}C). The chemical shifts are referenced to $^{13}CDCl_3$ and $CDCl_3$ solvent signals at 77.0 and 7.26 ppm, respectively. Standard pulses sequences were employed for magnitude COSY. HMQC and HMBC experiments were optimized for $^{1}J_{C-H}=135$ Hz, $^{2,3}J_{C-H}=10$ Hz, respectively. Me_4Si was used as internal reference.

2.2. General procedure for the synthesis of 1-aryl-3-ethoxycarbonyl-pyrido[2,3-*g*]isoquinolin-5,10-diones (1a-4a), 1-aryl-3-ethoxycarbonyl-pyrido [3,2-*g*]isoquinolin-5,10-diones (1b-4b), 3-amino-3-ethoxycarbonyl-dihydrothieno[2,3-*g*]quinolin-4,9-dione (X) and 3-amino-3-ethoxycarbonyl-dihydrothieno [3,2-*g*]quinolin-4,9-dione (Y)

A mixture of 2-aryl-1,3-thiazolidine ethyl esters (1 mmol) and silver carbonate (1 mmol), in anhydrous acetonitrile (50 mL), at −20 °C, was added to a solution of quinolin-5,8-dione (1 mmol) in anhydrous acetonitrile (50 mL). After 15 min, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU, 1 mmol) was added. To the reaction mixture, stirred for 2 h at −20 °C and kept at

room temperature over night, diethyl ether was added (50 mL) and the solid residue containing silver was taken away. Diethyl ether HCl_{sat} (10 mL), was added to the organic layer and the mixture was stirred for 10 min. Two fractions were recovered, an organic layer and a brown precipitate.

The organic layer, washed with 10% $NaHCO_3$ solution and dried with Na_2SO_4 anhydrous afforded crude Diels Alder products **1-4 a**, **b**. The isomeric **a** and **b** products were separated chromatographically on silica gel plates using a mixture of carbon tetrachloride/ethyl acetate (1:1; v:v) as eluent. Aldehydes arising from **X** and **Y** formation were also recovered.

The brown precipitate dissolved in water, neutralized with 10% $NaHCO_3$ solution was extracted with chloroform yielding the dihydrothienoquinolindiones **X** and **Y** as free bases. The racemic mixtures of **X** and **Y** were separated by flash chromatography using diethyl ether/$CHCl_3$ (3:7; v:v).

2.2.1. 1-Phenyl-3-ethoxycarbonyl-pyrido[2,3-*g*]isoquinolin-5,10-dione (1a). Pale-yellow solid (yield 80.6 mg, 20 mol%), mp 205–206 °C; [found: C, 70.41; H, 3.93; N, 7.84. $C_{21}H_{14}N_2O_4$ requires C, 70.39; H, 3.94; N, 7.82%]; R_f (5% $Et_2O/CHCl_3$) 0.50; UV–vis ($CHCl_3$) λ_{max} (log ε) nm 358 (2.6); ν_{max} (KBr) 3154–2975 (br), 1695, 1590, 1499 cm^{-1}; δ_H (500 MHz $CDCl_3$) 9.13 (1H, dd; J=4.8, 1.2 Hz), 8.82 (1H, s), 8.64 (1H, dd; J=7.8, 1.2 Hz), 7.79 (1H, dd; J=7.8, 4.8 Hz), 7.59 (2H, d; J=7.0 Hz), 7.47 (3H, d+t; J=7.0 Hz), 4.53 (2H, q; J=7.2 Hz), 1.50 (3H, t; J=7.2 Hz); δ_C (125 MHz, $CDCl_3$) 181.7 (s, C5), 180.9 (s, C10), 163.6 (s, COO), 162.5 (s, C1), 156.1 (d, C7), 151.8 (s, C3), 149.7 (s, C5a), 141.3 (s, C10a), 138.9 (d, C1′), 135.2 (d, C9), 128.8 (d, C8), 128.7 (s, C9a), 128.5 (2C d, C2′6′), 128.0 (2C d, C3′5′), 126.9 (d, C4a), 126.8 (d, C4′), 119.3 (d, C4), 62.6 (t, *CH_2*–CH_3), 14.2 (q, CH_2–*CH_3*). MS (EI) *m/z* 358 (M+).

2.2.2. 1-(4-Methylphenyl)-3-ethoxycarbonyl-pyrido[2,3-*g*]isoquinolin-5,10-diones (2a). Pale-yellow solid (yield 29.6 mg, 8 mol%), mp 203–4 °C; [found: C, 70.92; H, 4.32; N, 7.53. $C_{21}H_{14}N_2O_4$ requires $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52%]; R_f (5% $Et_2O/CHCl_3$) 0.45; UV–vis ($CHCl_3$) λ_{max} (log ε) nm 389 (3.3); ν_{max} (KBr) 3096–2930 (br), 1703, 1560, 1460 cm^{-1}; δ_H (500 MHz $CDCl_3$) 9.15 (1H, dd; J=4.8, 1.2 Hz), 8.89 (1H, s), 8.53 (1H, dd; J=7.8, 1.2 Hz), 7.76 (1H, dd; J=7.8, 4.8 Hz), 7.46 (2H, d; J=8.6 Hz), 7.30 (2H, d; J=8.6 Hz), 4.53 (2H, q; J=7.2 Hz), 2.42 (3H, s), 1.47 (3H, t; J=7.2 Hz). δ_C (125 MHz, $CDCl_3$) 181.7 (s, C5), 180.5 (s, C10), 163.7 (s, COO), 162.4 (s, C1), 156.0 (d, C7), 151.5 (s, C3), 149.5 (s, C5a), 141.3 (s, C10a), 139.4 (s, C1′), 136.0 (s, C4′), 135.1 (d, C9), 131.6 (s, C9a), 129.1 (2C d, C2′6′), 128.8 (2C d, C3′5′), 127.9 (d, C8), 125.6 (s, C4a), 118.9 (d, C4), 62.5 (t, *CH_2*–CH_3), 21.4 (q, CH_3), 14.1 (q, CH_2–*CH_3*). MS (EI) *m/z* 372 (M+).

2.2.3. 1-(4-Chlorophenyl)-3-ethoxycarbonyl-pyrido[2,3-*g*]isoquinolin-5,10-diones (3a). Pale-yellow solid (yield 82.3 mg, 21 mol%), mp 208–9 °C; [found: C, 64.30; H, 3.32; N, 7.14. $C_{21}H_{13}N_2O_4Cl$ requires C, 64.21; H, 3.34; N, 7.13%]; R_f (5% $Et_2O/CHCl_3$) 0.55; UV–vis ($CHCl_3$) λ_{max} (log ε) nm 369 (2.8); ν_{max} (KBr) 3094–2937 (br), 1710, 1665, 1537, 1409, 1110 cm^{-1}; δ_H (500 MHz $CDCl_3$) 9.16 (1H, dd; J=4.8, 1.2 Hz), 8.84 (1H, s), 8.65 (1H, dd; J=7.8, 1.2 Hz), 7.79 (1H, dd; J=7.8, 4.8 Hz), 7.55 (2H, d; J=8.6 Hz), 7.45 (2H, d; J=8.6 Hz), 4.54 (2H, q; J=7.2 Hz), 1.48 (3H, t; J=7.2 Hz). δ_C (125 MHz, $CDCl_3$) 181.7 (s, C10), 181.1 (s, C5), 163.7 (s, COO), 161.4 (s, C1), 156.4 (d, C7), 152.0 (s, C3), 149.5 (s, C5a), 141.6 (s, C10a), 130.5 (2C d, C2′6′), 137.6 (s, C4′), 135.9 (d, C9), 135.5 (d, C9a), 129.6 (s, C1′), 128.7 (2C d, C3′5′), 128.4 (d, C8), 126.8 (s, C4a), 119.99 (d, C4), 62.5 (t, *CH_2*–CH_3), 14.1 (q, CH_2–*CH_3*). MS *m/z* 392 (M+), 394 (M+2, 32% M+).

2.2.4. 1-(4-Nitrophenyl)-3-ethoxycarbonyl-pyrido[2,3-*g*]isoquinolin-5,10-diones (4a). Yellow solid (yield 96.1 mg, 22 mol%), mp 308–9 °C; [found: C, 62.63; H, 3.26; N, 10.40. $C_{21}H_{13}N_3O_6$ requires C, 62.53; H, 3.25; N, 10.42%]; R_f (5% $Et_2O/CHCl_3$) 0.40; UV–vis ($CHCl_3$) λ_{max} (log ε) nm 369 (2.8); ν_{max} (KBr) 3109–2975 (br), 2260, 1733, 1688, 1560, 1409 cm^{-1}; δ_H (500 MHz $CDCl_3$) 9.20 (1H, dd; J=4.8, 1.2 Hz), 9.02 (1H, s), 8.52 (1H, dd; J=7.8, 1.2 Hz), 8.37 (2H, d; J=8.6 Hz), 7.81 (1H, dd; J=7.8, 4.8 Hz), 7.69 (2H, d; J=8.6 Hz), 4.56 (2H, q; J=7.2 Hz), 1.48 (3H, t; J=7.2 Hz); δ_C (125 MHz, $CDCl_3$) 181.5 (s, C5), 180.5 (s, C10), 163.2 (s, COO), 161.8 (s, C1), 156.4 (d, C7), 151.7 (s, C3), 148.2 (s, C5a), 142.4 (s, C10a), 138.9 (s, C1′), 136.7 (d, C4′), 135.4 (d, C9), 132.2 (s, C9a), 130.1 (2C d, C3′5′), 129.0 (d, C8), 123.2 (2C d, C2′6′), 126.1 (s, C4a), 120.7 (d, C4), 62.7 (t, *CH_2*–CH_3), 14.2 (q, CH_2–*CH_3*). MS (EI) *m/z* 403 (M+).

2.2.5. 1-Phenyl-3-ethoxycarbonyl-pyrido[3,2-*g*]isoquinolin-5,10-dione (1b). Pale-yellow solid (yield 32.2 mg, 8 mol%), mp 209–10 °C; [found: C, 70.35; H, 3.95; N, 7.83. $C_{21}H_{14}N_2O_4$ requires C, 70.39; H, 3.94; N, 7.82%; R_f (5% $Et_2O/CHCl_3$) 0.50; UV–vis ($CHCl_3$) λ_{max} (log ε) nm 360 (2.9); ν_{max} (KBr) 3050–2960 (br), 1710, 1655, 1575, 1447 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.15 (1H, dd; J=4.8, 1.2 Hz), 8.92 (1H, s), 8.52 (1H, dd; J=7.8, 1.2 Hz), 7.77 (1H, dd; J=7.8, 4.8 Hz), 7.54 (2H, d; J=7.0 Hz), 7.51 (2H, t; J=7.2 Hz), 7.47 (1H, t; J=7.0 Hz), 4.53 (2H, q; J=7.2 Hz), 1.47 (3H, t; J=7.2 Hz). δ_C (125 MHz, $CDCl_3$) 181.6 (s, C10), 180.5 (s, C5), 163.5 (s, COO), 162.2 (s, C1), 155.4 (d, C8), 151.6 (s, C3), 147.7 (s, C9a), 141.7 (s, C10a), 139.4 (s, C1′), 135.8 (d, C6), 131.5 (s, C5a), 129.2 (2C d, C2′6′), 129.0 (2C d, C3′5′), 128.7 (d, C4′), 128.5 (d, C7), 125.5 (s, C4a), 120.0 (d, C4), 62.6 (t, *CH_2*–CH_3), 14.2 (q, CH_2–*CH_3*). MS *m/z* 358 (M+).

2.2.6. 1-(4-Methylphenyl)-3-ethoxycarbonyl-pyrido[3,2-*g*]isoquinolin-5,10-diones (2b). Pale-yellow solid (yield 29.6 mg, 8 mol%), mp 208–9 °C; [found: C, 70.96; H, 4.33; N, 7.50. $C_{22}H_{16}N_2O_4$ requires C, 70.96; H, 4.33; N, 7.52%]; R_f (5% $Et_2O/CHCl_3$) 0.40; UV–vis ($CHCl_3$) λ_{max} (log ε) nm: 391 (3.5); ν_{max} (KBr) 3109–2930 (br), 1733, 1665, 1499 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.16 (1H, dd; J=4.8, 1.2 Hz), 8.78 (1H, s), 8.64 (1H, dd; J=7.8, 1.2 Hz), 7.80 (1H, dd; J=7.8, 4.8 Hz), 7.51 (2H, d; J=8.6 Hz), 7.27 (2H, d; J=8.6 Hz), 4.53 (2H, q; J=7.2 Hz), 2.45 (3H, s), 1.46 (3H, t; J=7.2 Hz). δ_C (125 MHz, $CDCl_3$) 181.8 (s, C10), 181.1 (s, C5), 163.6 (s, COO), 162.3 (s, C1), 155.3 (d, C8), 151.8 (s, C3), 147.7 (s, C9a), 141.7 (s, C10a), 139.5 (s, C1′), 136.5 (s, C4′), 136.5 (d, C6), 129.9 (s, C5a), 129.3 (2C d, C2′6′), 128.9 (2C d, C3′,5′), 128.7 (d, C7), 126.9 (s, C4a),

119.7 (d, C4), 62.5 (t, *CH*$_2$–CH$_3$), 21.3 (q, CH$_3$), 14.2 (q, CH$_2$–*CH*$_3$). MS *m/z* 372 (M+).

2.2.7. 1-(4-Chlorophenyl)-3-ethoxycarbonyl-pyrido[3,2-*g*] isoquinolin-5,10-diones (3b). Pale-yellow solid (yield 43.1 mg, 11 mol%), mp 217–8 °C; [found: C, 64.41; H, 3.35; N, 7.15. $C_{21}H_{13}N_2O_4Cl$ requires C, 64.21; H, 3.34; N, 7.13%]; R_f (5% Et$_2$O/CHCl$_3$) 0.45;); UV–vis (CHCl$_3$) λ_{max} (log ε) nm: 370 (2.9); ν_{max} (KBr) 3070–2980 (br), 1675, 1575, 1409, 1110 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 9.17 (1H, dd; *J*=4.8, 1.2 Hz), 8.94 (1H, s), 8.54 (1H, dd; *J*=7.8, 1.2 Hz), 7.82 (1H, dd; *J*=7.8, 4.8 Hz), 7.50 (2H, d; *J*=8.6 Hz), 7.47 (2H, d; *J*=8.6 Hz), 4.55 (2H, q; *J*=7.2 Hz), 1.46 (3H, t; *J*=7.2 Hz). δ_C (125 MHz, CDCl$_3$) 181.6 (s, C10), 180.2 (s, C5), 163.4 (s, COO), 160.9 (s, C1), 155.5 (d, C7), 152.3 (s, C3), 147.7 (s, C9a), 141.3 (s, C10a), 137.1 (2C d, C2′6′), 135.8 (d, C6), 135.6 (s, C4′), 130.4. (s, C1′), 129.4 (s, C5a), 128.6 (d, C7), 128.5 (2C d, C3′5′), 125.7 (s, C4a), 120.3 (d, C4), 62.7 (t, *CH*$_2$–CH$_3$), 14.1 (q, CH$_2$–*CH*$_3$). MS (EI) *m/z* 392 (M+), 394 (M+2, 32% M+).

2.2.8. 1-(4-Nitrophenyl)-3-ethoxycarbonyl-pyrido[3,2-*g*] isoquinolin-5,10-diones (4b). Yellow solid (yield 52.4 mg, 12 mol%), mp 311–2 °C; [found: C, 62.58; H, 3.26; N, 10.41. $C_{21}H_{13}N_3O_6$ requires C, 62.53; H, 3.25; N, 10.42%]; R_f (5% Et$_2$O/CHCl$_3$) 0.55; UV–vis (CHCl$_3$) λ_{max} (log ε) nm 371 (3.0); ν_{max} (KBr) 3190–2975 (br), 1733, 1655, 1590, 1432 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 9.17 (1H, dd; *J*=4.8, 1.2 Hz), 8.93 (1H, s), 8.68 (1H, dd; *J*=7.8, 1.2 Hz), 8.34 (2H, d; *J*=8.6 Hz), 7.82 (1H, dd; *J*=7.8, 4.8 Hz), 7.73 (2H, d; *J*=8.6 Hz), 4.56 (2H, q; *J*=7.2 Hz), 1.48 (3H, t; *J*=7.2 Hz); δ_C (125 MHz, CDCl$_3$) 182.1 (s, C10), 181.9 (s, C5), 163.3 (s, COO), 162.5 (s, C1), 155.9 (d, C8), 152.1 (s, C3), 148.9 (s, C9a), 142.9 (s, C10a), 139.3 (s, C1′), 136.5 (d, C4′), 135.9 (d, C6), 130.0 (2C d, C3′5′), 129.5 (d, C5a), 128.4 (d, C7), 125.5 (s, C4a), 123.2 (2C d, C2′6′), 121.3 (d, C4), 63.0 (t, *CH*$_2$–CH$_3$), 14.1 (q, CH$_2$–*CH*$_3$). MS *m/z* 403 (M+).

2.2.9. 3-Amino-3-ethoxycarbonyl-dihydrothieno[2,3-*g*] quinolin-4,9-dione (X). Orange solid (yields from the reaction between **QQ** and **T$_1$** (54.7 mg, 18 mol%), **T$_2$** (30.4 mg, 10 mol%), **T$_3$** (18.2 mg, 6 mol%), **T$_4$** (27.3 mg, 9 mol%), and **T$_5$** (39.3 mg, 14 mol%), mp >200 °C dec.; ν_{max} (KBr) 3216–2945 (br), 1733, 1635, 1567, 1437 cm^{-1}; UV–vis (CHCl$_3$) λ_{max} (log ε) nm 418 (3.6); R_f (5% MeOH/CHCl$_3$) 0.55; δ_H (500 MHz, CDCl$_3$); 9.01 (1H, dd; *J*=4.3, 1.6 Hz), 8.40 (1H, dd; *J*=8.2, 1.6 Hz), 7.64 (1H, dd; *J*=8.2, 4.3 Hz), 4.27 (2H, q; *J*=7.2 Hz), 3.87 (1H, d; *J*=12.4 Hz), 3.34 (1H, d; *J*=12.4 Hz), 2.37 (2H, bs; NH$_2$), 1.27 (3H, t; *J*=7.2 Hz); δ_C (125 MHz, CDCl$_3$) 180.7 (s, C9), 179.9 (s, C4), 172.5 (s, COO), 154.9 (s, C9a), 154.3 (d, C6), 146.7 (s, C4a), 142.0 (s, C3a), 136.7 (d, C8), 129.1 (s, C8a), 128.2 (d, C7), 73.3 (s, C3), 62.6 (t, *CH*$_2$–CH$_3$), 42.4 (t, C2), 14.0 (q, CH$_2$–*CH*$_3$). MS (EI) *m/z* 304 (M+), 306 (M+2, 11% M+), 308 (M+4, 4% M+).

2.2.10. 3-Acetylamino-3-ethoxycarbonyl-dihydrothieno [2,3-*g*]quinolin-4,9-dione (X′). Compound **X** (30 mg), dissolved in dichloromethane (25 mL), treated with acetyl chloride (10% excess) was stirred for 2 h. The reaction mixture washed with 10% NaHCO$_3$ solution and dried with Na$_2$SO$_4$ anhydrous afforded crude the acetyl derivative **X′** (yield 31 mg, 90%), which was crystallized from ethanol. Yellow solid, mp 208–9 °C; [found: C, 55.36; H, 3.98; N, 9.23. $C_{16}H_{14}N_2O_5S$ requires C, 55.26; H, 3.97; N, 9.21]; UV–vis (CHCl$_3$) λ_{max} (log ε) nm 401 (3.0); ν_{max} (KBr) 3065–2975 (br), 2267, 1718, 1635, 1605 cm^{-1}; R_f (3% MeOH/CHCl$_3$) 0.65; δ_H (500 MHz, CDCl$_3$) 9.01 (1H, dd; *J*=4.3, 1.6 Hz), 8.36 (1H, dd; *J*=8.2, 1.6 Hz), 7.67 (1H, dd; *J*=8.2, 4.3 Hz), 7.58 (1H, s; NH), 4.32 (2H, q; *J*=7.2 Hz), 4.03 (1H, d; *J*=12.6 Hz), 3.90 (1H, d; *J*=12.6 Hz), 2.18 (3H, s), 1.26 (3H, t; *J*=7.2 Hz); δ_C (125 MHz, CDCl$_3$) 179.5 (s, C9), 178.0 (s, C5), 170.2 (s, COO), 169.5 (CONH), 155.2 (d, C6), 154.9 (s, C9a), 147.6 (s, C4a), 142.0 (s, C3a), 129.0 (s, C8a), 135.1 (d, C8), 125.9 (d, C7), 73.1 (s, C3), 62.4 (t, *CH*$_2$–CH$_3$), 41.6 (t, C2), 19.9 (q, CH$_3$), 14.0 (q, CH$_2$–*CH*$_3$). MS (EI) *m/z* 346 (M+), 348 (M+2, 121% M+), 350 (M+4, 4% M+).

2.2.11. 3-Amino-3-ethoxycarbonyl-dihydrothieno[3,2-*g*] quinolin-4,9-dione (Y). Orange solid (yields from the reaction between **QQ** and **T$_1$** (12.2 mg, 4 mol%), **T$_2$** (21.2 mg, 7 mol%), **T$_3$** (6.1 mg, 2 mol%), **T$_4$** (24.3 mg, 8 mol%), and **T$_5$** (18.2 mg, 6 mol%), mp >200 °C dec.; [found: C, 55.28; H, 3.97; N, 9.23. $C_{16}H_{14}N_2O_5S$ requires C, 55.26; H, 3.97; N, 9.21%]; R_f (5% MeOH/CHCl$_3$) 0.40; UV–vis (CHCl$_3$) λ_{max} (log ε) nm 413 (3.2); ν_{max} (KBr) 3336–2937 (br), 1733, 1642, 1575, 1432 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 9.00 (1H, dd; *J*=4.3, 1.6 Hz), 8.38 (1H, dd; *J*=8.2, 1.6 Hz), 7.62 (1H, dd; *J*=8.2, 4.3 Hz), 4.27 (2H, q; *J*=7.2 Hz), 3.85 (1H, d; *J*=12.4 Hz), 3.36 (1H, d; *J*=12.4 Hz), 2.28 (2H, bs; NH$_2$), 1.27 (3H, t; *J*=7.2 Hz); δ_C (125 MHz, CDCl$_3$) 180.1 (s, C9), 180.0 (s, C4), 171.9 (s, COO), 155.5 (d, C7), 154.7 (s, C9a), 146.8 (s, C8a), 142.2 (s, C3a), 135.8 (d, C5), 128.9 (s, C4a), 128.5 (d, C6), 72.0 (s, C3), 62.5 (t, *CH*$_2$–CH$_3$), 43.1 (t, C2), 14.1 (q, CH$_2$–*CH*$_3$). MS (EI) *m/z* 304 (M+), 306 (M+2, 11% M+), 308 (M+4, 4% M+).

2.2.12. 3-(4′-NO$_2$-Benzyliden)amino-3-ethoxycarbonyl-dihydrothieno[2,3-*g*]quinolin-4,9-dione (4Z). Orange oil (yields 3.5 mg, 0.8 mol%); [found: C, 57.69; H, 3.44; N, 9.64. $C_{16}H_{14}N_2O_5S$ requires C, 57.66; H, 3.46; N, 9.61%]; R_f (5% MeOH/CHCl$_3$) 0.60; UV–vis (CHCl$_3$) λ_{max} (log ε) nm 421 (3.0); ν_{max} (KBr) 3099, 2996, 2606, 1703, 1665, 1620, 1590, 1510, 1432 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 9.05 (1H, dd; *J*=4.8, 1.8 Hz), 8.54 (1H, s), 8.43 (1H, dd; *J*=7.2, 1.8 Hz), 8.24 (2H, d; *J*=8.4 Hz), 7.94 (2H, d; *J*=8.4 Hz), 7.66 (1H, dd; *J*=7.2, 4.8 Hz), 4.30 (2H, q; *J*=7.2 Hz), 4.13 (1H, d; *J*=11.8 Hz), 3.80 (1H, d; *J*=11.8 Hz), 1.26 (3H, t; *J*=7.2 Hz); δ_C (125 MHz, CDCl$_3$) 13.9 (q, *CH*$_2$–CH$_3$), 44.0 (t, S–*CH*$_2$), 61.8 (*CH*$_2$–CH$_3$), 72.6 (s, N–*C*–CO), 124.1 (d, 2C3′), 127.1 (d, C6), 128.7 (s, C4a), 128.8 (d, 2C2′), 134.5 (d, C5), 142.7 (s, C9a), 143.7 (s, C1′), 150.3 (s, C4′), 151.1 (s, C3a), 155.1 (s, C8a), 156.2 (d, C7), 162.1 (d, N=*CH*), 169.9 (s, C4) 177.4 (s, C9), 178.3 (s, CO ester). MS (EI) *m/z* 437 (M+), 439 (M+2, 11% M+), 441 (M+4, 4% M+).

2.2.13. 3-(4′-NO$_2$-Benzyliden)amino-3-ethoxycarbonyl-dihydrothieno[3,2-*g*]quinolin-4,9-dione (4Z′). Orange oil (yields 2,5 mg, 0.5 mol%); [found: C, 57.71; H, 3.47; N, 9.64. $C_{16}H_{14}N_2O_5S$ requires C, 57.66; H, 3.46; N, 9.61%]; R_f (3% MeOH/CHCl$_3$) 0.50; UV–vis (CHCl$_3$) λ_{max} (log ε) nm 423 (3.0); ν_{max} (KBr) 3096, 2965, 2614, 1703,

1620, 1447 cm^{-1}; δ_H (500 MHz $CDCl_3$) 9.03 (1H, dd; J= 4.8, 1.8 Hz), 8.54 (1H, s), 8.40 (1H, dd; J=7.2, 1.8 Hz), 8.21 (2H, d; J=8.4 Hz), 7.93 (2H, d; J=8.4 Hz), 7.64 (1H, dd; J=7.2, 4.8 Hz), 4.32 (2H, q; J=7.2 Hz), 4.14 (1H, d; J=11.8 Hz), 3.81 (1H, d; J=11.8 Hz), 1.28 (3H, t; J= 7.2 Hz); δ_C (125 MHz, $CDCl_3$) 14.1 (q, CH_2–CH_3), 40.2 (t, S–CH_2), 62.1 (CH_2–CH_3), 72.5 (s, N–*C*–CO), 124.3 (d, 2C3′), 127.3 (d, C6), 128.9 (s+d, C4a+2C2′), 134.5 (d, C5), 141.8 (s, C9a), 142.7 (s, C1′), 151.2 (s, C4′), 151.4 (s, C3a), 155.1 (s, C8a), 156.4 (d, C7), 162.1 (d, N=*CH*), 170.9 (s, C4) 177.1 (s, C9), 178.3 (s, CO ester). MS (EI) *m/z* 437 (M+), 439 (M+2, 11% M+), 441 (M+4, 4% M+).

Acknowledgements

The authors thank the Centro Interdipartimentale di Metodologie Chimico-Fisiche and the Centro Interdipartimentale di Analisi Strumentale dell'Università di Napoli "Federico II". This work was supported by a grant from Ministero dell'Università e della Ricerca Scientifica.

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Asymmetric synthesis of 1-deoxynojirimycin and its congeners from a common chiral building block

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Received 19 May 2004; accepted 16 June 2004

Available online 21 July 2004

Abstract—A new, promising chiral building block **9** for the synthesis of 1-deoxy-4,5-*trans*-oriented azasugars such as 1-deoxynojirimycin (**1**) was prepared in only four steps from the Garner aldehyde **10** using catalytic ring-closing metathesis (RCM) for the construction of the piperidine ring. In practical test, the first synthesis of all four isomers (**1** and **6**-**8**) of *trans*-4,5-orientated 1-deoxyiminosugars using **9** as a common chiral building block was demonstrated.

1. Introduction

Interest in polyhydroxylated piperidines has undergone a remarkable expansion in recent years[1] since the discovery of nojirimycin, a glycosidase inhibitor that mimics glucose (by analogy with the glycosyl oxocarbenium intermediate produced during the enzymatic cleavage of glycosides).[2] The biological properties of iminosugars can be attributed to their structural resemblance to oxygenated analogues found in natural substrates. Thus, because of these mimetic properties, iminosugars could be of great value in treating a variety of diseases such as diabetes,[3] viral infections,[4] and tumor metastasis.[5] Typical examples of natural products that have shown potent glycosidase inhibition properties are 1-deoxynojirimycin **1**,[6] 1-deoxygalactstatin **2**,[7] and fagomine **3**,[8] which have varying levels of oxygenation and a stereochemical array on the piperidine ring (Fig. 1). The therapeutic importance of these compounds has increasing interest in developing methods for their preparation.

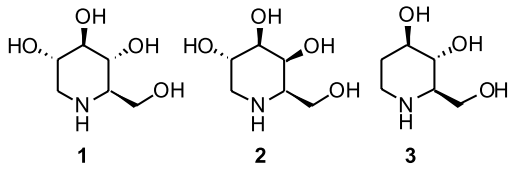
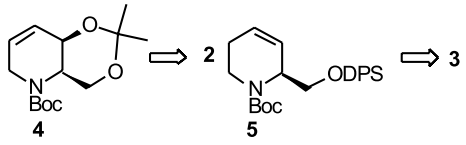


Figure 1.

In previous studies, we reported on the straightforward and stereoselective synthesis of **2** and **3** using dioxanylpiperidene **4**,[9] and hydroxymethylpiperidene **5**,[10] respectively, as chiral building blocks (Scheme 1).



Scheme 1.

However, **1** and its three stereoisomers, that is, 1-deoxyaltronojirimycin (**6**), 1-deoxymannonojirimycin (**7**), and 1-deoxyallonojirimycin (**8**) of *trans*-4,5-substituted 1-deoxyazasugars (nojirimycin-type) have been not synthesized from a common chiral building block (Fig. 2). In a project focused on the asymmetric synthesis of glycosidase inhibitors, we envisioned dioxanylpiperidene **9** as a new common chiral building block, which represents an ideal precursor for synthesis of 1-deoxynojirimycin (**1**) and its congeners (Fig. 2). Herein we describe a straightforward synthesis of 1-deoxynojirimycin (**1**) and its congeners **6**-**8** via **9** starting from the Garner aldehyde **10** using catalytic ring-closing metathesis (RCM)[11] to construct the piperidine ring (Scheme 2).

Keywords: Iminosugars; Garner aldehyde; Asymmetric synthesis.
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doi:10.1016/j.tet.2004.06.112

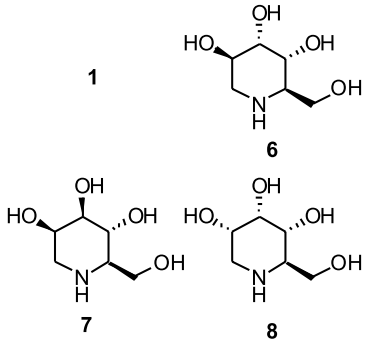
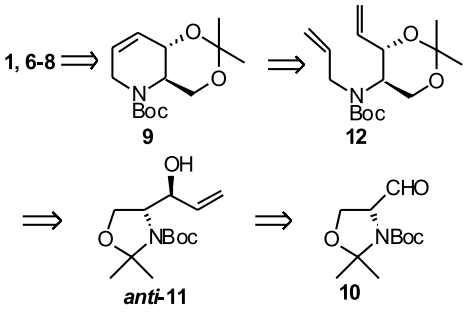


Figure 2. Structures of 1-deoxynojirimycin and its congeners.

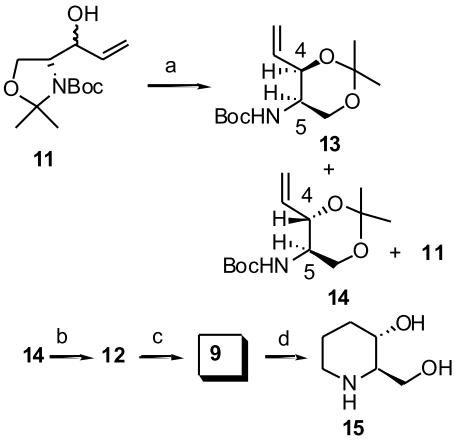


Scheme 2. Retrosynthesis of **1**, **6**, **7**, and **8**.

2. Results and discussion

Our retorosynthetic analysis of 1-deoxyazasugars **1**, **6**-**8** is outlined in Scheme 2. The proposed preparation of the common intermediate **9** involves the RCM of diolefin **12**, produced by the stereoselctive coupling of **10** with vinyl metals.

The D-serine-derived Garner aldehyde **10** provided an attractive starting point for the synthesis since it reacts with organometalic reagents with a high degree of diastereoselectivity and racemization is minimal.[12] The diastereoselective addition of vinyl metals to **10** could furnish the *anti*-vinyl alcohol *anti*-**11**, depending on the reaction conditions used.[13] The results are summarized in Table 1. While the use of HMPA as a cosolvent accounts for the high *anti*-selectivity (entry 5). The diastereoselectivity is convincingly accounted for by considering the preferred transition state in each reaction. According to the well-known Felkin-Anh model, the nucleophile preferentially attacks the si-face of aldehyde **10** thereby leading to the *anti*-configuration. The chromatographic separation of a diastereomeric mixture of alcohols **11** was not successful.

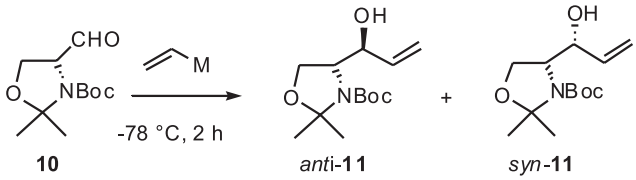


Scheme 3. Reagents and conditions: (a) 0.15 N HCl gas in $CHCl_3$, rt, overnight, **13** (1.8%), **14** (47%), **11** (32%); (b) allyl iodide, NaH, THF, 0 °C, overnight, 95%; (c) cat. $(Cl_2(Cy_3P_2)Ru{=}CHPh$, CH_2Cl_2, rt, 2 h, 97%; (d) (i) H_2, cat. 10% Pd–C, MeOH, rt, overnight; (ii) 5 N HCl, MeOH, 60 °C, 2 h, 91%.

Accordingly, treatment of **11** (*anti*:*syn*=5.2:1) prepared from entry 5 with HCl in chloroform afforded the readily separable 1,3-acetonides **13** (1.8%), **14** (47%), and **11** (32%).[14] The relative configuration at the C-4 and C-5 of **14** was confirmed from the H–H-coupling constant ($J_{4,5}$), which is 9.5 Hz for the *trans* configuration.[15] The *N*-allylation of **14** with allyl iodide using NaH as a base gave the diolefin product **12** in 95% yield. Finally, **12** was subjected to RCM in the presence of Grubbs' catalyst [$(Cl_2(Cy_3P)_2$-Ru=CHPh)] in dichloromethane. Under these conditions, the desired piperidene **9** was obtained in 97% yield. In addition, the stereochemistry of **9** was unambiguously confirmed by its transformation to the known *trans*-3-hydroxy-2-hydroxymethyl piperidine (**15**) (Scheme 3).[16,17]

With the promising chiral building block **9** in hand, our interest was directed to synthesis of 1-deoxynojirimycin compounds **1** and **6**-**8**. We first converted the double bond to

Table 1. Reaction of the Garner aldehyde with vinyl metals

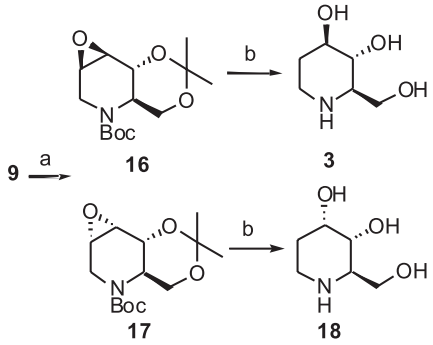


Entry	M	Additive	Solvent	*anti*:*syn*[a]	Yield %
1	MgBr	None	Toluene/THF (1:1)	4.0:1	68
2	Li	None	Et_2O	2.0:1	94
3	Li	HMPA	Toluene/Et_2O (1:1)	3.6:1	92
4	Li	HMPA	THF	3.7:1	86
5	Li	HMPA	Et_2O	5.2:1	91
6	Li	BF_3–Et_2O	Et_2O	1.3:1	85

[a] Ratios were determined by ^1H NMR (300 MHz) of acetates of **11**.

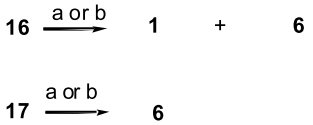
an epoxy-functionality to give both **1** and **6** containing a *trans* diol in the 3 and 4 positions. The dioxirane, generated in situ from Oxone® with 1,1,1-trifuluoroacetone was reacted with **9** to give the *anti* epoxide **16** and *syn* epoxide **17** in 45 and 44% yields, respectively. The use of *m*-CPBA also resulted in low stereoselectivity to provide **16** and **17** in a ratio of 47:27 in 74% yield.

The stereochemistry of the epoxy products was determined by stereoselective cleavage of the epoxy ring using Super-Hydride®. Treatment of **16** with Super-Hydride® in THF led to the hydroxylated product which, upon deprotection using hydrochloric acid in methanol followed by treatment of the resulting salts with an ion-exchange resin afforded the known fagomine **3**[10,17] in 65% overall yield. The application of an analogous procedure to **17** provided 3-*epi*-fagomine **18**[10,17] in 52% overall yield (Scheme 4).

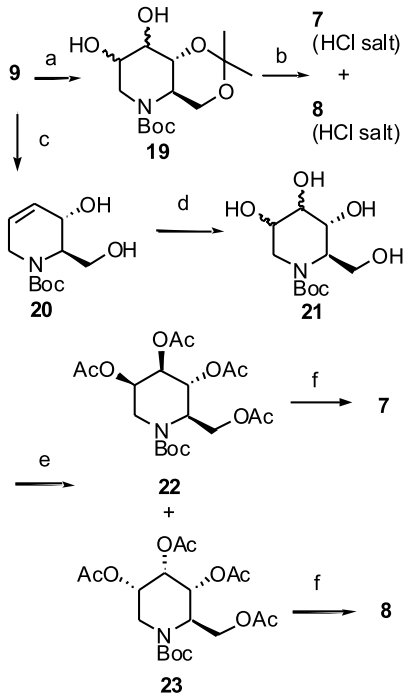


Scheme 4. Reagents and conditions (a) Na_2EDTA, $CF_3COCH_3NaHCO_3$, Oxone, CH_3CN, 0 °C, 1 h, **16** (45%), **17** (44%); (b) (i) Super-Hydride, THF, 0 °H, 3 h, 78%; (ii) 6 N HCl, MeOH, 60 °C, 2 h; (iii) DOWEX-50wX8, **3** (65%), **18** (52%).

Acid hydrolysis of the epoxy ring of **16** was examined with a 0.2/3/2 mixture of H_2SO_4/dioxane/H_2O,[18] followed by treatment with the ion-exchange resin to give 1-deoxynojirimycin (**1**)[17,19] and 1-deoxyaltronojirimycin (**6**)[17,20] in a ratio of 1:1 in 89% yield. Basic cleavage of the epoxide **16** using a mixture of KOH/dioxane/H_2O gave **6**, preferentially in a ratio of 1:1.5 (**1** to **6**) in 99% yield. In contrast, both acidic hydrolysis and basic cleavage of the *syn* epoxide **17** afforded only 1-deoxyaltronojirimycin (**6**) in 63 and 68% yields, respectively, after treatment with ion-exchange resin. Although a rationale of these stereoselectivity remains unclear, we consider the following explanation. It is known that opening of cyclohexene oxides generally proceeds in the diaxial reaction.[21] The epoxy substituents at 2 position of **16** and at 3 position of **17** are in quasi-equiatrial orientation, because *anti*-dioxanyl ring is diequatrial orientation. Accordingly, it is expected that axial attacks occur at 2 position of **16** and 3 position of **17**. In the case of



Scheme 5. Reagents and conditions: (a) (i) cH_2SO_4, 1,4-dioxane, H_20, reflux, 3 h, (ii), dowex-50wX8 **1** and **6** (1:1, 89%) from **16**, **6** (63%) from **17**; (b) (i) 3 M KOH, 1,4-dioxane, reflux, overnight, (ii) DOWEX-1X2, **1** (33%), **6** (51%) from **16**, **6** (63%) from **17**.



Scheme 6. Reagents and conditions; (a) cat. $K_2OsO_4\cdot 2H_2O$, NMO, acetone, rt, overnight, 95% or AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH–H_2O, 0 °C, 2 overnights; (b) 6 N HCl, 60 °C, 1 h; (c) *p*TsOH·H_2O, MeOH, rt, 2 h, 94%; (d) cat. $K_2OsO_4\cdot 2H_2O$, NMO, acetone, rt, overnight, 87%; (e) Ac_2O, pyridine, rt, overnight, **22** (45%), **23** (49%); (f) 6 N HCl, MeOH, reflux, 8 h; DOWEX-50wX8, **7** (94%) from **22**, **8** (91%) from **23**.

16, however, a steric repulsion between a nucleophile and substituent at 4 position would exist. Hence, the nucleophile may attack at remote site (2 position) of **16** (Scheme 5).

The stereoselective dihydroxylation of the double bond was next examined. Under modified Upjohn conditions, treatment of **9** with a catalytic amount of $K_2OsO_4\cdot 2H_2O$ (5 mol%) and 4-methylmorphorine *N*-oxide (NMO) as a cooxidant gave diol **19** as a diastereomeric mixture, which was deprotected with HCl in methanol to afford an inseparable mixture of the hydrochloride salts of 1-deoxymannojirimycin (**7**) and 1-deoxyallonojirimycin (**8**) in a ratio of 1:4.2 (**7** to **8**) in 95% combined yield. Analogously, AD-mix-β mediated dihydoxylation of **9** provided a mixture of the hydrochlorides of **7** and **8** in a ratio (1:8.2) (**7** to **8**) in 93% overall yield. Unfortunatly, their separation with ion-exchange resin resulted in insufficiency. Deprotection of the acetonide with *p*-TsOH in methanol gave diol **20** (94%), which was treated under above modified Upjohn conditions to give an inseparable mixture of tetraols **21** in 87% yield. Fortunately, acetylation of the tetraols gave a mixture of separable tetraacetates **22** and **23**, which were isolated in 45 and 49% yields. Finally, exposure of **22** and **23** to 5 N HCl in methanol followed by treatment with the ion-exchange resin provided 1-deoxymannojirimycin (**7**)[17,22] and 1-deoxyallonojirimycin (**8**)[17,23] in 94 and 91% yields, respectively (Scheme 6).

3. Conclusion

In summary, the new promising chiral building block **9** for

the synthesis of 1-deoxy-4,5-*trans*-oriented azasugars was prepared in only four steps from the Garner aldehyde **10**. In practice, the first synthesis of all four isomers **1** and **6**-**8** of *trans*-4,5-orientated 1-deoxyiminosugars using **9** as a common chiral building block was achieved. In addition, 1,2,3-trideoxy and 1,2-dideoxy-*trans*-4,5-oriented azasugars **15**, **3**, and **18** were also prepared.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were measured with a JASCO A102 and a Perkin–Elmer 1600 spectrophotometers. ^{1}H NMR and ^{13}C spectra were recorded on a JEOL FX 270, Varian Gemini-300, and Varian Unity-500. MS and HRMS were taken on a JEOL-JMS D-200 spectrometer using the electron ionization. Elemental analyses were performed by a Perkin–Elmer 2400 Elemental Analyzer. Optical rotations were measured with a JASCO-DIP-1000 digital polarimeter.

4.1.1. (4*R*,5*R*)-(2,2-Dimethyl-4-vinyl-[1,3]-dioxan-5-yl)-carbamic acid *tert*-butyl ester (13) and (4*S*,5*R*)-(2,2-dimethyl-4-vinyl-[1,3]-dioxan-5-yl)-carbamic acid *tert*-butyl ester (14). A solution of 1.18 M MeLi (6.79 mL, 8 mmol) in Et_2O was added to a solution of tetravinyltin (0.36 mL, 2 mmol) in Et_2O (15 mL) at 0 °C and the mixture was stirred for 15 min at the same temperature. Then HMPA (1.4 mL, 8 mmol) was added to the mixture at −78 °C. A solution of **10** (458.5 mg, 2 mmol) in Et_2O (5 mL) was slowly added to the mixture at −78 °C. The reaction was stirred at the same trempertature for 2 h. Saturated NH_4Cl was added to the mixture with ice cooling. Organic layer was separated and the aqueous layer was extracted with Et_2O twice. The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (*n*-hexane/ethyl acetate 5:1) to give a mixture of *anti* and *syn* **11** (*anti*:*syn*=5.2:1) (466 mg, 91%) as pale yellow solids. 0.15 N HCl in $CHCl_3$ (11 mL) was added to a solution of **11** (*anti*:*syn*=5.2:1) (14.18 g, 55.1 mmol) in $CHCl_3$ (633 mL). The mixture was stirred overnight at room temperature and concentrated. The residue was purified by chromatography (*n*-hexane/ethyl acetate=15:1–2:1) to give **13** (0.21 g, 1.8%), **14** (6.7 g, 47%), and **11** (4.54 g, 32%). **13**: oil; $[\alpha]_D^{23}$ +10.0° (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.45 (s, 3H), 1.49 (s, 3H), 3.59 (dd, *J*=9.6, 1.6 Hz, 1H), 3.78 (dd, *J*=12.0, 1.3 Hz, 1H), 4.10 (dd, *J*=11.9, 1.5 Hz,1H), 4.46–4.52 (m, 1H), 5.21 (d, *J*=10.7 Hz, 1H), 5.27 (br s, 1H), 5.33 (d, *J*=17.3 Hz, 1H), 5.77 (ddd, *J*=17.1, 10.7, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 28.2, 29.5, 47.2, 64.6, 71.5, 79.2, 98.9, 116.5, 134.5, 155.4; IR (neat) 3350.0, 1700.2, 1498.6 cm^{-1}; HRMS Calcd for $C_{13}H_{23}NO_4$ (M^+) 257.1670, found 257.1613. **14**: mp 74–75 °C; $[\alpha]_D^{19}$ −10.6° (*c* 1.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 12H), 1.47 (s, 3H), 3.44–3.58 (m, 1H), 3.63 (br t, *J*=10.0 Hz, 1H), 3.95 (dd, *J*=11.0, 5.0 Hz, 1H), 4.00–4.11 (m, 1H), 4.39 (br d, *J*=8.2 Hz, 1H), 5.24 (dd, *J*=9.6, 0.8 Hz, 1H), 5.32 (dd, *J*=15.6, 0.8 Hz, 1H), 5.83 (ddd, *J*=17.2, 10.4, 6.8 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.6, 28.0, 2821, 28.28, 28.3, 28.4, 48.9, 63.0, 74.5, 98.7, 135.4, 135.7, 155.0; IR (neat) 3350.5, 1689.4, 1521.4 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.70; H, 8.94; N, 5.49.

4.1.2. (4*S*,5*R*)-Allyl-(2,2-dimethyl-4-vinyl-[1,3]-dioxan-5-yl)-carbamic acid *tert*-butyl ester (12). A mixture of 60% NaH in oil (324 mg, 8.1 mmol) was added to a solution of **14** (1.39 g, 5.4 mmol) in THF (32.2 mL) with ice cooling and the mixture was stirred for 1 h. Allyl iodide (0.74 mL, 8.1 mmol) was added to the mixture and the mixture was stirred overnight with ice cooling. The mixture was quenched with saturated NH_4Cl and the whole mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography (*n*-hexane/ethyl acetate=15:1) to give **12** (1.53 g, 95%) as an oil. **12**; $[\alpha]_D^{20}$ −38.7° (*c* 1.78, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$)[24] δ 1.38–1.58 (m, 15H), 3.32 (br s, 1H), 3.58–3.73 (m, 2H), 3.82–3.89 (m, 1H), 4.10 (m, 0.5H), 4.25–4.28 (m, 0.5H), 4.65 (m, 0.5H), 4.90 (m, 0.5H), 5.08–5.30 (m, 4H), 5.70–5.79 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$)[24] δ 20.1, 28.3, 28.4, 51.5, 56.6, 57.3, 60.5, 61.2, 70.7, 71.7, 79.8, 80.5, 98.6, 116.6, 117.0, 117.8, 118.1, 134.8, 136.0, 154.6; IR (neat) 3081, 1851, 1694 cm^{-1}. HRMS Calcd for $C_{16}H_{27}NO_4$ (M^+) 297.1940, found 297.1925.

4.1.3. (4a*R*,8a*S*)-2,2-Dimethyl-4,4a,6,8a-terahydro-[1,3]-dioxino[5,4-*b*]pyridine-5-carboxylic acid *tert*-butyl ester (9). Grubbs' catalyst 63.1 mg (5 mol%) was added to a solution of **12** (492.3 mg, 1.65 mmol) in CH_2Cl_2 (73 mL) and the mixture was stirred for 2 h at room temperature. After evaporation, the residue was purified by chromatography (*n*-hexane/ethyl acetate=15:1) to give **9** (432.3 mg, 97%) as an oil; $[\alpha]_D^{20}$ −3.20° (*c* 1.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.45 (s, 9H), 1.55 (s, 3H), 1.60 (s, 1H), 3.06 (td, *J*=9.5, 4.4 Hz, 1H), 3.65 (dd, *J*=18.4, 1.1 Hz, 1H), 4.19–4.37 (m, 3H), 4.55 (t, *J*=11.2 Hz, 1H), 5.66–5.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 28.6, 29.6, 46.3, 56.2, 63.2, 68.2, 80.7, 99.0, 126.0, 128.0, 184.0; IR (neat) 1702 cm^{-1}. HRMS Calcd for $C_{14}H_{23}NO_4$ (M^+): 269.1627, found 269.1494.

4.1.4. (2*R*,3*S*)-2-Hydroxymethylpiperidin-3-ol (15). A suspension of **9** (214.3 mg, 0.797 mmol) and 10%Pd–C (50%wet 10 mg) in methanol (3.5 mL) was stirred at hydrogene atmosphere overnight. The mixture was filtered off and the filtrate was evaporated. 5 N-HCl (22.9 mL) was added to a solution of the residue in methanol (6.8 mL). The mixture was heated at 60 °C for 2 h and evaporated. Two drops of 30% NaOH were added to the residue with ice cooling. A mixture of $CHCl_3$: isopropyl ether (4:1) (34 mL) was added to the mixture and dried over K_2CO_3. After evaporation, the residue was purified by chromatography ($CHCl_3$/methanol=10:1–5:1) to afford **15** (95.1 mg, 91%) as a solid; mp 154–155 °C, lit.[16] mp 154–155 °C for enantiomer of **15**; $[\alpha]_D^{19}$ +58.3° (*c* 1.06, MeOH), [lit.[16] $[\alpha]_D$ −59.8° (MeOH) for enantiomer of **15**]; ^{1}H NMR (500 MHz, D_2O): δ 1.27 (br d, *J*=10.2 Hz, 1H), 1.40 (br d, *J*=10.2 Hz, 1H), 1.65 (m, 1H), 1.93 (br s, 1H), 2.46 (br s, 2H), 2.91 (br d, *J*=9.4 Hz, 1H), 3.34 (br s, 1H), 3.51 (m, 1H), 3.74 (br s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 24.1, 32.9, 45.0, 61.9, 63.1, 68.1 (free); ^{13}C NMR (125 MHz,

D_2O) δ 21.0, 31.1, 44.1, 58.6, 62.2, 65.2 (HCl). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found C, 54.66; H, 9.71; N, 10.55.

4.1.5. (1*R*,3a*R*,7a*R*,8*R*)-6,6-Dimethylhexahydro-1,5,7-trioxa-3-azacyclopropa[a]naphthalene-3-carboxylic acid *tert*-butyl ester (16) and (1*S*,3a*R*,7a*R*,8*S*)-6,6-dimethylhexahydro-1,5,7-trioxa-3-azacyclopropa[*a*]-naphthalene-3-carboxylic acid *tert*-butyl ester (17). To a solution of **9** (97.5 mg, 0.36 mmol) in CH_3CN (2.7 mL) was successively added 4×10^{-4} M Na_2EDTA (1.8 mL) and CF_3COCH_3 (0.36 mL) at 0 °C. A mixture of $NaHCO_3$ (235 mg) and Oxone (1.10 g) was added to the reaction mixture over 1 h at 0 °C and the whole mixture was stirred at the same temperature for 30 min. H_2O (2 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried and evaporated. The residue was purified by chromatography (*n*-hexane/ethyl acetate=15:1–7:1) to yield **16** (46.2 mg, 45%) and **17** (44.9 mg, 44%) as oils. **16**: oil; $[\alpha]_D^{24}$ +42.4° (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 1.42 (s, 3H), 1.44 (s, 9H), 1.55 (s, 2H), 1.63 (s, 1H), 2.79 (td, *J*=10.5, 4.5 Hz, 1H), 3.15 (s, 2H), 3.26 (d, *J*=15 Hz, 1H), 3.93 (dd, *J*=11.2, 4.3 Hz, 1H), 4.00 (d, *J*=10.5 Hz, 1H), 4.41 (d, *J*=15 Hz, 1H), 4.70 (br t, *J*=10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 28.6, 29.5, 46.6, 50.3, 55.1, 56.4, 62.9, 65.5, 81.0, 100.0, 155.3; IR (neat) 1698.1, 1380.7, 1251.6, 1085.4 cm^{-1}. HRMS Calcd for $C_{14}H_{23}NO_5$ (M^+) 285.1576. found 285.1554. **17**: oil; $[\alpha]_D^{23}$ −1.15° (*c* 2.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s,9H), 1.46 (s, 3H), 1.51 (s, 1H), 1.52 (s, 2H), 3.21–3.39 (m, 3H), 3.62 (d, *J*=15.3 Hz, 1H) 3.95 (dd, *J*=15.3, 3.3 Hz, 1H), 3.79–4.06 (m, 1H), 4.18–4.06 (m, 1H), 4.18–4.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 27.9, 28.6, 29.3, 43.7, 50.7, 52.0, 52.5, 62.6, 69.8, 81.1, 99.4, 154.6; IR (neat) 1770.8, 1698.2, 1381.8, 1198.0, 1103.6 cm^{-1}. HRMS Calcd for $C_{14}H_{23}NO_5$ (M^+) 285.1576. found 285.1511.

4.1.6. Fagomine (3). Super-Hydride® (0.91 mL, 0.91 mmol) was added to a solution of **16** (130 mg, 0.456 mmol) in THF (2.8 mL) and the mixture was stirred at 0 °C for 3 h. Several pieces of ice were added to the mixture. After the mixture was stirred for 15 min, H_2O (1.29 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (10 mL) four times. The extracts were dried and evaporated. The residue was purified with chromatography as eluent (hexane/ethyl acetate=7: 1) to yield (4a*R*,8*R*,8a*R*)-*tert*-butyl hexahydro-8-hydroxy-2,2-dimethyl-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylate (102 mg, 78%) as an oil; $[\alpha]_D^{24}$ +4.52° (*c* 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.43 (s, 9H), 1.51 (s, 3H), 1.74 (s, 1H), 1.93–1.98 (m, 1H), 2.62 (br s, 1H), 2.75 (t, *J*=13.5 Hz, 1H), 2.96 (td, *J*=10.5, 4.9 Hz, 1H), 3.50–3.61 (m, 2H), 4.10 (br d, *J*=3.0 Hz, 1H), 4.31 (dd, *J*=11.6, 5.0Hz, 1H), 4.43 (t, *J*=11.2Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 19.6, 28.6, 29.6, 31.4, 44.4, 55.6, 62.3, 71.9, 75.7, 80.7, 99.0, 154.4; IR (neat) 3471.8, 2977.9, 1694.1, 1165.6 cm^{-1}. HRMS Calcd for $C_{14}H_{25}NO_5$ (M^+) 287.1732. found 287.1722. A solution of the above oil (85 mg, 0.296 mmol) and 6 N HCl (6 mL) in methanol (2.7 mL) was heated at 60 °C for 2 h. The mixture was evaporated, the residue was treated with cation-exchange resin (DOWEX-50wX8) to **3** (36.3 mg, 83%) as a solid; mp 185–186 °C; $[\alpha]_D^{22}$ +22.1° (*c* 0.60, H_2O), [lit.[7] $[\alpha]_D$ +19.5° (*c* 1.0, H_2O)]; ^{1}H NMR (300 MHz, D_2O) δ 1.32 (qd, *J*=12.3, 4.4Hz, 1H), 1.86 (br d, *J*=12.9 Hz, 1H), 2.37–2.52 (m, 2H), 2.88 (br d, *J*=11.2 Hz, 1H), 3.04 (1H, t, *J*=9.3 Hz, 1H), 3.37–3.53 (m, 2H), 3.72 (dd, *J*=11.5, 2.2 Hz, 1H); ^{13}C NMR (75 MHz, D_2O/ HCl salt) δ 29.30, 42.57, 58.41, 60.77, 70.25, 71.12; ^{13}C NMR (75 MHz, D_2O) δ 33.40, 43.42, 61.68, 62.33, 73.88, 73.95; Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.93; H, 8.90; N, 9.47.

4.1.7. 3-*epi*-Fagomine (18). Super-Hydride® (0.79 mL, 0.79 mmol) was added to a solution of **17** (113 mg, 0.39 mmol) in THF (2.2 mL) and the mixture was stirred at 0 °C for 3 h. Several pieces of ice were added to the mixture. After the mixture was stirred for 15 min, H_2O (1.29 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (10 mL) four times. The extracts were dried and evaporated. The residue was purified with chromatography as eluent (*n*-hexane/ethyl acetate=7: 1) to yield (4a*R*,8*S*,8a*R*)-*tert*-butyl hexahydro-8-hydroxy-2,2-dimethyl-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylate (80 mg, 70%) as an oil; $[\alpha]_D^{23}$ −47.9° (*c* 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.43 (s, 9H), 1.52 (s, 3H), 1.64–1.76 (m, 1H),1.85 (dd, *J*=14.4, 2.6 Hz, 1H), 2.46 (s, 1H), 3.11 (td, *J*=13.2, 2.4 Hz, 1H), 3.46 (td, *J*=10.5, 4.9 Hz, 1H), 3.74 (dd, *J*=10.4, 2.4 Hz,1H), 3.84 (br d, *J*=13.1 Hz, 1H), 3.95 (d, *J*=2.4 Hz, 1H) 4.24 (dd, *J*=11.8, 4.9 Hz, 1H), 4.53 (t, *J*=11.2 Hz, 1H); ^{13}C NMR(75 MHz, D_2O) δ 19.8, 28.7, 29.5, 30.5, 41.6, 51.9, 62.3, 66.1, 72.1, 80.4, 99.0, 154.6; IR$^-$ (neat) 3486.2, 1698.0, 1167.8 cm^{-1}. HRMS Calcd for $C_{14}H_{25}NO_5$ (M^+) 287.1737. found 287.1732. A solution of the above oil (80 mg, 0.278 mmol) and 6 N HCl (7.6 mL) in methanol (2.5 mL) was heated at 60 °C for 2 h. The mixture was evaporated, the residue was treated with cation-exchange resin (DOWEX-50wX8) to **18** (30.2 mg, 74%) as a solid; mp 218–219 °C, lit.[10a] mp 220–222 °C; $[\alpha]_D^{24}$ +77.15° (*c* 0.68, H_2O), [lit.[10a] $[\alpha]_D^{26}$ +74.4° (*c* 0.68, H_2O)]; ^{1}H NMR (300 MHz, D_2O) δ 1.57–1.72 (m, 2H), 2.62–2.74 (m, 3H), 3.32 (br d, *J*=9.9 Hz, 1H), 3.47 (dd, *J*=11.5, 6.6 Hz, 1H), 3.67 (dd, *J*=11.4, 2.3 Hz, 1H), 3.94 (br s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 31.89, 39.17, 56.50, 62.89, 68.66, 70.35. Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.94; H, 8.98; N, 9.49.

4.1.8. D-1-Deoxynojirimycin (1) and D-1-deoxyaltrojirimycin (6). *Acidic hydrolysis*. A mixture of **16** (84.8 mg, 0.29 mmol), 1,4-dioxane (1.8 mL), H_2O (1.2 mL), and *c* H_2SO_4 (210 mg) was refluxed for 3 h. After evaporation of the reaction mixture, the residue was treated with ion-exchange resin DOWEX-50wX8 using water as eluent to yield a mixture of **1** and **6** (43.3 mg, 89%) as a ratio (1:1). By similar procedure described the above, **17** (62.1 mg, 0.217 mmol) provided **6** (22.4 mg, 63%) as oil. *Basic hydrolysis*. A mixture of **16** (160 mg, 0.56 mmol), 1,4-dioxane (13.8 mL), (.3 M KOH (28 mL) was refluxed overnight. After evaporation, methanol (5.1 mL) and 6 N HCl (15.4 mL) were added to the residue. The mixture was heated at 60 °C for 1 h and evaporated. The residue was treated with ion-exchange resin DOWEX-1X2 (OH^- form) using water as eluent to yield **1** (29.7 mg, 33%) and **6** (46.9 mg, 51%)/. By similar procedure described the above, **17** (120 mg, 0.42 mmol) provided **6** (43 mg, 63%) as oil. **1**:

mp 199–199.5 °C; $[\alpha]_D^{23}$ +40.3° (*c* 1.47, H_2O); [lit.[25] mp 199–201 °C, $[\alpha]_D^{25}$ +42.1° (*c* 1, H_2O)]; ^1H NMR (500 MHz, D_2O) δ 2.35 (td, J=8.4, 1.2 Hz,1H), 2.41–2.45 (m, 1H), 3.00 (dd, J=7.5, 3.0 Hz, 1H), 3.12 (td, J=10.6, 1.7 Hz, 1H), 3.20 (td, J=8.9, 2.1 Hz, 1H), 3.35–3.40 (m, 1H), 3.52 (ddd, J=12.0, 6.2, 1.9 Hz, 1H) 3.72 (1dd, J=11.5, 2.5 Hz, 1H); ^{13}C NMR(125 MHz, D_2O) δ 49.46, 61.28, 62.13, 71.66, 72.27, 79.16. **6**: oil; $[\alpha]_D^{24}$ +19.5° (*c* 2.15, H_2O); [lit.[23b] $[\alpha]_D$ +17.9° (*c* 1.3, H_2O)]; ^1H NMR (500 MHz, D_2O) δ 2.61–2.70 (m, 2H), 2.82 (dd, J=14.5, 2.5 Hz, 1H), 3.58–3.65 (m, 2H), 3.68 (dd, J=9.6, 3.2 Hz, 1H), 3.74–3.76 (m, 1H), 3.80–3.81 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 45.30, 56.36, 61.62, 66.96, 70.17, 71.44. HRMS Calcd for $C_6H_{13}NO_4$ (M^+) 163.0788, found 163.0856. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16;; H, 8.03; N, 8.58. Found: C, 44.23; H, 7.81; N, 8.54.

4.1.9. Dihydroxylation of 9. A solution of 50% NMO (99.4 μL) in water and a solution of $K_2OsO_4\cdot 2H_2O$ (0.74 mg, 0.5 mol%) in water (0.29 mL) were successively added to a solution of **9** (114 mg, 0.42 mmol) in acetone (2.9 mL) and the mixture was stirred at room temperature overnight. Na_2SO_3 (100 mg) was added to the mixture and the mixture was stirred for 30 min. The insoluble materials were filtered off and the filtrate was evaporated. The residue was purified by chromatography (*n*-hexane/ethyl acetate=2:3) to yield the diols (122 mg, 95%) as a diasteromeric mixture. 6 N HCl (6 mL) was added to a solution of the above diol. The mixture was heated at 60 °C for 1 h and evaporated to yield a mixture of hydrochlorides of **7** and **8** (88 mg, 100%). Their ratio was estimated by C^{13} NMR to be 1:4.2. The hydrochloride of **7**: ^{13}C NMR (125 MHz, D_2O) δ 48.3 (C-1), The hydrochloride of **8**: ^{13}C NMR (125 MHz, D_2O) δ 42.4 (C-1). To a mixture of AD-mix-β (840 mg) in H_2O (3 mL) was added a solution of **9** (162 mg, 0.6 mmol) in *t*-BuOH (3 mL) and $CH_3SO_2NH_2$ (57 mg) at 0 °C. The mixture was stirred at the same temperature 2 overnights. After addition of Na_2SO_3 (50 mg), the mixture was stirred for 0.5 h and extracted with ethyl acetate three times. The organic solvent was washed with water, dried, and evaporated added. The residue was purified by chromatography (*n*-hexane/ethyl acetate=2:3) to yield the diols (169 mg, 93%) as a diasteromeric mixture. 6 N HCl (8 mL) was added to a solution of the above diol. The mixture was heated at 60 °C for 1 h and evaporated to yield a mixture of hydrochlorides of **7** and **8** (111 mg, 100%). The ratio was 1:8.2.

4.1.10. (2*R*,3*S*)-3-Hydroxy-2-hydroxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (20). *p*TsOH·H_2O (53.7 mg) was added to a solution of **9** (540 mg, 2 mmol) in methanol (25 mL). The mixture was stirred for 2 h at room temperature and evaporated. The residue was purified by chromatography ($CHCl_3$/methanol=20:1) to yield **20** (430 mg, 94%) as an oil; $[\alpha]_D^{24}$ +86.2° (*c* 2.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.25–2.87 (br s, 1H), 2.87–3.41 (br s, 1H), 3.44–3.59 (m, 3H), 4.06–4.25 (t, J=7.4 Hz, 2H), 5.83–5.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 41.2, 60.6, 61.1, 63.3, 80.7, 124.8, 127.4, 156.5; IR (neat) 3391.9, 1681.7, 1417.2 cm^{-1}. HRMS Calcd for $C_{11}H_{19}NO_4$ (M^+-CH_2OH) 198.1048, found 198.1150.

4.1.11. 2,3,4,6-Tetra-*O*-acetyl-*N*-*tert*-butyloxycarbonyl-1,5-imino-D-mannitol (22) and 2,3,4,6-tetra-*O*-acetyl-*N*-*tert*-butyloxycarbonyl-1,5-imino-D-allitol (23). A solution of 50% NMO (180 μL) in water and a solution of $K_2OsO_4\cdot 2H_2O$ (1.33 mg, 0.5 mol%) in water (0.5 mL) were successively added to a solution of **9** (165 mg, 0.72 mmol) in acetone (5.5 mL) and the mixture was stirred at room temperature three overnights. Na_2SO_3 (170 mg) was added to the mixture and the mixture was stirred for 30 min. The insoluble materials were filtered off and the filtrate was evaporated. The residue was purified by chromatography ($CHCl_3$/methanol=12:1) to yield **21** (165 mg, 87%) as a solid of a diasteromeric mixture. Ac_2O (1.74 mL) was added to a mixture of **21** (107 mg, 0.41 mmol) in pyridine (4.1 mL) with ice cooling. The mixture was stirred at room temperature overnight, diluted with H_2O, and extracted with ethyl acetate three times. The extracts were successively washed with 1 N HCl, sat. $NaHCO_3$, H_2O, and brine. The organic layer was dried and evaporated. The residue was purified by chromatography (*n*-hexane/ethyl acetate=2:1–1:1) to yield **22** (79.7 mg, 45%) and **23** (86.2 mg, 49%) as oils. **22**: oil; $[\alpha]_D^{24}$ −28.3° (*c* 2.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.98 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 3.09 (m, 1H), 3.95–4.21 (m, 2H), 4.42 (t, J=10.0 Hz, 1H), 4.57 (br s, 1H), 4.91 (br s, 1H), 5.01–5.08 (m, 1H), 5.25 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 20.7, 28.1, 59.8, 65.0, 67.0, 68.0, 80.7, 154.4, 168.7, 168.8, 169.2; IR (neat) 1747.6, 1698.7, 1369.5, 1226.3, 1155.6, 1054.8, 1026.3 cm^{-1}. HRMS Calcd for $C_{19}H_{29}NO_{10}$ (M^++1) 432.1862, found 432.1876. **23**: oil; $[\alpha]_D^{23}$ −1.97° (*c* 2.41, $CHCl_3$); δ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.01 (s, 6H), 2.08 (s, 3H), 3.17 (br d, J=15.3 Hz, 1H), 4.14 (dd, J=11.5, 5.7 Hz, 1H), 4.28–4.41 (m, 2H), 4.75 (br t, J=6.1 Hz, 1H), 5.11 (br s,1H), 5.16 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 20.9, 21.0, 28.3, 42.3, 54.1, 61.0, 66.7, 67.0, 80.5, 155.0; IR (neat) 1744.8, 1701.0, 1369.0, 1230.4, 1145.7, 1068.6 cm^{-1}. HRMS Calcd for $C_{19}H_{29}NO_{10}$ (M^++1) 432.1868, found 432.1872.

4.1.12. D-1-Deoxymannojirimycin (7). A mixture of **22** (65.8 mg, 0.15 mmol) and 6 N HCl (4.58 mL) in methanol (1.5 mL) was refluxed for 8 h and evaporated. The residue was treated with ion-exchange resin DOWEX-50wX8 (H^+ form) using water as eluent to yield **7** (23.3 mg, 94%) as white solid. mp (dec.) 179–180 °C; [lit.[26] mp (dec.) 182–184 °C]; $[\alpha]_D^{25}$ −40.2° (*c* 0.33, H_2O); [lit.[27] $[\alpha]_D$ −41.4° (H_2O)]; ^1H NMR (300 MHz, D_2O/ HCl salt) δ 3.03–3.09 (m, 1H), 3.15 (br d, J=13.5 Hz, 1H), 3.32 (dd, J=13.5, 2.9 Hz, 1H), 3.60 (dd, J=9.5, 2.9 Hz, 1H), 3.71–3.80 (m, 2H), 3.90 (dd, J=12.6, 3.0 Hz, 1H), 4.15 (br s, 1H); ^{13}C NMR (75 MHz, D_2O / HCl salt) δ 48.2, 58.8, 61.0, 66.4, 66.6, 73.1; ^1H NMR (300 MHz, D_2O) δ 2.41–2.43 (m, 1H), 2.70 (d, J=14.2 Hz, 1H), 2.95 (d, J=14.2 Hz, 1H), 3.53–3.56 (m, 2H), 3.72 (d, J=2.7 Hz, 2H), 3.94 (br s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 48.9, 61.1, 61.4, 69.0, 69.8, 75.2. HRMS Calcd for $C_6H_{13}NO_4$ (M^+-CH_2OH) 132.0537, found 132.0853. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.06; H, 7.98; N, 8.57.

4.1.13. D-1-Deoxyallonojirimycin (8). A mixture of **23** (59.9 mg, 0.14 mmol) and 6 N HCl (3.78 mL) in methanol (1.2 mL) was refluxed for 8 h and evaporated. The residue

was treated with ion-exchange resin DOWEX-50wX8 (H^+ form) using water as eluent to yield **8** (20.6 mg, 91%) as white solid. mp 165 °C; $[\alpha]_D^{25}$ +36.2° (*c* 0.83, methanol), [lit.[28] $[\alpha]_D^{20}$ +35.2° (methanol)]; ^{1}H NMR (300 MHz, D_2O/HCl salt) δ 2.99 (t, J=11.8 Hz,1H), 3.12–3.22 (m, 2H), 3.68–3.78 (m, 3H), 3.84–3.90 (m, 1H), 4.04 (br s, 1H); ^{13}C NMR (75 MHz, D_2O /HCl salt) δ 44.0, 57.2, 60.1, 67.0, 67.8, 72.4; ^{1}H NMR (300 MHz, D_2O) δ 2.55–2.67 (m, 2H), 2.76 (dd, J=12.0, 4.9 Hz, 1H), 3.38 (dd, J=10.1, 2.5 Hz, 1H), 3.52–3.63 (m, 2H), 3.71 (dd, J=11.5, 2.5 Hz, 1H), 4.00 (br s, 1H); ^{13}C NMR (75 MHz, D_2O) δ 44.5, 55.3, 62.2, 69.0, 69.5, 72.3. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.21; H, 7.97; N, 8.44.

Acknowledgements

This research was supported by the Uehara Memorial Foundation and a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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Enantioselective synthesis of afzelechin and *epi*afzelechin

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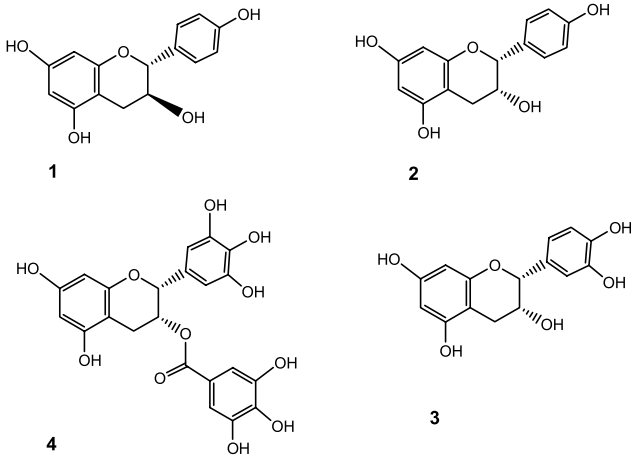
Received 2 April 2004; revised 10 June 2004; accepted 16 June 2004

Available online 21 July 2004

Abstract—The flavonoids afzelechin and *epi*afzelechin as well as their gallate esters were synthesized enantioselectively via Sharpless hydroxylation followed by regioselective cyclization.

1. Introduction

The flavonoids afzelechin (**1**) and *epi*afzelechin (**2**) have been found in numerous plants. Some recent reports of isolation of **1** and **2** include the following species: *Typha capensis* (Rohrb.) N. E. Br, commonly referred to as bulrush in South Africa;[1] *Artocarpus dadah*, known as 'Tampang' in Indonesia;[2] *Celastrus orbiculatus* Thunb. (Celastraceae), a perennial shrub[3] and *Calophyllum apetalum* from India.[4] In addition, many plants contain also proanthocyanidins which are oligomers formed by the condensation of **1** and **2** as well as similar flavonoids.[5] Many of these compounds and their derivatives show a range of biological activities. Potent proliferative effects on MCF-7 and osteoblastic cells have been found for a number of *epi*afzelechin (**2**) derivatives.[6] (−)-*Epi*afzelechin showed selective inhibitory activities against cyclooxygenase-1 (COX-1) over COX-2.[2] Condensed tannin derived from *epi*afzelechin and *epi*-catechin (**3**), isolated from the Chinese herbal drug 'Wen Guan Mu', showed inhibitory effects on HIV-1 protease.[7] Selligueain A, a proanthocyanidin trimer composed of **1** and **2** units, isolated from the rhizomes of *Selliguea feei*, was rated by a taste panel as being ca. 35 times sweeter than a 2% w/v aqueous sucrose solution.[8] Because of our interest in the potential of green tea catechins as cancer preventive agents, we have embarked on a program in preparing synthetic analogs of *epi*gallocatechin-3-gallate (EGCG, **4**).[9] We have engaged in the enantioselective synthesis of **1** and **2** as well as their gallate esters. As far as we are aware, no de novo syntheses of these compounds have been reported in the literature.[10]



2. Results and discussion

The synthesis of afzelechin (**1**) is outlined in Scheme 1. Friedel–Craft alkylation of 3,5-dibenzyloxyphenol (**5**)[11] with **6** under strictly controlled conditions gave the alkylation product **7**. Compound **7** was first protected as the *t*-butyldimethylsilyl ether and then subject to Sharpless hydroxylation with AD-mix α, followed by de-silylation to give the (+)-(1*S*,2*S*)-diol **8**. Direct hydroxylation of **7** without protection did not proceed well under the Sharpless conditions. The assignment of the absolute configurations at the two stereogenic centres in **8** was based on the stereochemical outcome normally formulated according to Sharpless hydroxylation of alkenes.[12] Cyclization of **8** under the orthoformate/acidic conditions followed by base hydrolysis of the formate ester gave the protected flavan-3-ol **9**. The *trans* stereochemistry of **9** was evident from its

Keywords: Enantioselective synthesis; *Typha capensis*; *Calophyllum apetalum*; Afzelechin; *epi*Afzelechin.
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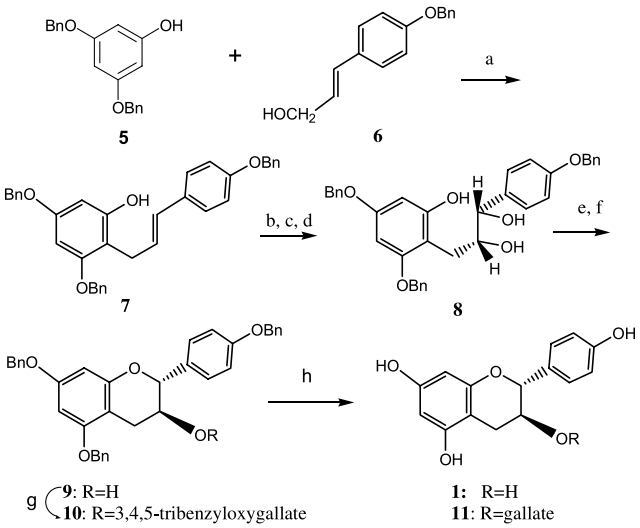
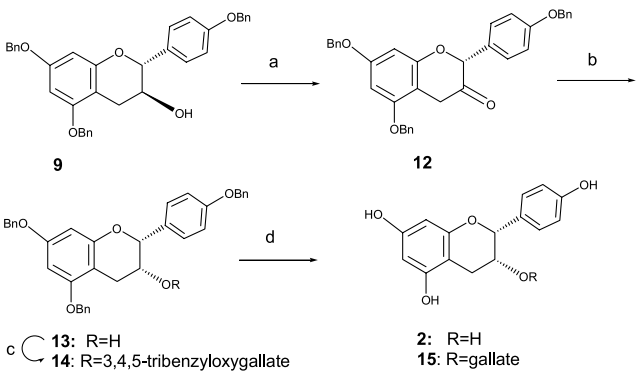
doi:10.1016/j.tet.2004.06.113



Scheme 1. (a) $H_2SO_4(SiO_2)/CH_2Cl_2$, rt; (b) TBSCl/imidazole/DMF, rt; (c) AD-mix/$CH_3SO_2NH_2/H_2O/t$-BuOH/CH_2Cl_2, 0 °C; (d) TBAF/THF, rt; (e) $CH(OEt)_3$/PPTS/$(CH_2Cl)_2$, rt; (f) K_2CO_3/MeOH/DME, rt; (g) 3,4,5-tris(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; (h) $H_2/Pd(OH)_2$ on charcoal/MeOH/THF, rt.

^{1}H NMR spectrum.[13] This is in agreement with a inversion of stereochemistry at C-2 during cyclization, giving the 2*R*,3*S* product. Hydrogenolysis of **9** to remove the benzyl protecting group gave (+)-**1**. The optical activity of the synthetic (+)-**1** was found to be the same as that reported in the literature.[15] Alternately, compound **9** was first acylated with 3,4,5-tribenzyloxybenzoyl chloride to give the corresponding ester **10**, which on hydrogenolysis gave (+)-(2*R*,3*S*)-afzelechin-3-gallate (**11**).

To obtain *epi*afzelechin, compound **9** was first oxidized by Dess–Martin periodinane[14] to the corresponding ketone **12**. Reduction of the carbonyl function with L-selectride at −78 °C gave exclusively the *cis*-substituted compound **13**. The stereochemistry of **13** was also evident from its ^{1}H NMR where the coupling of H-2 and H-3 is distinctly different from that of compound **9**. Hydrogenolysis of **13** gave then (−)-(2*R*,3*R*)-**2** (Scheme 2). The synthetic (−)-**2** had an optical rotation, $[\alpha]_D = -59$ ($c=3$, EtOH), similar to the literature value for the natural compound, $[\alpha]_D = -58.9$ ($c=3$, EtOH).[15] Similarly, the 3-gallate ester **15** was



Scheme 2. (a) Dess-Martin periodinane/CH_2Cl_2, rt; (b) L-Selectride/THF, −78 °C–rt; (c) 3,4,5-Tris(benzyloxy)benzoyl chloride/DMAP/CH_2Cl_2, rt; (d) $H_2/Pd(OH)_2$ on charcoal/MeOH/THF, rt.

obtained after formation of the ester **14** followed by hydrogenolysis.

In conclusion, the natural occurring flavonoids afzelechin (**1**) and *epi*afzelechin (**2**) have been synthesized enantioselectively for the first time in 12 and 7% overall yield, respectively. The biological studies of these synthetic compounds will be reported elsewhere.

3. Experimental

3.1. General

The starting materials and reagents, purchased from commercial suppliers, were used without further purification. Anhydrous THF was distilled under nitrogen from sodium benzophenone ketyl. Anhydrous methylene chloride was distilled under nitrogen from CaH_2. Anhydrous DMF was distilled under vacuum from CaH_2. Reaction flasks were flame-dried under a stream of N_2. All moisture-sensitive reactions were conducted under a nitrogen atmosphere. Flash chromatography was carried out using silica-gel 60 (70–230 mesh). The melting points were uncorrected. ^{1}H NMR and ^{13}C NMR (400 MHz) spectra were measured with TMS as an internal standard when $CDCl_3$ and acetone-d_6 were used as a solvent. High-resolution (ESI) MS spectra were recorded using a QTOF-2 Micromass spectrometer.

3.1.1. (*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-(4-benzyloxy)phenyl]propene (7). At rt under an N_2 atmosphere, 25% H_2SO_4/SiO_2 (1.6 g, 4 mmol) was added in one batch to the stirred mixture of 3,5-bis(benzyloxy)phenol (3.06 g, 10 mmol) and (*E*)-4-benzyloxycinnamyl alcohol (2.40 g, 10 mmol) in dry CH_2Cl_2 (50 mL). The resulting mixture was stirred at rt overnight. After filtration and evaporation, the residue was purified by flash chromatography on silica gel (benzene) to afford the desired compound as white solid (2.0 g, 38% yield): mp 132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.30 (m, 15H), 7.30 (A of AB, $J=8.7$ Hz, 2H), 6.89 (B of AB, $J=8.7$ Hz, 2H), 6.43 (A of AB, $J=15.8$ Hz, 1H), 6.27 (d, $J=2.1$ Hz, 1H), 6.17 (d, $J=2.1$ Hz, 1H), 6.20 (B of ABt, $J=15.8$, 6.3 Hz, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 4.99 (s, 2H), 3.57 (d, $J=6.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.7, 158.0, 157.7, 155.7, 137.0, 136.9, 136.8, 130.2, 129.9, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.5, 127.4, 127.2, 126.1, 114.8, 106.9, 95.0, 93.6, 77.2. 70.3, 70.0, 69.9, 26.4; HRMS (ESI) calcd for $C_{36}H_{33}O_4$ (M+H) 529.2379, found 529.2385.

3.1.2. (+)-(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-(4-benzyloxyphenyl)propane-1,2-diol ((+)-8). The propene **7** (2.3 g, 4.4 mmol) was dissolved in dry DMF (30 mL), and to this solution imidazole (0.9 g, 13.2 mmol) and TBSCl (1.3 g) were added successively. The resulting mixture was stirred at rt overnight, and then saturated Na_2CO_3 solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatograph on silica gel (*n*-hexane and EtOAc=9:1 v/v) to afford [3,5-bis(benzyloxy)-2-[3-(4-benzyloxyphenyl)allyl]phenoxy]-*tert*-butyldimethylsilane.

This material was used in next step without further purification.

AD-mixα (11.4 g) and methanesulfonamide (0.76 g) were dissolved in a solvent mixture of *t*-BuOH (50 mL) and H_2O (50 mL). The resulting mixture was stirred at rt for 5 min, then the mixture was cooled to 0 °C and a solution of the above [3,5-bis(benzyloxy)-2-[3-(4-benzyloxyphenyl)allyl-phenoxy]-*tert*-butyldimethylsilane in dichloromethane (50 mL) was added. After the mixture had been stirred overnight, a total of four batches of AD-mixα (5.7 g each) and methanesulfonamide (0.38 g each) were added in 24 h intervals. After another 24 h of stirring at 0 °C, TLC showed that the reaction was completed. Then a 10% $Na_2S_2O_3$ solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic phases were combined, dried ($MgSO_4$) and evaporated. The residue was redissolved in THF (30 mL), and TBAF (10 mL, 1 M in THF) was added. The resulting mixture was stirred at rt for 4 h, and the saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc, and the organic layers were combined, dried (MgSO4) and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc in CH_3Cl) and then recrystallized in EtOAc to give a white solid (1.3 g, 53% yield): mp 150–152 °C; $[\alpha]_D=+2.1$ ($c=0.9$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.19 (m, 15H), 7.10 (A of AB, $J=8.6$ Hz, 2H), 6.84 (B of AB, $J=8.6$ Hz, 2H), 6.27 (d, $J=2.2$ Hz, 1H), 6.19 (d, $J=2.2$ Hz, 1H), 4.98 (s, 2H), 4.94 (s, 2H), 4.85 (AB, $J=11.7$ Hz, 2H), 4.48 (d, $J=7.4$ Hz, 1H), 4.03–3.98 (m, 1H), 2.93 (A of ABt, $J=14.7$, 3.1 Hz, 1H), 2.74 (B of ABt, $J=14.7$, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 159.0, 158.7, 157.7, 157.5, 136.9, 136.8, 136.7, 132.5, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 127.4, 126.8, 114.8, 106.1, 95.9, 93.3, 77.2, 70.0, 69.9, 69.8, 26.3; HRMS (ESI) calcd for $C_{36}H_{34}O_6Na$ (M+Na) 585.2253, found 585.2246.

3.1.3. (+)-(2*R*,3*S*)-*trans*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)chroman-3-ol ((+)-9). To a suspension of (1*S*,2*S*)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-(4-benzyloxy-phenyl)propane-1,2-diol (1.3 g, 2.3 mmol) in 1,2-dichloro-ethane (30 mL) was added triethyl orthoformate (1 mL), followed by PPTS (340 mg, 1.4 mmol). The mixture was stirred at rt for 20 min and the solid dissolved, then heated the mixture to 60 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was redissolved in DME (20 mL) and MeOH (20 mL), K_2CO_3 (400 mg) was added, and the mixture was stirred at rt overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane=1:3 v/v) to afford the desired product as white solid (0.95 g, 75% yield): mp 134–136 °C; $[\alpha]_D=+5.8$ ($c=2.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.32 (m, 17H), 7.01 (d, $J=8.5$ Hz, 2H), 6.26 (s, 1H), 6.21 (s, 1H), 5.06 (s, 2H), 5.01 (s, 2H), 4.97 (s, 2H), 4.69 (d, $J=8.2$ Hz, 1H), 4.08 (m, 1H), 3.15 (A of ABt, $J=16.3$, 5.6 Hz, 1H), 2.69 (B of ABt, $J=16.3$, 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 159.0, 158.7, 157.7, 155.3, 136.9, 136.8, 136.7, 130.1, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 127.4, 127.0, 115.1, 102.2, 94.3, 93.7, 81.4, 70.0, 69.9, 69.8, 68.1, 27.9; HRMS (ESI) calcd for $C_{36}H_{33}O_5$ (M+H) 545.2328, found 545.2319.

3.1.4. (+)-Afzelechin ((+)-1). Under an H_2 atmosphere, $Pd(OH)_2$/C (20%, 200 mg) was added to a solution of (+)-**9** (300 mg, 0.55 mmol) in a sovent mixture of THF/MeOH (1:1 v/v, 30 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h, TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatograph on silica gel (20% MeOH in CH_2Cl_2) to afford (+)-afzelechin (44 mg, 81% yield): mp 252–254 °C (decompose); $[\alpha]_D=+20$ ($c=4$, Me_2CO); lit. $[\alpha]_D=+20.6$ ($c=5$, Me_2CO);[15] ^{1}H NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 7.34 (A of AB, $J=8.5$ Hz, 2H), 6.95 (B of AB, $J=8.5$ Hz, 2H), 6.14 (d, $J=2.2$ Hz, 1H), 5.97 (d, $J=2.2$ Hz, 1H), 4.73 (d, $J=8.0$ Hz, 1H), 4.14 (dd, $J=8.0$, 2.8 Hz, 1H), 3.01 (A of ABt, $J=16.1$, 5.5 Hz, 1H), 2.66 (B of ABt, $J=16.1$, 8.5 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz) δ 151.7, 151.3, 151.0, 150.5, 124.9, 123.6, 109.8, 94.6, 90.2, 89.3, 76.2, 62.1, 22.7; HRMS (ESI) calcd for $C_{15}H_{15}O_5$ (M+H) 275.0919, found 275.0910.

3.1.5. (+)-(2*R*,3*S*)-*trans*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)chroman-3-yl 3,4,5-tris(benzyloxy)benzoate ((+)-10). Under an N_2 atmosphere, a solution of 3,4,5-tris(benzyloxy)benzoic acid (200 mg, 0.45 mmol) was refluxed with $(COCl)_2$ (1 mL) in dry CH_2Cl_2 (10 mL) and one drop of DMF for 3 h. The excess of $(COCl)_2$ and the solvent were removed by distillation and the residue was dried under vacuum for 3 h and dissolved in CH_2Cl_2 (5 mL). This solution was added dropwise to a solution of (+)-**9** (120 mg, 0.3 mmol) and DMAP (75 mg, 0.22 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at rt overnight, then saturated $NaHCO_3$ aqueous solution was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc/benzene) to afford the desired compound (170 mg, 80%). Recrystallization from $CHCl_3$ and ether gave a white powder: mp 131–132 °C; $[\alpha]_D=+5.1$ ($c=2.0$, CH_3Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.19 (m, 34H), 6.92 (d, $J=8.6$ Hz, 2H), 6.29 (s, 2H), 5.50 (bs, 1H), 5.12 (d, $J=7.0$ Hz, 1H), 5.08 (s, 2H), 5.03 (s, 4H), 5.00 (s, 2H), 4.99 (s, 4H), 3.15 (A of ABt, $J=16.7$, 5.1 Hz, 1H), 2.87 (B of ABt, $J=16.7$, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 165.0, 158.9, 158.7, 157.6, 155.0, 152.3, 142.3, 137.3, 136.7, 136.5, 130.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 124.9, 114.8, 108.9, 101.4, 94.3, 93.7, 78.4, 77.2, 75.0, 71.0, 70.1, 69.9, 24.5; HRMS (ESI) calcd for $C_{64}H_{55}O_9$ (M+H) 967.3846, found 967.3854.

3.1.6. (+)-Afzelechin gallate ((+)-11). Under an H_2 atmosphere, $Pd(OH)_2$/C (20%, 200 mg) was added to a solution of (+)-**10** (360 mg, 0.24 mmol) in a sovent mixture of THF/MeOH (1:1 v/v, 30 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h. TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatograph on silica gel (20% MeOH in CH_2Cl_2) to afford

(+)-afzelechin gallate (130 mg, 82% yield): mp 257–259 °C (decompose); $[\alpha]_D$=45.5 (c=0.5, Me_2CO); ^1H NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 7.39 (A of AB, J=7.3 Hz, 2H), 7.12 (s, 2H), 6.92 (B of AB, J=7.3 Hz, 2H), 6.17 (s, 1H), 6.06 (s, 1H), 5.45 (bs, 1H), 5.20 (d, J=6.8 Hz, 1H), 3.08 (A of ABt, J=16.4, 4.9 Hz, 1H), 2.84 (B of ABt, J=16.4, 6.8 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 160.0, 151.2, 151.0, 150.6, 150.5, 149.5, 139.3, 132.7, 123.4, 122.3, 114.3, 109.4, 103.3, 92.6, 89.9, 88.7, 18.5; HRMS (ESI) calcd for $C_{22}H_{19}O_9$ (M+H) 427.1029, found 427.1024.

3.1.7. (+)-(2*R*)-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)-chroman-3-one ((+)-12). Dess-Martin periodinane (6.3 mL, 15% g/mL in CH_2Cl_2, 2.2 mmol) was added in one batch to a stirred solution of (+)-**9** (600 mg, 1.1 mmol) in CH_2Cl_2 (30 mL) under an N_2 atmosphere. The mixture was stirred at rt for about 2 h till TLC showed the absence of starting material. Subsequently, saturated $NaHCO_3$ solution (15 mL) and 10% $Na_2S_2O_3$ aqueous solution (15 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (benzene) and then recrystallized in $CHCl_3$ and ether to afford the desired compound (448 mg, 75%): mp 141–143 °C, $[\alpha]_D$=+46 (c=1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.30 (m, 15H), 7.27 (A of AB, J=8.7 Hz, 2H), 6.95 (B of AB, J=8.7 Hz, 2H), 6.37 (d, J=2.1 Hz, 1H), 6.34 (d, J=2.1 Hz, 1H), 5.26 (s, 1H), 5.03 (s, 2H), 5.01 (s, 2H), 4.99 (s, 2H), 3.68 (AB, J=21.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 205.3, 159.3, 158.9, 156.9, 154.6, 136.7, 136.5, 136.4, 128.6, 128.5, 128.1, 128.0, 127.9, 127.5, 127.3, 127.1, 114.9, 102.0, 95.7, 95.0, 83.1, 70.1, 70.0, 69.9, 33.8; HRMS (ESI) calcd for $C_{36}H_{31}O_5$ (M+H) 543.2171, found 543.2190.

3.1.8. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)-chroman-3-ol ((−)-13). Under an N_2 atmosphere, the ketone ((+)-**12**) (280 mg, 0.51 mmol) was dissolved in dry THF (10 mL), and the solution was cooled to −78 °C. Then L-selectride (1 mL, 1 M solution in THF, 1 mmol) was added dropwise. The resulting solution was stirred at −78 °C overnight. When TLC showed the reaction was completed, saturated $NaHCO_3$ aqueous solution (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatograph on silca gel (5% EtOAC/benzene) and then recrystallized with ethanol and EtOAC to afford the desired product (200 mg, 71%) as a white solid: mp 110–111 °C, $[\alpha]_D$=−5.7 (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.22 (m, 17H), 6.93 (d, J=8.7 Hz, 2H), 6.18 (s, 2H), 4.98 (s, 2H), 4.92 (s, 2H), 4.90 (s, 2H), 4.87 (d, J=4.4 Hz, 1H), 4.16 (bs, 1H), 2.95 (A of ABt, J=17.4, 1.8 Hz, 1H), 2.87 (B of ABt, J=17.4, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 158.7, 158.5, 158.2, 155.3, 136.9, 136.8, 130.5, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 127.4, 127.1, 114.8, 100.9, 94.6, 93.9, 78.3, 70.0, 69.9, 69.8, 66.2, 28.3; HRMS (ESI) calcd for $C_{36}H_{33}O_5$ (M+H) 545.2328, found 545.2320.

3.1.9. (−)-*epi*Afzelechin ((−)-2). The compound was prepared following the synthetic method of (+)-afzelechin with (−)-**13** as the starting marterial. The yield was 82%; mp 196–198 °C; $[\alpha]_D$=−59 (c=3, Me_2CO); lit. $[\alpha]_D$=−58.9 (c=3, EtOH);[15] ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (A of AB, J=8.6 Hz, 2H), 6.91 (B of AB, J=8.6 Hz, 2H), 6.12 (d, J=2.3 Hz, 1H), 6.02 (d, J=2.3 Hz, 1H), 5.00 (bs, 1H), 4.32 (bs, 1H), 2.95 (A of ABt, J=16.6, 4.5 Hz, 1H), 2.77 (B of ABt, J=16.6, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 150.4, 150.2, 150.0, 124.2, 122.8, 122.3, 108.8, 106.3, 93.2, 93.1, 89.5, 88.8, 72.4, 59.8, 21.7; HRMS (ESI) calcd for $C_{15}H_{15}O_5$ (M+H) 275.0919, found 275.0932.

3.1.10. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-(4-benzyloxyphenyl)-chroman-3-yl 3,4,5-tris(benzyloxy)benzoate ((−)-14)). Following the preparation procedure for (+)-**10**, compound (−)-**14** was synthesized with (−)-**13** as starting material. The yield was 82%; mp 134–135 °C; $[\alpha]_D$=−51.3 (c=1.0, CH_3Cl); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.25 (m, 32H), 6.85 (d, J=8.7 Hz, 2H), 6.37 (d, J=2.2 Hz, 1H), 6.30 (d, J=2.2 Hz, 1H), 5.5 (bs, 1H), 5.10 (d, J=4.9 Hz, 1H), 5.08 (s, 2H), 5.03 (s, 2H), 5.02 (s, 2H), 5.01 (s, 2H), 4.99 (s, 2H), 4.97 (s, 2H), 3.08 (bs, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 165.1, 158.7, 158.4, 157.9, 155.6, 152.1, 142.1, 137.8, 136.8, 136.7, 136.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 124.9, 114.5, 108.9, 100.8, 94.5, 93.7, 77.3, 75.0, 70.8, 70.0, 69.8, 68.7, 25.9; HRMS (ESI) calcd for $C_{64}H_{55}O_9$ (M+H) 967.3846, found 967.3862.

3.1.11. (−)-*epi*Afzelechin gallate ((−)-15). The compound was prepared following the synthetic method of (+)-afzelechin gallate with (−)-**14** as the starting material. The yield was 80%; mp 242–244 °C (decompose); $[\alpha]_D$=−177 (c=0.9, Me_2CO); lit. −181.9 (c=0.9, Me_2CO);[15] ^1H NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 7.49 (A of AB, J=8.6 Hz, 2H), 7.13 (s, 2H), 6.92 (B of AB, J=8.6 Hz, 2H), 6.16 (d, J=2.2 Hz, 1H), 6.12 (d, J=2.2 Hz, 1H), 5.56 (bs, 1H), 5.25 (bs, 1H), 3.16 (A of ABt, J=17.4, 4.5 Hz, 1H), 3.02 (B of AB, J=17.4 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3:1, v/v, 400 MHz): δ 160.3, 151.0, 150.7, 150.2, 139.3, 132.6, 123.6, 122.3, 114.5, 109.1, 103.4, 92.2, 89.9, 89.0, 71.4, 63.3, 19.9; HRMS (ESI) calcd for $C_{22}H_{19}O_9$ (M+H) 427.1029, found 427.1045.

Acknowledgements

This work was supported by the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (Project No. AoE/P-10/01). We thank the Hong Kong Polytechnic University for financial support. T. H. C. acknowledges the support of McGill University for the granting of a leave.

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On the oxidative coupling of *N,N*-disubstituted 2-aminothiophenes—synthesis of *N,N′*-persubstituted 5,5′-diamino-2,2′-bithiophenes

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Received 1 April 2004; revised 9 June 2004; accepted 16 June 2004

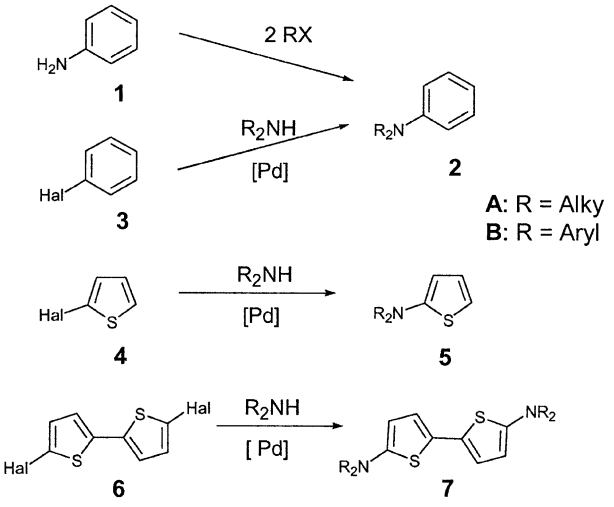
Available online 29 July 2004

Abstract—The oxidative coupling of *N,N*-disubstituted 2-aminothiophenes performed by several heavy-metal free oxidizing agents gives rise to the formation of *N,N′*-persubstituted 5,5′-diamino-2,2′-bithiophenes which are of interest as hole-transport materials for optoelectronic applications.

1. Introduction

Metal-catalysed coupling reactions are advantageous alternatives in the synthesis of *N,N*-disubstituted aromatic amines **2**, for example, from their *N*-unsubstituted parent compounds **1** by reaction with alkyl halides.[1] For preparing *N,N*-diaryl substituted anilines **2B** (R = Aryl) they are the only methods. Whereas in the past copper-catalysed coupling reactions, originally invented by Ullmann,[2] have been used, recently palladium-catalysed coupling reactions, invented by Hartwig,[3] Buchwald,[4] and others,[5] are applied to them. Thus, *N,N*-diaryl substituted anilines **2B** (R = Aryl) have been prepared in mostly satisfactory yields by reaction of iodo or bromobenzenes **3** with diarylamines.[6]

The heavy metal-catalysed *C,N*-coupling reaction has also been successfully applied for the synthesis of *N,N*-disubstituted 2-aminothiophenes **5** as well as for the synthesis of *N,N′*-persubstituted 5,5′-diamino-2,2′bithiophenes **7** from their corresponding bromo derivatives **4** or **6**, respectively. Thus, 2-diarylaminothiophenes **5B**[7] and 5,5′-bis-(diarylamino)-2,2′-bithiophenes **7B**[8] (R = Aryl) have been prepared by palladium-catalysed coupling reactions of diarylamines with 2-bromothiophene **4** or 5,5′-dibromo-2,2′-bithiophene **6** (Hal = Br).



Previously, the *N*-peraryl-substituted 2-aminothiophenes **5B** and 5,5′-diamino-2,2′-bithiophenes **7B** so prepared received a lot of interest as building blocks for new optoelectronic materials, such as dyes with pronounced non-linear optical properties[9] or for compounds with a strong electroluminescence[10] or a tunable electric conductivity.[11] For applying these compounds in the mentioned fields they must have an extremely high purity. Specifically traces of heavy metals, for example, originating from their synthesis, have to be removed completely. This procedure normally requires high time- and cost-consuming separation processes which raise, in general, the prices of the highly purified products

Keywords: 2-Aminothiophenes; 5,5′-Diamino-2,2′-bithiophenes; 5,5′-Dihydro-2,2′-bithiophene-5,5′-diiminium salts; Oxidative coupling; Hetaryl–hetaryl coupling.
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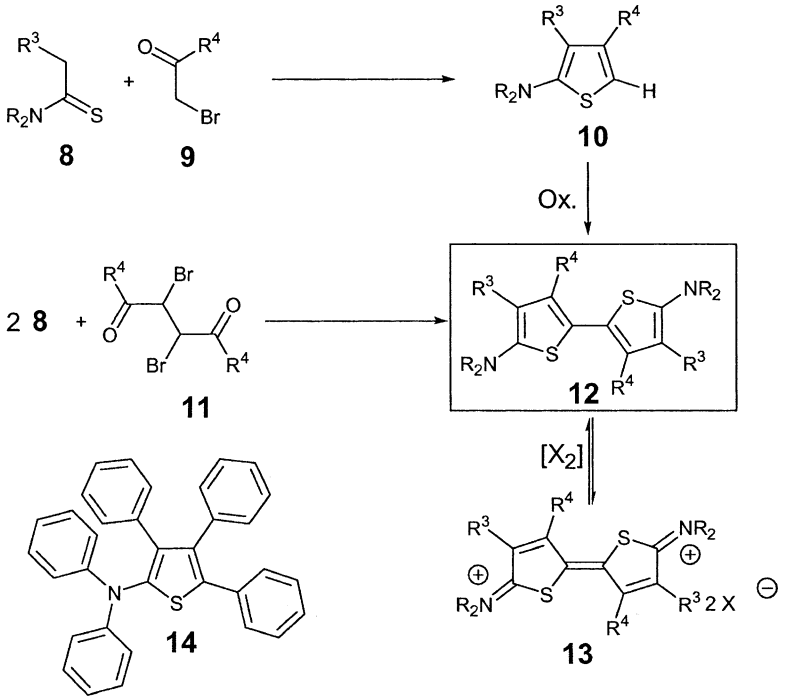
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.107

significantly. Therefore, metal-free methods for preparing such compounds in a technique extent are highly desirable.

Although for the synthesis of triarylamines **2B** such reactions are not in sight today, such synthetic routes are available, in principle, for the synthesis of their heterocyclic thiophene analogues. Thus, for the synthesis of *N,N*-disubstituted 2-aminothiophenes **5** a heavy metal-free synthesis using a heterocyclisation procedure starting from easily available *N,N*-disubstituted thioacetamides **8** and 2-bromoethanones **9** has been elaborated and recently used for a series of compounds **10** which are substituted at their thiophene moieties by further aryl groups.[12]

Recently, this method was also been used to the synthesis of *N,N*-persubstituted 5,5′-diamino-2,2′bithiophenes **12**.[13] Although this method allows the preparation of diamino-2,2′bithiophenes **12** with aryl substitutents at their thiophene moieties, it could not be used hitherto, owing to the failure of a simple access to the necessary 2,3-dibromobutane-1,4-diones **11** as starting compounds and also in contrast to the synthesis of a series of *N,N*-disubtituted 2-aminothiophenes **10**, for synthesis of a larger variety of products.



10 12, 13	R_2N	R^3	R^4
a	$(C_6H_5)_2N$	C_6H_5	C_6H_5
b	$(C_6H_5)_2N$	C_6H_5	4-C_6H_5-C_6H_4
c	$(C_6H_5)_2N$	C_6H_5	4-Me-C_6H_4
d	$(C_6H_5)_2N$	C_6H_5	4-MeO-C_6H_4
e	$(C_6H_5)_2N$	C_6H_5	2-$C_{10}H_7$
f	(4-Me-$C_6H_4)_2N$	C_6H_5	C_6H_5
g	(4-Me-$C_6H_4)_2N$	C_6H_5	4-Me-C_6H_4
h	(4-Me-$C_6H_4)_2N$	4-Me-C_6H_4	4-Me-C_6H_4
i	(4-MeO-$C_6H_4)_2N$	C_6H_5	C_6H_5
j	(4-MeO-$C_6H_4)_2N$	(4-MeO-$C_6H_4)_2N$	(4-MeO-$C_6H_4)_2N$
k	1-$C_{10}H_7(C_6H_5)N$	C_6H_5	C_6H_5
l	2-$C_{10}H_7(C_6H_5)N$	C_6H_5	C_6H_5
m	2-$C_{10}H_7(C_6H_5)N$	C_6H_5	2-$C_{10}H_7$
n	$O(C_2H_4)_2N$	C_6H_5	C_6H_5
o	$O(C_2H_4)_2N$	4-Me-C_6H_4	C_6H_5
p	$O(C_2H_4)_2N$	4-MeO-C_6H_4	C_6H_5
q	$O(C_2H_4)_2N$	4-Me-C_6H_4	4-Br-C_6H_4
r	$O(C_2H_4)_2N$	C_6H_5	4-Cl-C_6H_4

2. Results and discussion

We found a simple, heavy metal-free route for synthesising the interesting *N,N*-persubstituted 5,5′-diamino-2,2′bithiophenes **12**. It consists of the oxidative coupling of the *N,N*-disubstituted 2-aminothiophenes **10**. This coupling reaction avoids, other than a reported method which uses $TiCl_4$ as oxidizing agent,[14] the use of heavy metals and can be performed by means of different type of oxidising agents, such as iodine, bromine, or thionyl chloride. It gives rise to products whose structures depend, to a certain extent, on the compounds and methods used as well as on the conditions applied.

Thus, the reaction of *N,N*-disubstituted 2-aminothiophenes **10** with stoichiometric amounts of iodine is one of the possibilities (method *A*) to transform these compound into their corresponding dimers. It works satisfactorily, however, only in few cases. With iodine in excess or with bromine or thionylchloride as oxidizing agents dicationic products of the structure **13** were formed, primarily. The raw products so obtained were isolated, after the addition of diethyl ether, by filtration and subsequently treated, after washing with diethyl ether and dissolving in a mixture of methanol and acetone without further characterisation, with $NaBH_4$. Thereby the *N,N′*-persubstituted 5,5′-diamino-2,2′-bithiophenes **12** were obtained in nearly quantitative yields (method *B*).

In Table 1 all the 5,5′-diamino-2,2′-bithiophenes **12** so obtained by the methods described are depicted. The structures of the compounds obtained have been confirmed by means of elemental analyses, mass spectra, as well as NMR spectroscopy. These data are compiled in Table 2. The most characteristic NMR signals which were recorded are the ^1H signals for the morpholino moieties in compounds **12p–12t** at about 3.0–4.0 ppm and for the methyl or methoxy groups at the aryl substituents in several compounds between 2.0 and 3.7 ppm as well as the ^{13}C signals at about 20 and 50 ppm in the methyl or methoxy substituted compounds and at about 153 ppm in the 2-morpholino substituted compounds. Further characteristic ^{13}C signals were found in all the 2-diarylamino substituted compounds **12a–12o** at about 147 ppm. These signals can be attributed to *C*(2) of the thiophene moieties.

Although at first glance there seems little doubt, by considering the analytic data of the compounds prepared, on the structure of the *N,N′*-persubstituted 5,5′-diamino-2,2′bithiophenes **12** as oxidation product of the *N,N*-

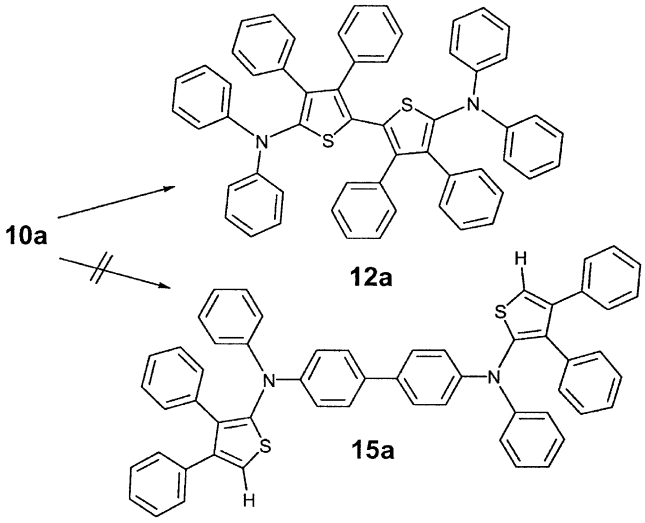
Table 1. Characteristic substance data of compounds **12**

Entry	R_2N	Ar^3	Ar^4	Yield [%] (method)	Mp [°C]	Formula calcd (m.w.) found	C	H	N	S
12a	$(C_6H_5)_2N$	C_6H_5	C_6H_5	46 (A)	263–265	$C_{56}H_{40}N_2S_2$	83.58	4.97	3.48	7.96
				69 (B1)		(805.07)	83.41	5.02	3.59	7.74
12b	$(C_6H_5)_2N$	C_6H_5	4-C_6H_5–C_6H_4	42 (A)	202–203	$C_{68}H_{48}N_2S_2$	85.35	5.02	2.93	6.69
				67 (B1)		(957.26)	85.27	5.11	2.92	6.70
12c	$(C_6H_5)_2N$	C_6H_5	4-CH_3–C_6H_4	82	232–234	$C_{58}H_{44}N_2S_2$	83.65	5.29	3.36	7.69
				(B1)		(833.12)	83.61	5.32	3.33	7.76
12d	$(C_6H_5)_2N$	C_6H_5	4-CH_3O–C_6H_4	84	247–248	$C_{58}H_{44}N_2O_2S_2$	80.55	5.09	3.24	7.41
				(B1)		(865.12)	80.15	5.31	3.22	7.63
12e	$(C_6H_5)_2N$	C_6H_5	2-$C_{10}H_7$	65	176–177	$C_{64}H_{44}N_2S_2$	84.95	4.86	3.10	7.08
				(B1)		(905.19)	84.78	4.85	3.02	7.21
12f	$(4\text{-}CH_3\text{–}C_6H_4)_2N$	C_6H_5	C_6H_5	85	157–158	$C_{60}H_{48}N_2S_2$	83.72	5.58	3.25	7.44
				(B1)		(861.17)	83.64	5.61	3.13	7.72
12g	$(4\text{-}CH_3\text{–}C_6H_4)_2N$	C_6H_5	4-CH_3–C_6H_4	83	223–225	$C_{62}H_{52}N_2S_2$	83.78	5.85	3.15	7.21
				(B1)		(889.23)	83.69	6.10	3.09	7.52
12h	$(4\text{-}CH_3\text{–}C_6H_4)_2N$	4-CH_3–C_6H_4	4-CH_3–C_6H_4	79	272–274	$C_{64}H_{56}N_2S_2$	83.72	6.10	3.05	6.98
				(B1)		(917.28)	83.17	6.32	3.06	6.74
12i	$(4\text{-}CH_3O\text{–}C_6H_4)_2N$	C_6H_5	C_6H_5	66	190–192	$C_{60}H_{48}N_2O_4S_2$	77.82	5.19	3.03	6.92
				(B1)		(925.17)	77.44	5.19	3.02	6.71
12j	$(4\text{-}CH_3O\text{–}C_6H_4)_2N$	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	69	209–210	$C_{64}H_{56}N_2O_8S_2$	73.47	5.36	2.68	6.12
				(B1)		(1045.28)	73.23	5.41	2.52	5.98
12k	1-$C_{10}H_7$–$(C_6H_5)N$	C_6H_5	C_6H_5	68	270–272	$C_{64}H_{44}N_2S_2$	84.95	4.86	3.10	7.08
				(B1)		(905.19)	84.84	4.93	3.17	7.22
12l	2-$C_{10}H_7$–$(C_6H_5)N$	C_6H_5	C_6H_5	76	191–192	$C_{64}H_{44}N_2S_2$	84.95	4.86	3.10	7.08
				(B1)		(905.19)	84.89	4.92	3.06	7.23
12m	2-$C_{10}H_7$–$(C_6H_5)N$	C_6H_5	2-$C_{10}H_7$	67	143–144	$C_{72}H_{48}N_2S_2$	86.23	4.79	2.79	6.39
				(B1)		(1005.31)	86.04	4.87	2.73	6.42
12n	$O(CH_2CH_2)_2N$	C_6H_5	C_6H_5	67 (B2)	280–281	$C_{40}H_{36}N_2O_2S_2$	75.00	5.62	4.37	10.00
				73 (B3)		(640.86)	74.77	5.81	4.19	10.12
12o	$O(CH_2CH_2)_2N$	4-CH_3–C_6H_4	C_6H_5	72 (B2)	255	$C_{42}H_{40}N_2O_2S_2$	75.45	5.99	4.19	9.58
				83 (B3)		(668.91)	75.39	6.06	4.10	9.63
12p	$O(CH_2CH_2)_2N$	4-CH_3O–C_6H_4	C_6H_5	79 (B2)	205–206	$C_{42}H_{40}N_2O_4S_2$	72.00	5.71	4.00	9.14
				82 (B3)		(700.91)	71.90	5.77	4.09	9.21
12q	$O(CH_2CH_2)_2N$	4-CH_3–C_6H_4	4-Br–C_6H_4	56 (B2)	304–306	$C_{42}H_{38}Br_2N_2O_2S_2$	61.02	4.60	3.39	7.75
				59 (B3)		(826.70)	60.97	4.67	3.29	7.80
12r	$O(CH_2CH_2)_2N$	C_6H_5	4-Cl–C_6H_4	81 (B3)	304–305	$C_{40}H_{34}N_2O_2S_2Cl_2$	60.15	4.26	3.51	8.02
						709.75	60.08	4.27	3.51	8.11

disubtituted 2-aminothiophenes **10**, some doubts may arise. However, keeping in mind that most of the starting materials contain further *N*-linked aryl moieties which are principally able to be coupled oxidatively via their *C*(4) postions also. For instances, triphenylamine can be oxidatively transformed into *N,N′*-tetraphenylbenzidine or its dicationic consecutive product.[15]

Therefore, some of the 2-diarylamino-substituted thiophenes, such as the compounds **12a**–**12e** and **12k**–**12m**, could be principally dimerise at their aryl moieties. Thus, from compound **10a**, for example, the dimerisation product **12a** or **15a** could be expected. Whereas the compound **12a** results from an oxidative coupling of its 2-aminothiophene moiety at its 5-position, the compound **15a** should result from an oxidative coupling at the 4-position in one of its aniline moiety.

Because both the compounds **12a** and **15a** are isomeric to each other their analytic and spectroscopic data should be very similar and a decision between one of those seems not simply possible. Thus, the signal of the proton at *C*(5) of the thiophene moiety in the starting compound **10a** is hidden beneath the proton signals of the its aryl moieties, so that the actual coupling position is not easily detected by ^{1}H NMR.



A simple proof for the actual structure of the coupling product obtained **12a** can be derived, however, from its ^{1}H and ^{13}C NMR spectrum. These spectra are identical with the ones of compound **12a** which has been prepared by reaction of two equivalents of *C,N,N*-triphenyl-thioacetamide **8** (R/R^3=phenyl) with one equivalent of 2,3-dibromo-1,4-diphenylbutane-1,4-dione **11** (R^4=phenyl). In contrast,

Table 2. Spectroscopic data of the compound **12** prepared

Entry	*m/z*	^{1}H NMR, δ-values, in $CDCl_3$ (ppm) (assignment)	^{13}C NMR, δ-values, in $CDCl_3$ (ppm)
12a	804 (100%), 402 (8%)	6.79–6.84 (m, 4 arom.. H), 6.85–6.97 (m, 22 arom. H), 7.03–7.16 (m, 14 arom. H)	122.26, 122.87, 127.21, 127.31, 128.13, 128.15, 128.56, 129.42, 130.42, 131.36, 135.51, 136.20, 138.63, 141.68, 146.42, 147.80
12b	956 (100%), 478 (14%)	6.82–7.00 (m, 24 arom. H), 7.08–7.15 (m, 8 arom. H), 7.26–7.35 (m, 8H, arom. H), 7.37–7.43 (m, 4 arom. H), 751–7.55(m, 4 arom. H)	122.31, 122.94, 126.7, 127.26, 127.55, 127.84, 128.24, 128.70, 129.39, 129.46, 130.47, 131.60, 135.24, 135.48, 138.75, 139.68, 140.9, 141.53, 146.53, 147.82
12c	832 (100%), 416 (7%)	2.28 (s, 6H, CH_3), 6.83–7.0 (m, 30 arom. H), 7.09–7.16 (m, 8 arom. H)	21.97, 122.23, 122.78, 127.14, 128.13, 128.59, 128.91, 129.37, 130.47, 131.29, 132.28, 135.69, 136.91, 138.68, 141.5, 146.19, 147.81
12d	864 (100%), 432 (9%)	3.73 (s, 6H, OCH_3), 6.61–6.65 (m, 4 arom. H), 6.8–6.98 (m, 26 arom. H), 7.08–7.15(m, 8 arom. H)	55.78, 113.68, 122.25, 122.81, 127.17, 128.17, 128.37, 128.74, 129.38, 130.47, 132.52, 135.68, 138.61, 141.08, 146.20, 147.81, 159.10
12e	904 (100%), 452 (16%)	6.65–7.72 (m, 44 arom. H)	121.48, 122.18, 125.52, 125.64, 126.52, 126.66, 127.48, 127.49, 127.78, 128.22, 128.29, 128.73, 129.60, 129.62, 131.98, 132.96, 132.98, 134.58, 138.01, 140.83, 145.83, 147.02
12f	860 (100%), 430 (13%)	2.27 (s, 6H, CH_3), 6.8–6.91 (m, 6 arom. H), 6.92–7.01 (m, 7 arom. H), 7.04–7.09 (m, 2 arom. H), 7.14–7.20 (3 arom. H)	20.64, 121.37, 126.37, 126.45, 127.34, 127.37, 127.66, 129.26, 129.72, 130.63, 131.42, 134.89, 135.57, 137.49, 140.79, 144.93, 146.10
12g	888 (100%), 444 (26%)	2.25 (s, 12H, CH_3), 2.28 (s, 6H, CH_3), 6.72–7.03 (m, 34H, arom.H)	20.64, 21.25, 121.35, 126.3, 127.36, 127.71, 128.13, 129.22, 129.79, 130.57, 131.3, 132.66, 135.10, 136.02, 137.55, 140.57, 144.96, 145.86
12h	916 (100%), 458 (29%)	2.18 (s, 6H, CH_3), 2.25 (s, 12H, CH_3), 2.29 (s, 6H, CH_3), 6.75–6.8 (m, 12 arom. H), 6.81, 6.83 (d, 4 arom. H), 6.86, 6.88 (d, 4 arom. H), 6.90–6.96 (m, 12 arom. H)	20.72, 21.19, 21.35, 121.59, 128.24, 128.45, 128.54, 129.64, 129.96, 130.99, 131.91, 132.46, 133.31, 136.55, 136.74, 138.10, 141.20, 145.37, 145.95
12i	923 (100%), 924 (71%), 462 (21%)	3.72 (s, 12H, OCH_3), 6.65, 6.67 (d, 8 arom. H), 6.78–7.07 (m, 28 arom. H)	55.48, 114.08, 122.69, 126.35, 126.42, 127.12, 127.34, 127.39, 129.78, 130.64, 135.04, 135.62, 136.68, 140.71, 141.23, 146.83, 154.86
12j	1044 (100%), 522 (27%)	3.67 (s, 6H, OCH_3), 3.72 (s, 12H, OCH_3), 3.75 (s, 6H, OCH_3), 6.55, 6.57 (d, 4 arom. H), 6.67–6.81 (m, 24 arom. H), 6.88 (d, 4 arom. H)	55.32, 55.40, 55.76, 113.21, 113.25, 114.37, 122.97, 127.38, 127.93, 128.69, 131.28, 132.26, 136.87, 140.79, 141.58, 146.52, 155.33, 158.60, 158.85
12k	904 (100%), 452 (18%)	6.77–6.9 (m, 20 arom. H), 6.99–7.08 (m, 8 arom. H), 7.1–7.19(m, 6 arom. H), 7.25–7.38 (m, 6 arom. H), 7.56, 7.59(d, J=8.4 Hz, 2 arom. H), 7.61(d, J=8.1 Hz, 2 arom. H), 7.73, 7.75(d, J=8.1 Hz, 2 arom. H)	117.91, 120.34, 124.45, 125.33, 125.55, 125.62, 125.76, 126.28, 126.38, 126.39, 127.19, 127.31, 127.39, 127.92, 128.67, 129.89, 129.91, 130.55, 134.62, 135.12, 135.50, 137.21, 140.83, 142.30, 146.75, 149.76
12l	904 (100%), 452 (35%)	6.85–7.02 (m, 20 arom. H), 7.07–7.20 (m, 12 arom. H), 7.27–7.35(m, 4 arom. H), 7.35–7.42 (t, 2 arom. H), 7.57–7.63 (t, J=9.1 Hz, 4 arom. H), 7.68–7.74 (d, J=8.0 Hz, 2 arom. H)	117.77, 121.72, 121.96, 122.39, 123.23, 126.16, 126.55, 126.68, 126.94, 127.45, 127.46, 127.47, 127.96, 128.41, 128.76, 129.65, 129.69, 130.67, 134.08, 134.68, 135.43, 138.04, 141.03, 144.77, 145.64, 146.94
12m	1002 (100%), 860 (14%), 502 (26%),	6.76 (d, 1 arom. H, J=1.8 Hz), 6.78–6.98 (m, 15 arom. H), 7.08–7.16 (m, 6 arom. H), 7.27–7.45 (m, 13 arom. H), 7.48–7.58 (m, 5 arom. H), 7.67–7.72 (m, 4 arom. H)	117.75, 121.72, 121.92, 122.44, 124.24, 125.59, 125.69, 126.15, 126.57, 126.73, 126.99, 127.46, 127.50, 127.51, 127.83, 128.29, 128.31, 128.46, 128.79, 129.61, 129.67, 129.69, 132.03, 132.95, 133.08, 134.05, 134.53, 138.16, 140.93, 144.74, 145.79, 146.95
12n	640 (100%), 320 (9%)	2.80 (t, 8H, CH_2), 3.59 (t, 8H, J=4.5 Hz, CH_2), 6.63 (d, 4H arom. H, J=6.0 Hz), 6.9–7.16(m, 16 arom. H)	52.82, 66.66, 122.29, 125.98, 126.12, 127.33, 127.65, 128.37, 130.22, 130.52, 135.9, 135.93, 140.42, 153.85
12o	334 (9%) 668 (100%),	2.24 (s, 6H, CH_3), 2.8(t, 8H, CH_2), 3.6(t, 8H, J=3.9 Hz, CH_2), 6.63 (d, 4 arom. H, J=6.6 Hz), 6.9–7.01(m, 14 arom. H)	21.13, 52.74, 66.66, 122.27, 125.89, 127.30, 128.26, 128.36, 129.98, 130.53, 132.98, 135.54, 136.06, 140.42, 153.51
12p	700 (100%), 350 (10%)	2.80 (t, 8H, CH_2), 3.61(t, 8H, CH_2), 3.71(s, 6H, OCH_3), 6.64(m, 8 arom. H), 6.90–7.01(m, 10 arom. H)	52.66, 54.92, 66.67, 113.03, 122.18, 125.86, 127.3, 127.83, 128.17, 130.51, 131.19, 136.05, 140.34, 153.37, 157.7
12q	826 (100%), 413 (9%)	2.24 (s, 6H, CH_3), 2.83 (q, 8H, J=4.4 Hz, CH_2), 3.62 (t, 8H, J=4.8 Hz, CH_2), 6.28 (d, 4 arom. H), 6.88–6.98 (m, 12 arom. H)[a]	21.18, 52.81, 66.71, 120.11, 122.01, 128.23, 128.63, 129.96, 130.39, 131.77, 132.38, 134.87, 135.95, 138.59, 154.01
12r	708 (100%), 354 (4%)	2.83 (t, 8H, CH_2), 3.61 (t, 8H, CH_2), 6.36 (d, 4 arom. H, J=7.8 Hz), 6.83 (d, 4 arom. H, J=8.1 Hz), 6.98–7.18 (m, 10H, arom. H)	52.87, 66.60, 122.21, 126.48, 127.51, 127.95, 128.47, 130.19, 131.43, 131.95, 134.26, 135.48, 138.70, 154.10

[a] Measured in CD_2Cl_2.

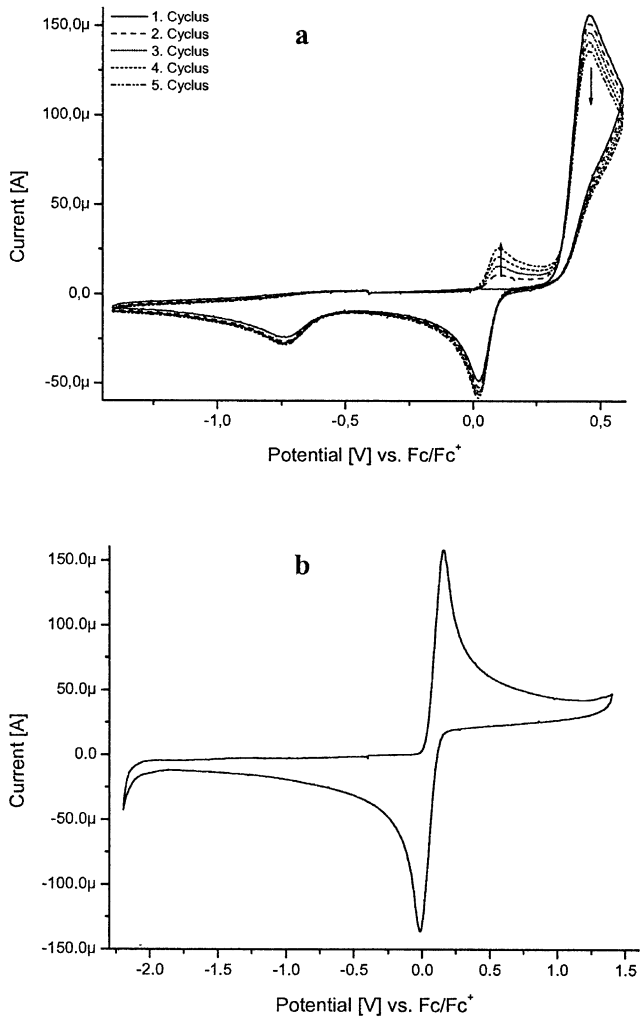


Figure 1. Cylic voltammogram of compounds **10g** (a) and **12g** (b).

the ^{1}H and ^{13}C NMR spectra of compound **12a** (mp 261–262 °C) are not identical with the ones of compound **15a** (mp 276 °C) which was available by reaction of 1 equiv. of *N,N′*-bis(thiophenylacetyl)-*N,N′*-diphenylbenzdine with two equivalent of phenacyl bromide.[13]

Further arguments for the correct structures of the coupling products **12** results from an oxidative coupling of *N,N*-disubstituted 2-aminothiophenes which are, like the compound **14**, substituted by a phenyl group at *C*(5) in the thiophene moiety, or, like the compound **10f** or **10g**, by two 4-tolyl groups at their 2-amino moieties. Whereas the compound **14** (prepared from *C,N,N*-triphenythioacetamide **8a** and desylbromide accordingly to ref. [13]) is unable to give a bithiophene derivative by its oxidative coupling under the usual applied coupling conditions, the compounds **10f** or **10g** couple oxidatively without problems to yield corresponding bithiophene derivatives **12f** and **12g**, respectively.

The different oxidative coupling behaviour of the compound **14** in respect to the one of compounds which are, like the compounds **10f** and **10g**, non-substituted at *C*(5) of their 2-aminothiphene moiety can be studied also by means of cyclic voltammetry. For instance, the compound **10g** exhibits in its cyclic voltammogram two characteristic

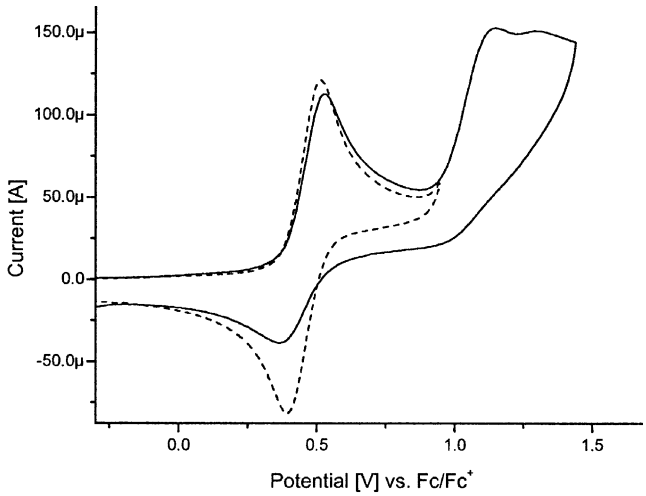


Figure 2. Cylic voltammogram of compound **14**.

peaks at +0.45 and +0.06 V their intensities vary with the number of scans (see Fig. 1a). In the first scan only one peak is observed at+0.45 V. This peak is strongly irreversible and can be attributed, therefore, to the formation of a corresponding radical cation which is formed primarily from the starting 2-aminothiophene by the loss of one electron and which dimerise, due to its high reactivity, accordingly to a RRD or RSC mechanism.[16] The second peak appearing in the next scans only is completely reversible.

This peak originates, therefore, from the 5,5′-diamino-2,2′-bithiophene derivative **12g** which is formed in course of the anodic processes and exhibits, as studied independently with an authentic sample (see Fig. 1b), an oxidation peak at exactly the same potential.

In contrast, compound **14** exhibit in its cyclic voltammogram, as depicted in Figure 2, two peaks at+0.44 and+1.11 V. Whereas the second peak is irreversible, the first peak is reversible and corresponds to an one-electron process. It was measured nearly at the same potential as for compound **12g** indicating, hence, the formation of stabilised oxidation products unable to dimerise under the conditions of measurement.

From these findings it can be concluded, therefore, that the presence of proton at *C*(5) of the thiophene moieties in the starting compounds **10** is a necessary precondition for their oxidative dimerisation. It gives rise to the formation of dimers of the general structure **12** as well as corresponding dicationic products of the structure **13** and, subsequently, not to the formation of dimers with a benzidine structure **15**. The oxidative dimerisation here used has some relations to a heavy metal-free coupling reaction performed with phenyliodine bis(trifluoroacetate) and used for the oxidative dimerisation of alkyl-substituted thiophenes.[17]

3. Experimental

3.1. General information

The following instruments and analytical techniques were

used: *melting points*: Kofler hot-stage microscope, corrected; *NMR*: Inova 500 'max 2'. Varian 300 MHz spectrometer Gemini 300; $CDCl_3$ was used as solvent; *elemental analysis*: LECO analyzer CHNS 932; *MS*: AMO spectrometer 402 (70 eV, EI); *cyclic voltammetry*: Autolab instrument PGSTAT 20. The electrochemical measurements were performed under argon in benzonitrile containing Bu_4NPF_6 as supporting electrolyte with a scan rate of 0.1 V s^{-1} using a stationary platinum working electrode, a platinum counter electrode, and a stationary platinum reference electrode. Standard redox potentials have been estimated versus ferrocen/ferrocenium in benzonitrile as a reference redox system with nearly reversible electrode processes; *mass spectra*: ESI, LCQ, Finnigan MAT.

3.2. Materials

The *N,N*-disubstituted 2-aminothiophenes **10** used as starting materials for the oxidative coupling reactions described have been prepared accordingly to Ref. 12. *N,N′*-Bis(phenyl)-*N,N′*-bis(3.4-diphenyl-2-thienyl) benzidine **15a** was prepared accordingly to Ref. 13.

3.2.1. Preparation of *N,N′*-persubstituted 5,5′-diamino-3,4,3′,4′-tetraaryl-2,2′-bithiophenes 12 (general procedures). *Method A*. A solution of iodine in acetonitrile (5%) was slowly added to a solution of a 2-diarylaminothiophene **10a**–**10m** (0.01 mol) in acetonitrile (100 mL) under reflux until the educt used was not more detectable by TLC. The solution was evaporated and the precipitate formed was isolated by filtration and washed with methanol.

Methode B. To a solution of the dicationic intermediates **13** prepared by the subsequent procedures and dissolved in a mixture of acetone (100 mL) and methanol (10 mL), $NaBH_4$ was added under reflux until the solution becomes colourless. After evaporation of the solvent, the products **12** were precipitated by addition of methanol, isolated by filtration, and purified by recrystallisation or column chromatography on silica using a mixture of toluene/cyclohexane as eluent.

3.2.2. Preparation of 3,4,3′,4′-tetraaryl-5,5′-dihydro-2,2′-bithiophene-5,5′-diiminium salts 13 (general procedures). *Method B1*. A solution of a *N,N*-diarylaminothiophene **12a**–**12m** (0.01 mol) and iodine (0.05 mol, 12.7 g) in dichloromethane (100 mL) was refluxed 0.5 h. After concentration of the solution the blue-green solid product of **13**, precipitated by cooling, was separated by filtration and washed with diethyl ether.

Method B2. To a solution of a 2-morpholinothiophene **10n**–**10r** (0.01 mol) in 70 ml dichloromethane, thionylchloride (0.025 mol, 3.0 g) was added and the resulting mixture, which turned red, was refluxed for 0.5 h. After cooling at room temperature and addition of diethyl ether (50 mL) to the mixture, the products **13** formed were isolated by filtration and washed with diethyl ether.

Method B3. To a solution of a 2-morpholinothiophene **10n**–**10r** (0.01 mol) in dichloromethane (70 mL), bromine (0.015 mol, 2.4 g), dissolved in dichloromethane (50 mL), was added. After refluxing the mixture for 0.5 h, it was concentrated and cooled. The red-coloured products **13** that precipitated were isolated by filtration after the addition of diethyl ether.

3.2.3. 2-(*N,N*-Diphenylamino)-3,4,5-triphenylthiophene 14. A solution of *N,N*-(diphenyl)phenylthioacetamide (0.01 mol, 3.03 g) and desylbromide (0.01 mol, 2.75 g) in ethanol (70 mL) was refluxed for 6 h. A white solid precipitated was isolated by filtration and recrystallised from ethanol.

Yield: 3.62 g, (75%), mp 173 °C.

^{1}H NMR ($CDCl_3$): 6.84–7.24 (m, 25 arom. H).

^{13}C NMR ($CDCl_3$): 122.46, 122.59, 127.19, 127.32, 127.84, 128.15, 128.54, 128.90, 129.51, 130.01, 130.55, 131.58, 135.14, 135.85, 136.37, 136.87, 137.91, 140.10, 145.05, 148.11.

Ms: 479 (100%), 121 (10%).

Anal. calcd for $C_{34}H_{25}NS$ (479.64): C, 85.06; H, 5.21; N, 2.92; S, 7.09. Found: C, 84.80; H, 5.32; N, 3.06; S, 7.17.

Acknowledgements

The authors wish to thank the Deutsche Forschungsgemeinschaft for generous financial support as well as Dr. Dirk Rohde for his support with some electrochemical measurements.

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Tetrahedron 60 (2004) 8221–8231
Tetrahedron

Enantioselective nucleophilic addition of organometallic reagents to quinoline: regio-, stereo- and enantioselectivity

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Received 31 March 2004; revised 9 June 2004; accepted 16 June 2004

Available online 8 July 2004

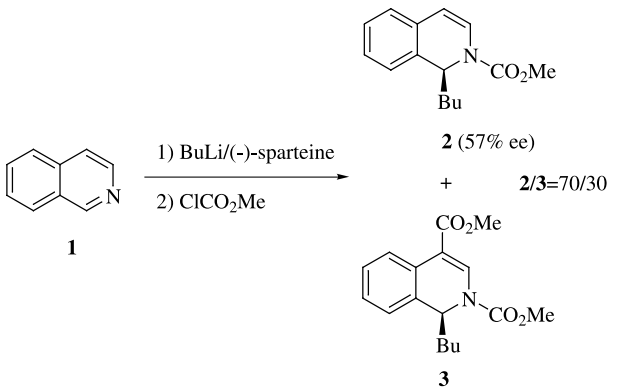
Abstract—Some 2-alkyl-1,2-dihydroquinoline and some 2-aryl-1,2-dihydroquinoline were obtained by enantioselective addition of methyl-, butyl-, phenyl- and 1-naphthyllithium on quinoline. Bisoxazolines were used as external chiral ligands, giving enantiomeric excess up to 79%. The ligand could be used in catalytic amounts without significant loss of enantioselectivity.

1. Introduction

The nucleophilic 1,2 addition of organometallic reagents on imines and related compounds is a well-known method to synthesise amines. The asymmetric version has extensively been studied, both with stoichiometric covalent auxiliaries[1] and with external chiral ligands, in stoichiometric or catalytic amounts.[2] In the particular case of azaaromatic compounds, the nucleophilic addition is more difficult because of the already poor reactivity of the C=N double bond and the aromatic nature of these systems.[3] Even fewer examples concern quinoline.

Quinoline derivatives are compounds of biological interest[4] and nucleophilic addition of an organometallic reagent, such as organolithiums and Grignards, is a good method to obtain a racemic 1,2- or 1,4-dihydroquinoline.[5] The use of quinolinium salts, to enhance the reactivity, often improves the results.[6] Nevertheless, not much is known about the synthesis of non-racemic alkylated 1,2-dihydroquinolines. Diastereoselective[4d,5h] and an enantioselective synthesis are known, using chiral aminals as auxiliary.[7] Excellent enantiomeric excess could be obtained with phenyl and naphthyl Grignard. To our knowledge, only the cyanation of the quinoline has been reported with catalytic amounts of chiral ligand to give the corresponding dihydroquinoline with 80% ee.[8] The enantioselective addition of organometallic reagents, as carbon nucleophiles, does not seem to have been explored with quinoline.

In our earlier work, we reported the first enantioselective addition of organolithium reagents on isoquinoline in the presence of (−)-sparteine.[9] Even a catalytic amount of ligand could be used. We have shown that a direct addition of butyllithium on isoquinoline gave a chiral 1,2-dihydroisoquinoline with an enantiomeric excess of 57% (Scheme 1).



Scheme 1. Enantioselective addition of butyllithium to isoquinoline.

The regioselectivity of this nucleophilic addition was complete at the benzylic position 1, but stabilisation of the adduct with methylchloroformate gave a mixture of N-acylated product **2** and bisacylated product **3**. The ratio of these two products was invariably 70/30 when temperature, solvent and amount of reagents were changed. Within the framework of our study on heteroaromatic compounds, we are now interested in enlarging the method previously described with isoquinoline, to quinoline as aromatic imine.

2. Results and discussion

The regioselectivity of the nucleophilic addition was studied with methyllithium, a relatively less reactive organolithium

Keywords: 1,2-Dihydroquinoline; Enantioselective addition; Chiral ligand; Organolithium reagents; Organometallics; Bioxazoline.
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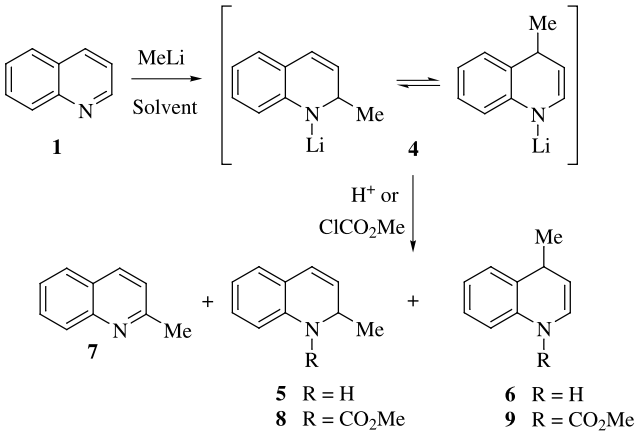
doi:10.1016/j.tet.2004.06.088

Table 1. Regioselectivity of the addition of methyllithium to quinoline



Entries	Solvent	T [°C]	Time (min)	Ligand	Ratio **5/6** or **8**	Yield or conversion [%]
1	Toluene	−20	60	—	100/0	65[a]
2	Toluene	−20	60	DME (0.5 equiv)	100/0	100[a]
3	Toluene	−20	60	TMEDA (0.5 equiv)	100/0	100[a]
4	Et_2O	−40	10	—	100	0[b]
5	Et_2O	−20	10	—	100	18[b]
6	Et_2O	−20	10	DME (0.5 equiv)	100	81[b]

[a] Conversion estimated of crude NMR spectra.
[b] Yield of isolated product.

reagent. Table 1 shows that only the 1,2 addition was observed, giving the 2-methyl-1,2-dihydroquinoline **5** in 65% conversion after 1 h. No re-aromatised product **7** was observed in the crude mixture and the final dihydroquinoline **5** was stable enough to be studied by crude NMR analysis. However, this product could hardly be purified by flash chromatography on silicagel without a large part of re-aromatisation.

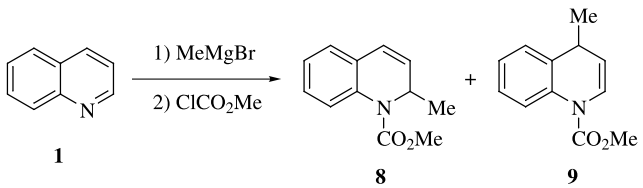
When dimethoxyethane (DME) was used as a non-chiral ligand (entry 2), the conversion was complete under the same conditions, indicating that the presence of a 1,2 diether enhanced the rate of the reaction. No change in the regioselectivity was observed and only the 1,2 adduct **5** was obtained. A similar behaviour was observed with a diamine, such as tetramethylethylenediamine (TMEDA) (entry 3).

Using the method previously explored with isoquinoline, the lithiated intermediate **4** was trapped, in Et_2O, with methylchloroformate after 10 min (Table 1). In this case, only the N-acylation was observed. The regioselectivity was not affected and the 1,2-dihydroquinoline **8** was the unique product. The influence of the temperature was determined and we can see that at −40 °C no reaction was observed after 10 min (entry 4). This also shows that methylchloroformate did not activate the imine moiety[6a] in the nucleophilic addition but only stabilises the adduct. When the temperature rose to −20 °C, the 1,2-dihydroquinoline **8** could be obtained in 18% yield (entry 5). However, the presence of sub-stoichiometric amounts of DME increased dramatically the yield up to 81% (entry 6).

These results show that the nucleophilic addition of an alkyllithium reagent on quinoline is completely regioselective and the 1,2-dihydroquinoline can be isolated in good yield without any by-product. Even more importantly, with asymmetric catalysis in view, the nucleophile can be activated by sub-stoichiometric amounts of an external ligand like DME or TMEDA in toluene or in Et_2O. These results had comforted us in the possibility of an enantioselective activation of this nucleophilic addition.

The rate of the reaction was also studied with methyl Grignard as carbon nucleophile (Table 2). In the absence of methyl chloroformate, no reaction took place. Therefore, an activation of quinoline, as its quinolinium salt is needed.

Table 2. Regioselectivity of the addition of methyl Grignard to the quinoline

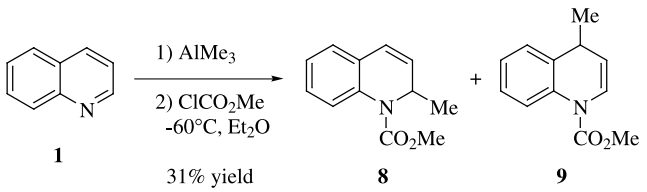


Entries	Solvent	T [°C]	Ligand	Yield [%]	**8/9**
1	Et_2O	−20	—	41	100/0
2	Et_2O	−20	DME 0.5 equiv	16	100/0
3	THF	−20	—	28	100/0
4	Toluene	−20	—	59	100/0
5	Toluene	−20	DME 0.5 equiv	34	100/0
6	CH_2Cl_2	−20	—	94	100/0
7	CH_2Cl_2	−20	DME 0.5 equiv	60	100/0

At −20 °C, methylchloroformate was added 10 min after the nucleophile in order to observe a significant rate of reaction. In Et_2O, without any ligand, the isolated yield of dihydroquinoline **8** was 41% (entry 1). Only the 1,2 adduct was observed. With 0.5 equiv. of dimethoxyethane, the isolated yield was only 16% (entry 2) but the

regioselectivity was complete. In tetrahydrofuran, the yield was worse than in Et_2O with 28% of isolated product (entry 3). In toluene, dihydroquinoline **8** was obtained in 59% yield (entry 4) but the presence of 0.5 equiv of dimethoxyethane decreased the yield down to 34% (entry 5). The best result was obtained in dichloromethane (entry 6) with 94% yield of the 1,2 adduct. Thus, in striking contrast to organolithium reagents, dimethoxyethane had a detrimental effect, the dihydroquinoline being obtained in only 60% yield. In all these experiments, the regioselectivity was complete at position 2 and no trace of 1,4 adduct **9** was observed. Unfortunately, the presence of a bidentate ligand such DME, dramatically decreased the yield of dihydroquinoline.

This regioselective 1,2 addition was also observed with trimethylaluminum (Scheme 2).

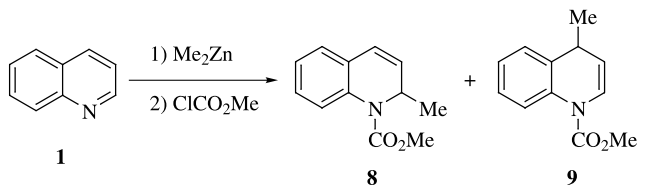


Scheme 2. Regioselectivity of the addition of $AlMe_3$ to quinoline.

Trimethylaluminum did not react after 12 h at room temperature. This nucleophile was not reactive enough with quinoline and activation as iminium salt with methylchloroformate was again required. In this case, the 1,2-dihydroquinoline **8** could be obtained in 31% yield at −60 °C. The regioselectivity was determined by NMR analysis of the crude and only the 1,2 adduct could be observed.

As for trimethylaluminum, dimethylzinc did not react with quinoline and methylchloroformate was used as an activating agent (Table 3).

Table 3. Regioselectivity of the addition of dimethylzinc to quinoline



Entries	Solvent	T [°C]	Ligand	Yield [%]	**8/9**
1	THF	−20	—	30	75/25
2	Et_2O	−20	—	18	>90/10
3	Et_2O	−20	DME 0.5 equiv	16	55/45

Methylchloroformate was added 10 min after the dimethylzinc. In tetrahydrofuran at −20 °C, a modest yield of 30% was observed and the ratio **8/9**, determined by NMR analysis, was found to be 75/25 (entry 1). In Et_2O, under the same conditions, the regioselectivity was better (entry 2) but the yield of isolated product was only 18%. The presence of a diether in the solution did not increase the yield and decreased dramatically the regioselectivity. In this case the ratio of 1,2- and 1,4-dihydroquinoline was 55/45 (entry 3).

2.1. Enantioselective additions with chiral diether 10

In summary, we can say that with organometallics such as alkyl Grignard, dimethylzinc and trimethylaluminum, quinoline has to be activated as a quinolinium salt. In all these cases, the yields were not as good as with organolithium reagents, which is able to add directly on the imine moiety. The presence of a diether decreased the yield, and the regioselectivity in the case of dimethylzinc. For these reasons, alkyllithium reagents appeared to us to be the best candidates for the 1,2 enantioselective nucleophilic addition to quinoline. So far, they were tested in the presence of three different ligands: the chiral 1,2 diether **10**,[10] developed by Tomioka, (−)-sparteine[11] **11** as a 1,2 diamine, and the bisoxazolines **12a**, **12b** and **12c** (Fig. 1).

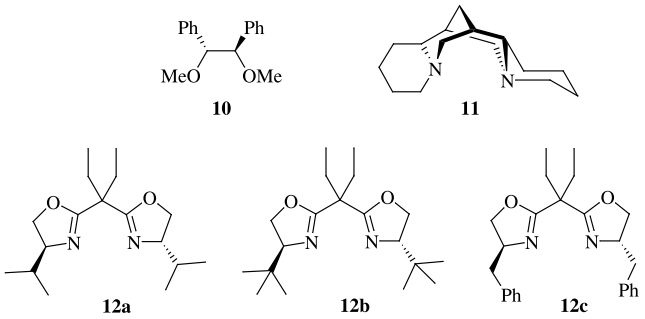


Figure 1. (*R*,*R*)-Dimethoxydiphenylethane **10**, (−)-sparteine **11**, bisoxazolines **12a**, **12b** and **12c**.

Firstly, methyllithium was used in the presence of 1 equiv of the chiral diether **10** (Table 4, entry 1). The desired dihydroquinoline was obtained in 67% isolated yield but the enantiomeric excess, determined by chiral GC analysis, was only 20%.

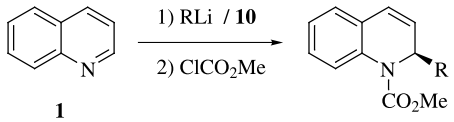
The catalytic version of this addition was tested with the more reactive *n*-butyllithium. Table 4 shows that conversion to the 2-butyl-1,2-dihydroquinoline **13** was good at low temperature in Et_2O or in toluene (entries 2–4). Unfortunately, the enantiomeric excess was very low. Phenyllithium (entries 5–9), as well as 1-naphthyllithium (entries 10 and 11), also showed very low enantioselectivity. However, it is striking to observe that, despite the very low yield, a moderate ee of 26% (although the best in this series!) could be obtained in toluene (entry 6). The yields were usually better with catalytic amount of ligand, indicating that the ligand might be destroyed by RLi, thus consuming most of this nucleophile.

2.2. Enantioselective additions with (−)-sparteine 11

The 1,2 diether **10** being rather inefficient, we have attempted to enhance the chiral induction by changing the nature of the chelating heteroatoms. (−)-Sparteine **11**, already known to be a good complexing chiral ligand for organolithium reagents,[11] appeared to us to be a good alternative. Using the same procedure as before, the organolithium reagent was firstly added to the mixture of (−)-sparteine **11** and quinoline **1** (Table 5).

In toluene at −40 °C, butyllithium gave the desired dihydroquinoline **13** with 15% ee in the presence of

Table 4. Enantioselective addition of organolithium reagent to quinoline in the presence of (*R*,*R*)-dimethoxydiphenylethane **10**



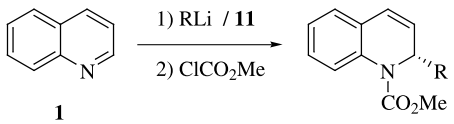
1

8 R = Me
13 R = Bu
14 R = Ph
15 R= Naphth

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yield [%]	ee [%]
1	Et_2O	Me	−20 1 h	1	67[a]	20
2	Et_2O	Bu	−60 1 h	0.2	86[a]	4
3	Toluene	Bu	−60 1 h	0.2	68[a]	0
4	Toluene	Bu	−78 1 h	0.2	53[a]	4
5	Et_2O	Ph[b]	−78 2 h	1	16	<2
6	Toluene	Ph[b]	−78 2 h	1	7	26
7	Toluene	Ph[b]	−78 2 h	0.2	54	<2
8	Toluene	Ph[b]	−60 2 h	1	20	12
9	Toluene	Ph[b]	−60 2 h	0.2	74	<2
10	Toluene	Naphth[b]	−50 2 h	1	57	<4
11	Toluene	Naphth[b]	−50 2 h	0.2	45	5

[a] Conversion determined by crude NMR analysis.
[b] PhLi and NaphthLi were prepared by halogen–metal exchange between PhI or NaphthI and *n*-BuLi.

Table 5. Enantioselective addition of butyllithium and methyllithium to quinoline in the presence of (−)-sparteine



1

8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	(−)-Sparteine [equiv]	Yield [%]	ee [%]
1	Toluene	Bu	−40 1 h	0.2	67	15
2	Toluene	Bu	−40 1 h	1	98	18
3	Toluene	Bu	−80 1 h	1	86	19
4	Et_2O	Bu	−40 1 h	1	98	16
5	Et_2O	Bu	−40 1 h	0.2	100	13
6	Et_2O	Bu	−60 1 h	1	99	18
7	Et_2O	Bu	−80 1 h	1	86	16
8[a]	Et_2O	Bu	−40 1 h	1	100	10
9[a]	Et_2O	Bu	−60 1 h	1	76	12
10	Et_2O	Me	−20 1 h	1	69	5

[a] By precomplexing the butyllithium and (−)-sparteine.

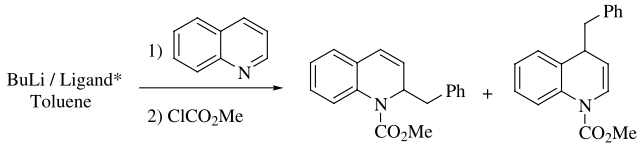
0.2 equiv of ligand (entry 1). Increasing the amount of ligand up to 1 equiv under the same conditions allowed to improve the yield up to 98% of isolated product, but the enantiomeric excess was only 18% (entry 2). This result could not be enhanced by cooling the temperature to −80 °C and enantiomeric excess was still 19% (entry 3). Using Et_2O instead of toluene gave lower enantiomeric excess with 1 equiv (entry 4), or 0.2 equiv of ligand (entry 5), even at lower temperatures (entries 6 and 7). Compared to diether **10**, (−)-sparteine **11** gave both higher yields and ee's. Finally, methyllithium was tested with stoichiometric amounts of ligand (entry 10). Both yield and enantiomeric excess of the dihydroquinoline **8** were comparable than before, with diphenyldimethoxyethane **10** as ligand.

Compared to isoquinoline, (−)-sparteine gave disappointingly low results with quinoline. So far, we have attempted to optimise the chiral induction by pre-complexing the ligand and the organolithium reagent before the reaction with quinoline. The precomplexation was done by stirring *n*-BuLi and (−)-sparteine at room temperature, for 30 min, then cooling this complex at the desired reaction temperature. Table 5 shows that 1 equiv of (−)-sparteine gave the dihydroquinoline **13** with 10% ee at −40 °C (entry 8), which was lower than without any pre-complexation (entry 4). At −60 °C, an enantiomeric excess of 12% could be observed (entry 9).

The same precomplexation procedure was repeated in toluene. However, we observed, this time, the nucleophilic addition of benzyl lithium, rather than of *n*-BuLi.

This organolithium reagent was formed by deprotonation of the solvent, toluene, in the presence of a diamine, such as

Table 6. Nucleophilic addition of benzyl lithium to quinoline by deprotonation of toluene in the presence of ligand



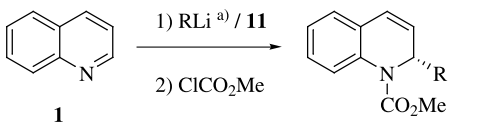
Entries	*T* [°C]	Ligand	Yield [%]	**16a/16b**[a]	ee [%] **16a/16b**
1	−60 1 h	**11** (1 equiv)	62	83/17	44/0
2	−60 1 h	TMCDA (1 equiv)	80	79/21	26/3

[a] Determined by NMR analysis.

(−)-sparteine **11**. In addition, the reaction was not regioselective and two products, the 2-benzyl-1,2-dihydroquinoline **16a** and the 4-benzyl-1,2-dihydroquinoline **16b**, were isolated, in a 83/17 ratio. The enantiomeric excess of the 1,2 adduct, **16a**, was 44%, while the 1,4 adduct, **16b**, was racemic (Table 6, entry 1). Similar results were obtained with (*R*,*R*) N,N′-tetramethyl cyclohexane-1,2-diamine (TMCDA) (entry 2), but with a lower enantioselectivity. Attempts were also made in the presence of diether **10** or bisoxazoline **12a**; toluene was not deprotonated by *n*-BuLi, a result which is consistent with the previous observations made in the presence of TMEDA or DABCO.[12] However, no nucleophilic addition at all was observed on quinoline, indicating that *n*-BuLi was consumed on reaction with diether **10** or bisoxazoline **12a**, at room temperature.

Phenyllithium generally affords better enantioselecttivities with (−)-sparteine than with other ligands.[13] The addition of phenyllithium to quinoline in stoichiometric amount of sparteine gave the 1,2-dihydroquinoline **14** in 82% yield and with 66% ee (Table 7, entry 1). These values were obtained in toluene at −78 °C after 1 h (entry 1), as well as in ether at −60 °C after 2 h (entry 5). When 2 equiv of ligand were added, the yield was stable and a slightly lower ee was obtained (entry 3). By increasing the temperature to −60 °C, an enantiomeric excess of 63% could be described (entry 4). Under the same conditions, whenever ether was used instead of toluene, the ee and the yield were similar (entries 5, 7 and 8). Therefore, with 1 equiv of sparteine, the enantiomeric excess was still up to 66%. In presence of 0.2 equiv of ligand, at −78 °C after 1 h, we found that the ee decreased dramatically. In toluene (entry 2), that value was 7% and rose up to 24% in ether (entry 6). In all cases, the enantiomeric excess was the best result observed thus far.

Table 7. Enantioseletive addition of aryllithium to quinoline in the presence of (−)-sparteine



1

14 R = Ph
15 R= Naphth

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yield [%]	ee [%]
1	Toluene	Ph	−78 1 h	1	82	66
2	Toluene	Ph	−78 1 h	0.2	38	7
3	Toluene	Ph	−78 1 h	2	88	57
4	Toluene	Ph	−60 2 h	1	91	63
5	Et_2O	Ph	−78 1 h	1	55	67
6	Et_2O	Ph	−78 1 h	0.2	60	24
7	Et_2O	Ph	−60 2 h	1	82	66
8	Et_2O	Ph	−20 2 h	1	70	57
9	Toluene	Naphth	−78 2 h	1	69	17
10	Toluene	Naphth	−78 2 h	0.2	24	9
11	Toluene	Naphth	−50 2 h	1	37	16
12	Toluene	Naphth	−50 2 h	0.2	66	6
13	Et_2O	Naphth	−78 2 h	1	86	28
14	Et_2O	Naphth	−78 2 h	0.2	64	12

RLi was prepared by halogen–metal exchange between RI and *n*-BuLi.

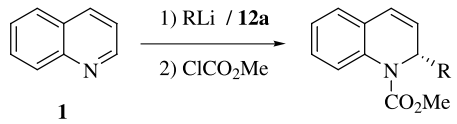
To extend this result, we also tested the addition of 1-naphthyllithium. The first observation was that the yield was satisfactory, but the enantiomeric excess was worse. In stoichiometric conditions, we have observed that in toluene at −78 °C (entry 9) or −50 °C (entry 11), the ee was the same with about 17%. Using Et_2O instead of toluene (entry 13), under the same conditions the enantiomeric excess increased to 28% and the yield was also better with 86%. Under catalytic conditions, in toluene (entries 10 and 12) or in ether (entry 14), the desired product **15** was obtained with a chiral induction, but the ee decreased, as before with phenyllitium.

2.3. Enantioselective additions with bisoxazolines 12a, 12b and 12c

The reactions with (−)-sparteine and alkyllithiums being a rather unselective, we have attempted to increase the enantiomeric excess of the 1,2-dihydroquinolines **8** and **13**, using more efficient ligands. Bisoxazolines were known to afford good results in enantioselective addition to acyclic imines.[13a] We therefore synthesised and tested bisoxazoline **12a** derived from L-valinol.

We have first tested the enantioselective addition with the bisoxazoline **12a** using methyllithium as carbon nucleophile (Table 8). The best result was obtained in toluene at −40 °C with one equiv of chiral ligand. An enantiomeric excess of 63% could be observed (entry 1). Catalytic amounts of this bisoxazoline under the same conditions gave the dihydroquinoline **8** in 43% isolated yield with an enantiomeric excess of 30% (entry 2). Decreasing the temperature to −60 °C did not allow a better enantiomeric excess (entry 3). Using Et_2O instead of toluene (entry 4) gave similar results in term of enantioselectivity. Nevertheless, bisoxazoline

Table 8. Enantioselective addition of alkyllithium to quinoline in the presence of bisoxazoline **12a**



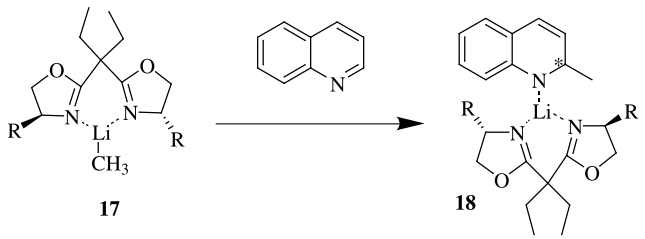
1

8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yied [%]	ee [%][a]
1	Toluene	Me	−40 2 h	1	47	63
2	Toluene	Me	−40 1 h	0.2	43	30
3	Toluene	Me	−60 2 h	0.2	40	32
4	Et_2O	Me	−60 2 h	0.2	31	31
5	Toluene	Me	−40 15 min	0.2	30[b]	62
6	Toluene	Me	−40 30 min	0.2	42[b]	57
7	Toluene	Me	−40 45 min	0.2	44[b]	59
8	Toluene	Me	−40 75 min	0.2	54[b]	54
9	Toluene	Bu	−60 1 h	1	63	72
10	Toluene	Bu	−70 1 h	1	85	79
11	Toluene	Bu	−60 1 h	0.2	75	66
12	Toluene	Bu	−70 1 h	0.2	63	67
13	Toluene	Bu	−80 1 h	0.2	55	67
14	Et_2O	Bu	−60 1 h	0.2	90	42
15	Et_2O	Bu	−70 1 h	0.2	79	45
16	Et_2O	Bu	−80 1 h	0.2	87	39

[a] Determined by chiral GC.
[b] Conversion determined by crude NMR analysis.

12a appeared to be the best chiral ligand for this reaction and we wanted to check what were the limitations of such an enantioselective nucleophilic addition in the presence of an external chiral ligand. Particularly, we wanted to know if the chiral ligand, associated to the organolithium reagent, was trapped by the lithiated amide intermediate produced by the nucleophilic addition, as indicated in Scheme 3.



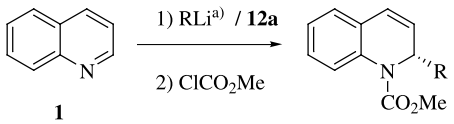
17 **18**

Scheme 3. Trapping of the chiral ligand by the lithiated intermediate.

The chiral ligand would then become inefficient for another catalytic cycle and the enantioselectivity would decrease during the reaction. In order to verify this hypothesis, the reaction was reproduced in toluene at −40 °C in the presence of catalytic amount of chiral bisoxazoline **12a**. Methylchloroformate was added after 15, 30, 45, or 75 min and in each reaction, the enantiomeric excess was compared to the conversion (Table 8). At 15 min, an enantiomeric excess of 62% was observed for a conversion of 30% (entry 5). This enantiomeric excess is higher than those observed in catalytic version, and it is closer to the stoichiometric version (entry 1). After 30 min, the conversion rose up to 42% but the enantiomeric excess decreased to 57% (entry 6). We observed that the reaction was slower than in the first 15 min, indicating that the acceleration of the reaction, due to the ligand, was not so well pronounced. After 75 min (entry 8), the decrease of the enantiomeric excess down to 54% was significant enough to be taken into consideration, and the conversion was only 54%. In regard to these two results: decrease of the enantiomeric excess and slow down the reaction rate, it appeared clear to us that the catalyst loses its efficiency during the reaction and this tends to prove the trapping of the ligand by the lithiated intermediate.

With butyllithium and a stoichiometric amount of ligand **12a** we obtained the 1,2-dihydroquinoline **13** in 63% isolated yield with 72% ee at −60 °C in toluene (Table 8, entry 9). By decreasing the temperature to −70 °C, an enantiomeric excess of 79% could be observed (entry 10). When catalytic amounts (0.2 equiv) of ligand were used under the same conditions, the enantiomeric excess was still up to 66% (entry 11). In this case, decreasing the temperature to −70 °C (entry 12) or −80 °C (entry 13) did not allow a better enantioselectivity, but rather decreased the yield of the reaction. Changing the solvent to Et_2O gave better yields but lower enantiomeric excess (entries 14–16). Thus, toluene appeared to be the best solvent in this reaction.

Table 9. Enantioselective addition of phenyl- and naphthyllithium to quinoline in the presence of bisoxazoline **12a**



1

14 R = Ph
15 R= Naphth

Entries	Solvent	R[a]	*T* [°C]	Ligand [equiv]	Yield [%]	ee [%]
1	Toluene	Ph	−78 1 h 00 min	1	6	<4
2	Toluene	Ph	−78 1 h 30 min	0.2	28	0
3	Toluene	Ph	−55 1 h 30 min	0.2	57	<4
4	Et_2O	Ph	−78 1 h 30 min	0.2	63	0
5	Et_2O	Ph	−55 1 h 30 min	0.2	82	0
6	Toluene	Naphth	−70 2 h	0.2	20	8
7	Toluene	Naphth	−50 2 h	0.2	55	0
8	Et_2O	Naphth	−78 2 h	0.2	36	0
9	Et_2O	Naphth	−50 2 h	0.2	65	0

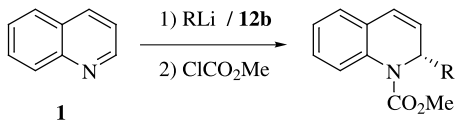
[a] RLi was prepared by halogen–metal exchange between RI and *n*-BuLi.

It was expected that phenyllithium would not behave favourably with bisoxazoline ligands.[13] This is indeed the case (Table 9).

Table 9, shows that only a trace amount of compounds **14**, with low ee, was obtained when the addition of phenyllithium to quinoline was carried out in toluene, at −78 °C and with 1 equiv of ligand (entry 1). Catalytic amounts of bisoxazoline **12a** gave the 2-phenyl- and 2-naphthyldihydroquinoline **14** and **15** with a better yield. The yields were better in ether than in toluene, but only racemates were obtained. Furthermore, the temperature influenced this value. In the case of the addition of phenyllithium, in toluene the yield was 28% at −78 °C (entry 2) and was enhanced to 57% at −55 °C (entry 3). In ether, the values were, respectively 63 and 82% (entries 4 and 5). Nevertheless, the increase of temperature did not change the enantiomeric excess.

So far, bisoxazoline **12a** gave an enantiomeric excess of 79% with *n*-BuLi, and the chiral induction with MeLi allowed an enantiomeric excess of around 63% in stoichiometric version or at the beginning of the catalytic reaction. The limitation of such a catalytic reaction is the trapping of the chiral ligand by the amine produced during the reaction. Bisoxazoline **12b**, having a tertiobutyl instead of an isopropyl group, is usually a better enantiodiscriminating ligand, due to the increased steric interactions. We therefore prepared and tested this new ligand (Table 10).

Table 10. Enantioselective addition of alkyllithium to quinoline in the presence of bisoxazoline **12b**



1

8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yied [%]	ee [%][a]
1	Toluene	Me	−40 2 h	0.2	<5	nd
2	Toluene	Bu	−70 1 h	1	80	32
3	Toluene	Bu	−70 1 h	0.2	70	37
4	Toluene	Bu	−40 1 h	0.2	69	7
5	Et_2O	Bu	−70 1 h	0.2	80	8

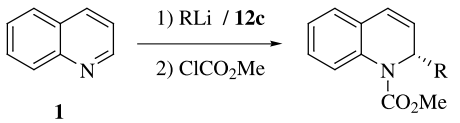
[a] Determined by chiral GC.

Methyllithium and catalytic amount of ligand **12b**, in toluene, did not afford significant addition product (entry 1). With the more reactive butyllithium, an enantiomeric excess of 37% was measured, with a good isolated yield (entry 3). Increasing the amount of ligand **12b** to 1 equiv, improved the yield to 80% but lowered the ee to 32%. Increasing the temperature or using ether instead of toluene, dramatically reduced the enantioselectivity (entries 4 and 5).

In a last attempt to optimise these results, we have used the benzylbisoxazoline **12c**, thinking that π-staking interactions with the substrate would have a favourable role.

With butyllithium as nucleophile, Table 11 shows that an enantiomeric excess of 69% could be obtained with 1 equiv of this ligand (entry 3), indicating that the bisoxazoline **12c**, with a benzyl group, gave a lower enantiomeric excess than the bisoxazoline **12a**, but a better than ligand **12b**. Nevertheless, catalytic amount of ligand can be used with a small loss of enantioselectivity (entries 4 and 5). Again, in ether, the ee are considerably lower than in toluene (entry 6). With ligand **12c**, methyllithium reacts normally, affording an ee of 21–22%, both in ether and toluene. Thus, bisoxazoline **12c** has an intermediate behaviour, compared to **12a** and **12b**. In view of the insignificant enantioselectivity observed with phenyllithium and bisoxazoline **12a**, no attempts were made with the other bisoxazolines.

Table 11. Enantioselective addition of alkyllithium to quinoline in the presence of bisoxazoline **12c**



1

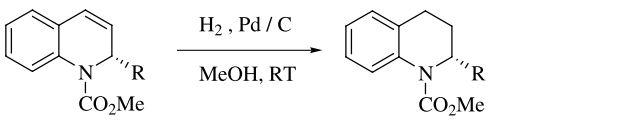
8 R = Me
13 R = Bu

Entries	Solvent	R	*T* [°C]	Ligand [equiv]	Yied [%]	ee [%][a]
1	Toluene	Me	−40 1 h	0.2	69	21
2	Et_2O	Me	−40 2 h	0.2	86	22
3	Toluene	Bu	−70 2 h	1	57	69
4	Toluene	Bu	−70 2 h	0.2	79	41
5	Toluene	Bu	−40 2 h	0.2	89	40
6	Et_2O	Bu	−70 2 h	0.2	96	20

[a] Determined by chiral GC.

2.4. Determination of the absolute configuration

In order to determine the absolute configuration of the addition products, 1,2-dihydroquinolines **13** and **14** were converted to the known tetrahydroquinolines **19** and **20**.[14] Thus, **13** and **14** were hydrogenated with palladium on charcoal to afford tetrahydroquinolines **17** and **18**, in 98 and 81% yield respectively (Scheme 4).

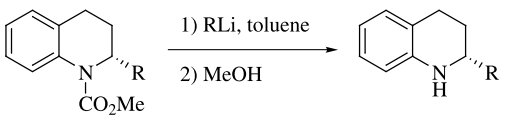


13 R = Bu
14 R = Ph

17 R = Bu (98% yield)
18 R = Ph (81% yield)

Scheme 4. Hydrogenation of 1,2-dihydroquinolines **13** and **14**.

Then, the carbamate functionality was removed by a Bouveault reaction with alkyllithium to provide the known products[14] **19** and **20** with the same enantiomeric excess as the starting 1,2-dihydroquinolines **13** and **14** and with a moderate non-optimised yield (31–35%) (Scheme 5).



17 R = Bu
18 R = Ph

19 R = Bu (31% yield)
20 R = Ph (35% yield)

Scheme 5. Removal of the carbamate of 1,2,3,4-tetrahydroquinolines **19** and **20**.

The specific rotation of 2-butyl-1,2,3,4-tetrahydroquinoline **19** gave a negative value of −39 for an enantiomeric excess of 41%, showing, by comparison with the literature data,[14] that the nucleophilic addition of *n*-butyllithium on quinoline, with bisoxazoline **12c** as ligand, gave (*S*)-2-butyl-1,2-dihydroquinoline **13**. For 2-phenyl-1,2,3,4-tetrahydroquinoline **20**, the sign of the specific rotation was negative with −31.4 for an enantiomeric excess of 64.6%. Thus, according to the literature data,[14] the nucleophilic addition of phenyllithium on quinoline, with sparteine as ligand, gave (*R*)-2-phenyl-1,2-dihydroquinolines **14**.

3. Conclusion

In conclusion, we have shown that it was possible to synthesise alkyl and aryl 1,2-dihydroquinolines from quinoline by direct addition of organometallic reagents. This reaction was completely regioselective with organolithium reagents, methyl Grignard and trimethylaluminum, and only the 1,2 addition was observed. Dimethylzinc gave a mixture of 1,2 and 1,4 adduct, depending on the experimental conditions. Organolithium reagents could react without any activation of the imine moiety. By this way, the N-acylation of the lithiated intermediate did not induced any by-product and allowed very good yields. With alkyllithium reagents, in the presence of a chiral ligand, an enantiomeric excess up to 79% could be obtained with butyllithium, using the bisoxazoline **12a** as an external ligand. The catalytic version gave lower enantiomeric excess due to the trapping of the ligand, but optimisation of these results will be done, using more efficient chiral ligands. With aryllithium reagents, (−)-sparteine **11** gave enantiomeric excess up to 66%, in stoichiometric conditions. So, in this case, the diamines as external ligands appeared to be good candidates to optimise this reaction.

4. Experimental

4.1. General remarks

All the reactions were carried out under argon atmosphere with magnetic stirring, unless otherwise specified. Two necked flasks were used with an internal thermometer. Solvents were dried by distillation from a drying agent as follow: Et_2O (Na/benzophenone), THF (Na/benzophenone), toluene (CaH_2), CH_2Cl_2 (CaH_2). Commercial MeLi Fluka in THF/Cumene 1/1, commercial *n*-BuLi Fluka in hexane, were used. Flash chromatography column: SiO_2 (Brunschwig 32–63, 60 Å). Gas chromatography: Hewlett Packard 5790A, integrator HP 3390A, HP-1 Capillary column, 10psi H_2. Chiral GC: Hewlett Packard, Lipodex E column 200034-32. Programs are written as follow: Initial temperature (°C)-initial time (min)-increasing temperature (°C/min)-final temperature (°C)-final time (min). Supercritical Fluid Chromatography (SFC): Berger, Column Chiralcel OJ and OD-H. Melting Point: Kofler hot stage. $[\alpha]_D^{20}$: Perkin–Elmer 241 polarimeter. ^1H NMR: Varian Gemini-200 at 200 MHz and Brucker DRX-400 at 400 MHz in $CDCl_3$, standard $CDCl_3$ (7.27 ppm). Coupling constants are expressed in Hz (multiplicity: singlet 's', doublet 'd', triplet 't', quadruplet 'q', multiplet 'm'). ^{13}C NMR: Varian Gemini-200 at 50 MHz and Brucker DRX-400 at 100 MHz in $CDCl_3$, standard $CDCl_3$ (77.0 ppm). Infra-red spectra (IR): FT-IR Perkin–Elmer 1600. The high-resolution mass spectra (HRMS) were recorded in the EI (70 eV) mode.

4.1.1. 2-Methyl-1,2-dihydroquinoline (5). To a stirred solution of quinoline (0.3 mL; 2.5 mmol) in dry toluene (10 mL) was added DME (1.3 mL; 1.25 mmol) under an argon atmosphere at −20 °C. Then methyllithium (3.1 mL; 5 mmol) was added. After 1 h, the solution was hydrolysed with water, extracted with Et_2O (3×20 mL), dried with $MgSO_4$, and filtered. The solvent was evaporated. The crude product was purified by flash chromatography on silicagel with cyclohexane/Et_2O (80/20) and the dihydroquinoline **5** was obtained in 57% yield as yellow oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.0–6.35 (m, 4H); 6.30 (m, 1H); 5.50 (m, 1H); 4.42 (m, 1H); 3.70 (s, 1H); 1.30 (d, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 144.4; 129; 127.6; 127.2; 125.6; 120.9; 117.9; 113.1; 48.8; 24.7. IR: 3388; 3033; 2963; 1639; 1602; 1487; 1453; 1318; 1277; 1122; 1038 cm^{-1}.

4.1.2. 2-Methyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (8). *With MeMgBr.* To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) in dry dichloromethane (20 mL) was added methylmagnesium bromide (1 mL, 3 mmol as a 3 M solution in Et_2O) at −20 °C under an argon atmosphere. After 10 min at −20 °C, methylchloroformate (2.2 mL, 3 mmol) was added dropwise. After 15 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with dichloromethane (3×20 mL), dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography with cyclohexane/Et_2O (90/10) as eluent and the desired 1,2-dihydroquinoline **8** was obtained in 94% yield.

With Me_2Zn. To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) in dry tetrahydrofuran (10 mL) was added Me_2Zn (1.2 mL, 3 mmol as a 2 M solution in toluene) at −20 °C under an argon atmosphere. After 10 min, methylchloroformate (2.2 mL, 3 mmol) was added dropwise. After 15 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (3×20 mL), dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel using cyclohexane/Et_2O (95/5) as eluent. A mixture of inseparable 1,2-dihydroquinoline **8** and 1,4-dihydroquinoline **9** was obtained in 30% yield.

With Me_3Al. To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) Et_2O was added Me_3Al (2 mL, 4 mmol as a 2 M solution in toluene) under an argon atmosphere at −20 °C. Methylchloroformate (2.2 mL, 3 mmol) was then added dropwise. After 1 h 30 min at −20 °C, the solution was hydrolysed with water, extracted with Et_2O (3×20 mL), dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel using cyclohexane/Et_2O (95/5). The 1,2-dihydroquinoline **8** was obtained in 31% yield.

4.1.3. *(S)*−2-Methyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (8). To a stirred solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) and bisoxazoline **12a**

(747 mg, 0.5 mmol) in dry toluene (20 mL) was added methyllithium (3 mL, 3 mmol as a 1 M solution in THF/cumene 1/1) at −60 °C. After 2 h methylchloroformate (0.23 mL, 3 mmol) was added. After 10 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (2×20 mL) and dichloromethane (2×20 mL), dried with $MgSO_4$ and filtered. The crude solution was purified by flash chromatography on silicagel with cyclohexane/Et_2O (80/20) as eluent and the dihydroquinoline **8** was obtained in 47% yield as pale pink oil. The enantiomeric excess was found to be 63% by chiral GC. TLC: R_f=0.42 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.6–7.0 (m, 4H); 6.4 (d, 1H, J=9.5 Hz); 6.0 (dd, 1H, J_1=5.9 Hz, J_2=9.7 Hz); 5.10 (q, 1H, J=6.3 Hz); 3.79 (s, 3H); 1.10 (d, 3H, J=6.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.1; 134; 130; 131.1; 127.8; 127.4; 124.9; 126.6; 124.6. IR: 2955; 1710; 1491; 1439; 1316; 1129; 765 cm^{-1}. MS-EI: *m/z* (relative intensity) 203 (19); 188 (100); 144 (89); 129 (18); 115 (10); 102 (9); 77 (11); 59 (15). Anal. calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89. Found: C, 69.46; H, 6.63; N, 6.52. Program of GC analysis: 90-1-170. $[\alpha]_D^{20}$=+22.9 (c=1.2 in $CHCl_3$) for an ee of 63%.

4.1.4. (*S*)-2-Butyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (13). To a solution of freshly distilled quinoline (0.3 mL, 2.5 mmol) and bisoxazoline **12a** (735 mg, 2.5 mmol) in dry toluene (20 mL) was added *n*-BuLi (1.8 mL, 3 mmol as a 1.6 M solution in hexane) at −70 °C under an argon atmosphere. After 1 h, methylchloroformate (0.23 mL, 3 mmol) was added. After 10 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (2×20 mL) and dichloromethane (2×20 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel with cyclohexane/Et_2O (80/20) as eluent and gave the 1,2-dihydroquinoline **13** in 80% yield as yellow oil. The enantiomeric excess of 79% was determined by chiral GC analysis using the Lipodex E column. TLC: R_f=0.50 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.23–7.08 (m, 4H); 6.46 (d, 1H, J=8 Hz); 6.09 (m, 1H); 5.00 (m, 1H); 3.81 (s, 3H); 1.45–1.27 (m, 6H); 0.88 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9; 134.3; 130.1; 127.4; 127.1; 126; 124.7; 124.4; 124.2; 52.8; 32.5; 27.3; 22.3; 13.9. IR: 2931; 1699; 1490; 1438; 1325; 1250; 1131; 764 cm^{-1}. MS-EI: *m/z* (relative intensity) 245 (3); 188 (100); 144 (68); 129 (16); 102 (6); 77 (6); 59 (11). Anal. calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.89; N, 5.48. Program of chiral GC: 90-1-170-20. $[\alpha]_D^{20}$=+35.7 (c=1.02 in $CHCl_3$) for an ee of 79%.

4.1.5. (*R*)-2-Phenyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (14). To a solution of iodobenzene (0.34 mL, 3 mmol, 1.2 equiv) and (−)-sparteine (0.57 mL, 2.5 mmol, 1 equiv) in dry toluene (10 mL) was added dropwise *n*-BuLi (1.88 mL, 3 mmol, as a 1.6 M solution in hexane) at −78 °C under an argon atmosphere. The solution was stirred during 1 h at −78 °C, and was diluted with 11 mL of toluene. Then quinoline (0.29 mL, 2.5 mmol, 1 equiv) was added, and the yellow reaction turned orange, with time. After 1 h at −78 °C, methylchloroformate (0.23 mL, 3 mmol, 1.2 equiv) was added and the solution became yellow. After 10 min, the solution was quenched with a solution of NH_4Cl, extracted with ether (2×20 mL) and dichloromethane (2×20 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **14** was obtained in 82% yield as yellow oil. An enantiomeric excess of 66% was determined by chiral SFC analysis, using the column chiralcel OD-H. TLC: R_f=0.30 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s br, 1H); 7.43–7.37 (m, 2H); 7.37–7.24 (m, 4H); 7.21 (dd, 1H, J_1=7.6 Hz, J_2=1.8 Hz); 7.15 (t, 1H, J=7.3 Hz); 6.74 (m, 1H); 6.35–6.24 (m, 2H); 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3; 139.7; 134.7; 128.6; 128.3; 127.9; 127.2; 127.1; 126.4; 125.4; 124.7; 124.4; 55.7; 53.3. IR: 2953, 1694; 1488; 1436; 1377; 1324; 1270; 1125; 1028; 844; 760; 695 cm^{-1}. MS-EI: *m/z* (relative intensity) 265 (41); 188 (100); 144 (66); 129 (19); 102 (11); 77 (17); 59 (15). HRMS: calcd for $C_{17}H_{15}NO_2$ ($M^{+\cdot}$) 265.1103. Found: 265.1087. Program of chiral SFC: OD-H 6%-6-1-15%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{25}$=−438.2 (c=3.1 in $CHCl_3$) for an ee of 66%.

4.1.6. (*R*)-2-Naphthyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (15). To a solution of 1-iodonaphthalene (1.8 mL, 1.2 mmol, 1.2 equiv) and (−)-sparteine (0.23 mL, 1 mmol, 1 equiv) in dry Et_2O (3.5 mL) was added dropwise *n*-BuLi (0.75 mL, 1.2 mmol, as a 1.6 M solution in hexane) at −78 °C under an argon atmosphere. The solution was stirred during 1 h at −78 °C, and was diluted with 3.5 mL of Et_2O. Then quinoline (0.12 mL, 1 mmol, 1 equiv) was added, and the yellow reaction turned orange, with time. After 2 h at −78 °C, methylchloroformate (0.09 mL, 1.2 mmol, 1.2 equiv) was added and the solution became yellow. After 10 min, the solution was quenched with a solution of NH_4Cl, extracted with ether (2×7 mL) and dichloromethane (2×7 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **15** was obtained in 85.6% yield as yellow oil. An enantiomeric excess of 27.5% was determined by chiral SFC analysis, using the column chiralcel OJ. TLC: R_f=0.31 using cyclohexane/Et_2O (9/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (d, 1H, J=7.8 Hz); 7.92 (d, 1H, J=8.1 Hz); 7.79 (d, 1H, J=8.1 Hz); 7.71 (t, 1H, J=7.7 Hz); 7.59 (t, 1H, J=7.6 Hz); 7.40 (d, 1H, J=7.1 Hz); 7.33–7.24 (m, 2H); 7.24–7.14 (m, 3H); 7.09 (d, 1H, J=5.8 Hz); 6.73 (d, 1H, J=9.6 Hz); 6.38 (dd, 1H, J_1=9.6 Hz, J_2=6.1 Hz); 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4; 135.3; 135.2; 134.1; 130.4; 129.0; 128.9; 128.6; 127.8; 127.3; 126.6; 126.3; 125.7; 125.4; 125.2; 124.8; 123.7; 52.9; 53.4. IR: 2953; 1697; 1489; 1437; 1300; 1265; 1123; 1040; 754 cm^{-1}. MS-EI: *m/z* (relative intensity) 315 (51); 256 (62); 188 (100); 128 (17); 101 (5); 77 (9); 59 (10). HRMS: calcd for $C_{21}H_{17}NO_2$ ($M^{+\cdot}$) 315.1259. Found: 315.1247. Program of chiral SFC: OJ 10%-2-1-25%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{25}$=−169.5 (c=1.305 in $CHCl_3$) for an ee of 27.5%.

4.1.7. 2-Benzyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (16a) and 4-benzyl-1,2-dihydro-[N-methoxycarbonyl]-quinoline (16b). To a solution of (−)-sparteine (0.23 mL, 1 mmol, 1 equiv) in dry toluene (8 mL) was

added *n*-BuLi (0.75 mL, 1.2 mmol as a 1.6 M in hexane) at 25 °C under an argon atmosphere. The solution was stirred for 30 min. The temperature was then cooled to −60 °C and quinoline (0.12 mL, 1 mmol) was added. After 1 h at −60 °C, methylchloroformate (0.09 mL, 1.2 mmol) was added. After 10 min, the solution was hydrolysed with a solution of NH_4Cl, extracted with Et_2O (2×10 mL) and dichloromethane (2×10 mL). The organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silicagel with cyclohexane/Et_2O (95/5) as eluent and the products **16a** and **16b** were obtained in 62% global yield as yellow oil. Enantiomerics excess of 44% for **16a** and 0% for **16b** were determined by chiral SFC analysis, using the column chiralcel OD-H.

Product **16a**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.71 (s br, 1H); 7.35–7.13 (m, 9H); 6.55 (d, 1H, J=9.6 Hz); 6.00 (dd, 1H, J_1=5.8 Hz, J_2=9.6 Hz); 5.27 (s br, 1H); 3.66 (s, 3H); 2.75 (dd, 1H, J_1=2.8 Hz, J_2=7.5 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.0; 138.9; 137.8; 131.4; 129.9; 129.0; 128.8; 128.7; 126.8; 125.7; 124.8; 121.9; 113.1; 54.6; 53.3; 40.7. Program of chiral SFC: OD-H 2%-2-1-20%; MeOH; 200 Bar; 2 mL/min; 30 °C. $[\alpha]_D^{20}$=−162.3 (c=1.1 in $CHCl_3$) for an ee of 44%.

Product **16b**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.93 (d, 1H, J=8.4 Hz); 7.28–7.18 (m, 4H); 7.10 (t, 1H, J=7.3 Hz); 7.04–6.93 (m, 4H); 5.28 (dd, 1H, J_1=5.8 Hz, J_2=7.6 Hz); 3.82 (s, 3H); 3.62 (q, 1H, J=6.4 Hz); 2.85 (d, 2H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.8; 138.4; 136.5; 130.8; 129.5; 128.3; 127.9; 126.5; 126.3; 126.0; 124.7; 121.3; 112.6; 53.1; 44.4; 40.1. Program of chiral SFC: OD-H 2%-2-1-20%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C.

4.1.8. (*S*)-2-Butyl-1,2,3,4-tetrahydro-[N-methoxy carbonyl]-quinoline (17). To a solution of **13** of 40.4% ee (181.5 mg, 0.74 mmol, 1 equiv) in methanol (15 mL) was added 2 mol% of palladium on activated charcoal. The hydrogenation was performed at room temperature under H_2 (1 atm) for 3 h. The crude product was then filtered through Celite and the solvent was evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **17** was obtained in 98% yield as yellow oil. TLC: R_f=0.23 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 1H, J=7.8 Hz); 7.21–7.14 (m, 1H); 7.13–7.08 (m, 1H); 7.04 (t, 1H, J=7.3 Hz); 4.61–4.52 (m, 1H); 3.78 (s, 3H); 2.77–2.63 (m, 2H); 2.26–2.14 (m, 1H); 1.70–1.60 (m, 1H); 1.59–1.50 (m, 1H); 1.42–1.20 (m, 5H); 0.95–0.79 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4; 136.6; 131.2; 127.9; 125.8; 125.5; 124.0; 52.8; 52.6; 32.3; 28.8; 28.0; 24.4; 22.4; 13.9. IR: 2930; 1697; 1492; 1438; 1388; 1323; 1213; 1128; 1057; 911; 765; 716 cm^{-1}. MS-EI: m/z (relative intensity) 247 (19); 190 (100); 130 (14); 118 (16); 91 (7); 77 (6); 59 (7). $[\alpha]_D^{25}$=+36.7 (c=1.145 in $CHCl_3$). The enantiomeric excess was not determined.

4.1.9. (*R*)-2-Phenyl-1,2,3,4-tetrahydro-[N-methoxy carbonyl]-quinoline (18). To a solution of **14** of 65.5% ee (132.8 mg, 0.5 mmol, 1 equiv) in methanol (10 mL) was added 2 mol% of palladium on activated charcoal. The hydrogenation was performed at room temperature under H_2 (1 atm) for 3 h. The crude product was then filtered through Celite and the solvent was evaporated. The crude oil was purified by chromatography on silica gel with cyclohexane/ether (85/15) as eluent, and the product **18** was obtained in 81% yield as yellow oil. TLC: R_f=0.20 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, 1H, J=7.8 Hz); 7.34–7.19 (m, 6H); 7.16–7.06 (m, 2H); 5.52 (t, 1H, J=7.7 Hz); 3.74 (s, 3H); 2.75–2.61 (m, 2H); 2.57–2.48 (m, 1H); 1.98–1.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5; 143.3; 137.6; 132.6; 128.3; 127.5; 126.7; 126.4; 125.9; 124.8; 124.0; 58.2; 52.8; 33.1; 26.0. IR: 2952; 1698; 1491; 1438; 1380; 1323; 1236; 1133; 1056; 908; 727; 647 cm^{-1}. MS-EI: m/z (relative intensity) 267 (100); 235 (15); 208 (68); 176 (20); 144 (6); 130 (24); 91 (45); 77 (25); 51 (9). Anal. calcd for $C_{17}H_{17}NO_2$ (267.33): C, 76.38; H, 6.41; N, 5.24. Found: C, 75.32; H, 6.52; N, 4.96. $[\alpha]_D^{25}$=−76.3 (c=1.355 in $CHCl_3$). The enantiomeric excess was not determined.

4.1.10. (*S*)-2-Butyl-1,2,3,4-tetrahydroquinoline (19). To a solution of **17** (125.2 mg, 0.51 mmol, 1 equiv) in dry ether (5 mL) was added dropwise *n*-BuLi (1.25 mL, 2 mmol, as a 1.6 M solution in hexane) at −20 °C under an argon atmosphere. The mixture was stirred and the temperature was allowed to rise to room temperature. After 3 h, the solution was quenched with methanol, and the solvents were evaporated. The crude product was purified by chromatography on silica gel with cyclohexane/ether (98/2) as eluent, and the product **19** was obtained in 31% yield as yellow oil. An enantiomeric excess of 40.8% was determined by chiral SFC analysis, using the column chiralcel AD. TLC: R_f=0.63 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01–6.95 (m, 2H); 6.62 (t, 1H, J=7.6 Hz); 6.50 (d, 1H, J=7.3 Hz); 3.85 (s br, 1H); 3.30–3.20 (m, 1H); 2.88–2.69 (m, 2H); 2.03–1.93 (m, 1H); 1.67–1.55 (m, 1H); 1.55–1.47 (m, 2H); 1.46–1.33 (m, 4H); 0.95 (t, 1H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6; 129.2; 126.7; 121.5; 117.0; 114.1; 51.6; 36.3; 28.1; 27.9; 26.4; 22.8; 14.1. IR: 2927; 1608; 1485; 1352; 1310; 1276; 1214; 745 cm^{-1}. MS-EI: m/z (relative intensity) 189 (17); 144 (2); 132 (100); 117 (8); 77 (5); 51 (1). Program of chiral SFC: AD 5%-2-1-15%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{26}$=−38.7 (c=0.54 in $CHCl_3$) for an ee of 40.8%. The absolute configuration was assigned as (*S*) by analogy to the lit. data. (Lit.[14] $[\alpha]_D^{25}$=+79.9 (c=1 in $CHCl_3$) for an ee of 92% for *(R)* stereochemistry).

4.1.11. (*R*)-2-Phenyl-1,2,3,4-tetrahydroquinoline (20). To a solution of **18** (144.8 mg, 0.55 mmol, 1 equiv) in dry toluene (4 mL) was added dropwise MeLi (2.2 mL, 2.2 mmol, as a 1 M solution in THF/cumene: 1/1) at −20 °C under an argon atmosphere. The mixture was stirred and the temperature was allowed to rise to room temperature. After 1 h, the solution solution was quenched with methanol, and the solvents were evaporated. The crude product was purified by chromatography on silica gel with cyclohexane/ether (98/2) as eluent, and the product **20** was obtained in 35% yield as yellow oil. An enantiomeric excess of 64.6% was determined by chiral SFC analysis, using the column chiralcel AS. TLC: R_f=0.62 using cyclohexane/Et_2O (85/15). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.34 (m, 4H);

7.32–7.27 (m, 1H); 7.06–7.6.99 (m, 2H); 6.67 (t, 1H, J=7.4 Hz); 6.56 (d, 1H, J=7.6 Hz); 4.46 (dd, 1H, J=9.3, 3.4 Hz); 4.16 (s br, 1H); 2.99–2.89 (m, 1H); 7.15 (dt, 1H, J=16.3, 4.7 Hz); 2.17–2.10 (m, 1H); 2.06–1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7; 129.3; 128.8; 128.6; 127.4; 126.9; 126.5; 121.0; 117.3; 114.1; 56.3; 30.9; 26.4. IR: 3396; 2924; 1598; 1491; 1310; 1273; 831; 747; 698 cm^{-1}. MS-EI: m/z (relative intensity) 209 (92); 194 (15); 132 (100); 118 (17); 104 (13); 91 (25); 77 (24); 51 (10). Anal. calcd for $C_{15}H_{15}N$ (209.29): C, 86.08; H, 7.22; N, 6.69. Found: C, 84.90; H, 7.38; N, 5.44. Program of chiral SFC: AS 10%-2-1-25%; elute: MeOH; pressure: 200 Bar; flow rate: 2 mL/min; 30 °C. $[\alpha]_D^{27}=-31.4$ (c=1.26 in $CHCl_3$) for an ee of 64.6%. The absolute configuration was assigned as *(R)* by analogy to the lit. data. (Lit.[14] $[\alpha]_D^{25}=+69.9$ (c=1 in $CHCl_3$) for an ee of 72% for *(S)* stereochemistry).

Acknowledgements

The Swiss National Science Foundation, grant N° 2000-68095.02, is acknowledged for the financial support.

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Tetrahedron 60 (2004) 8233–8243

Large scale enantiomeric synthesis, purification, and characterization of ω-unsaturated amino acids via a Gly-Ni(II)-BPB-complex

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Received 16 March 2004; revised 3 June 2004; accepted 16 June 2004

Available online 28 July 2004

Abstract—The enantiomeric syntheses of ω-unsaturated amino acids and β-substituted ω-unsaturated amino acids were accomplished by using Gly-Ni-2[*N*-(*N*′-benzylprolyl)amino]benzophenone (BPB) as a chiral auxiliary. The synthesis provides excellent yields and high diastereoselectivities. The product crystallization followed by isomer epimerization strategy makes the reaction practical and useful for large-scale preparations. Dialkylation of the Ni(II)-complex, which was designed for mechanistic considerations, revealed that high diastereoselectivity is obtained due to the thermodynamic conformational stability of the Ni(II)-complex. The assignment of absolute configuration was accomplished by NMR, which is supported by corresponding X-ray structure and optical rotation data. Both enantiomerically pure amino acids can be synthesized in this alkylation–hydrolysis two-step strategy in multi gram scales.

1. Introduction

Proteinogenic amino acids have been extensively applied to the area of synthetic organic chemistry.[1] However, opportunities for the use of these naturally occurring amino acids for synthetic purposes are hampered by the limited number of functional groups on the side chains. In addition, replacing natural amino acids with nonproteinogenic counterparts often is applied to peptides and proteins in order to change their secondary structure and functionalities in order to enhance binding to specific receptors,[2] or to obtain more potent inhibition of target enzymes.[3] ω-Unsaturated amino acids are of value in terms of their biological importance and their utility as asymmetric synthetic building blocks.[4] The double bond is a masked functional group, and is stable to most acidic and basic reaction conditions. As a precursor, it can be easily transferred to ω-hydroxyl, ω-halogen, ω-epoxy, ω-amino, aldehyde, and carboxyl amino acids.[5] They also have been used in cyclization of peptides through ring closing metathesis.[6] They act as precursors of boron containing biomolecules,[7] which are interesting for application in boron neutron capture therapy.[8] The masked diol, obtained by osmylation of the double bond, is a useful equivalent of an α-amino acid aldehyde.[9]

In the course of our ongoing peptide and nonpeptidomimetic research, a practical large-scale synthesis of enantiomerically pure ω-unsaturated amino acids **1** and **2** (Fig. 1) has become required in several of our research projects. For example, both the enantiomerically pure forms of allylglycine were used as precursors in the synthesis of [3.3.0]-BTD[2,3] (bicyclic β-turn dipeptide) Leu-enkephalin analogues.[10] The two enantiomers of homoallylglycine have been used in the development of a novel strategy for [6,5]-bicyclic β-turn dipeptides.[11] Homoallylglycine and bishomoallylglycine, both in enantiomerically pure forms, currently are being used for the synthesis of [4.3.0]- and [5.3.0]-BTD[2,3]-Leu-enkephalin analogues. ω-Unsaturated

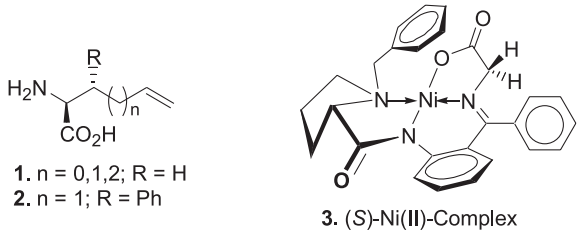

Figure 1. Structures of the ω-unsaturated amino acids and the (*S*)-Ni(II)-complex auxiliary.

Keywords: Ni(II)-complex chiral auxiliary; Alkylation; Diastereoselectivity; Epimerization; Amino acids.

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doi:10.1016/j.tet.2004.06.087

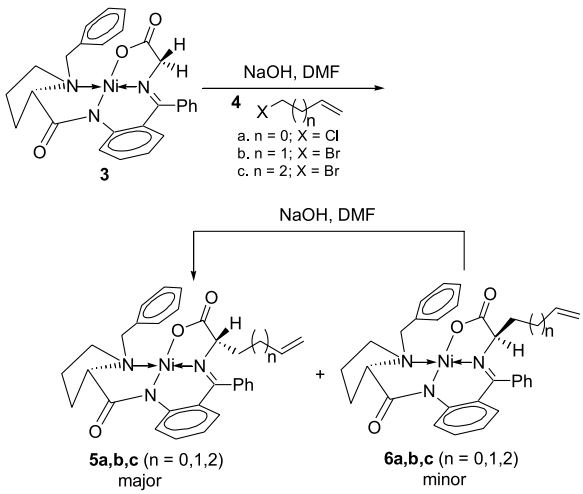
amino acids with β-substituents provide further constraints and functionality at β-positions.[12] β-Phenyl-δ, ϵ-unsaturated amino acid **2** was the first example we synthesized using a Ni(II)-complex, and it was used in the synthesis of functionalized thiazolizidinone [4.3.0]-bicyclic β-turn mimetics.[13] For all of these projects and other potential applications, enantiomerically pure ω-unsaturated amino acids are needed in multi-gram quantities.

Some ω-unsaturated amino acids have been isolated from mushrooms. For example, (*S*)-allylglycine was isolated from *Amanita*, while (*S*)-homoallylglycine was found in *Amanita gymnopus*.[14] *S*- and *R*-allylglycine are commercially available (Acros, Pittsburgh, PA, USA) and the enzymatic separation of *S*-allylglycine from its racemate is well described.[15] ω-Unsaturated amino acid analogue synthesis from Sharpless asymmetric epoxidation also has been reported.[16] However, it is more direct and less expensive to synthesize them by using a Ni(II)-complex in a two-step strategy, because the essential part of auxiliary, (*S*)-BPB {2-[*N*-(*N*′-benzylprolyl)amino]benzophenone}, can be reused in the synthesis of the Gly-Ni(II)-BPB-complex. This chiral auxiliary has been widely used in amino acid synthesis since it was developed by Belokon et al. in 1985.[17] Many different types of amino acids have been synthesized using different reactions, such as alkylation,[18] Michael addition,[19] and the aldol reactions.[20] Although these synthetic methodologies can introduce different side chain groups, the introduction of an ω-terminal double bond using a Ni(II)-complex was only reported by Collet et al. with low yields and limited preparative applications.[7,21] Application of Ni(II)-complexes for the synthesis of unsaturated amino acids as synthetic building blocks for constrained amino acids, and dipeptides is, however, limited by undeveloped methods especially for large-scale synthesis. We report herein a full account of the preparation of these amino acids on multi-gram scales. The mechanistic considerations involved in the alkylation, characterization of the stereochemical outcome, and the diastereoselectivities of the Ni(II)-complex products also were investigated and are discussed.

2. Results and discussion

2.1. Monoalkylation of Ni(II)-complex

The Ni(II)-complex was synthesized in three steps on a 50–100 g scale based on a reported method.[22] The alkylation of 4-bromo-1-butene **4b** on Ni(II)-complex has been reported in low yield,[7,21] which may be attributed to the limited solubility of Ni(II)-complex (<40 mg/mL) and sodium hydroxide in acetonitrile. The alkylation reaction was optimized by first modifying the solvent, and then temperature conditions were investigated. We found that although the Ni(II)-complex was soluble in methanol, the alkylation was slow and TLC showed only a 25% conversion in 16 h. The reaction can be accelerated by using excess NaOMe as base instead of sodium hydroxide. However, the reaction was not completed in 24 h and the Ni(II)-complex suffered significant decomposition during the prolonged reaction time under argon atmosphere. THF was not an efficient solvent either, but DMF gave much better results and also provided a homogenous reaction (Scheme 1). The enolate generation, which was indicated by formation of a green color occurred within 2 min, and the reaction was completed in 3 min at room temperature. No difference was observed when ground KOH was used instead of ground NaOH.



Scheme 1. The alkylation of the Ni(II)-complex.

The alkylation in DMF was optimized using different temperatures (Table 1). It was found that the reaction was prolonged at lower temperatures, and gave poorer diastereoselectivities, while elevated temperatures gave inconclusive results, and the Ni(II)-complex was partially decomposed. The best diastereoselectivity was obtained at ambient temperature with a reaction time of less than 5 min. Based on these reaction results and considering an exothermic reaction in a large scale synthesis, we scaled up the alkylation at ambient temperature in a water bath in 5 min, and the reaction was very efficient (Table 1).

5-Bromo-1-pentene **4c** was used in the Ni(II)-complex alkylation under the same reaction conditions with high diastereoselectivity (Table 1). When allyl bromide was used as an electrophile, an unidentified byproduct was generated, and lowing the reaction temperature to 0 °C did not result in any improvement. However, when the allylic chloride **4a** was used at room temperature, the reaction was very clean and gave a diastereoselectivity of 87:13. In order to avoid dialkylation, all the above electrophilic halides **4a**~**c** were

Table 1. The alkylation conditions and results in DMF

	Electrophile	Reaction temp. (°C)	Reaction time (min)	Isomer ratio[a]	Yield (%)[b]
1	**4b**	−30	35	92:8	95
2	**4b**	0	10	91:9	95
3	**4b**	20	5	95:5[c]	98
4	**4b**	20	10	95:5	96
5	**4b**	20	20	95:5	96
6	**4b**	50	5	Inconclusive	<80
7	**4a**	20	5	87:13[c]	96
8	**4c**	20	5	93:7[c]	98

[a] The diastereomeric ratio (2*S*/2*R*) was determined by ^{1}H NMR.
[b] Combined yield of two diastereomers.
[c] The diastereomeric ratios were obtained in the reactions on a 20 g scale. All the other results were obtained in <1 g scale.

used in slightly less than 1 equiv. For the 20 g scale reactions, no secondary alkylation was observed under these reaction conditions, and no elimination of halogen was detected.

The crude product mixture was dissolved in benzene and washed with brine four times to remove DMF. We also tried using toluene but the Ni(II)-alkylation product has limited solubility in it. While DCM and chloroform are good solvents, washing with brine was not efficient with these solvents. Fractional recrystallization was used to isolate the products, because the minor products often overlap on TLC (hexane/acetone=1:1), and thus it was not always easy to purify these diastereomers with flash liquid chromatograph. The enantiomeric purity of the major isomer **5a** and **5b** was improved by fractional recrystallization from a mixture of DCM and ether. A fast flash chromatograph was usually employed for the mother liquor after the first crystallization to separate the remaining diastereomeric mixture from impurities which came from the starting material of the Ni(II)-complex and from decomposition in the reaction. The reddish eluent was used for further recrystallization, and finally the minor enriched mixture was subjected to the same alkylation reaction conditions for 5 min. Epimerization transferred the minor product to the major one with the same diastereomeric ratio (Scheme 1). In this way, over 90–95% yield of alkylation products can be collected with >98% de. The *S*(2*R*) allyl alkylation product **6a** in mother liquor was further purified on an analytical silica gel HPLC column (IBM Silica 2872053, hexane/2-propanol=98:2, UV detector at 232 nm) for characterization. Attempts to characterize the minor product *S*(2*R*) of homoallyl alkylation **6b** using the same HPLC column failed due to poor resolution. In the case of 5-bromo-1-pentenyl bromide alkylation, both the major **5c** and minor **6c** products crystallize out in DCM/ether solution at the same time but as different crystals. The mother liquor, however, became a pure solution of major product **5c**. The crystal mixture was subjected to three fractional crystallizations until the mixture became enriched with the *S*(2*R*)-product.

The configuration of the major product generated from the *si*-face of the glycine enolate was assigned as *S*(2*S*).[18,19] The diastereomeric ratio was determined from the relative intensity of the peaks in the region of 8.0–8.5 ppm (Fig. 2) in the ^{1}H NMR of the crude product. The two most downfield proton peaks are doublets of the *ortho* protons H_a and H_b in a ratio of 1:2 in the Ni(II)-complex and its products, as indicated by the following results observed in DQF-COSY and 1D NOE experiments. The spin systems in aromatic ring B and C, identified in the DQF-COSY spectrum, were differentiated by the NOE correlation between the H_b protons and both α and δ protons in proline. The spin system in ring A is unique. The resonance from the H_a and H_d protons were unambiguously assigned using the NOE's between H_d and the protons in ring C, and between H_a and the protons in ring B. All the *S*(2*S*) products **5** have their H_a and H_b protons at about 8.0–8.2 ppm (Fig. 2, item ii). However, in the *S*(2*R*) products **6** proton spectra, the H_a proton resonance shifts downfield (~8.5 ppm), while an upfield shift occurs for the H_b (<8.0 ppm) (Fig. 2, item iii).

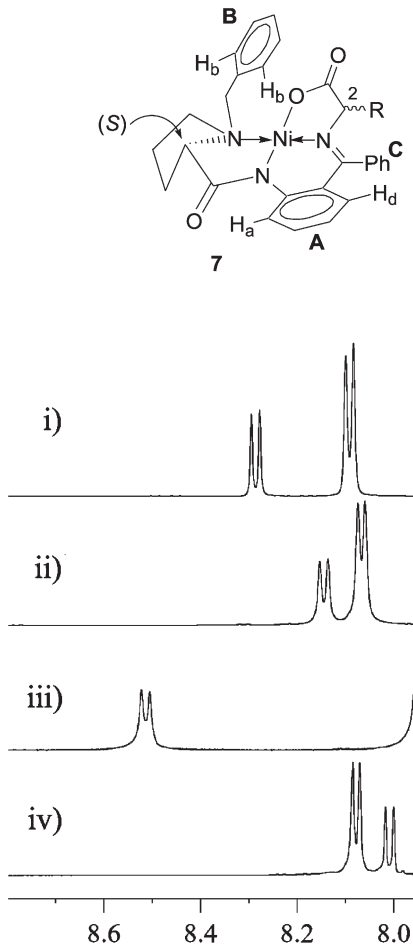
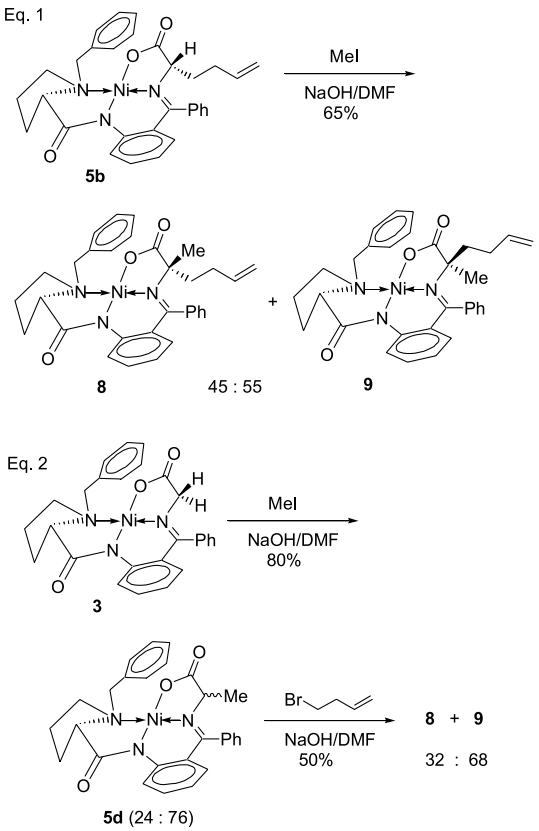


Figure 2. The proton NMR spectra of the downfield protons H_a and H_b of unalkylated and various alkylated complexes. (i) Ni(II)-complex **3**; (ii) *S*(2*S*)-monoalkylated product; (iii) *S*(2*R*)-monoalkylated product; (iv) dialkylated product.

2.2. Dialkylation and face selectivity

Previous studies have attempted to understand the origin of the high diastereoselectivity in alkylation reactions of the Gly-Ni(II)-BPB-complex.[18,19] Although the kinetic controlled reaction has been studied for dialkylation,[23] the difficulty in understanding the absolute configuration of the α, α-dimethyl product makes the results unclear. Since the exact model to mimic the kinetic vs thermodynamic selectivity in monoalkylation is not available due to fast epimerization, we designed the following dialkylation reactions (Scheme 2) by using different aliphatic electrophiles so that the kinetic ratio for reaction in dialkylation could be trapped. The reactions were accomplished in DMF and 10 equiv. of NaOH at ambient temperature. The dialkylation reaction times and their diastereoselectivities are listed in Table 2. For comparison, the monoalkylation of 4-bromo-1-butene **4b** and MeI also is listed.

In our first attempt at dialkylation, the purified homoallyl Gly-Ni-(*S*)-BPB **5b** was used in a reaction with MeI (Scheme 2). The reaction cannot be monitored because the product **9** shared the same R_f value as the starting material **5b** on TLC (acetone/hexane=1:1, R_f=0.45). The reaction was optimized for completion in 3 h by adding another



Scheme 2. Dialkylation of the Ni(II)-complex and their diastereoselectivity.

Table 2. Alkylation and their diastereoselectivities

Starting material	Electrophile	Reaction time	Diastereomeric ratio[a]		Yield
Ni(II)-**3**	**4b**	5 min	2*R*/2*S*	5:95	98
5b	MeI	3 h	**8/9**	45:55	65
Ni(II)-**3**	MeI	5 min	2*R*/2*S*	24:76	80
5d	**4b**	1.5 h	**8/9**	32:68	50

[a] The diastereomeric ratio was determined by ^{1}H NMR.

3 equiv. of MeI after the 1.5 h reaction. However, the diastereoselectivity was only 45:55; almost no *si*-face preference. We also synthesized the methyl Gly-Ni-(*S*)-BPB **5d** from the Ni(II)-complex as starting material (Scheme 2). This gave a 24:76 diastereomeric mixture. This mixture also can be obtained by using racemic alanine in generation of the Ni(II)-complex. However, an attempt to isolate the pure diastereomeric products by fractional crystallization failed. The mixture then was used for alkylation with 4-bromo-1-butene, and the reaction was completed in about 1.5 h. Although this reaction was faster than the first one, it was not as clean. The diastereomeric ratio was 32:68. Both of these kinetic control selectivities are much lower than the thermodynamic control monoalkylation results we observed in Table 1.

From the above results, we conclude that the kinetic *si*-face selectivity for monoalkylation is very limited. For the small electrophile, the *si*-face selectivity is not that obviously favored over the *re*-face reaction. We suggest that the high diastereoselectivity in alkylation actually may be generated by epimerization. The epimerization reaction proved to be very fast in transferring the minor enriched mixture to the major product. It explains why the room temperature reaction actually can provide better diastereoselectivity. We also found that the diastereoselectivity in asymmetric dialkylation increased if a large electrophile (1-bromo-4-butene compare to methyl iodide) was used in the second alkylation.

It should be pointed out that the newly generated chiral configuration in dialkylation products cannot be determined based on the most downfield proton peaks in NMR spectra. Both products gave H_a and H_b close to 8.2 ppm (see Fig. 2, item iv), Interestingly, we were able to determine the weak NOE interactions between the protons on the side chains and *N*^{P}-benzyl ring in both **8** and **9**. These unexpected results indicated that the *N*^{P}-benzyl ring stays on the Ni(II)-complex plane. This assumption was confirmed by the X-ray structure of **8** (Fig. 3), which is consistent with NMR NOE results. The α-configurations of **8** and **9** were assigned as in Scheme 2, relating them to the known absolute configuration of proline.

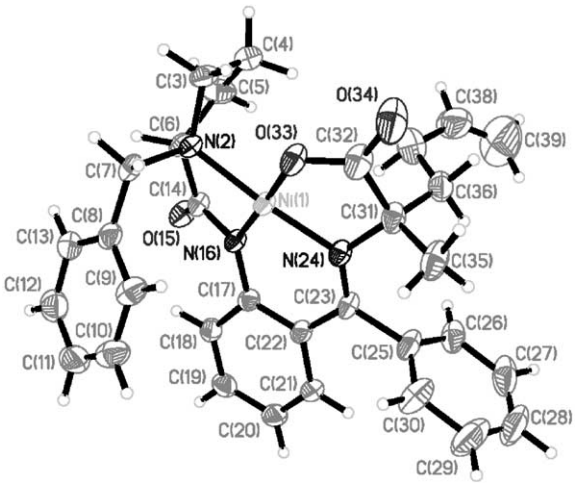


Figure 3. X-ray structure of the dialkylation product **8**.

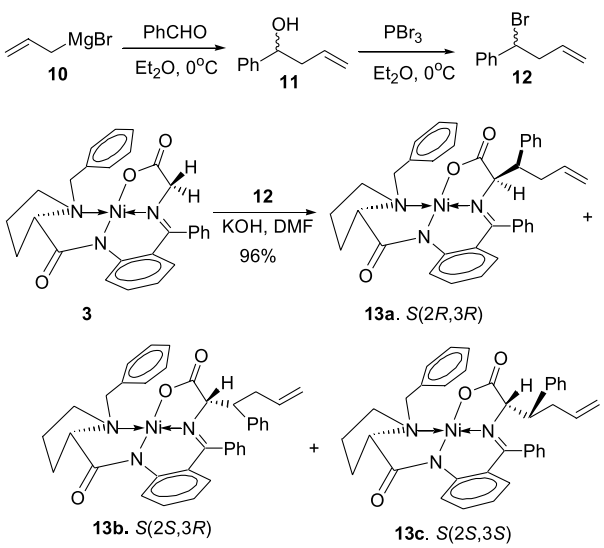
It is interesting to note that the chemical shifts of the most downfield protons H_a and H_b of the dialkylation products are similar by comparison to the starting material **3** and other *S*(2*S*) monoalkylation products **4a**–**c**. By examining all of the crystal structures,[19d,24] we found that the NMR results are consistent with the X-ray structure conformation. For the *S*(2*R*) products, the *N*^{P}-benzyl ring moves outside of Ni(II)-complex plane which results in no NOE interactions between the proton H_a and H_b in the Ni(II)-complex products. As a result, both the chemical shifts of H_a (8.5 ppm) and H_b (<8.0 ppm) became 'normal'. When the *N*^{P}-benzyl ring covers the top of Ni(II)-complex plane, the H_a was shielded and shifts upfield, while H_b was deshielded and shifts downfield. It is not completely clear why, in dialkylation products, the *N*^{P}-benzyl ring can stay on top of the Ni(II)-complex plane and both products **8** and **9** show H_a and H_b proton close to 8.1 ppm. However, it is noteworthy that all *S*(2*R*) products gave negative data for their optical rotations while the others are always positive. Presumably

these results also are related and consistent with different conformations of the Ni(II)-complex in these isomers.

From the above analysis, we assume that the face selectivity in Ni(II)-complex is not caused simply by the steric hindrance of the *N*[P]-benzyl ring[25] because it can move outside of the Ni(II)-complex plane. There is no evidence for the α-H existing in a pseudo-axial or pseudo-equatorial position[19a], because in the transition state, the Gly-Ni(II)-5-membered ring can be very close to planar. However, the difference in the thermodynamic stability of the two alkylated products, due to their different conformations, gives high diastereoselectivity. Efforts to increase the selectivity by increasing the steric hindrance of the *N*[P]-substituted benzyl ring[25] is not necessary in monoalkylation, because the minor product can be converted to the major one by epimerization. Asymmetric synthesis of α, α-dialkylated amino acids[26] using different nucleophiles also is not a practical method, due to the low diastereoselectivity and low isolated yield.

2.3. Alkylation with racemic secondary bromide

When a secondary bromide is used in the alkylation reaction, four possible isomers of the β-substituted alkylation products can be generated.[18b] The secondary bromide 1-bromo-3-butenyl-benzene **12** was synthesized in two steps from commercially available starting materials in moderate yield (Scheme 3).[27] Both the alcohol and bromide were purified by liquid chromatograph. Alkylation of the secondary bromide **12**, generated a mixture of three diastereomers (Scheme 3). This reaction was examined using different amounts of bromide at ambient temperature and the results are summarized in Table 3. The results showed that the diastereomeric ratio increased as the amount of bromide increased to 2.8 equiv. Although the diastereoselectivity was increased as the temperature decreased,[13] the selectivity dropped when the reaction was scaled up due to the exothermic nature of the reaction. In practice, 3.0 equiv. of racemic bromide was used so that the reaction gives high diastereoselectivity.



Scheme 3. The synthesis of a secondary bromide and its alkylation.

Table 3. The secondary bromide in alkylation

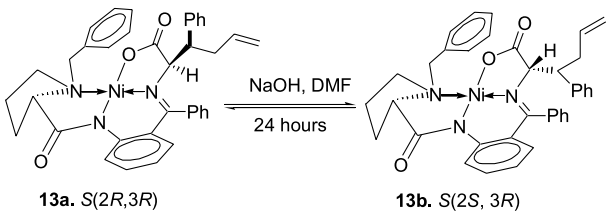
Entry	**12** (equiv.)	S.M.	**13a**[a]	**13b**[a]	**13c**[a]
1	1	7	21	10	62
2	2	0	15	6	76
3	2.5	0	15	4	81
4	2.8	0	10	4	86
5	3	0	11	3	86
6	4	0	9	6	85

[a] The diastereomeric ratios were determined by ^{1}H NMR.

High diastereoselectivity of *S*(2*S*,3*S*)/*S*(2*R*,3*R*) is generated from *si*-face selectivity. Again, it is lower than the results in Table 1, even though the electrophile is much bulkier due to the β-substitution. The major product *S*(2*S*,3*S*) is a kinetic product, while the *S*(2*S*,3*R*) minor product may have been produced from epimerization of the *S*(2*R*,3*R*) product. The high selectivity for *S*(2*S*,3*S*)/*S*(2*S*,3*R*) at position 3 is difficult to understand. A model in previous work[18a] suggested that one of the electrophilic enantiomers is matched in the reaction transition state. This explains why high diastereoselectivity was obtained when using 3 equiv. of bromide. As a matter of fact, we recovered the remaining bromide from the column, presumably an (*R*)-enriched form if the reaction is a typical S_N2 reaction. This enriched compound has an optical rotation of $[\alpha]_D^{24}=+8.9°$ (c=2.4, $CHCl_3$). However, when we used this enantiomerically enriched bromide (2 or 3 equiv.) in an alkylation with the (*R*)-Ni(II)-complex, presumably a matched case, the reaction did not provide any obvious diastereomeric improvement. It should be pointed out that although about 1.5 equiv. of bromide can be recovered and reused in the alkylation, its optical activity drops (racemized) dramatically during storage.

A fast flash column chromatograph was used to recover the bromide and to purify the product mixture before fractional crystallization. In the process, a 1:1 mixture of *S*(2*S*,3*S*) and *S*(2*R*,3*R*) crystals and an *S*(2*S*,3*S*) enriched mother liquor was obtained. A crystal carefully prepared for single X-ray crystallography, was found to be a diastereomeric co-crystal of *S*(2*S*, 3*S*) and *S*(2*R*, 3*R*).[24] Interaction between the racemic side chain groups could be the major packing force in initial crystalline formation, which can explain why a diastereomeric co-crystal forms. This 1:1 co-crystal mixture can be further isolated by flash liquid chromatograph. The *S*(2*S*,3*R*) **13b** minor product (~3%), which has a similar R_f value as the *S*(2*S*,3*S*) product, always coexisted in the mother liquor [R_f=0.62 for *S*(2*S*,3*S*) and 0.59 for *S*(2*R*,3*R*) in a 1:1 mixture of hexane and acetone]. The purity of the major product in the mother liquor was further improved by crystallization.

The unique NMR spectra of these monoalkylation products can be used to assign their configurations at position 2. Both the major *S*(2*S*,3*S*) and minor *S*(2*S*,3*R*) products have the typical H_a and H_b signal near 8.2 ppm (Fig. 2). The minor product *S*(2*R*,3*R*) has its H_a proton at 8.6 ppm, while the H_b is even further upfield, overlapping with the other aromatic protons. The 3*S* configuration in the major product *S*(2*S*,3*S*) was further confirmed by NOE studies of the [6,5]-bicyclic β-turn dipeptide[13] and by the X-ray structure of the co-crystal.[24] The minor product *S*(2*R*,3*R*) was crystallized



Scheme 4. Epimerization of the *S*(2*R*,3*R*) to the *S*(2*S*,3*R*) product.

and its single X-ray structure was obtained.[24] It was found that the crystalline form had two conformers that showed the *N*[P]-benzyl ring was outside of the Ni(II)-complex plane, which is consistent with the NMR result. The stereoisomer relationship of the *S*(2*R*,3*R*) and *S*(2*S*,3*R*) compounds can be confirmed by epimerization (Scheme 4). The assigned *S*(2*R*,3*R*) **13a** minor product was subjected to the same reaction conditions of alkylation, but at ambient temperature and at different reaction times, with the results shown in Table 4. The reaction gave a mixture of *S*(2*R*,3*R*):*S*(2*S*,3*R*)=16:84 at equilibrium after 20 h reaction. However, decomposition occurred frequently with more than half of the material destroyed in about 2 h, and over 70% of the starting material was decomposed in the 20 h reaction. The major product *S*(2*S*,3*R*) was isolated from the *S*(2*R*,3*R*) isomer by liquid chromatograph. This epimerization provides a unique way to obtain this pure minor product for characterization.

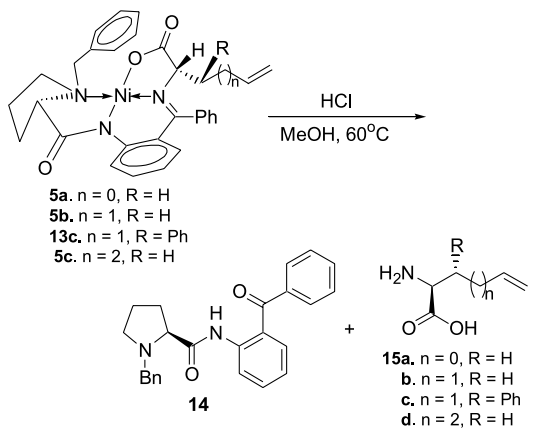
Table 4. The epimerization of Ni(II)-alkylation product

Entry	Reaction time (min)	Starting material[a]	Product[a] *S*(2*S*, 3*R*)
1	20	82	18
2	40	43	57
3	120	23	77
4	360	19	81
5	20 h	16	84

[a] The percentages were determined by ^{1}H NMR.

2.4. Hydrolysis of the Ni(II)-complex

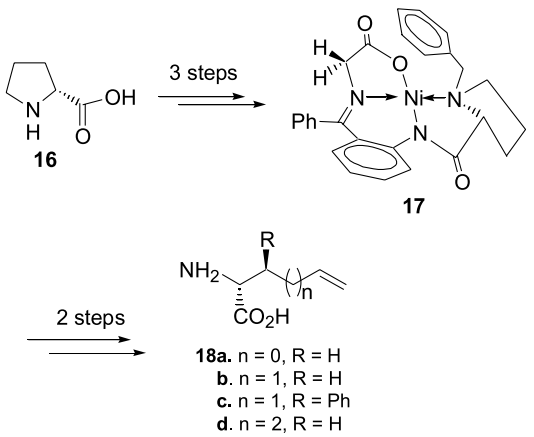
Amino acids **15a**–**d** were generated by decomposition of the Ni(II)-complex products with 3 N HCl in methanol (1:1) (Scheme 5). A mixture of methanol and DCM (approx. 2:1) was used to increase the solubility of the Ni(II)-alkylated product. Hydrolysis of β-phenyl-homoallylglycine **13c** was very slow and the disappearance of the reddish color



Scheme 5. Hydrolysis of the alkylated Ni(II)-complex.

indicated the completeness of hydrolysis. After evaporation, the above products mixture was diluted in aqueous solution, and (*S*)-BPB **14** was extracted with $CHCl_3$, recovering 96%. This byproduct can be used in the regeneration of Ni(II)-complex **3** without further purification. The mixture of amino acid and Ni^{2+} salt in aqueous phase was then concentrated and loaded on an H^+ form ion exchange resin column. It is very important to wash the column with deionized water to pH=7 before washing with the concentrated aqueous ammonia and water (4:1) mixture. For **15c** and **d**, a mixture of ammonia, water and ethanol (4:1:2) is needed for fast collection of the amino acid. The Ni^{2+} salt remained on the column which was regenerated with 1 N HCl solution. The amino acids were collected after evaporation of the ammonia aqueous solution and the residue was redissolved in small amounts of water and dried by lyophilization. All the amino acids can be collected in this way in over 95% yield.

(*R*)-Amino acids are important in peptidomimetics at position 2 of Leu-enkephalin analogues[28] and at position 7 in α-MSH analogues.[29] Thus *R*-allylglycine, *R*-homoallylglycine, and *R*-bishomoallylglycine derivatives have been synthesized in 3 g scales from the (*R*)-Ni(II)-complex, which was synthesized from (*R*)-proline in comparable yields (Scheme 6). (*R*)-2-Amino-hept-6-enyl carboxylic acid was synthesized on a 1 g scale by using bromide **12** as an electrophile.



Scheme 6. Synthesis of the (*R*)-Ni(II)-complex and the *R*-amino acids.

During purification of (*R*)-4-pentenyl-glycine-Ni(II)-BPB-complex, a purple minor product, *R*(2*S*), crystallized out before the red major product, *R*(2*R*). Both the *R*(2*R*) and *R*(2*S*) products were characterized using samples collected by hand picking individual crystals. It is interesting to note that visually the *R*(2*S*) minor product is a notably darker color, and apparently a different crystal form compared with its *S*(2*R*) enantiomer, which was synthesized from the (*S*)-Ni(II)-complex. However, in attempts to obtain better purity crystals in small scales for X-ray analysis, we found that the *R*(2*S*) and *S*(2*R*) compounds grew as identical red-orange plate-like crystals. Because of the visual differences, we were curious to see if a racemic crystal could be grown. When equal quantities of *R*(2*S*) and *S*(2*R*) were mixed in DCM and ether, red-orange plates were again obtained. X-ray diffraction determined that these crystals are identical to the pure individual enantiomers and thus indicates that

spontaneous self-resolution has occurred. The X-ray diffraction results of these molecules will be reported elsewhere.

3. Conclusions

The Ni(II)-complex derived from a glycine Schiff base with 2-[*N*-(*N*′-benzylprolyl)amino]benzophenone was found to be an ideal equivalent of nucleophilic glycine in reactions with various alkyl halides affording an efficient, generalized and practically useful method for the large scale preparation of enantiomerically pure ω-unsaturated amino acids. High diastereoselectivities and high yields were achieved by homogenous reaction and epimerization. The fractional crystallization employed in this method has been a reliable way to prepare diastereomerically pure Ni(II)-complex products on about a 20 g scale, which after hydrolysis affords multi-gram amounts of enantiomerically pure amino acids. This synthetic strategy and the crystallization purification methods are not limited to the synthesis of ω-unsaturated amino acids but to all the possible electrophiles that can be used in Ni(II)-complex alkylation. It should be indicated that the above simple but efficient method could not be used for the synthesis of vinylglycine analogues and β-substituted allylglycine analogues. A novel methodology to synthesize these ω-unsaturated amino acids by using the Ni(II)-complex as a chiral auxiliary are presently under investigation.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 MHz NMR spectrometer equipped with a Nalorac triple-resonance 3-axis gradient 5-mm probe. The chemical shifts were reported in δ, parts per million (ppm), relative to TMS (δ=0.00 ppm) as an internal standard. For amino acids in D_2O, ^{1}H chemical shifts were referenced to the HOD peak at 4.76 ppm, and ^{13}C chemical shifts were indirectly referenced to $CDCl_3$ at 7.26 ppm. In DMSO, the spectra were referenced to solvent peaks at 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. The DQF-COSY[30a,b] and 1D transient selective NOE[30c,d] (350 ms mixing time) spectra were acquired. Mass spectrometric analyses were conducted by the Mass Spectrometry Facility at the Department of Chemistry of the University of Arizona on a Jeol HX-110A. Optical rotations were measured on a JASCO P1010 polarimeter. All the reagents and solvents, unless otherwise stated, are commercially available and were used as received. Flash column chromatograph was performed with 230–400 mesh size silica gel which was purchased from Aldrich Chemical Co. Thin-layer chromatograph (TLC) was performed with Merck silica gel 60 F_{254}. Melting points (Mp) are uncorrected and were obtained in open capillaries. The compounds were characterized by Mp, $[\alpha]_D$, ^{1}H, ^{13}C NMR and high resolution mass spectrometry (HRMS). All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy. Unless otherwise stated, all reactions were run under an atmosphere of argon.

4.1.1. 1-Bromo-3-butenyl-benzene (12). In a 500-mL flame-dried flask, 1 M allyl magnesium bromide in diethyl ether (100 mL, 100 mmol) was diluted with 140 mL of anhydrous ether. The solution was cooled down to 0 °C before benzaldehyde (10.1 mL, 100 mmol) was added slowly. It was kept at 0 °C for 1 h before being quenched by slowly adding 60 mL of 10% H_2SO_4. The organic phase was then separated and washed with $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo and the crude material was purified by flash liquid chromatograph. A colorless liquid product (**11**) was obtained (14.1 g, 95% yield).

The above alcohol **11** (14.1 g, 95 mmol) was dissolved in 250 mL anhydrous ether in a 500-mL flame-dried flask. The solution was cooled down to 0 °C and then PBr_3 (4.75 mL, 150 mmol) was added. The reaction was kept at 0 °C until completed in 45 min. It was quenched by saturated NH_4Cl aqueous solution (150 mL). The organic phase was then separated and washed with $NaHCO_3$ and brine, and dried over $MgSO_4$. The product solution was then concentrated in vacuo, and the residue was purified on a silica gel column using hexane. A slight yellowish liquid (12.8 g, 65% yield) was obtained. R_f=0.33 (hexane); ^{1}H (500 MHz, $CDCl_3$), δ 2.95–3.05 (2H, m), 4.96 (1H, t, *J*=7.5 Hz), 5.09–5.15 (2H, m), 5.70–5.77 (1H, m), 7.26–7.41 (5H, m); ^{13}C (125 MHz, $CDCl_3$), δ 44.2, 54.0, 118.1, 127.3, 128.4, 128.7, 134.7, 141.6; HRMS (FAB) calcd for $(C_{10}H_{11})^+$ 131.0861, found 131.0857.

4.2. General procedure for alkylation of Ni(II)-complex

Ni(II)-complex **3** (1 equiv.) and ground NaOH (10 equiv.) were added to a flask which was purged two times with argon. Anhydrous DMF (4 mL/mmol) was added by syringe and the mixture was allowed to react for 5 min at room temperature before bromide **4a**, **4b**, **4c** (0.98 equiv. each) or **12** (3.0 equiv.) was added in one portion, respectively. The reaction was then kept at room temperature for another 5 min (for bromide **12**, 1-bromo-but-3-enyl-benzene, 3 equiv., −30 °C, 45 min reaction). The solution was decanted into an aqueous solution (40 mL/mmol) containing 5% of HOAc. The suspension was dissolved in benzene (20 mL/mmol) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×40 mL/mmol) and dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was first purified by fractional recrystallization in DCM/ether solution. The mother liquor was purified by flash liquid chromatograph before they were further purified by fractional recrystallization. The alkylation with electrophiles **4a**, **4b**, **4c** were performed in 20 g scales, while the alkylation with electrophile **12** was performed in 10 g scale.

4.2.1. (*S*)-Allylglycine-Ni-(*S*)-BPB (5a). Yield 83.5%, Mp: 203–205 °C; $[\alpha]_D^{24}$=+2440° (*c* 0.012, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 2.07–2.16 (2H, m), 2.41–2.57 (3H, m), 2.82 (1H, bs), 3.48 (1H, dd, *J*=6.0, 10.5 Hz), 3.49–3.64 (3H, m), 4.05 (1H, dd, *J*=4.0, 6.0 Hz), 4.46 (1H, d, *J*=12.5 Hz), 5.21 (1H, d, *J*=17.0 Hz), 5.42 (1H, d, *J*=10.0 Hz),

6.44–6.49 (1H, m), 6.65–6.70 (2H, m), 6.98 (1H, d, J=7.0 Hz), 7.17 (1H, t, J=7.0 Hz), 7.22 (1H, t, J=7.0 Hz), 7.29 (1H, bs), 7.37 (2H, t, J=7.5 Hz), 7.49–7.55 (3H, m), 8.07 (2H, d, J=7.0 Hz), 8.20 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.3, 30.7, 38.4, 56.8, 63.1, 70.3 (two carbons), 119.7, 120.6, 123.6, 126.4, 127.0, 127.7, 128.79, 128.83, 128.9, 129.7, 131.5, 132.1, 133.1, 133.2, 133.9, 142.4, 170.8, 178.8, 180.3; HRMS (FAB) MH^+ calcd for $C_{30}H_{30}N_3NiO_3$ 538.1641, found 538.1638.

4.2.2. (*R*)-Allylglycine-Ni-(*R*)-BPB. Yield 85%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (*S*)-allylglycine-Ni-(*S*)-BPB (**5a**).

4.2.3. (*R*)-Allylglycine-Ni-(*S*)-BPB (6a). Yield 12.5%, $[\alpha]_D^{24}=-1190°$ (*c* 0.049, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.87 (1H, bs), 2.06–2.10 (1H, m), 2.21–2.24 (1H, m), 2.50–2.64 (3H, m), 3.63 (1H, dd, J=4.0, 10.0 Hz), 3.73 (1H, d, J=13.0 Hz), 3.93 (1H, dd, J=3.5, 7.5 Hz), 4.10–4.14 (1H, m), 4.63 (1H, d, J=13.0 Hz), 5.03 (1H, d, J=17.0 Hz), 5.23 (1H, d, J=9.5 Hz), 6.04–6.10 (1H, m), 6.72 (1H, t, J=7.5 Hz), 6.79 (1H, d, J=7.5 Hz), 7.06 (1H, d, J=4.0 Hz), 7.20 (1H, bs), 7.28 (1H, m), 7.44–7.51 (6H, m), 7.93 (2H, d, J=7.0 Hz), 8.5 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.4, 30.7, 39.3, 58.0, 61.6, 68.9, 70.5, 119.0, 120.7, 123.7, 125.8, 126.9, 128.1, 128.6, 129.0, 129.1, 129.3, 129.7, 131.7, 132.3, 132.5, 133.1, 133.7, 134.2, 142.9, 171.4, 179.1, 182.3; HRMS (FAB) MH^+ calcd for $C_{30}H_{30}N_3NiO_3$ 538.1641, found 538.1644.

4.2.4. (*S*)-But-3-enyl-glycine-Ni-(*S*)-BPB (5b). Yield 93%, Mp: 207–209 °C (lit.,[21] 210 °C); $[\alpha]_D^{24}=+4471°$ (*c* 0.014, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.73 (1H, bs), 2.07–2.12 (1H, m), 2.17–2.21 (1H, m), 2.28–2.31 (1H, m), 2.53–2.58 (1H, m), 2.78 (1H, bs), 3.48–3.57 (2H, m), 3.61 (2H, d, J=12.5 Hz), 3.93 (1H, d, J=6.0 Hz), 4.47 (1H, d, J=12.5 Hz), 4.89 (1H, d, J=10.5 Hz), 4.99 (1H, d, J=17.0 Hz), 5.54–5.59 (1H, m), 6.65–6.71 (2H, m), 6.95 (1H, d, J=7.5 Hz), 7.16 (1H, t, J=7.0 Hz), 7.22 (1H, t, J=7.0 Hz), 7.29 (1H, bs), 7.38 (2H, t, J=7.5 Hz), 7.48–7.49 (1H, m), 7.51–7.54 (2H, m), 8.08 (2H, d, J=7.5 Hz), 8.15 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.7, 29.4, 30.7, 35.0, 57.0, 63.1, 69.9, 70.2, 115.7, 120.7, 123.7, 126.5, 127.3, 127.5, 128.8, 128.89, 128.91, 128.93, 129.7, 131.5, 132.1, 133.2, 136.6, 142.2, 170.4, 179.1, 180.4; HRMS (FAB) MH^+ calcd for $C_{31}H_{32}N_3NiO_3$ 552.1797, found 552.1807.

4.2.5. (*R*)-But-3-enyl-glycine-Ni-(*R*)-BPB. Yield 91%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (*S*)-allylglycine-Ni-(*S*)-BPB (**5b**).

4.2.6. (*S*)-Pent-4-enyl-glycine-Ni-(*S*)-BPB (5c). Yield 86%, Mp: 191–192 °C (lit.,[21] 192 °C); $[\alpha]_D^{24}=+2560°$ (*c* 0.033, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.65–1.67 (2H, m), 1.91–2.07 (4H, m), 2.14–2.23 (2H, m), 2.50–2.55 (1H, m), 2.76 (1H, bs), 3.47 (1H, dd, J=6.0, 10.0 Hz), 3.52–3.60 (3H, m), 3.91 (1H, d, J=5.0 Hz), 4.44 (1H, d, J=12.5 Hz), 4.95–5.00 (2H, m), 5.70–5.75 (1H, m), 6.62–6.67 (2H, m), 6.92 (1H, d, J=6.5 Hz), 7.14 (1H, t, J=7.0 Hz), 7.19 (1H, t, J=7.0 Hz), 7.27 (1H, bs), 7.34 (2H, t, J=7.0 Hz), 7.45–7.50 (3H, m), 8.05 (2H, d, J=7.0 Hz), 8.13 (1H, d, J=8.0 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.6, 24.6, 30.7, 33.2, 34.8, 56.9, 63.0, 70.2, 70.3, 115.2, 120.7, 123.6, 126.5, 127.1, 127.6, 128.82, 128.85, 128.87, 129.6, 131.5, 132.1, 133.15, 133.17, 136.8, 137.7, 142.2, 170.3, 179.3, 180.3; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1954.

4.2.7. (*S*)-Pent-4-enyl-glycine-Ni-(*S*)-BPB (5c). Yield 85%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (*S*)-pent-4-enyl-glycine-Ni-(*S*)-BPB (**5c**).

4.2.8. (*R*)-Pent-4-enyl-glycine-Ni-(*S*)-BPB (6c). Yield 9%, $[\alpha]_D^{24}=-1180°$ (*c* 0.040, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.50–1.52 (2H, m), 1.84–1.91 (4H, m), 1.98–1.20 (1H, m), 2.12–2.18 (1H, m), 2.22–2.24 (1H, m), 2.52–2.58 (1H, m), 2.64–2.69 (1H, m), 3.59 (1H, d, J=13.0 Hz), 3.67 (1H, d, J=6.0 Hz), 3.79 (1H, d, J=6.5 Hz), 4.21 (1H, t, J=5.0 Hz), 4.48 (1H, d, J=13.0 Hz), 4.93–4.97 (2H, m), 5.63–5.69 (1H, m), 6.72 (1H, t, J=7.5 Hz), 6.76 (1H, d, J=8.0 Hz), 7.00 (1H, d, J=6.5 Hz), 7.19 (1H, bs), 7.26 (1H, bs), 7.45–7.50 (6H, m), 7.99 (2H, d, J=7.0 Hz), 8.50 (1H, d, J=9.0 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.3, 24.6, 30.5, 33.2, 35.4, 58.6, 61.5, 69.1, 70.4, 115.1, 120.7, 123.7, 125.9, 126.9, 127.9, 128.6, 129.0, 129.1, 129.6, 131.6, 132.4, 133.5, 133.7, 134.1, 137.9, 142.8, 170.8, 179.7, 182.3; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1954.

4.2.9. (2*S*,3*S*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (13c). Yield 82%, Mp: 135–137 °C; $[\alpha]_D^{24}=+2183°$ (*c* 0.033, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.37–1.45 (1H, m), 1.68–1.76 (1H, m), 1.95 (1H, dt, J=7.0, 11.0 Hz), 2.12–2.23 (2H, m), 2.79 (1H, dt, J=6.0, 11.5 Hz), 3.24 (1H, t, J=8.5 Hz), 3.38 (1H, d, J=12.5 Hz), 4.21 (1H, d, J=12.5 Hz), 4.28 (1H, d, J=3.0 Hz), 4.63 (1H, dd, J=3.0, 9.0 Hz), 4.75–4.86 (1H, m), 4.82 (1H, d, J=3.0 Hz), 6.64–6.69 (2H, m), 7.08 (1H, t, J=7.5 Hz), 7.13 (2H, t, J=13.5 Hz), 7.27 (2H, t, J=7.5 Hz), 7.31 (1H, d, J=7.0 Hz), 7.38 (2H, d, J=7.0 Hz), 7.45–7.60 (6H, m), 8.00 (2H, d, J=7.5 Hz), 8.25 (1H, d, J=9.0 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.0, 30.7, 36.3, 50.2, 57.4, 63.6, 70.4, 73.2, 117.3, 120.4, 123.1, 126.1, 127.6, 127.7, 128.2, 128.65, 128.71, 128.91, 128.93, 129.3, 129.7, 129.9, 131.5, 132.3, 133.3, 133.5, 134.4, 135.0, 139.9, 143.0, 170.9, 177.4, 180.4; HRMS (FAB) MH^+ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2122.

4.2.10. (2*R*,3*R*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*R*)-BPB. Yield 83%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (2*S*,3*S*)-(1-phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (**13c**).

4.2.11. (2*R*,3*R*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (13a). Yield 10%, Mp: 187–189 °C; $[\alpha]_D^{24}=-2030°$ (*c* 0.024, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.14–1.18 (1H, m), 1.31–1.35 (1H, m), 1.80–1.84 (1H, m), 2.04–2.10 (1H, m), 2.38–2.42 (1H, m), 2.48–2.56 (2H, m), 2.81 (1H, bs), 3.32–3.34 (1H, m), 3.37 (2H, AB, J=14.0, 35.5 Hz), 3.79 (1H, m), 4.29 (1H, d, J=2.5 Hz), 4.63–4.65 (1H, m), 4.85–4.95 (1H, m), 4.88 (1H, d, J=3.5 Hz), 6.76 (1H, t, J=7.5 Hz), 6.82 (1H, d, J=7.5 Hz), 7.13 (1H, d, J=6.0 Hz), 7.17 (1H, d, J=5.0 Hz), 7.28–7.34 (5H, m), 7.50 (1H, t, J=7.0 Hz), 7.53–7.60 (7H, m), 8.44 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.7, 31.4, 35.5, 50.9, 55.0, 59.2, 68.6, 73.5, 117.4, 120.7, 123.5, 126.4, 127.6, 127.9, 128.2, 128.66, 128.71, 128.90, 128.93, 129.3, 129.8, 130.5, 131.8,

131.9, 132.6, 133.8, 134.3, 134.9, 141.1, 143.2, 170.7, 176.9, 181.8; HRMS (FAB) MH^+ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2119.

4.2.12. (2*S*,3*R*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (13b). The above purified (2*R*, 3*R*)-product (170 mg, 0.271 mmol) and ground NaOH (120 mg, 3.0 mmol) were added to a 10-mL flask. The flask was purged with argon two times and anhydrous DMF (2 mL) was added by syringe. The mixture was kept at room temperature for 20 h before it was quenched by an aqueous acidic solution (20 mL, 5% HOAc). The product mixture was treated as in the general procedure for Ni(II)-complex alkylation, and the product was isolated by flash chromatograph. $[\alpha]_D^{24}$=+1565° (*c* 0.061, $CHCl_3$); ^1H (500 MHz, $CDCl_3$), δ 2.10–2.21 (1H, m), 2.61–2.67 (1H, m), 2.81–2.87 (1H, m), 2.90–2.95 (1H, m), 3.46–3.53 (3H, m), 3.57 (1H, d, *J*=12.5 Hz), 3.83–3.92 (1H, m), 4.10 (1H, d, *J*=6.0 Hz), 4.45 (1H, d, *J*=12.0 Hz), 4.94 (1H, dd, *J*=1.0, 10.0 Hz), 5.09 (1H, dd, *J*=1.0, 17.0 Hz), 5.54–5.61 (1H, m), 6.17 (1H, d, *J*=8.0 Hz), 6.53 (1H, dd, *J*=1.5, 8.5 Hz), 6.63 (1H, t, *J*=7.5 Hz), 6.72 (2H, d, *J*=7.0 Hz), 7.06–7.24 (7H, m), 7.30 (2H, t, *J*=7.5 Hz), 7.43–7.46 (2H, m), 8.05 (2H, d, *J*=7.0 Hz), 8.21 (1H, d, *J*=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.4, 30.9, 34.8, 52.1, 56.9, 63.0, 70.7, 75.7, 117.1, 120.6, 123.1, 126.5, 127.0, 127.5, 128.3, 128.6, 128.71, 128.79, 128.81, 128.84, 128.88, 129.5, 131.5, 132.4, 133.1, 133.6, 134.7, 135.7, 138.2, 142.6, 170.7, 177.0, 180.1; HRMS (FAB) MH^+ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2114.

4.3. Dialkylation of Ni(II)-complex

Eq. 1. Monoalkylated Ni(II)-product **5b** (277 mg, 0.5 mmol) and ground NaOH (40 mg, 5.0 mmol) were added to a flask which was purged two times with argon. Anhydrous DMF (2 mL) was added by syringe and the mixture was allowed to react for 5 min at room temperature before methyl iodide (94 μL, 1.5 mmol) was added. The reaction was then kept at room temperature for 90 min before a second addition of methyl iodide (94 μL, 1.5 mmol). After another 90 min reaction, the solution was decanted into an aqueous solution (40 mL) containing 5% of HOAc. The suspension was dissolved in benzene (40 mL) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash liquid chromatograph, and product **8** (83 mg) and product **9** (100 mg) were obtained (65% total yield).

Eq. 2. Ni(II)-complex **3** (1.5 g, 3.0 mmol) and ground NaOH (1.2 g, 30 mmol) were added to a flask which was purged two times with argon. Anhydrous DMF (12 mL) was added by syringe and the mixture was allowed to react for 5 min before it was cooled to 0 °C. Methyl iodide (184 μL, 2.9 mmol) was added in one portion and the reaction was kept for another 5 min at 0 °C before quenching with an aqueous solution (120 mL) containing 5% of HOAc. The suspension was dissolved in benzene (120 mL) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×80 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization in DCM/ether solution and product **5d** (1.22 g, 80% yield) was obtained as a diastereomeric mixture.

The above methyl-Ni(II) product **5d** (256 mg, 0.5 mmol) and ground NaOH (40 mg, 5.0 mmol) were added to a flask which was purged two times with argon. Anhydrous DMF (2 mL) was added by syringe and the mixture was allowed to react for 5 min at room temperature before 1-bromo-4-butene (102 μL, 1.0 mmol) was added. The reaction was then kept at room temperature for 90 min before it was decanted into an aqueous solution (40 mL) containing 5% of HOAc. The suspension was dissolved in benzene (40 mL) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash liquid chromatograph, and product **8** (45 mg) and product **9** (96 mg) were obtained (50% total yield).

4.3.1. (2*R*)-2-Buten-3′-yl-2-methyl-glycine-Ni(II)-(*S*)-BPB (8). $[\alpha]_D^{24}$=+1451° (*c* 0.032, $CHCl_3$); ^1H (500 MHz, $CDCl_3$), δ 1.26 (3H, s), 1.73 (1H, dt, *J*=4.0, 13.0 Hz), 1.83 (1H, dt, *J*=4.5, 13.0 Hz), 2.03–2.08 (2H, m), 2.46–2.51 (1H, m), 2.67–2.71 (2H, m), 2.98–3.03 (1H, m), 3.24–3.27 (1H, m), 3.44 (1H, dd, *J*=5.5, 10.5 Hz), 3.65 (1H, d, *J*=10.0 Hz), 3.69 (1H, d, *J*=13.0 Hz), 4.48 (1H, d, *J*=12.5 Hz), 5.03 (1H, d, *J*=10.0 Hz), 5.11 (1H, d, *J*=17.0 Hz), 5.78–5.84 (1H, m), 6.61–6.66 (2H, m), 6.99 (1H, d, *J*=7.5 Hz), 7.13 (1H, t, *J*=6.5 Hz), 7.29–7.32 (2H, m), 7.37–7.46 (3H, m), 7.46–7.47 (2H, m), 8.01 (1H, d, *J*=8.5 Hz), 8.08 (1H, d, *J*=7.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.2, 29.4, 29.8, 30.6, 39.2, 57.0, 63.3, 69.9, 77.6, 115.4, 120.7, 123.9, 126.9, 127.2, 127.9, 128.5, 128.8, 128.9, 129.3, 130.1, 131.5, 131.6, 133.3, 136.4, 136.8, 141.4, 172.5, 180.4, 182.1; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1968.

4.3.2. (2*S*)-2-Buten-3′-yl-2-methyl-glycine-Ni(II)-(*S*)-BPB (9). $[\alpha]_D^{24}$=+960° (*c* 0.031, $CHCl_3$); ^1H (500 MHz, $CDCl_3$), δ 1.46–1.50 (1H, m), 1.52 (3H, s), 1.75–1.79 (1H, m), 2.04–2.13 (4H, m), 2.46–2.51 (1H, m), 2.60–2.65 (1H, m), 3.33–3.39 (1H, m), 3.45 (1H, dd, *J*=5.5, 11.0 Hz), 3.64 (1H, d, *J*=12.5 Hz), 3.72 (1H, dd, *J*=6.0, 10.0 Hz), 4.39 (1H, d, *J*=12.5 Hz), 5.00 (1H, d, *J*=10.0 Hz), 5.04 (1H, dd, *J*=1.0, 17.0 Hz), 5.70–5.75 (1H, m), 6.61–6.67 (2H, m), 7.03 (1H, d, *J*=7.5 Hz), 7.12 (1H, dt, *J*=1.5, 7.5 Hz), 7.26–7.31 (2H, m), 7.36–7.49 (5H, m), 7.96 (1H, d, *J*=8.5 Hz), 8.14 (1H, d, *J*=7.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.7, 27.8, 28.9, 30.6, 38.9, 57.6, 63.7, 70.4, 77.6, 115.1, 120.7, 124.1, 127.1, 127.7, 128.2, 128.3, 128.7, 128.9, 129.0, 129.4, 131.39, 131.43, 133.1, 133.9, 136.1, 136.8, 141.3, 172.4, 180.5, 182.6; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1958.

4.4. General procedure for hydrolysis of alkylation product of Ni(II)-complex

The Ni(II)-alkylated product (**5a**,**b**,**c** and **13c**) (1 equiv.) was dissolved in a methanol and DCM mixture (2:1, 3 mL/mmol) and added dropwise into a mixture of HCl (3 N, 2 mL/mmol) and methanol (2 mL/mmol) solution at 60 °C. The solution turned green (for the β-phenyl-substituted

product **13c**, 6 N HCl at 60 °C for 1 h). The methanol–water solution was evaporated and the residue was re-dissolved in water (3×5 mL/mmol) and evaporated to remove the HCl. NH_4OH (5 mL/mmol), and then water (5 mL/mmol) was added and the mixture was concentrated in vacuo to dryness. The residue was then dissolved in water (5 mL/mmol) and $CHCl_3$ (5 mL/mmol). The organic phase was separated and the water phase was washed with $CHCl_3$ (2×5 mL/mmol). The combined organic phase was washed with brine and dried over $MgSO_4$, and then concentrated in vacuo. (*S*)-BPB (about 96%) was recovered. The aqueous phase was evaporated to 10 mL and loaded on an ion-exchange column (DOWEX 50Wx2-100 resin) which was pre-washed with water to neutral pH. The column was eluted by water to pH=7 and then washed with ammonium hydroxide/water (4:1) until all the amino acid was washed out (for **5c** and **13c**, a mixture of ammonium hydroxide/water/ethanol (4:1:2) was used). The column can be regenerated by 1 N HCl. The aqueous solution collected from the column was concentrated and the colorless amino acid was collected after lyophilization.

4.4.1. (*S*)-2-Allylglycine (15a). Yield 96%, Mp: >275 °C (decomp.) (lit.,[7] 208 °C); $[\alpha]_D^{24}$=+21.1° (*c* 1.53, H_2O); ^1H (500 MHz, DMSO), δ 2.46–2.57 (2H, m), 3.69 (1H, t, *J*=5.5 Hz), 5.13–5.18 (2H, m), 5.62–5.70 (1H, m); ^{13}C (125 MHz, DMSO), δ 35.2, 54.3, 120.8, 131.7, 174.4; HRMS (FAB) MH^+ calcd for $C_5H_{10}NO_2$ 116.0712, found 116.0717.

4.4.2. (*R*)-2-Allylglycine (18a). Yield 90%, ^1H and ^{13}C (DMSO) spectra are identical to (*S*)-2-allylglycine (**15a**).

4.4.3. (*S*)-2-Amino-5-hexenoic acid (15b). Yield 96%, Mp: >270 °C; $[\alpha]_D^{24}$=+13.1° (*c* 1.30, H_2O) (lit.,[21] +13.6°); ^1H (500 MHz, DMSO), δ 1.83–1.87 (2H, m), 2.02–2.07 (1H, m), 2.14–2.19 (1H, m), 3.80 (1H, t, *J*=6.0 Hz), 4.96 (1H, d, *J*=10.5 Hz), 5.03 (1H, d, *J*=17.5 Hz), 5.71–5.77 (1H, m); ^{13}C (125 MHz, DMSO), δ 28.7, 29.2, 51.5, 116.3, 137.1, 170.8; HRMS (FAB) MH^+ calcd for $C_6H_{11}NO_2$ 130.0868, found 130.0870.

4.4.4. (*R*)-2-Amino-5-hexenoic acid (18b). Yield 92%, ^1H and ^{13}C (DMSO) spectra are identical to (*S*)-2-amino-5-hexenoic acid (**15b**).

4.4.5. (*S*)-2-Amino-6-heptenoic acid (15d). Yield 96%, Mp: 225 °C (decomp); $[\alpha]_D^{24}$=+10.0° (*c* 1.02, H_2O) (lit.,[21] +8.4°); ^1H (500 MHz, D_2O), δ 1.37–1.42 (2H, m), 1.73–1.80 (2H, m), 2.00–2.04 (2H, q, *J*=7.0 Hz), 3.64 (1H, t, *J*=5.5 Hz), 4.93 (1H, d, *J*=10.0 Hz), 4.98 (1H, d, *J*=17.0 Hz), 5.76–5.80 (1H, m); ^{13}C (125 MHz, D_2O), δ 23.9, 30.2, 32.9, 55.1, 115.4, 139.0, 175.3; HRMS (FAB) MH^+ calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1021.

4.4.6. (*R*)-2-Amino-6-heptenoic acid (18d). Yield 90%, ^1H and ^{13}C (D_2O) spectra are identical to (*S*)-2-amino-6-eptenoic acid (**15d**).

4.4.7. (2*S*, 3*S*)-2-Amino-3-phenyl-hexenoic acid (15c). Yield 98%, Mp: 132–135 °C; $[\alpha]_D^{24}$=+2.98° (*c* 4.3, H_2O); ^1H (500 MHz, D_2O), δ 2.61–2.74 (2H, m), 3.34 (1H, dt, *J*=5.0, 10.0 Hz), 4.17 (1H, d, *J*=5.0 Hz), 4.95 (1H, d, *J*=10.0 Hz), 5.06 (1H, d, *J*=17.0 Hz), 5.61–5.68 (1H, m), 7.26 (2H, d, *J*=7.0 Hz), 7.32 (1H, t, *J*=7.0 Hz), 7.37 (2H, t, *J*=7.0 Hz); ^{13}C (125 MHz, D_2O), δ 34.2, 45.7, 57.8, 117.6, 128.2, 128.6, 129.1, 135.3, 136.8, 171.1; HRMS (FAB) MH^+ calcd for $C_{12}H_{15}NO_2$ 206.1181, found 206.1184.

4.4.8. (2*R*, 3*R*)-2-Amino-3-phenyl-hexenoic acid (18c). Yield 95%, ^1H and ^{13}C (D_2O) spectra are identical to (2*S*,3*S*)-2-amino-3-phenyl-hexenoic acid (**15c**).

Crystallographic data (excluding structure factors) for the structure **8** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 231756. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This research was supported by grants from the US Public Health Service DA 13449, DA 06284, and DK 17420. The DRX 500 MHz spectrometer was obtained by a grant from the NSF (9729350). This work was supported in part by a fellowship to J.Y. from Merck Research Laboratories.

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Tetrahedron 60 (2004) 8245–8256

Polylithiumorganic compounds. Part 29: C,C Bond cleavage of phenyl substituted and strained carbocycles using lithium metal☆

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Received 23 February 2004; revised 14 June 2004; accepted 16 June 2004

Available online 27 July 2004

Abstract—The reaction of phenyl substituted cyclopropanes phenylcyclopropane and 1,1-diphenylcyclopropane, phenyl substituted bicyclobutanes 1-phenylbicyclobutane, 1-methyl-3-phenylbicyclobutane, 1-methyl-2,2-diphenylbicyclobutane, as well as phenyl substituted spiropentanes phenylspiropentane and 1,1-diphenylspiropentane with lithium metal or lithium di-*t*-butylbiphenyl (LiDBB) was investigated. Under suitable reaction conditions and choice of solvent in all cases cleavage of the single bond next to the activating phenyl group was observed. The dilithiumorganic compounds thus obtained are sufficiently stable and can be trapped with electrophiles. Lithium hydride elimination is observed as follow-up reaction only in a few cases. The corresponding anions of the strained ring systems 1-lithio-2,2-diphenylcyclopropane, 1-lithio-3-phenylbicyclobutane, 1-lithio-3-methyl-2,2-diphenylbicyclobutane, and 1-lithio-4-phenylspiropentane, which can be obtained by lithium bromine exchange or by metalation of the unsubstituted carbocycle, do not show any cleavage upon reaction with lithium metal.

1. Introduction

The reaction of small ring carbocycles with lithium metal is a straightforward method for accessing dilithiumorganic compounds that means carbon-centred 1,ω-dilithioalkanes or 1,ω-dilithioalkenes are obtained upon ring cleavage. The reactions reported in the literature so far are summarized elsewhere.[2] However, these ring systems have to be activated by suitable functional groups, the unsubstituted hydrocarbons, that is, cyclopropane, cyclobutane, bicyclobutane,[3] or spiropentane do not react with lithium metal. As activating groups, exocyclic double bonds (like methylidene,[4] ethenylidene,[1] vinylidene,[1] vinyl[5] or phenyl substituents) or triple bonds[6] can be employed. Two different types of activation and subsequent mechanisms of cleavage can be distinguished in a simplifying way, when classifying the different substituents in α or β position.

(i) The activating group reacts with lithium metal and the cleavage of the carbocycle is a follow-up reaction. This stepwise reaction is observed, for example, in the reaction of phenyl cyclopropyl acetylene **1**, the primary addition product of lithium to the triple bond **2**, which is stable at temperatures below −30 °C, rearranges with cleavage of the ring and formation of **3** (Scheme 1).[7] Another typical example is the cleavage of methylenecyclopropane (**4a**) to the 1,3-dilithioalkene **6a**; here the intermediate addition product cannot be trapped. Investigations of this reaction with suitably substituted methylenecylopropanes (**4b** affords **6b**) demonstrate that the cleavage is not occurring on the level of the intermediate radical anion **7b**, which can be expected to form the more stable, that is, higher substituted radical anion **8b**.[8]

(ii) Another class of activating groups consists of substituents like the phenyl group, which ease the transfer of one electron into an energetically low-lying σ* orbital of the cyclic framework, usually by lowering the energy of the σ* orbital by conjugation. Here the electron is intermediately, if at all, transferred into a π* orbital of the substituent and then into the σ* orbital of the ring system. Addition of lithium metal to the phenyl substituent can be excluded, as the energy of activation would be much higher due to the loss of aromaticity. So, among a few examples, the reductive cleavage of propellane with lithium metal can be mentioned,[9] here, no activating substituent is necessary at all. Another example is the cleavage of substituted phenylcyclopropane with potassium in THF as the solvent, the primary reaction products, however, cannot be found as fast follow-up reactions occur with the solvent.[10]

☆For Part 28, see Ref. 1

Keywords: Carbanions; Cleavage reactions; Lithium; Small ring systems; Polylithiumorganic compounds.
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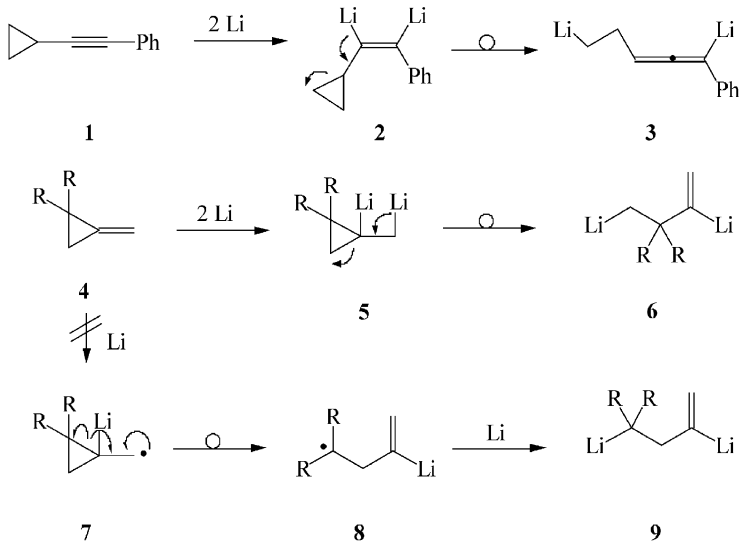
doi:10.1016/j.tet.2004.06.105

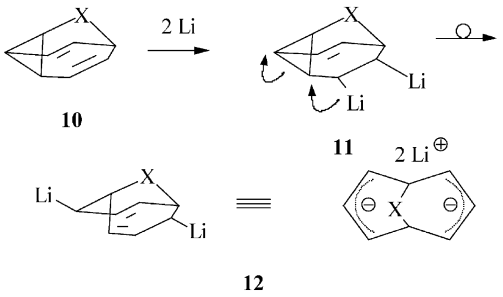


a) R = H, b) R = Me

Scheme 1.

The known reactions of semibullvalene (**10a**),[11] bullvalene (**10b**),[12] and barbaralane (**10c**)[13] belong to the first group mentioned above, the activating and in these cases endocyclic double bonds of the polycyclic rings can be anticipated as being the electron acceptor, leading in a subsequent cleavage of the intermediates **11a–c** to the bisallyl systems **12a–c**. These intermediates **11a–c** have been pictured in Scheme 2 as 1,2-dilithioalkanes, without detailed knowledge of the actual structure of the cleaving intermediates.

The reaction of a number of ring systems with lithium metal has not been examined systematically, here we present our results obtained in the reaction of phenylcyclopropane (**13**), 1,1-diphenylcyclopropane (**20**), 1-phenylbicyclobutane (**26**), 1-methyl-3-phenylbicyclobutane (**31**), 1-methyl-2,2-diphenylbicyclobutane (**36**), phenylspiropentane (**41a**), and 1,1-diphenylspiropentane (**41b**) with lithium metal. It is known that ethylene, as well as its monolithiated derivative vinyllithium, reacts with lithium metal,[14] thus the analogous reaction of the corresponding monolithiated ring systems with lithium metal were investigated as well in order to investigate the synthetic approach to higher lithiated derivatives.



a) X = - b) X = CH_2 c) X = CH=CH

Scheme 2.

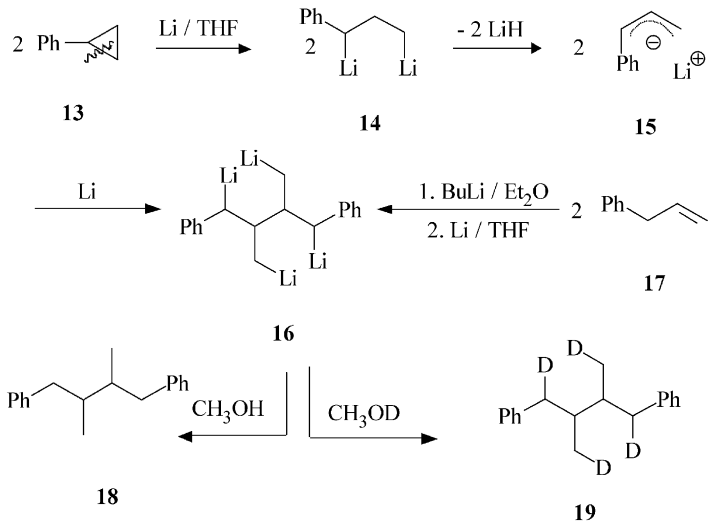
2. Results and discussion

The synthesis of the starting materials is described in Section 4. In all reactions highly reactive lithium dust[15] containing 2% sodium was employed. Due to the formation of polymeric material in the cleavage reactions, all reaction mixtures were purified by bulb-to-bulb distillation in order to isolate the derivatives of mono- and dimeric lithiation products, the nature of the polymeric material was not investigated.

2.1. Cleavage of substituted cyclopropanes with lithium metal

2.1.1. Cleavage of phenylcyclopropane (13). In order to bring about a reaction of phenylcyclopropane (**13**) with lithium, it is necessary to treat **13** with ultrasonication at 20 °C in THF with lithium. After hydrolysis, 2,3-dimethyl-1,4-diphenylbutane (**18**) is obtained as a mixture of *meso* and *d,l* isomers in up to 55% yield. Quenching with methanol-d_1 affords the corresponding tetradeuterated derivative **19**. The formation of **16** can be explained by assuming ring cleavage of phenylcyclopropane (**13**) to the dilithioalkane **14**, subsequent elimination of lithium hydride to cinnamyllithium **15** and dimerization induced by electron transfer (Scheme 3). This mechanism is proved by characterization of the isolated lithium hydride by powder diffraction. Furthermore, independent synthesis of **16** by metalation of allylbenzene (**17**) using *n*-butyllithium in diethyl ether followed by reaction with lithium metal in THF affords identical products. This type of dimerization induced by electron transfer is known and has been reported for the reaction of 1,3-diphenylallyllithium with potassium.[16] The above-mentioned cleavage of 1,2-dimethyl-3-phenylcyclopropane with potassium works the same way, however, the potassiumorganic compound is not stable in the solvent THF.[10]

2.1.2. Cleavage of 1,1-diphenylcyclopropane (20). 1,1-Diphenylcyclopropane (**20**) has a smaller ring strain



Scheme 3.

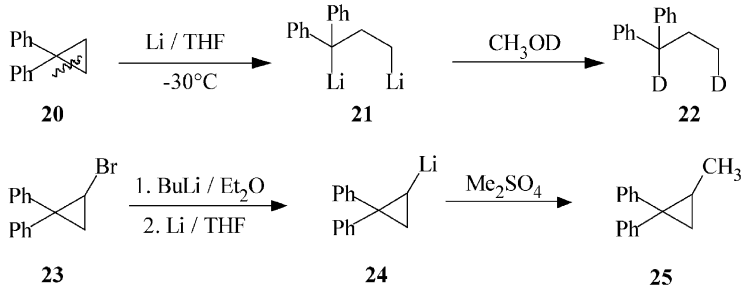
compared to phenylcyclopropane (**13**), and conjugation between the phenyl substituents and the ring is higher. **20** reacts easily within 5 h with lithium metal at −30 °C (at lower temperatures the turnover is not complete) in THF to 1,3-dilithiopropane **21** as a red-coloured solution, affording the corresponding hydrocarbons after quenching with methanol and methanol-d_1 respectively, in up to 88% yield (Scheme 4). Elimination of lithium hydride is not observed under the reaction conditions.

2.1.3. Attempted cleavage of 1-lithio-2,2-diphenylcyclopropane (24). The lithium derivative of **20**, that is, 1-lithio-2,2-diphenylcyclopropane (**24**), which is obtained by bromine lithium exchange of the bromide **24** with *n*-butyllithium in diethyl ether, shows no tendency to react with lithium metal even at rt and upon addition of THF to the reaction mixture. By derivatization with dimethyl sulfate the methyl derivative **25** is isolated in 74% yield. There is no evidence for any cleavage reaction. So the negative charge is deactivating the electron transfer in cyclopropanes in general, the reaction is not comparable to the reaction of vinyllithium, which reacts easily with lithium metal.[4]

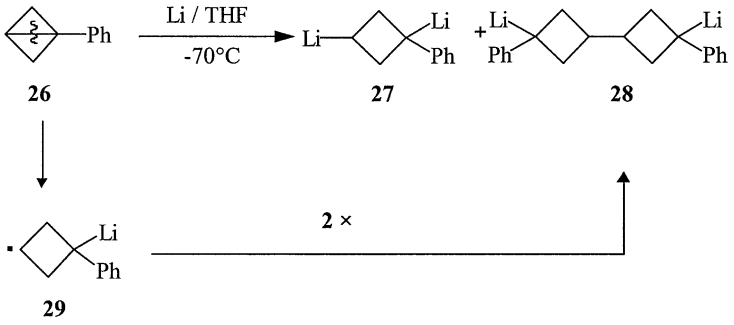
2.2. Cleavage of substituted bicyclobutanes with lithium metal

2.2.1. Cleavage of 1-phenylbicyclobutane (26). 26 reacts smoothly at −70 °C in THF with lithium with cleavage of the 0-bridge bond. Upon quenching with dimethyl sulfate besides polymeric material an isomeric mixture of monomeric (25%) and dimeric (20%) dimethyl derivatives are found, that is **27** and **28** (Me instead of Li). Furthermore 11% of the metalated starting material are evidenced by the formation of **31**, and a product of partial hydrolysis (1-methyl-1-phenylcyclobutane, 3%) can be identified. The formation of dimers via dimerization of the radical anion **29** is reasonably assumed, this type of head-to-head dimers is also found in radical induced polymerization of **26**,[17] furthermore it is known that neither *n*- nor *t*-butyllithium adds to 1-phenylbicyclobutane, so reaction of the even less nucleophilic **27** to the starting material can be excluded. Similar results are obtained upon quenching of the reaction mixture with either methanol or methanol-d_1, so after hydrolysis 14% of the cyclobutane derivative **27** (H instead of Li) are found and 26% of a mixture of isomers originating from **28**. Similarly, after deuterolysis, 31% of derivatives of **27** and 11% of derivatives of **28** are yielded (Scheme 5). In both reactions also minor amounts of products can be identified, which are formed by metalation of the starting material and reactions with the solvent THF, the details are given in Section 4.

2.2.2. Attempted cleavage of 1-lithio-3-phenylbicyclobutane (30). 30 is obtained by metalation of 1-phenylbicyclobutane (**26**) using *t*-butyllithium in THF at temperatures between −70 and −40 °C. Even with a fourfold excess of *n*-butyllithium in THF at higher temperatures (0 °C) this metalation is not complete. **30** is reacted with lithium di-*t*-butylbiphenyl (LiDBB) either at −70 or −20 °C. The



Scheme 4.

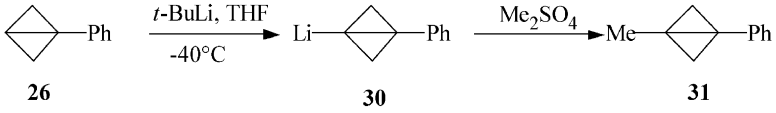


Scheme 5.

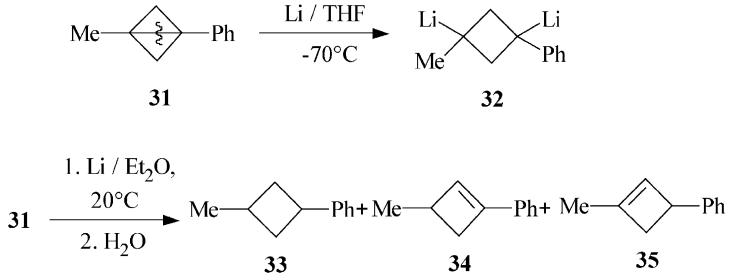
excess of LiDBB is destroyed by the addition of *t*-butyl chloride, however, after quenching with dimethyl sulfate, **31** is the sole product isolated, with 39 and 86% yield, respectively. No further reaction with lithium occurs (Scheme 6).

2.2.3. Cleavage of 1-methyl-3-phenylbicyclobutane (31). The reaction of **31** with lithium metal affords 1,3-dilithio-1-methyl-3-phenylcyclobutane (**32**) as a mixture of *cis*/*trans*-isomers under similar experimental conditions, which were used for **26** in THF as the solvent. The corresponding products obtained by derivatization with either methanol or methanol-d_1, which were obtained in a yield of about 70%, could not be separated on a preparative scale and were characterized as such. Upon quenching of the dilithiumorganic compound with dimethyl sulfate, besides products of partial hydrolysis the trimethylcyclobutane **32** (Me instead of Li) is obtained in 59% yield. The reaction takes the same course, which was observed for **26**, the 0-bridge bond is cleaved exclusively, however, due to the methyl substituent in position 1 dimerization of the intermediate radical anion is suppressed. At higher reaction temperatures using diethyl ether as the solvent the dilithiumorganic compound decomposes, the total yield is only 29%, besides this, elimination of lithium hydride occurs, which is evidenced by the formation of cyclobutenes **34** and **35** formed from the corresponding allyllithium system, which are found after hydrolysis. The details of the product composition are given in Section 4 (Scheme 7).

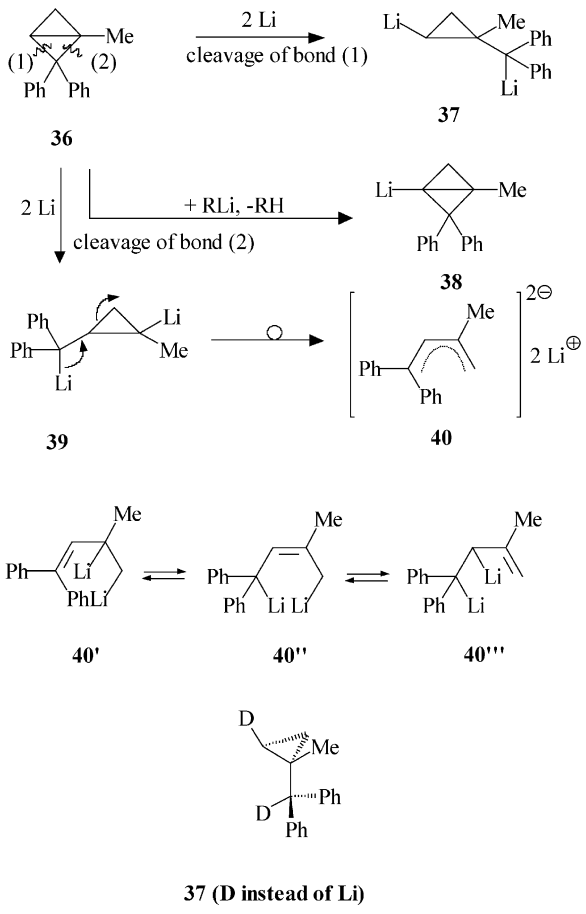
2.2.4. Cleavage of 1-methyl-2,2-diphenylbicyclobutane (36). The reaction of **36** with lithium metal is achieved at −70 °C in THF, in diethyl ether, even at rt no reaction occurs, neither can the reaction be brought about using LiDBB in THF at −60 °C. The products obtained after deuterolysis of the reaction mixture confirm the cleavage of the bicyclobutane ring with intermediate formation of a dilithiumorganic structure. Thus, the dideuterated cyclopropane **37** (D instead of Li) and the dideuterated diphenyl-2-butene **40″** (D instead of Li) are identified in a ratio of 1:1 and a yield of 33% each. The isolated 1-methyl-2,2-diphenylbicyclobutane (13%) shows incorporation of one deuterium equivalent, so **38** (D instead of Li) is formed by metalation of the starting material. Hydrolysis of the reaction mixture affords the same ratio of products, the cyclopropyl derivative **37** (H instead of Li), the benzhydryl derivative **40″** (H instead of Li) and **36** are identified in 32, 31 and 11%, respectively. When the reaction mixture is quenched with dimethyl sulfate, the composition of the crude product is more complex because products of partial hydrolysis are formed as well and complete separation cannot be achieved. The formation of the two different cleavage products **37** and **40** can be explained by reductive cleavage of one of the bonds next to the activating phenyl groups, bond (1) or bond (2), see Scheme 8. The methyl substituent in position 1 does not influence the ratio in a significant manner. The unsubstituted 1,1-diphenylcyclopropylmethyllithium is known to be stable in THF,[18] so the stability of the primary cleavage products, the cyclopropyl



Scheme 6.



Scheme 7.



Scheme 8.

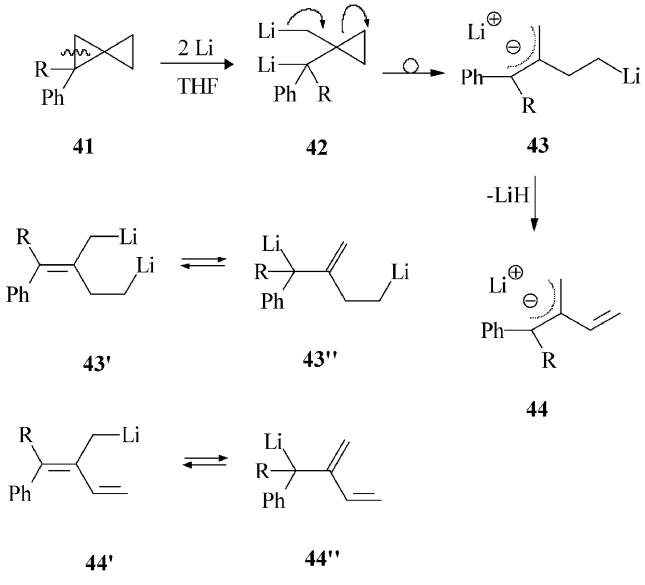
derivatives **37** and **39**, can be expected. Interestingly, no evidence for derivatives originating from **39** are found, it rearranges completely to **40**. An explanation for the instability of **39** is steric hindrance between the benzhydryl substituent and the cyclopropyl substituent, together with this effect less stabilization and thus a second cleavage of the cyclopropyl moiety is occurring.

According to NOE NMR experiments on **37** (D instead of Li) only *trans* configuration is evidenced, so together with cleavage of bond (1) inversion on the carbon center occurs, this type of isomerization is known and has been observed in the reaction of substituted phenylcyclopropanes with alkali metals before.[10]

2.2.5. Attempted cleavage of 1-lithio-3-methyl-2,2-diphenylbicyclobutane (38). Complete metalation of **36** is achieved using 3 equiv. of *t*-butyllithium at −40 °C in THF. A solution of **38** is brought to reaction with an excess of lithium metal with reaction temperatures up to 0 °C, however, after quenching with dimethyl sulfate the monomethyl derivative **38** (Me instead of Li) is isolated in 94% as the sole product. A similar result is obtained when additionally catalytic amounts of DBB are added to the reaction mixture and the LiDBB formed is destroyed with *t*-butyl chloride, here the same product is found in 99% yield. There is no evidence for any cleavage products of **38** in the reaction with lithium.

2.3. Cleavage of substituted spiropentanes with lithium metal

2.3.1. Cleavage of phenylspiropentane (41a). The reaction of **41a** with lithium is possible at temperatures of about −30 °C, using again THF as the solvent, upon quenching of the reaction mixture with dimethyl sulfate as main product 2-(1-phenylethyl)-1-pentene (**43a″**, Me instead of Li) is obtained in 48% yield, besides minor amounts of isomeric derivatives and unreacted starting material. Both rings of **41a** are broken during the course of the reaction. It can be assumed that the bond between the carbon atoms 1 and 2 is cleaved first, with formation of the cyclopropylmethylanion **42a**, which rearranges to the allyllithium derivative **43a** (Scheme 9). Cleavage of the bond between carbon atoms 1 and 3 is not observed in the kinetically controlled reaction. Depending on the type of reagent used for quenching, derivatives originating either from **43′** or **43″** are found in a ratio of about 4 to 1, upon hydrolysis and deuterolysis 74 and 70% deriving from **43a′** and 21 and 18% deriving from **43a″** are yielded, respectively. In the above described reaction of **41a** with dimethyl sulfate, the corresponding derivative of **43′** is formed only to a small extent, so identification is not possible in this case.

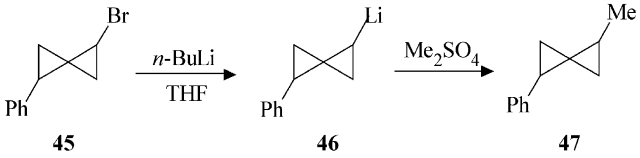


a: R = H, b: R = Ph

Scheme 9.

2.3.2. Cleavage of 1,1-diphenylspiropentane (41b). The reaction takes the same course when **41b** is reacted in THF with lithium metal, again temperatures of up to −30 °C are necessary. Upon hydrolysis and deuterolysis the two products deriving from **43′** and **43″** are found in a ratio of about 1 to 1 (34:34%, and 34:37%, respectively). Furthermore another follow-up product can be identified, **44b′** (H or D instead of Li) is formed by lithium hydride elimination, in 10 and 15%. Upon quenching of the reaction mixture with dimethyl sulfate the main product is **43b″** (Me instead of Li) in a yield of 71%. The product deriving from **43b′** is found only in 2% yield, lithium hydride elimination is occurring to about 5%.

2.3.3. Attempted cleavage of 1-lithio-4-phenylspiropentane (46). The lithium derivative of **41a**, that is, 1-lithio-4-phenylcyclopropane (**46**), which is obtained by bromine lithium exchange of the bromide **45** with *n*-butyllithium in THF, shows no tendency to react with lithium metal at temperatures between −30 and −10 °C, and the addition of catalytic amounts of DBB does not change the outcome of the reaction. After quenching with dimethyl sulfate 1-methyl-4-phenylspiropentane (**47**) is the major product isolated, in 93 and 80%, respectively. Only traces of products of hydrolysis are found, there is, however, no evidence for any cleavage reaction of **46** (Scheme 10).



Scheme 10.

3. Conclusions

For the strained carbocycles under investigation, the cyclopropanes **13** and **20**, the bicyclobutanes **26**, **31**, and **36**, and the spiropentanes **41a** and **41b**, in all cases reaction with lithium metal with cleavage of the bond next to the activating phenyl group is observed. Also, in all cases THF is the most suitable solvent, the dilithiumorganic compounds form red-coloured solutions. In the few cases where the less activating and stabilizing solvent diethyl ether can be used, higher reaction temperatures are required and follow-up reactions are observed. These follow-up reactions and other side reactions found in this investigation are of the general type known for di- and polylithiumorganic compounds,[2] that is elimination of lithium hydride, dimerization of the intermediate radical anion, rearrangement of cyclopropylmethyl anions or hydrolysis by reaction with the solvent or acidic protons of the starting material.

The ring strain reported for the different carbocycles cannot be used for the prediction of the reactivity towards lithium metal, for cyclopropane a value of 27 kcal/mol is given,[19] for bicyclobutanes a value of 64 kcal/mol is reported,[19] for spirobutane 63 kcal/mol.[20] For the diphenyl derivatives according to the Thorpe–Ingold effect less ring strain can be assumed.[21] All attempts to bring about the reaction of the lithiated strained carbocycles **24**, **30**, **38**, and **46**, with lithium metal—for 1-lithiobicyclobutane a value of 40.7 kcal/mol for the ring strain is given[22]—did not afford any cleavage products, even when using LiDBB in homogenous solution for this metalation.

The regioselectivity of the reaction of 1-methyl-2,2-diphenylbicyclobutane **36** with lithium metal and the different stability of the primarily formed cyclopropylmethyllithium derivatives **37** and **39** is very interesting, a better understanding of the effects responsible for the stability will require a more detailed investigation, for example of 2,2-diphenylbicyclobutanes with a different substitution pattern.

4. Experimental

4.1. General remarks

All reactions with air sensitive compounds were carried out under an atmosphere of dried argon (99.996%). Ethereal solvents were purified by adsorptive filtration over basic aluminium oxide (activity I) and freshly distilled under argon from sodium-benzophenone ketyl. Dimethyl sulfate was distilled in vacuo and stored over molecular sieve (3 Å). Electron impact (EI) mass spectra were obtained with an ionization energy of 70 eV using GC/MS coupling on a HP 5988A mass spectrometer (hp5 capillary); *m/z* values are reported followed by the relative intensity in parentheses. The 10 strongest peaks and, if not enclosed, the intensity of the molecular ion is given. Nuclear magnetic resonance (^{1}H, ^{2}H and ^{13}C) spectra were recorded on the Bruker instruments AM 400, AC 200, and WH 80. All NMR spectra were recorded in $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Coupling constants (*J*) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), m (multiplet), br. (broad signal). For separations of the reaction mixtures a preparative gas chromatograph (Hupe und Busch, HP 1075c prep. GC) was used. For analytical gas chromatography a HP 5890 with a SE30 column (25 m) and FID was used. Elemental analysis were performed by the Mikroanalytisches Labor, Beller (Göttingen). Melting points were recorded with a Thiele (Büchi SMP-20) melting point apparatus and are not corrected.

4.2. Starting materials

Phenylcyclopropane (**13**)[23] and 1,1-diphenylcyclopropane (**20**)[24] were obtained according to the given literature procedures, 1-bromo-2,2-diphenylcyclopropane (**23**) was synthesized from 1,1-dibromo-2,2-diphenylcyclopropane[25] by treatment with *n*-butyllithium in THF and subsequent hydrolysis analogous to Nozaki et al.[26] 1-Phenylbicyclobutane (**26**) was obtained in several steps from 3-phenylcyclobutanol[27] analogous to the procedure given by Jain et al.,[28] which was also used for the synthesis of 1-methyl-3-phenylbicyclobutane (**31**). 1-Methyl-2,2-diphenylbicyclobutane (**36**) was prepared as reported by Moore and Hill.[29]

4.2.1. Phenylspiropentane (41a)[30]. Contrary to the reference procedure,[30] 1,1-dibromo-4-phenylspiropentane could not be completely reduced to phenylspiropentane using zinc dust and hydrochloric acid, mixtures were obtained instead, therefore, the following two-step procedure was used.

1-Bromo-4-phenylspiropentane (**45**). To a solution of 145 g (0.48 mol) of 1,1-dibromo-4-phenylspiropentane[31] in a mixture of 540 mL of THF, 180 mL of diethyl ether, and 180 mL of pentane were added at −100 °C 330 mL of a 1.6 M solution of *n*-butyllithium in hexane (0.53 mol) while keeping the temperature of the mixture below −95 °C. After the addition was completed and an additional stirring of 15 min a solution of 40 mL of methanol in 160 mL of THF was added, again keeping the temperature of the reaction mixture below −100 °C. After warming to −20 °C

100 mL of aqueous ammonium chloride and 100 mL of water were added. After separation, the aqueous layer was extracted with three 150 mL portions of diethyl ether; the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuum. The remainder was subjected to fractional distillation to afford 86.1 g (0.39 mol, 80%) of **45** as a mixture of isomers (85:15), bp 64–80 °C (0.01 Torr). ^{1}H NMR (200 MHz) δ 1.23, 1.36, 1.48, 1.63 (4×m, 4H, H-2/H-4), 2.49 (m, 1H, H-5), 7.00–7.29 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 15.2 (C-2), 17.2 (C-4), 23.6 (C-5), 24.9 (C-1), 25.3 (C-3), 125.9 (C_{ar}-3), 126.4 (C_{ar}-4), 128.2 (C_{ar}-2), 140.9 (C_{ar}-1). MS of the first eluting isomer: *m/z* 143 (53), 141 (18), 128 (67), 116 (28), 115 (75), 51 (60), 50 (40), 39 (100), 38 (20), 27 (41). MS of the second isomer: *m/z* 143 (67), 141 (23), 128 (78), 116 (26), 115 (79), 104 (21), 51 (60), 50 (39), 39 (100), 27 (42). Calcd for $C_{11}H_{11}Br$ (M_r 223.11) C, 59.22%, H, 4.97%; found C, 59.70%, H, 4.95%.

To a solution of 20 g (90 mmol) of **45** in 200 mL of THF were added 200 mL of a 1.6 M solution (0.32 mol) of *n*-butyllithium in hexane at −30 °C. After 45 min at −20 °C 100 mL of a saturated solution of aqueous ammonium chloride and 300 mL of water were added; the aqueous layer was extracted with three portions of diethyl ether. The workup was performed as described above, two consecutive fractional distillations afforded 6.1 g (42 mmol, 47%) of 1-phenylspiropentane, bp 75 °C (12 Torr). The ^{1}H NMR data was in accordance with reference data.[30] ^{13}C NMR (50 MHz) δ 4.9 (C-2), 7.3 (C-1), 17.6 (C-4), 18.5 (C-3), 22.5 (C-5), 125.2 (C_{ar}-4), 126.1 (C_{ar}-3), 128.1 (C_{ar}-2), 143.2 (C_{ar}-1). MS *m/z* 144 (M^+, 6), 129 (100), 128 (33), 116 (34), 115 (90), 104 (24), 51 (65), 50 (40), 39 (93), 38 (20), 27 (39).

4.2.2. 1,1-Diphenylspiropentane (41b). 1-Bromo-1-methyl-2,2-diphenylcyclopropane. To a solution of 138 g (0.39 mol) of 1,1-dibromo-2,2-diphenylcyclopropane[25] and 116 g (0.82 mol) of methyl iodide in 1 l of THF at −90 °C were added 270 mL of a 1.6 M solution (0.43 mol) of *n*-butyllithium in hexane. After stirring for 45 min at this temperature the reaction mixture was allowed to warm to rt, then the workup was performed as usual by addition of 800 mL of diethyl ether and 200 mL of saturated aqueous ammonium chloride solution. After drying and evaporation of the solvent in vacuum the remainder was recrystallized from methanol to afford 99 g (0.35 mol, 88%) of the product with mp 79–80 °C. ^{1}H NMR (200 MHz) δ 1.70/1.96 (2×d, J=6.4 Hz, 2×1H, H-2), 1.74 (s, 3H, CH_3), 7.13–7.53 (m, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 29.0 (C-4), 29.3 (C-2), 40.8 (C-1), 42.3 (C-3), 126.6 (C_{ar}-4), 128.0/128.5 (2×C_{ar}-3/C_{ar}-4), 129.1/129.6 (C_{ar}-2), 141.8/144.2 (C_{ar}-1). MS *m/z* 208 (23), 207 (100), 206 (51), 191 (52), 178 (23), 165 (26), 129 (90), 128 (29), 91 (83), 89 (26). Calcd for $C_{16}H_{15}Br$ (M_r 287.20) C, 66.91%, H, 5.26%; found C, 67.10%, H, 5.48%.

1-Methylene-2,2-diphenylcyclopropane. A solution of 60 g (5.4 mol) of potassium-*t*-butoxide in 350 mL of dimethyl sulfoxide (DMSO) was added within 20 min to a solution of 97 g (0.34 mol) of 1-bromo-1-methyl-2,2-diphenylcyclopropane in 500 mL of DMSO while keeping the temperature below 25 °C. Then the mixture was stirred for 1 h at 38 °C. The excess of base was destroyed by the addition of ice, then 500 mL of water were added and the mixture was extracted with four 350 mL-portions of pentane. After drying over magnesium sulfate and evaporation of the solvent the remainder was subjected to fractional distillation to afford 63.0 g (0.31 mol, 90%) of the product, bp 91–105 °C (0.01 Torr). The ^{1}H NMR data were in accordance with literature values.[32] MS *m/z* 206 (M^+, 100), 205 (35), 203 (21), 202 (22), 191 (83), 189 (26), 128 (26), 101 (27), 91 (43), 89 (26).

1,1-Dibromo-4,4-diphenylspiropentane. 300 mL of a 50% aqueous sodium hydroxide solution (6.0 mol) were added with vigorous stirring to a solution of 44.5 g (0.22 mol) of 1-methylene-2,2-diphenylcyclopropane, 243 g (0.96 mol) of bromoform, 4 mL of ethanol and 0.8 g of triethylbenzylammonium chloride in 200 mL of dichloromethane (DCM). The mixture was then heated to reflux for another 4 h and stirred overnight. Then 200 mL of DCM were added, the organic layer was separated, the aqueous layer was diluted with 600 mL of water and extracted with three 150 mL-portions of DCM. The combined organic layers were washed with water and brine, the solvent evaporated in vacuum, finally at 40 °C under high vacuum (0.1 Torr). The remainder was extracted with three 800 mL-portions of hexane, which were filtered through alumina (basic, activity I). The hexane was distilled off, together with remaining starting material (8.4 g, 41 mmol). The remainder was crystallized twice from hexane to afford 30.6 g (81 mmol, 45%) of the product, mp 93–94 °C. ^{1}H NMR (200 MHz) δ 1.93–2.13 (m, 4H, H-2, H-4), 7.01–7.40 (m, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 27.6 (C-2), 28.9 (C-3), 29.7 (C-4), 38.8 (C-5), 40.4 (C-1), 125.9 (C_{ar}-4), 127.2 (C_{ar}-3, C_{ar}-4), 127.9 (C_{ar}-2), 128.6 (C_{ar}-3), 129.8 (C_{ar}-2), 140.7/141.1 (C_{ar}-1). MS *m/z* 218 (100), 217 (92), 215 (32), 203 (32), 202 (48), 192 (31), 191 (70), 165 (41), 108 (35), 91 (68). Calcd for $C_{17}H_{14}Br_2$ (M_r 378.11) C, 54.00%, H, 3.73%; found C, 53.92%, H, 3.61%.

1-Bromo-4,4-diphenylspiropentane. 56 mL of a 1.6 M solution (89 mmol) of *n*-butyllithium was added to a solution of 30.6 g (80 mmol) of 1,1-dibromo-4,4-diphenylspiropentane in 200 mL of THF and 90 mL of diethyl ether at −100 °C while keeping the temperature of the reaction mixture below −100 °C. After an additional 20 min at −100 °C was added a solution of 7 mL of methanol in 20 mL of THF. After warming to rt, the usual workup was performed by addition of saturated aqueous ammonium chloride, extraction with diethyl ether, washing of the combined organic layers with brine, drying over magnesium sulfate and evaporation of the solvent in vacuum. The remainder was dissolved in 80 mL of boiling ethanol from this solution the product crystallized at −20 °C as a 6:4 mixture of isomers in a yield of 18 g (60 mmol, 75%). One isomer could by obtained in pure form by recrystallization from ethanol with mp 105–106 °C and was characterized as follows. ^{1}H NMR (200 MHz) δ 1.32–1.52 (m, 2H, H-5), 1.88 (AB doublet, J=6.8 Hz, 2H, H-2), 3.56–3.70 (m, 1H, H-4), 7.04–7.43 (m, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 17.1 (C-2), 23.4 (C-5), 25.8 (C-4), 28.9 (C-3), 35.6 (C-1), 125.7/126.7 (C_{ar}-4), 127.4/130.0 (C_{ar}-2), 127.7/128.5 (C_{ar}-3), 141.8/142.1 (C_{ar}-1). MS *m/z* 219 (45), 204 (20), 203 (19), 202 (17), 191 (34), 178 (18), 165 (23), 141 (32), 115 (20), 91

(100). Calcd for $C_{17}H_{15}Br$ (M_r 299.21) C, 68.24%, H, 5.05%; found C, 68.15%, H, 5.28%.

1,1-Diphenylspiropentane (**41b**). To a solution of 13.9 g (47 mmol) of 1-bromo-4,4-diphenylspiropentane in 200 mL of THF were added at −40 °C 120 mL of a 1.6 M solution (190 mmol) of *n*-butyllithium in hexane. Then the reaction mixture was stirred for 45 min at this temperature, then at −70 °C were added 20 mL of methanol in 40 mL of THF. After the usual workup the solvent was evaporated and the product was obtained by bulb-to-bulb condensation under high vacuum to afford 3.9 g (18 mmol, 38%) of **41b** besides a large amount of polymeric material. ^{1}H NMR (200 MHz) δ 0.97–1.03 (m, 4H, H-4, H-5), 1.70 (s, 2H, H-2), 7.10–7.31 (m, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 7.0 (C-4, C-5), 24.7 (C-3), 24.9 (C-2), 33.0 (C-1), 125.7 (C_{ar}-4), 128.0 (C_{ar}-3), 128.4 (C_{ar}-2), 144.6 (C_{ar}-1). MS *m*/*z* 220 (M^+, 14), 205 (68), 192 (74), 191 (100), 189 (34), 174 (41), 165 (54), 129 (63), 128 (33), 115 (33), 91 (36). Calcd for $C_{17}H_{16}$ (M_r 220.13) C, 92.68%, H, 7.32%; found C 92.77%, H, 7.31%.

4.3. General procedure for the reaction of carbocycles with lithium and subsequent derivatization

If not stated otherwise, the carbocycles were added slowly as diluted solutions to a suspension of lithium dust in the solvent given, with vigorous magnetic stirring. A small amount of the starting material was added at a temperature slightly higher than the stated reaction temperature until the reaction started, which was usually noticeable by a coloration of the reaction mixture, which turned to a deep red solution during the addition of the educt. After filtration under inert gas conditions through a glass sinter frit, quenching of the reaction mixture was performed by addition of a solution of the electrophile as a solution in the solvent employed and the reaction mixture was allowed to warm to rt. In order to destroy the excess of dimethyl sulfate a concentrated solution of ammonia was added and the mixture stirred at rt overnight. The aqueous layer was extracted with diethyl ether, dried over sodium sulfate, and the solvents were evaporated using a rotary evaporator. When quenching was performed by either addition of methanol in THF or methanol-d_1 or deuterium oxide in THF, saturated aqueous ammonium chloride was added to the reaction mixture before extraction with diethyl ether. The crude reaction products were further purified by bulb-to-bulb condensation under high vacuum conditions (below 0.01 Torr). The condensate was analyzed by GC and GC/MS coupling affording the percentage composition assuming identical gas chromatographic response factors.

4.3.1. Reaction of phenylcyclopropane (13) with lithium metal. 2.0 g (17 mmol) of **13** and 0.60 g (90 mmol) of lithium were stirred for 12 h at rt in 25 mL of THF and another 14 h ultrasonication was applied. Quenching was performed by adding dropwise 7 mL of methanol at −70 °C. Then 20 mL of water were added, the workup was performed as described in the general procedure. After evaporation of the solvents the remainder was purified by bulb-to-bulb condensation to afford 0.90 g (3.8 mmol, 44%) of **18** as a diastomeric mixture (61:39). ^{1}H NMR data were in accordance with reported values.[33] MS of the first eluting isomer *m*/*z* 238 (M^+, 7), 147 (5), 146 (5), 131 (5), 105 (29), 92 (21), 91 (100), 65 (8), 41 (10), 39 (6). Second eluting isomer *m*/*z* 238 (M^+, 8), 147 (6), 146 (5), 131 (5), 105 (30), 92 (17), 91 (100), 65 (6), 41 (9), 39 (5).

In a second experiment 3.7 g (30 mmol) of **13** and 1.5 g (0.22 mol) of lithium afforded after quenching with 7 mL of deuterium oxide in 20 mL of THF 2.0 g (8.3 mmol, 55%) of **19** as a mixture of diasteromers (62:38). ^{2}H NMR (^{1}H decoupled) δ 0.93, 2.49, 2.74, 2.90. MS of the first eluting isomer *m*/*z* 242 (M^+, 8), 133 (6), 107 (14), 106 (26), 93 (32), 92 (100), 91 (26), 66 (6), 43 (6), 42 (6). MS of the second eluting isomer *m*/*z* 242 (M^+, 8), 150 (6), 149 (6), 107 (14), 106 (30), 93 (27), 92 (100), 91 836), 43 (7), 42 (6).

In the same way 15.0 g (0.13 mol) of **13** and 2.6 g (0.37 mmol) of lithium were treated in 100 mL of THF for 30 h with ultrasonication. The excess of lithium was separated by filtration through a G2 frit, the lithium hydride was then isolated by a second filtration through a G3 frit, washed with THF and dried in vacuo, and transferred into a suitable tube for characterization by X-ray powder diffraction. Another aliquot of the lithium hydride was quenched with trimethylsilyl chloride and the trimethylsilane was identified using GC/MS coupling.

4.3.2. Reaction of 1,1-diphenylcyclopropane (20) with lithium metal. 3.0 g (16 mmol) of **20** were brought to reaction with 1.0 g (0.11 mmol) of lithium in 35 mL of THF at −30 °C. The mixture was stirred for 5 h at −25 °C, then quenching was performed at −50 °C with methanol-d_1. After the usual workup the remainder was purified by bulb-to-bulb condensation to afford 2.8 g (88%) of **22**. ^{1}H NMR (200 MHz) δ 0.85 (t, ^3J=7.0 Hz, additional splitting of the signals due to $^2J_{H,D}$, 2H, CH_2D), 2.02 (br t, ^3J=7.0 Hz, 2H, CH_2), 7.18 (s, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 12.5 (equal intensity triplet, CH_2D), 28.4 (CH_2), 52.8 (equal intensity triplet, CD), 126.0 (C_{ar}-4), 127.9 (C_{ar}-3), 128.3 (C_{ar}-2), 145.1 (C_{ar}-1). MS *m*/*z* 198 (M^+, 11), 169 (13), 168 (100), 167 (13), 166 (32), 165 (9), 153 (17), 152 (8), 51 (12), 30 (7). The degree of deuteration was determined with ca. 96% d_2, 4% d_1.

Another reaction was performed on the same scale, quenching was performed with methanol to afford 2.4 g (12 mol, 76%) of **22** (H instead of D). ^{1}H NMR data were in accordance with literature values.[34] ^{13}C NMR (50 MHz) δ 12.8 (CH_3), 28.6 (CH_2), 53.2 (CH), 126.0 (C_{ar}-4), 127.9 (C_{ar}-3), 128.3 (C_{ar}-2), 145.1 (C_{ar}-1). MS *m*/*z* 196 (M^+, 12), 168 (13), 167 (100), 166 (13), 165 (36), 152 (23), 115 (10), 91 (8), 51 (12), 39 (9).

4.3.3. Reaction of 1-lithio-2,2-diphenylcyclopropane (24) with lithium metal. To a solution of 2.0 g (7.3 mmol) of 2-bromo-1,1-diphenylcyclopropane in 25 mL of diethyl ether were added at −40 °C 20 mL of a 1.6 M solution (32 mmol) of *n*-butyllithium in hexane. The reaction mixture was allowed to warm to rt and a 10 mL aliquot was quenched with dimethyl sulfate. The remaining solution of **24** was cooled to −40 °C and 0.60 g (86 mmol) of lithium were added, this solution was allowed to slowly warm to rt. As no noticeable reaction took place, 20 mL of THF were added at −20 °C and the mixture was ultrasonicated for 3 h at rt. Then quenching was performed

by addition of dimethyl sulfate. After the usual workup and bulb-to-bulb condensation the products were analyzed by GC/MS coupling. Total yield of **25** 0.90 g (4.3 mmol, 74%). ^{1}H NMR data were in accordance with literature values.[35] MS *m/z* 208 (M^+, 33), 193 (34), 179 (21), 178 (32), 165 (37), 130 (54), 129 (37), 115 (100), 91 (37), 51 (39).

4.3.4. Reaction of 1-phenylbicyclobutane (26) with lithium metal. 0.70 g (5.4 mmol) of **26** in 15 mL of THF were slowly dropped at −70 °C to a suspension of 0.40 g (60 mmol) of lithium in 10 mL of THF. After stirring for one hour at −60 to −70 °C, the mixture was filtered through a G3 glass sinter frit and 3.0 mL of dimethyl sulfate (32 mmol) in 15 mL of THF were added slowly at −90 °C. After the usual workup the crude product was purified by bulb-to-bulb condensation to afford 0.46 g (3.2 mmol, 59%). The main component *cis/trans*-**27** (Me instead of Li) (25%) was enriched by preparative gas chromatography as a mixture of isomers (8:1), ^{1}H NMR (200 MHz) δ 1.05 (d, ^3J=6.7 Hz, 3H, 3-CH_3), 1.45 (s, 3H, 1-CH_3), 1.80–2.00 (m, 2H, H-2$_{endo}$), 2.22–2.30 (m, 2H, H-2$_{exo}$), 2.35–2.70 (m, 1H, H-3), 7.10–7.30 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 22.0 (3-CH_3), 24.3 (1-CH_3), 30.7 (C-3), 42.0 (C-2), 42.6 (C-1), 124.7 (C_{ar}-3), 125.0 (C_{ar}-4), 128.0 (C_{ar}-2), 153.2 (C_{ar}-1). MS of the minor isomer *m/z* 160 (M^+, 5), 145 (7), 119 (9), 118 (100), 117 (41), 91 (7), 78 (9), 77 (7), 51 (3), 39 (3). MS of the major isomer *m/z* 160 (M^+, 3), 145 (6), 119 (9), 118 (100), 117 (42), 115 (6), 103 (13), 91 (8), 78 (11), 77 (9). Calcd for $C_{12}H_{16}$ (M_r 160.13) C, 89.94%, H, 10.06%; found C, 89.84%, H, 10.03%.

Furthermore the formation of the following structures was made plausible by mass spectrometry. 3,3′-Di(1-methyl-1-phenylcyclobutyl) (**28**, Me instead of Li) mixture of isomers with 10, 7 and 2% with identical mass spectra. MS *m/z* 290 (M^+, not observed), 157 (13), 143 (16), 130 (31), 129 (35), 128 (13), 119 (10), 118 (100), 117 (27), 115 (21), 91 (27). 1-Methyl-3-phenylbicyclobutane (**31**) (11%), the synthesis of an authentic sample is described below. MS *m/z* 144 (M^+, 23), 129 (100), 128 (77), 127 (22), 115 (19), 91 (15), 77 (19), 51 (19), 39 (13), 28 (14). 1-Methyl-1-phenylcyclobutane (3%). MS *m/z* 146 (M^+, 8), 131 (16), 118 (100), 117 (54), 115 (8), 103 (22), 91 (11), 78 (15), 77 (13), 28 (28).

The same reaction was performed starting with 0.60 g (4.6 mmol) of **26** and 0.20 g (30 mmol) of lithium, quenching was performed after filtration with 2.0 mL (45 mmol) of methanol-d_1 at −90 °C. After bulb-to-bulb condensation 0.30 g (50%) were obtained, the main product was purified by preparative gas chromatography. Side products were made plausible by their mass spectra.

cis/trans-1,3-Dideuterio-1-phenylcyclobutane (*cis/trans*-**27**, D instead of Li) (31%): ^{1}H NMR (200 MHz) δ 1.82/1.92 (2×m, $^2J_{HD}$=1.6 Hz, 2×0.5H, H-3), 2.12/2.31 (2×m, 2×2H, H-2), 7.10–7.30 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 17.9 (equal intensity triplet, C-3), 29.4 (C-2), 39.9 (equal intensity triplet, C-1), 125.6 (C_{ar}-4), 126.2 (C_{ar}-3), 128.1 (C_{ar}-2), 146.1 (C_{ar}-1). MS *m/z* 134 (M^+, 12), 145 (7), 106 (9), 105 (100), 104 (21), 79 (14), 78 (15), 52 (4), 51 (8), 50 (4), 29 (5). Degree of deuteration: 2% d_0, 5% d_1, 91% d_2, 2% d_3. 3,3′-Di(1-deuterio-1-phenylcyclobutyl): (**28**, D instead of Li) mixture of isomers with 9, 1, and ca. 0.5% with identical mass spectra. MS *m/z* 264 (M^+, 4), 159 (27), 144 (30), 131 (26), 130 (100), 129 (74), 128 (24), 115 (37), 105 (62), 104 (30), 91 (31).

The same reaction was performed starting with 0.70 g (5.4 mmol) of **26** and 90 mg (13 mmol) of lithium, quenching was performed after filtration with 2.0 mL (49 mmol) of methanol at −90 °C. After bulb-to-bulb condensation 0.32 g (45%) were obtained, the main product was purified by preparative gas chromatography. Side products were made plausible by their mass spectra, furthermore 2% of starting material was found. Phenylcyclobutane (**27**, H instead of Li) (14%) ^{1}H NMR (200 MHz) δ 1.80–2.39 (m, 6H, H-2, H-3), 3.54 (quint., ^3J=8.6 Hz, 1H, H-1), 7.12–7.33 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 18.2 (C-3), 29.7 (C-2), 40.3 (C-1), 125.6 (C_{ar}-4), 126.2 (C_{ar}-2), 146.2 (C_{ar}-1). MS *m/z* 132 (M^+, 15), 115 (4), 105 (10), 104 (100), 103 (20), 102 (3), 91 (6), 78 (14), 77 (9), 51 (5). 3,3′-Di(1-phenylcyclobutyl) (**28**, H instead of Li): mixture of isomers with 14, 8 and 4% with identical mass spectra. MS *m/z* 262 (M^+, 8), 158 (44), 142 (41), 130 (100), 129 (91), 128 (35), 115 (43), 104 (73), 103 (21), 91 (38). 4-(1′-Phenylcyclobutyl)-1-butanol (2%). MS *m/z* 204 (M^+, 2), 188 (9), 130 (17), 129 (5), 104 (15), 103 (4), 91 (4), 77 (7), 76 (8), 75 (100), 61 (5).

4.3.5. Reaction of 1-lithio-3-phenylbicyclobutane (30) with lithium metal. To 0.70 g (5.4 mmol) of **26** in 30 mL of THF were added at −70 °C 18 mL of a 1.5 M solution of *t*-butyllithium in pentane (27 mmol). The mixture was allowed to warm to −40 °C within 1 h, then at −70 °C a solution of 5.2 g (19 mmol) of LiDBB in 30 mL of THF was added, this mixture was warmed to −20 °C for 90 min. After cooling to −70 °C the excess of LiDBB was destroyed with *t*-butyl chloride and was then quenched with dimethyl sulfate to afford after the usual workup 0.67 g (4.7 mmol, 86%) of **31**.

4.3.6. Reaction of 1-methyl-3-phenylbicyclobutane (31) with lithium metal. 0.70 g (4.9 mmol) of **31** in 15 mL of THF were brought to reaction with 0.50 g (70 mmol) of lithium at −80 to −60 °C for 2 h. Then 2.0 g (0.16 mol) of dimethyl sulfate in 5 mL of THF at −80 °C were added and the excess of lithium was destroyed by the addition of isopropanol. After the usual workup and bulb-to-bulb condensation 0.50 g (2.9 mmol, 59%) of **32** (Me instead of Li) were isolated. Further purification of an analytical sample was achieved by preparative gas chromatography. ^{1}H NMR (200 MHz) δ 0.98/1.23/1.42 (3×s, 3×3H, 3×CH_3), 2.04/2.33 (2×AB system, ^2J=11.9 Hz, 2×2H, H-2), 7.13–7.31 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 28.3 (C-2), 31.0/31.1/34.6 (3×CH_3), 35.2 (C-1), 47.6 (C-2/4), 124.8 (C_{ar}-4), 125.3 (C_{ar}-3), 128.0 (C_{ar}-2), 153.1 (C_{ar}-1). MS *m/z* 174 (M^+, 5), 119 (10), 118 (100), 117 (40), 115 (8), 103 (14), 91 (9), 78 (11), 77 (11), 41 (6). Calcd for $C_{13}H_{18}$ (M_r 174.14): C, 89.59%,H, 10.41%; found C, 89.92%,H, 10.14%.

0.50 g (3.5 mmol) of **31** in 5 mL of THF were brought to reaction with 0.20 g (29 mmol) of lithium at −70 °C for 1.5 h. Then 4.0 mL (96 mmol) of methanol-d_1 were added and the workup was performed as usual. A 61:39 mixture of

isomers was obtained in about 70% yield. ^{1}H NMR (200 MHz) of the mixture: δ 1.08/1.22 (2×s, 3H, CH_3), 1.77/1.98 (2×m, 2H, H-2$_{endo}$), 2.33 (m, 2H, H-2$_{exo}$) 7.25 (m, 5H, aryl-H). ^{2}H NMR (^{1}H decoupled) of the mixture: δ 2.44/2.51 (2×s, D-1), 3.40/3.73 (2×s, D-3). ^{13}C NMR (50 MHz) δ 21.4/21.8 (CH_3), 25.5/26.3 (2× equal intensity triplet, C-1), 35.7/35.8 (2× equal intensity triplet, C-3), 35.6/37.5 (C-2), 125.48/125.53 (C_{ar}-4), 126.3 (2 overlapping signals, C_{ar}-3), 128.08/128.14 (C_{ar}-2), 146.1/146.5 (C_{ar}-1). MS of the first eluting isomer *m/z* 148 (M^+, 6), 106 (9), 105 (100), 104 (19), 103 (4), 92 (3), 79 (9), 78 (12), 77 (6), 51 (4). Degree of deuteration: 83% d_2, 12% d_1, 5% d_0. MS of the second eluting isomer *m/z* 148 (M^+, 6), 106 (10), 105 (100), 104 (16), 103 (4), 92 (3), 79 (10), 78 (11), 77 (6), 51 (4). Degree of deuteration: 77% d_2, 13% d_1, 10% d_0.

Starting from 0.40 g (58 mmol) of lithium and 0.60 g (4.2 mmol) of **31** and subsequent hydrolysis a 66:34 mixture of **33** was obtained in a yield of 67% determined by GC analysis using tetradecane as external standard. ^{1}H NMR (200 MHz) δ 1.08 (d, J=6.0 Hz) and 1.23 (d, J=6.6 Hz, 3H, CH_3), 1.45–2.90 (m, 5H, H-1, H-2), 2.90–3.95 (m, 1H, H-3), 7.22 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 21.6/21.9 (CH_3), 35.8/36.1 (C-3), 36.2/37.7 (C-2), 125.46/125.51 (C_{ar}-4), 126.31/126.33 (C_{ar}-3), 128.07/128.14 (C_{ar}-2), 146.1/146.5 (C_{ar}-1). MS of the first eluting isomer *m/z* 146 (M^+, 7), 105 (9), 104 (100), 103 (11), 91 (6), 78 (14), 77 (9), 65 (3) (5), 50 (3), 41 (3). MS of the second eluting isomer *m/z* 146 (M^+, 7), 118 (22), 117 (8), 105 (13), 104 (100), 103 (15), 91 (8), 78 (19), 77 (12), 39 (6).

0.30 g of lithium (43 mmol) and 0.60 g (4.2 mmol) of **31** were brought to reaction in 25 mL of diethyl ether at rt for 48 h, and quenched at −50 °C with 6.0 mL of methanol. After the usual workup the following structures were made plausible by their mass spectra using tetradecane as standard. *trans*- and *cis*-1-methyl-3-phenylcyclobutane (*cis*/*trans*-**33**) (13 and 4%). 3-Methyl-1-phenyl-1-cyclobutene (**34**) (10%). MS *m/z* 144 (M^+, 30), 143 (12), 130 (10), 129 (100), 128 (63), 127 (17), 115 (9), 51 (16), 50 (8), 39 (9). 1-Methyl-3-phenyl-1-cyclobutene (**35**) (1%). MS *m/z* 144 (M^+, 18), 130 (11), 129 (100), 128 (25), 115 (10), 104 (50), 103 (15), 78 (14), 51 (17), 39 (13).

4.3.7. Reaction of 1-methyl-2,2-diphenylbicyclobutane (36) with lithium metal. 2.0 g (9.1 mmol) of **36** in 20 mL of THF were added to 0.70 g (0.10 mol) of lithium at −80 °C. The deep red reaction mixture was allowed to warm to −50 °C within 1H, the excess of lithium was filtered off and 2.0 mL (50 mmol) of methanol in 10 mL of THF were added at −80 °C. After the usual workup, the mixture was analyzed by GC/MS coupling and NMR spectroscopy, besides 11% of starting material, the following compounds were found. 1-Benzhydryl-1-methylcyclopropane (**37**, H instead of Li) (31%): ^{1}H NMR (200 MHz) δ 0.38–0.49 (AA′BB′-system, 4H, cyclopropyl-H), 1.09 (s, 3H, CH_3), 3.81 (s, 1H, CH), 7.14–7.30 (m, 10H, aryl-H). MS *m/z* 222 (M^+, 5), 194 (63), 193 (23), 179 (36), 167 (100), 165 (57), 152 (28), 118 (46), 115 (25), 91 (20). 2-Methyl-4,4-diphenyl-2-butene (**40″**, H instead of Li) (32%): ^{1}H NMR (200 MHz) δ 1.71/1.78 (2×s, 2×3H, 2×CH_3), 4.88 (d, J=9.6 Hz, 1H, CH), 5.63 (d, J=9.6 Hz, 1H, =CH), 7.04–7.30 (m, 10H, aryl-H). MS *m/z* 222 (M^+, 65), 207 (76), 179 (25), 178 (27), 165 (39), 129 (100), 128 (31), 115 (20), 91 (51), 77 (16).

Another reaction was performed on the same scale, quenching was performed by addition of 2.0 mL (50 mmol) of methanol-d_1 after filtration of the reaction mixture, usual workup, and bulb-to-bulb condensation of the crude product. *trans*-2-Deuterio-1-(1-deuteriobenzhydryl)-1-methylcyclopro-pane (**37**, D instead of Li) (33%): ^{1}H NMR (200 MHz) δ 0.39–0.44 (m, 3H, cyclopropyl-H), 1.08 (s, 3H, CH_3), 7.10 (m, 10H, aryl-H). MS *m/z* 224 (M^+, 5), 195 (60), 194 (20), 180 (32), 179 (19), 168 (100), 166 (44), 153 (21), 118 (33), 116 (18). Degree of deuteration: 2% d_0, 26% d_1, 72% d_2. 3-Deuterio-1-methyl-2,2-diphenylbicyclobutane (**38**, D instead of Li) (13%). MS *m/z* 221 (M^+, 4), 182 (16), 181 (100), 180 (65), 179 (27), 166 (41), 165 (17), 120 (25), 119 (57), 118 (12), 116 (11). Degree of deuteration: 20% d_0, 80% d_1. (*Z*)-1,4-Dideuterio-3-methyl-1,1-diphenyl-2-butene (**40″**, D instead of Li) (33%): ^{1}H NMR (200 MHz) δ 1.68–1.71 (m, 2H, CH_2), 1.78 (s, 3H, CH_3), 5.62 (s, 1H, =CH), 7.03–7.30 (m, 10H, aryl-H). MS *m/z* 224 (M^+, 42), 195 (52), 180 (50), 179 (35), 168 (100), 166 (74), 165 (33), 129 (32), 118 (32), 92 (31). Degree of deuteration: 1% d_0, 18% d_1, 81% d_2.

Another reaction was performed on the same scale, quenching was performed by addition of 5.0 mL (50 mmol) of dimethyl sulfate after filtration of the reaction mixture, usual workup, and bulb-to-bulb condensation 1.8 g (80%) of crude product were obtained. The following structures were made plausible by GC/MS coupling. *trans*-1-(1,1-Diphenylethyl)-1,3-dimethylcyclopropane (**37**, Me instead of Li) (16%). MS *m/z* 250 (M^+, 2), 208 (100), 193 (69), 181 (75), 178 (27), 165 (35), 132 (83), 115 (30), 103 (41), 91 (35). 1,3-Dimethyl-2,2-diphenylbicyclobutane (**38**, Me instead of Li) (14%). MS *m/z* 234 (M^+, 17), 220 (17), 219 (100), 205 (14), 204 (60), 203 (29), 202 (20), 141 (13), 115 (19), 91 (13). The synthesis of an authentic sample is described below. (*Z*)-4-Methyl-2,2-diphenyl-3-hexene (**40″**, Me instead of Li) (32%). MS *m/z* 250 (M^+, 47), 221 (100), 178 (17), 143 (99), 129 (18), 128 (26), 115 (24), 105 (52), 91 (81), 77 (19). 2-Methyl-4,4-diphenyl-2-pentene (4%). MS *m/z* 236 (M^+, 59), 221 (61), 143 (100), 131 (26), 129 (20), 128 (37), 115 (27), 105 (38), 91 (86), 77 (26). 1-(1,1-Diphenylethyl)-1-methylcyclopropane (14%). MS *m/z* 236 (M^+, 2), 208 (70), 193 (48), 181 (33), 165 (28), 118 (100), 115 (27), 103 (37), 91 (34), 77 (25).

4.3.8. Reaction of 1-lithio-3-methyl-2,2-diphenylbicyclobutane (38) with lithium metal. To a solution of 4.2 g (19 mmol) of **36** in 60 mL of THF were added 35 mL of a 1.5 M solution of *t*-butyllithium in pentane at −70 to −40 °C within 1.5 h. To one half of this solution 1.3 g (0.19 mol) of lithium were added, then the mixture was allowed to warm to 0 °C and quenched with dimethyl sulfate after filtration of the excess of lithium. To the other half was added a mixture of 1.2 g (0.17 mol) of lithium and 0.50 g (1.9 mmol) of DBB. This mixture was allowed to warm to 0 °C within 1 h, the excess of lithium was filtered off, excess of LiDBB was destroyed by addition of *t*-butyl chloride, and then derivatization was performed with dimethyl sulfate in the usual way. In both reactions **38** (Me instead of Li) was isolated as the sole product as a white solid with mp

60–62 °C, recrystallized from ethanol. ^{1}H NMR (200 MHz) δ 0.70 (s, 1H, H-4$_{endo}$), 1.11 (s, 1H, H-4$_{exo}$), 1.58 (2×s, 2×3H, 2×CH$_3$), 7.13–7.26 (m, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 9.6 (CH_3), 17.3 (C-1/3), 34.1 (C-4), 60.5 (C-2), 125.8/125.9 (C$_{ar}$-4), 127.8/128.2 (C$_{ar}$-3), 129.4/129.8 (C$_{ar}$-2), 140.4/142.0 (C$_{ar}$-1). Calcd for $C_{18}H_{18}$ (M_r 234.34): C, 92.26%,H, 7.74%; found C, 92.07%,H, 7.90%.

4.3.9. Reaction of phenylspiropentane (41a) with lithium metal. To 0.80 g (0.11 mol) of lithium were added at −90 °C a solution of 1.9 g (13 mmol) of **41a** in 20 mL of THF. The mixture, when allowed to slowly warm up, turned red at −50 °C and was stirred at −30 °C for 2 h. After filtering off the excess of lithium metal, the reaction was quenched with 3.2 g (25 mmol) of dimethyl sulfate, excess of dimethyl sulfate was destroyed as usual with 20% aqueous ammonia solution and the remainder was purified after the usual workup by bulb-to-bulb condensation to afford 1.5 g (8.6 mmol, 66%) of crude product. The main component was isolated by distillation at 35–44 °C (0.01 Torr) and further purified by preparative gas chromatography. 2-(1-Phenylethyl)-1-pentene (**43a″**, Me instead of Li): ^{1}H NMR (200 MHz) δ 0.83 (t, J=7.3 Hz, 3H, 5-CH$_3$), 1.36 (d, J=7.1 Hz, 3H, CH–CH_3), 1.41 (m, 2H, 4-CH$_2$), 1.85 (t, J=8.4 Hz, 2H, 3-CH$_2$), 3.39 (q, J=7.1 Hz, 1H, CH), 4.89/4.93 (2×m, 2×1H, =CH$_2$), 7.21 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 13.9 (C-5), 20.8 (CH–CH$_3$), 21.8 (C-4), 37.2 (C-3), 45.3 (CH–CH$_3$), 108.6 (C-1), 126.1 (C$_{ar}$-4), 127.6 (C$_{ar}$-3), 128.6 (C$_{ar}$-2), 145.6 (C$_{ar}$-1), 153.1 (C-1). MS *m/z* 174 (M^+, 19), 131 (100), 117 (49), 115 (21), 105 (32), 91 (32), 77 (19), 41 (25), 39 (25), 27 (29). Calcd for $C_{13}H_{18}$ (M_r 174.14): C, 89.59%, H, 10.41%; found C, 89.60%, H, 10.40%.

Another reaction was performed on the same scale and quenched with 2.5 mL of methanol-d_1 in 10 mL of THF. After the usual workup 1.7 g (11 mmol, 88%) of crude product were obtained after bulb-to-bulb condensation, the two components were further purified by preparative gas chromatography. (*E*)-2-(Methyl-d_1)-1-phenyl-1-butene-4-d_1 (**43a′**, D instead of Li) (70%). ^{1}H NMR (200 MHz) δ 1.09 (tt, J=7.4 Hz, J_{HD}=2.0 Hz, 2H, 4-CH$_2$D), 1.84 (t, J_{HD}=1.7 Hz, 2H, 2-CH$_2$D), 1.41 (m, 2H, 4-CH$_2$), 2.18 (t, J=7.4 Hz, 2H, 3-CH$_2$), 7.16–7.34 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 12.4 (equal intensity triplet, 4-CH$_2$D), 17.4 (equal intensity triplet, 2-CH$_2$D), 33.3 (C-3), 123.5 (C-1), 125.7 (C$_{ar}$-4), 127.9 (C$_{ar}$-3), 128.8 (C$_{ar}$-2), 138.7 (C$_{ar}$-1), 140.7 (C-2). MS *m/z* 148 (M^+, 49), 133 (13), 132 (100), 130 (13), 118 (12), 117 (12), 116 (22), 115 (11), 92 (23), 91 (27). 2-(1-Deuteriobenzyl)-1-butene-4-d_1 (**43a″**, D instead of Li) (18%). ^{1}H NMR (200 MHz) δ 1.00 (tt, J=7.4 Hz, J_{HD}=2.0 Hz, 2H, 4-CH$_2$D), 1.97 (t, J=7.4 Hz, 2H, 3-CH$_2$), 3.32 (br s, 1H, CH), 4.73/4.82 (2×m, 2×1H, =CH$_2$), 7.14–7.33 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 11.9 (equal intensity triplet, 4-CH$_2$D), 28.1 (C-3), 42.9 (equal intensity triplet, CHD), 109.8 (C-1), 126.0 (C$_{ar}$-4), 127.2 (C$_{ar}$-3), 128.9 (C$_{ar}$-2), 139.9 (C$_{ar}$-1), 150.6 (C-2). MS *m/z* 148 (M^+, 32), 133 (11), 132 (21), 119 (11), 118 (100), 116 (21), 105 (14), 92 (44), 91 (12), 66 (9).

Another reaction was performed as described above, methanol was used instead for quenching. (*E*)-2-Methyl-1-phenyl-1-butene (**43a′**, H instead of Li) (74%): ^{1}H NMR (200 MHz) δ 1.11 (t, J=7.4 Hz, 3H, 4-CH$_3$), 1.86 (s, 3H, 2-CH$_3$), 2.16 (q, J=7.4 Hz, 2H, CH$_2$), 5.25 (s, 1H, =CH), 7.13–7.34 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 12.7 (C-4), 17.7 (2-CH$_3$), 33.4 (C-3), 123.5 (C-1), 125.7 (C$_{ar}$-4), 127.9 (C$_{ar}$-3), 128.8 (C$_{ar}$-2), 138.7 (C$_{ar}$-1), 140.8 (C-2). MS *m/z* 146 (M^+, 50), 132 (11), 131 (100), 129 (15), 128 (9), 117 (15), 116 (16), 115 (25), 91 (44), 65 (7). 2-Benzyl-1-butene (**43a″**, H instead of Li) (21%): ^{1}H NMR (200 MHz) δ 1.02 (t, J=7.4 Hz, 3H, CH$_3$), 1.97 (q, J=7.4 Hz, 2H, 3-CH$_2$), 3.34 (s, 2H, Ph-CH_2), 4.73/4.81 (2×m, 2×1H, =CH$_2$), 7.15–7.31 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 12.2 (C-4), 28.1 (C-3), 43.2 (Ph-CH$_2$), 109.8 (C-1), 125.9 (C$_{ar}$-4), 128.2 (C$_{ar}$-3), 128.9 (C$_{ar}$-2), 139.9 (C$_{ar}$-1), 150.7 (C-2). MS *m/z* 146 (M^+, 33), 131 (30), 129 (7), 118 (10), 117 (100), 115 (29), 104 (21), 91 (58), 65 (15), 39 (10).

4.3.10. Reaction of 1,1-diphenylspiropentane (41b) with lithium metal. 0.55 g (2.5 mmol) of **41b** in 15 mL of THF were added to 0.50 g (71 mmol) of lithium at −60 °C. After 1.5 h at −30 °C the excess of lithium was filtered off and the solution was quenched with 2.0 mL (20 mmol) of dimethyl sulfate in 5 mL of THF at −70 °C. After the usual workup and bulb-to-bulb condensation 0.50 g (2.0 mmol, 80%) of crude product were obtained. 2-(1,1-Diphenylethyl)-1-pentene (**43b″**, Me instead of Li) (71%) was characterized as follows: ^{1}H NMR (200 MHz) δ 0.83 (t, J=7.3 Hz, 3H, 5-CH$_3$), 1.41 (m, 2H, 4CH$_2$), 1.88 (s, 3H, Ph$_2$C–CH_3), 1.92 (t, J=7.6 Hz, 2H, 3-CH$_2$), 4.66/5.08 (2×br s, 2×1H, =CH$_2$), 7.14–7.31 (m, 10H, aryl-H). ^{13}C NMR (50 MHz) δ 14.2 (5-CH$_3$), 22.0 (C-4), 27.8 (Ph$_2$C–CH$_3$), 35.4 (C-3), 54.2 (Ph$_2$C), 112.2 (C-1), 125.8 (C$_{ar}$-4), 127.7 (C$_{ar}$-3), 128.5 (C$_{ar}$-2), 147.3 (C$_{ar}$-1), 155.5 (C-2). MS *m/z* 250 (M^+, 17), 207 (100), 181 (81), 166 (21), 165 (31), 129 (42), 115 (19), 103 (37), 91 (60), 77 (21). Calcd for $C_{19}H_{22}$ (M_r 250.17): C, 91.14%, H, 8.86%; found C, 90.98%, H, 8.81%. Furthermore the following structures were made plausible by their mass spectra. 2-Ethyl-1,1-diphenyl-1-pentene (**43b′**, Me instead of Li) (2%). MS *m/z* 250 (M^+, 12), 234 (51), 219 (54), 207 (16), 178 (18), 143 (26), 141 (19), 129 (25), 128 (19), 115 (33), 91 (100). 2-Ethyl-1,1-diphenyl-1,3-butadiene (**44b′**, Me instead of Li) (5%). MS *m/z* 234 (M^+, 84), 219 (18), 206 (30), 205 (100), 204 (26), 203 (35), 202 (28), 191 (18), 101 (16), 91 (38). 2-(1,1-Diphenylethyl)-1-butene (2%). MS *m/z* 236 (M^+, 18), 207 (100), 181 (66), 179 (17), 166 (17), 165 (27), 129 (36), 128 (16), 103 (36), 91 (48).

Two further reactions were performed in the same manner, starting with 0.55 g (2.5 mmol) of **41b** and 1.0 g (0.14 mol) of lithium. One reaction mixture was quenched with 2.0 mL of methanol to afford 0.43 g (1.9 mmol 78%) of crude product, the other with 2.0 mL of methanol-d_1 yielded 0.48 g (2.1 mmol, 86%) after bulb-to-bulb condensation. The following mass spectra were obtained. 2-Methyl-1,1-diphenyl-1-butene (**43b′**, H instead of Li) (34%). MS *m/z* 222 (M^+, 97), 207 (46), 193 (37), 179 (23), 178 (35), 165 (34), 129 (100), 128 (27), 115 (27), 91 (62). 2-Benzhydryl-1-butene (**43b″**, H instead of Li) (34%). MS *m/z* 222 (M^+, 56), 193 (100), 179 (26), 178 (22), 167 (64), 165 (60), 152 (27), 129 (20), 115 (61), 91 (28). 2-Methyl-1,1-diphenyl-1,3-butadiene (**44b′**, H instead of Li) (10%). MS *m/z* 220 (M^+, 100), 205 (98), 204 (26), 203 (34), 202 (30), 191 (42), 178 (17), 128 (16), 101 (23).

Upon deuterolysis the following compounds were obtained: 2-(methyl-d_1)-1,1-diphenyl-1-butene-4-d_1 (**43b′**, D instead of Li) (34%). MS *m/z* 224 (M^+, 100), 208 (46), 194 (36), 179 (25), 178 (29), 165 (31), 130 (92), 129 (29), 92 (23), 91 (40). Degree of deuteration: 86% d_2, 14% d_1. 2-(1-Deuteriobenzhydryl)-1-butene-4-d_1 (**43b″**, D instead of Li) (37%). MS *m/z* 224 (M^+, 55), 195 (17), 194 (100), 179 (30), 168 (66), 167 (17), 166 (48), 165 (19), 153 (22), 116 (46). Degree of deuteration: 93% d_2, 7% d_1. 2-(Methyl-d_1)-1,1-diphenyl-1,3-butadiene (**44b′**, D instead of Li) (15%). MS *m/z* 221 (M^+, 100), 206 (23), 205 (98), 204 (30), 203 (36), 202 (25), 192 (13), 191 (41), 101 (17). Degree of deuteration: 1% d_3, 2% d_2, 89% d_1, 8% d_0.

4.3.11. Reaction of 1-lithio-4-phenylspiropentane (46) with lithium metal. To a solution of 20 mL of *n*-butyllithium in hexane (1.6 M, 32 mmol) were added at −25 °C 3.3 g (15 mmol) of **45** in 25 mL of THF. After 1 h at −20 °C the solution was transferred into a Schlenk flask containing 0.80 g (0.12 mol) of lithium. After a reaction time of 3 h at −30 to −10 °C the mixture was quenched with 8.4 g (70 mmol) of dimethyl sulfate and the workup was performed as usual. Thereby 2.2 g (14 mmol, 93%) of 1-methyl-4-phenylspiropentane (**47**) were obtained as diastereomeric mixture. An analytical sample was further purified by preparative gas chromatography. ^{1}H NMR (200 MHz) δ 0.36/0.54 (2×m, 2×1H, 2-H), 0.88 (m, 1H, 1-H), 1.06 (d, J=8.2 Hz, 3H, CH_3), 1.06 (d, J=6.7 Hz, 3H, CH_3), 1.20/1.44 (2×m, 2×2H, H-5), 2.17 (m, 1H, H-4), 7.20 (m, 5H, aryl-H). ^{13}C NMR (50 MHz) δ 12.1/12.3 (CH_3), 13.0/13.3 (C-2), 15.3/16.7 (C-1), 16.9/18.0 (C-3), 20.1/22.7 (C-5), 25.0/25.1 (C-4), 125.1/126.0 (C_{ar}-4), 126.2 (C_{ar}-3), 128.0 (C_{ar}-2), 143.3 (C_{ar}-1). MS of the first eluting isomer *m/z* 158 (M^+, 2), 143 (76), 129 (71), 128 (46), 116 (45), 115 (100), 104 (40), 51 (35), 50 (16), 39 (51). MS of the second eluting isomer *m/z* 158 (M^+, 3), 143 (67), 129 (52), 128 (38), 116 (40), 115 (100), 104 (56), 51 (40), 50 (18), 39 (58). Calcd for $C_{12}H_{14}$ (M_r 158.11): C, 91.08%, H, 8.92%; found C, 91.13%, H, 9.03%. When adding LiDBB instead of lithium metal in the reaction described above, again 1-methyl-4-phenylspiropentane was the sole product (80%).

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1,3,5-Triaryl-2-penten-1,5-dione anchored to insoluble supports as heterogeneous chromogenic chemosensor

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Received 5 February 2004; revised 4 June 2004; accepted 16 June 2004

Available online 21 July 2004

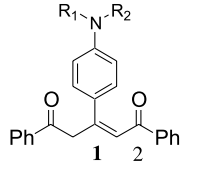
Abstract—*N*-Allyl substituted 1,5-diphenyl-3-(4-*N*-methylaminophenyl)-2-penten-1,5-dione (**1a**) has been immobilized on a polystyrene backbone, on the surface of mercaptopropyl-functionalized silica or inside the cavities of zeolite NaY. These solids either in suspension or in films act as chemosensors of Fe^{3+} and other strong Lewis acid metal ions such as Cu^{2+} and Pb^{2+} in buffered water or ethanol. Brönsted acids in low pH aqueous solutions also produce the response of the sensor. For sensing of Fe^{3+}, depending on the loading of **1a** (typically from 2.5 to 0.5 wt%) the solids can test from 10^{-2} to 10^{-4} M aqueous solutions. The time response can vary from tens of minutes to below a minute depending on hydrophilic/hydrophobic nature of the support and also on the **1a** loading. The solid sensor was reused up to 10 times by regenerating after every use the initial form with NaAcO treatment.

1. Introduction

A strategy to convert a soluble chemosensor into a heterogeneous sensing system could be anchoring covalently an appropriate derivative of the sensor molecule onto an insoluble support.[1,2] Analogous approach is commonly used in heterogeneous catalysis to immobilize active homogeneous catalysts.[3–5] Immobilization of the sensor allows to design systems for automatic continuous sensing. For this purpose organic polymers or inorganic oxides have been frequently used.[6,7] In contrasts, no much attention has been paid to the use of inorganic oxides as supports in spite that they offer the advantage of a large surface area and the possibility to have structured particles with micro- or mesoporosity, while organic polymers have an easy processability.[3,5,8,9]

When anchoring a sensor molecule onto a solid support some new factors, different from homogeneous sensing that require to be properly addressed, may arise influencing the performance of the sensor in solution. Most of differences between solution and surface-anchored sensor may derive from the interaction of the sensor with the solid surface. This interaction could play an unfavourable role reducing the affinity between the sensor and the analyte and leading to a reduced sensitivity of the anchored chemosensor. Also the accessibility of the sensor to the analyte may be reduced when the molecule is immobilized on the internal pores of a porous particle. All these factors may lead to a decrease on the sensitivity, increasing the detection threshold and the response time. These changes are negative in the use of the solids as sensors. On the other hand, reversibility and reusability is another issue of considerable importance for solids sensors that are never considered in solution.

Recently there has been a large interest in the use of 2-penten-1,5-dione derivatives of the type **1** as colorimetric sensors for a series of cations,[10] anions[2] and diacids.[10] Given the insolubility of these molecules in water, most of the analytic tests have been performed in organic solvents such as CH_2Cl_2, or water/organic solvent mixtures what may constitute a limitation of the homogeneous phase sensing methodology.



1 **2**

a: R_1=CH_3; R_2= CH_2-CH=CH_2

Keywords: Chemosensors; Pyrylium dye; Covalent functionalization.
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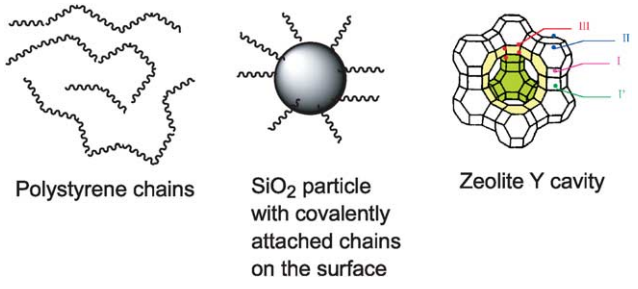
doi:10.1016/j.tet.2004.06.090

Given the generality of these pentendiones **1** as sensors and in order to develop a sensitive device for continuous operation, it would be of interest to support this molecule type on a series of solid supports and determine the ability of the resulting solids to respond as insoluble chemosensors. Herein we describe our results on the covalent anchoring of pentendione derivative, **1a**, on three insoluble supports. We will show our results towards the development of convenient solid chemosensors based on cyclizable pentendione, as well as limitations in response time, sensitivity and reusability and some ways to circumvent or minimize these general problems encountered in heterogeneous sensors.

2. Results and discussion

2.1. Synthesis of the solid chemosensors

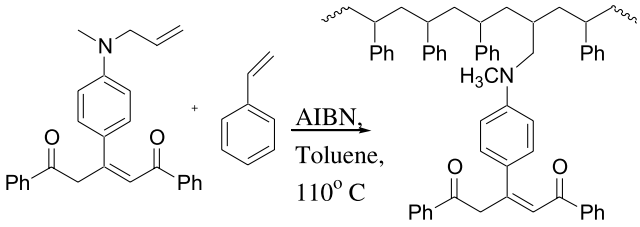
Among the solid supports selected, we tried to cover organic and inorganic supports. One of these supports is a polystyrene backbone to which some pentendione molecules **1a** were introduced during the polymerization step. The advantage of this polymer is that while it is insoluble in water, it can be dissolved in hot toluene so films of this polystyrene-bound sensor (**1a-PS**) can be cast on appropriate substrates. The other two supports are inorganic oxides namely silica and zeolite Y. In the case of the silica the pentendione **1a** can be bonded to the external surface of the amorphous particles (**1a-SiO$_2$**). In contrast NaY zeolite has a crystalline structure containing almost spherical cavities of 13 Å of diameter interconnected tetrahedrally through 12 oxygen ring windows of 7.4 Å in which the pentendione **1a** can be accommodated and immobilized inside the solid (**1a@NaY**). Scheme 1 shows the structure of the zeolite used in this work.



Scheme 1. Pictorial representation of the three supports on which compound **1a** has been immobilized.

To immobilize covalently the sensor to the solids we followed a flexible strategy based on the use of a common pentendione derivative containing an allylic functionality attached to the *N*-atom (**1a**). This compound was obtained by reacting *N*-methyl-*N*-allylaniline with 2,6-diphenylpyrylium ion followed by the opening of the heterocyclic ring. Scheme 2 indicates the reaction sequence followed to prepare the *N*-allyl functionalized pentendione **1a**.

The anchoring of this intermediate on a polystyrene backbone was simply accomplished through AIBN-initiated radical co-polymerization of **1a** and styrene (Scheme 3). The ratio styrene/**1a** was purposely high, so the polymer contains approximately between 0.5 and 2 wt% of chemosensor depending on the **1a** content used in the polymerization. The resulting **1a-PS** polymer is soluble in hot toluene, but insoluble in water and alcohols.

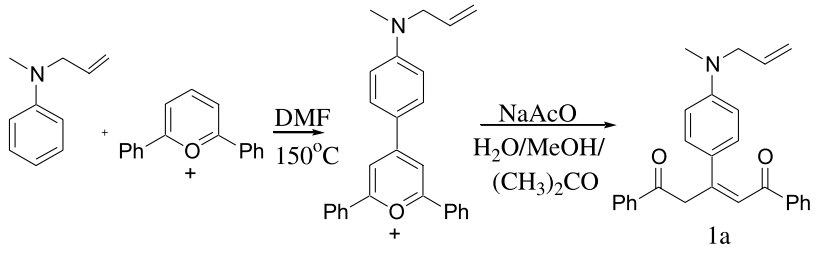


Scheme 3. Co-polymerization of compound **1a** and styrene to form **1a-PS**.

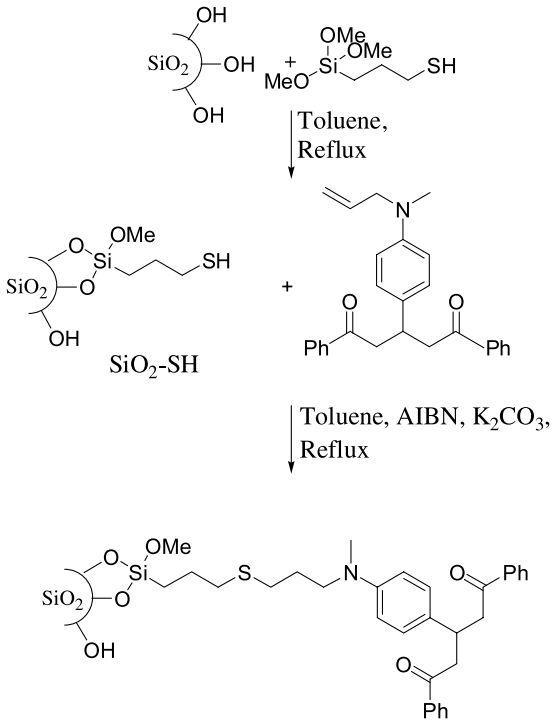
In the case of covalent anchoring of the allyl derivative **1a** on silica we followed a route consisting on the prior modification of the silica by introducing terminal mercapto groups by silylation of the silanol groups. The silica was modified by reaction with 3-mercaptopropyltrimethoxysilane in toluene. Scheme 4 shows the procedure used to anchor the chemosensor **1a** onto the functionalized silica.

Subsequently, modified silica support containing terminal mercapto group (**SiO$_2$-SH**) was reacted with the *N*-allyl-*N*-methyl derivative of pentendione **1a**, which undergoes a radical-chain thiol addition using AIBN as radical initiator as shown in Scheme 4.

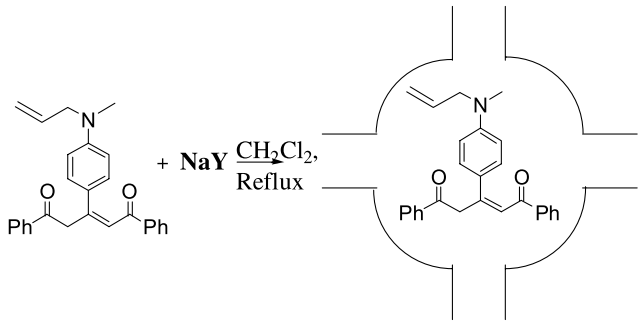
For the solid sensor in which pentendione **1a** is mechanically immobilized (as opposed to covalent anchoring) inside the cavities of porous NaY zeolite (**1a@NaY**), the *N*-allyl group does not play any role but derivative **1a** was also used for sake of synthetic economy. The major factor contributing to support the chemosensor within NaY is the high adsorption capacity of zeolites to include an organic guest in the micropore volume (Scheme 5).



Scheme 2. Synthetic route for the preparation of **1a**.



Scheme 4. Preparation procedure of sensor **1a**-SiO_2.

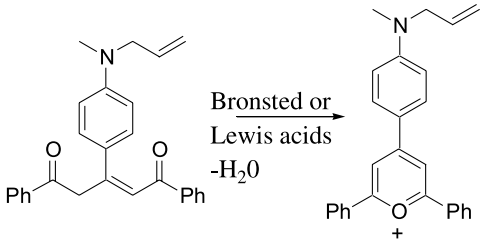


Scheme 5. Adsorption of compound **1a** into the cages of zeolite NaY to form **1a@NaY**.

Encapsulation of 1,3,5-triphenyl-2-penten-1,5-dione, analogous to the substrate **1a** used here, has been successfully achieved by Miranda, Braun et al. through a novel encapsulation strategy.[11] They reported that 2,4,6-triphenylpyrylium ion in water was completely adsorbed in zeolite NaY up to a loading of 25% in weight through the open 1,3,5-triphenyl-2-pentendione. In our case the pentendione **1a** was simply adsorbed into dehydrated NaY zeolite by stirring a suspension of the solid and the organic compound in dichloromethane at reflux temperature.

2.2. Characterization of the solid sensors

All the solids have common spectroscopic features arising from the presence of pentendione **1a**. Optical spectroscopy is particularly relevant since the colorimetric sensing relies on changes in the visible optical spectrum. Depending on whether the sensor can be dissolved (**1a-PS**) or is an insoluble opaque powder (**1a-SiO_2** or **1a@NaY**), transmission or diffuse reflectance modes were used to record the optical spectrum. In addition of the interest in optical spectroscopy to characterize spectrophotometrically the visual changes occurring during the sensing, UV/Vis spectroscopy served also to assess the absence or presence of some pyrylium ion **2a** formed spontaneously during manipulation of **1a** in the anchoring procedure according to Eq. (1). This is the reverse of the heterocycle opening shown in Scheme 1.



(1)

In UV spectroscopy the presence of the heterocyclic pyrylium ion can easily be revealed. This characterization

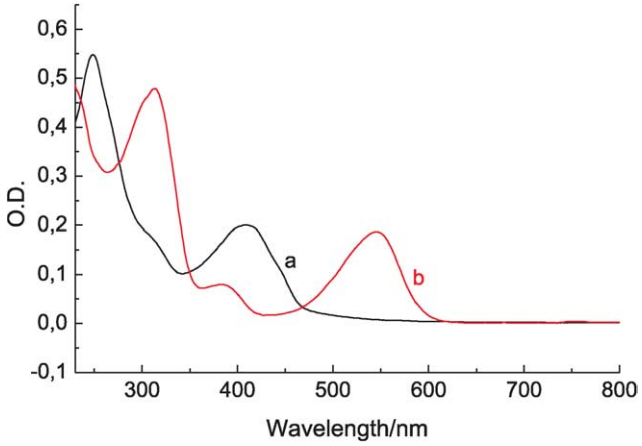


Figure 1. Transmission optical spectrum of pentendione **1a** (spectrum a) and pyrylium ion **2a** (spectrum b) recorded for 10^{-4} M solution in dichloromethane.

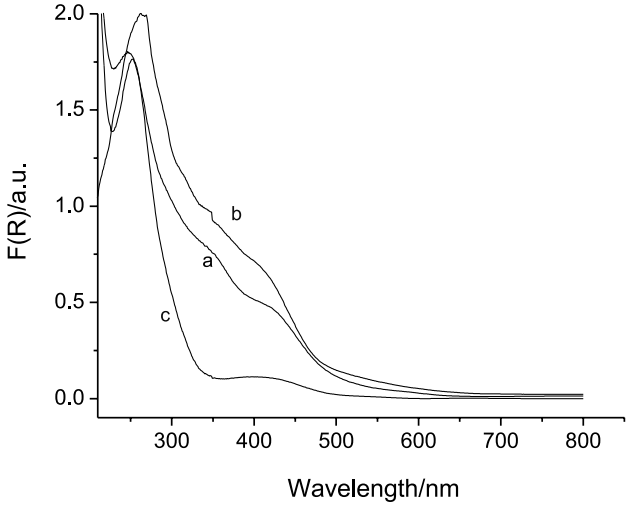


Figure 2. Diffuse reflectance UV/Vis spectra (plotted as the Kubelka–Munk function of the reflectance, F(R)) of **1a** covalently bonded to silica (spectrum a) and polystyrene (spectrum b) or absorbed on NaY (spectrum c).

of **2a** is based on the presence, or absence, of a specific peak, at $\lambda_{max}=560$ nm, that is responsible for the intense red color of the closed heterocyclic cation **2a**. This band is absent in the pentendione **1a**, that presents a yellow color and has characteristic absorption band at 410 nm. Figure 1 shows the UV/Vis spectra of the pentendione **1a** and pyrylium **2a** ion recorded in dichloromethane solution, while Figure 2 shows some spectra recorded for the solids containing pentendione **1a**.

Figure 2 establishes the absence of the band at 560 nm, indicating that the immobilization procedure has not produced the cyclization of the pentendione **1a**. This is also in agreement with the visual yellow color of all the supports after the immobilization procedure. The presence or absence of this band due to pyrylium ion **2a** will become more relevant later when discussing the chemosensing properties of these solids and the possibility of successful regeneration upon reuse. In some cases, for inorganic supports SiO_2 and NaY, we observed an extensive cyclization during the anchoring or the adsorption procedure as evidenced by the red color of the substrate and by the appearance of the pyrylium band in the visible region. According to Eq. (1) we believe that pyrylium **2a** arises from the acid catalysed cyclization of **1a** during the adsorption. To avoid or minimize the presence of acid sites on the inorganic supports, these solids were neutralized by contacting them with basic solutions.

IR spectroscopy is also a very convenient technique to distinguish between the pentendione **1a** and the pyrylium ion **2a**. While the former shows three bands at 1676, and 1642 cm^{-1} corresponding to the vibration of the carbonyl groups and the C=C double bond present in the dione, the most remarkable spectral feature of the pyrylium ion **2a** is the absence of these bands and the presence of a very intense peak at 1588 and 1573 cm^{-1} corresponding to the stretching mode of the $C{=}O^+$ bond present in the pyrylium ring. Figure 3 shows the IR of the two compounds.

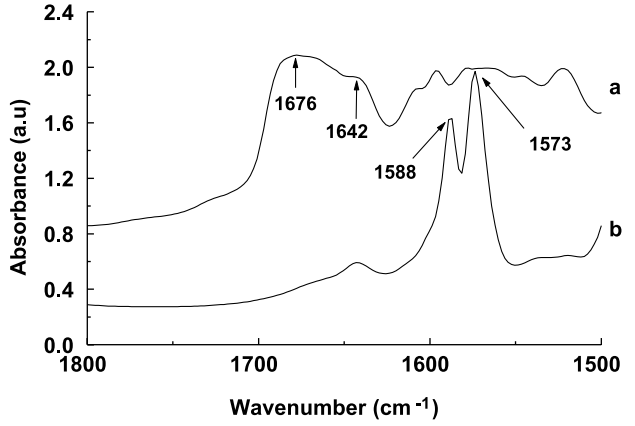


Figure 3. Carbonyl and aromatic region of the FT-IR spectra of compounds **1a** (a) and **2a** (b) recorded at room temperature on silicon wafers.

Previously we have reported[12] that the parent 2,4,6-triphenylpyrylium ion has an intense $C{=}O^+$ band at 1620 cm^{-1} and the large shift (about 30 cm^{-1}) observed for the *N*,*N*-dialkyl derivative **2a** can be attributed to the electron donor effect of the nitrogen atom being conjugated with the electron deficient pyrylium ring. In the case of the solid sensors the predominant absorption bands are obviously due to the polymeric or to the inorganic supports, but sufficient expansion of the carbonyl and aromatic region allows to detect weak broad bands that are attributable to the low amounts of the pentendione **1a** anchored to the support.

2.3. Use of solid sensors

As aspected in view of the behaviour of pentendione **1a** reported in solution,[1,2] all the solids change the color from yellow to red upon contacting with 10^{-2} M aqueous solutions of $Fe(NO_3)_3$, $Cu(NO_3)_2$ or $Pb(NO_3)_2$. In contrast, aqueous solutions of Al^{3+}, Mg^{2+} and Ca^{2+} or anions (Br^-, HPO_4^{2-}) did not give a positive test at this concentration. In accordance to Eq. (1), it is expected that the heterogeneous sensor systems based on the interconversion of **1a** to **2a** would respond to any Lewis acid cations with sufficient strength to provoke the cyclization of the pentendione through coordination with the N atom in the *para* position of the 4-aryl ring. In principle this cyclization can also be carried out by Bronsted acids and in fact aqueous solutions of HNO_3 (pH=1) are also able to produce the response of the solid sensors. For this reason, most of the experiments in aqueous media were carried out in buffered solution at pH=5 using HEPES. At this pH a blank control showed that cyclization of **1a** to **2a** does not occur for reasonable long periods of time.

Besides experiments in suspension performed stirring a solution of Lewis acid cations and the solid sensor, an alternative way of performing the tests was to place the solids as thin films on an inert substrate. For this set-up we covered a glass slide with a thin layer of each of the three water-insoluble solid sensors and assays were carried out by simply dropping a few microliters of the solutions of different cations on the sensor-covered glass.

Upon addition of aqueous solution of Fe^{3+} (pH=5) the change in the color was progressive in time. In the case of silica and zeolite Y at the lowest loading of **1a** employed (5 mg per g of support) the red coloration was evident in a few minutes and became complete after 30 min. According

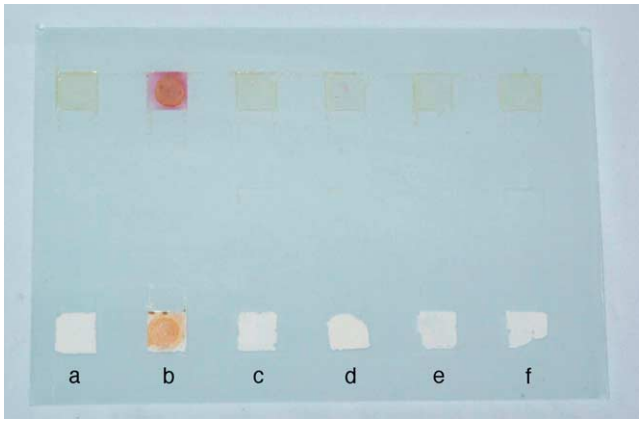


Figure 4. Photograph of a glass plate in which films of **1a-PS** (upper row) and **1a@NaY** (lower row) have been placed as squares. The image was recorded 1 h after dropping 50 μl of distilled water (a) or 10^{-2} M aqueous solution of: Fe^{3+} (b); Mg^{2+} (c); Al^{3+} (d); Br^- (e); HPO_4^- (f).

to the more hydrophobic nature of polystyrene backbone, when pentadione **1a** was covalently anchored on polystyrene the response of **1a-PS** was even significantly slower, the red color developing over 1 h and becoming complete in 5–6 h. Figure 4 shows a photograph of the sensing experiments in which the differences between positive or negative responses can be seen for some analytes.

In fact one of the major problems of the solid supports is the contact time required to observe the response. Obviously, in contrast to the solids sensors, for solution experiments the change in the color is almost instantaneous. As commented above this contact time depends on the hydrophilicity/hydrophobicity of the support. In this regard, the response time of **1a-PS** is dramatically reduced from hours up to less than 1 min when $Fe(NO_3)_3$ is dissolved in ethanol instead of water. Notably for these ethanolic solutions the response of **1a@NaY** requires longer time than for **1a-PS**. We also observed that the response time becomes shorter when solids sensors with more than 0.5 wt% contents of **1a** are used. Also the intensity of the color increase with loading of **1a**. Thus, by controlling the loading of **1a** on the solid one can on one hand shorten the response time and on the other to decrease the detection threshold of the film. The problem of using solids with high **1a** loading is the reusability as it will be commented above.

It was of interest to determine by optical spectroscopy whether or not the change in the color is accompanied by a partial chemical conversion between the pentendione and the pyrylium form as indicated in Eq. (1) in agreement with the chemosensing operation of the sensing system. We took the absorption bands at 440 and 550 nm as specific of the open form **1a** and heterocyclic form **2a** of the sensor system, respectively. We found that the red color, characteristic of the visual positive test as shown in Figure 4, corresponds to a true chemical change from **1a** to **2a**. Figure 5 shows a UV/Vis spectrum 30 min after addition of 10^{-2} M solution of $Fe(NO_3)_3$ in which the band at 550 nm is observed. This support the chemical interconversion between the open and the cyclic form.

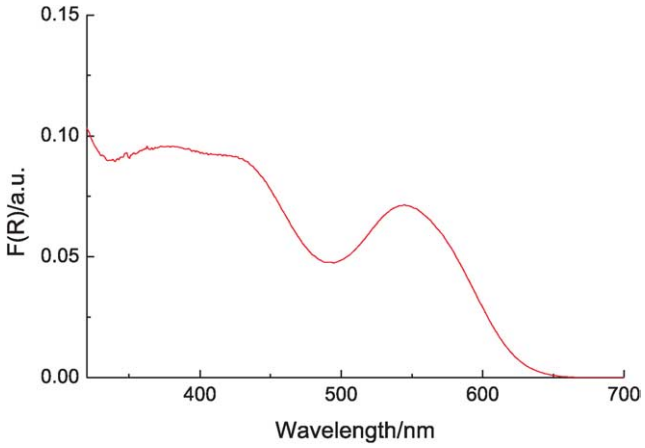


Figure 5. Diffuse reflectance UV/Vis spectrum of a **1a@NaY** solid 30 min after contacting with 1 ml of a 10^{-2} M aqueous solution of $Fe(NO_3)_3$. The visual appearance of the solid is red. For the initial diffuse reflectance spectrum of the sample see Figure 1.

The response of the glass coated sensors at 0.5 wt% loading of **1a** was also visually observable for 10^{-3} M concentration of Fe^{3+}, while for more diluted solutions not relevant response was observed.

As commented above, the detection threshold can be lowered, the visual response reaching 10^{-4} M when the concentration of **1a** is increased to 25 mg per gram of support. This loading also gives much faster response than lower contents of **1a**. However, high contents of **1a** give problems in terms of reusability.

2.4. Reuse of the solid sensors

In fact when working on solid chemosensors, one point of critical importance is the possibility of reuse by regeneration of the initial sensor form after the testing. In the case considered here and according to Scheme 2, it should be possible to reopen the heterocyclic pyrylium ion **2a** to pentendione **1a** by treatment with an aqueous base solution. As expected, upon addition of some drops of 10^{-1} M NaOAc onto the film of sensor the red color gradually turned into the yellow and the optical spectrum changed from the one corresponding to pyrylium to that of the pentendione. Figure 6 shows the spectra corresponding to three consecutive 10^{-2} M $Fe(NO_3)_3/10^{-1}$ NaOAc cycles using **1a@NaY** as heterogeneous sensor.

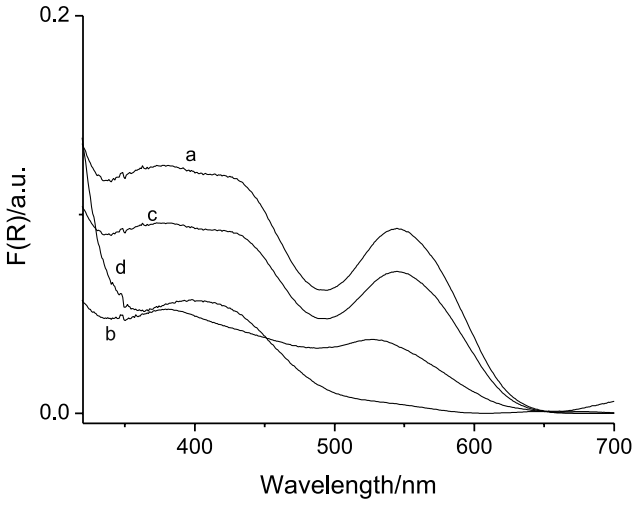


Figure 6. Diffuse reflectance UV/Vis spectra of the same sample of **1a@NaY** (loading 0.5 wt%) submitted, respectively, to the following treatments: (a) 10^{-2} M Fe^{3+}, 30 min; (b) 10^{-1} M NaAcO, 30 min; (c) 10^{-2} M Fe^{3+}, 30 min; (d) 10^{-1} M NaAcO, 30 min.

As it can be seen in this figure, UV/Vis spectroscopy reveals that the **1a@NaY** system undergoes a certain fatigue and the reversibility of the conversion between the open and the closed form is not complete after a few cycles as evidenced by the incomplete disappearance of the 560 nm band characteristic of **2a**. The higher the loading of **1a**, the lesser the reversibility of the system. It is worth commenting that **1a@NaY** is in fact the less reversible of the three insoluble solid sensors films since it is expected that Fe^{3+} will gradually exchange the Na^+ of the zeolite upon extensive reuse. In this regard **1a-SiO$_2$** or **1a-PS** are more reusable

Figure 7. Photograph of two dichloromethane solutions (3 ml) of **1a-PS** (50 mg in the first run) that has to be submitted to 10 consecutive test-recovery cycles. Left: upon addition of 500 μl of an 2.5×10^{-3} M ethanolic solution of $Mg(OAc)_2$. Right: after addition of 50 μl of an 2.5×10^{-3} M solution of $Fe(NO_3)_3$.

systems. For these two solids at 0.5 wt% loading the recycling of the sensor and the regeneration was performed at least 10 times without remarkable differences in the visual behaviour of the chemosensor. Figure 7 shows a photograph of a negative 2.5×10^{-3} M ethanolic solution of $Mg(OAc)_2$ and a positive 2.5×10^{-3} M ethanolic solution of $Fe(NO_3)_3$ test using **1a-PS** after 10 consecutive reuses regenerating every time the pentendione form by treatment with 10^{-2} NaOAc aqueous solution.

3. Conclusions

Covalently binding or adsorption of pentendione **1a** to several inorganic and organic supports is a viable strategy to transform this compound soluble in organic solvent into an insoluble solid sensor for Fe^{3+} and other strong Lewis acids and cations. In aqueous solution, the recoverable sensors also respond to Brönsted acids.

The three major problems are the increase in the response time, the lesser sensitivity and the reusability of the solids. The time of response and sensitivity are clearly modulated by the hydrophilicity of the support and the loading of the dye. Solid sensors containing 2.5 wt% of compound **1a** may show the response time below minutes and can detect below 10^{-3} M concentration. Reusability relies on the reversibility of the heterocyclic ring opening under basic conditions to regenerate the open pentendione form. The solid support plays a role in the system by hydrophobic/hydrophilic interaction with the solvent and also by promoting undesirable spontaneous cyclization of pentendione **1a**. Silica and zeolite are more adequate for sensing in water, while polystyrene gives shorter response time in ethanol. We are expanding this strategy to the development of other chromogenic heterogeneous sensors.

4. Experimental

4.1. Synthesis of organic compounds

4.1.1. Synthesis of *N*-allyl-*N*-methylaniline..[13] *N*-Methylaniline (535.5 mg, 5 mmol) was dissolved in dry THF (10 ml) and ^{t}BuOK (561.4 mg, 5 mmol) was added. The mixture was stirred for 1 h at 0 °C under N_2 atmosphere and allyl bromide (604.9 mg, 5 mmol) was added. The suspension was warmed at room temperature and magnetically stirred for 24 h. Then, the reaction was washed with a 1 M solution of HCl and extracted with CH_2Cl_2. The organic layer was washed with NaOH, dried with Na_2SO_4 and evaporated under vacuum. The compound (35%) was obtained as yellow oil after chromatography using a mixture of hexane/diethyl ether (10/1) as eluent. ^{1}H NMR ($CDCl_3$) δ: 2.98 (s, 3H, CH_3), 3.94 (d, $J=4.8$ Hz, 2H, CH_2N), 5.14–5.22 (m, 2H, CHCH_2), 5.77–5.90 (m, 1H, CHCH$_2$), 7.22–7.28 (5H, ArH). ^{13}C NMR ($CDCl_3$) δ: 36.6, 55.9, 113.0, 116.7, 117.0, 129.7, 134.4, 150.1.

4.1.2. Synthesis of compound 2a. *N*-Allyl-*N*-methylaniline (160.3 mg, 1.1 mmol) was dissolved in DMF (3 ml) and the 2,6-diphenylpyrylium perclorate (724.4 mg, 2.2 mmol), synthetized as described in the literature,[14,15] was added. The mixture was stirred at reflux temperature for 3 h, then cooled at room temperature and stirred for 20 h. The solvent was removed under reduced pressure and the resulting brownish, red oil used for the next step without purification.

4.1.3. Synthesis of compound 1a. Sodium acetate (183.3 mg, 2.23 mmol) was dissolved in a mixture of water (0.6 ml), methanol (1.9 ml) and acetone (3.8 ml). The crude compound **2a** was added, the mixture was stirred for 15 h at room temperature and for 10 h without stirring.

The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography using diethyl ether as eluent yielding pentendione **1a** (55%) as yellow oil.

^{1}H NMR ($CDCl_3$) δ: 3.01 (s, 3H, CH_3), 3.92 (d, $J=4.5$ Hz, 2H, CH_2N), 4.91 (s, 2H, CH_2COPh), 5.08–5.24 (m, 2H, CHCH_2), 5.63–5.96 (m, 1H, CHCH$_2$), 7.14–7.98 (m, 14H, ArH). ^{13}C NMR ($CDCl_3$) δ: 36.6, 55.9, 112.4, 116.8, 126.7, 127.0, 128.1, 128.6, 128.9, 129.2, 129.4, 129.6, 133.5, 135.7. HPLC-MS (electrospray) 396.2 ($M+H^+$). Combustion chemical analysis: Exp (%): C 80.40, H 6.50, N 3.09; calculated for $C_{27}H_{25}NO_2$ (%): C 82.00, H 6.37, N 3.54.

4.2. Preparation of the solid sensors

Compound **1a-PS**. Styrene (1 g) was dissolved in toluene (15 ml), a solution of **1a** (10 mg) in toluene (5 ml) and AIBN in catalytic amount were sequentially added. The mixture was stirred at reflux temperature under N_2 atmosphere for 3 h, then cooled at room temperature. The solvent was removed under reduced pressure yielding **1a-PS** as yellow solid.

Compound **1a@NaY**. The zeolite NaY (Aldrich, 1 g) was dehydrated by calcination at 500 °C for 6 h, then cooled under vacuum and suspended in CH_2Cl_2 (15 ml). A solution of **1a** (10 mg) in CH_2Cl_2 (5 ml) was slowly added and the mixture was stirred at 40 °C for 3 h. The solid **1a@NaY** was obtained as yellow powder after filtration and extensive washings with CH_2Cl_2.

Compound **1a-SiO$_2$**. Silica (BASF, 4 g) was dried at 300 °C under vacuum for 6 h and suspended in dry toluene (40 ml). 3-Mercaptopropyl trimethoxysilane (4 ml) was slowly

added and the mixture was stirred for 48 h at 110 °C. The resultant solid was filtered, dried and washed with CH_2Cl_2 in a Soxhlet apparatus to remove the unreacted silane. The modified SiO_2-SH (1 g) was then suspended in toluene (15 ml) and $NaHCO_3$ (200 mg) was added to neutralize the acidity. The suspension was stirred for 20 min then a solution of **1a** (10 mg) in toluene (5 ml) and AIBN, in catalytic amount were sequentially added. The reaction was stirred at reflux temperature for 24 h, then filtered and washed with CH_2Cl_2·yielding **1a-SiO$_2$** as yellow solid.

4.3. General sensing experiments.

Suspension test. The solid sensors **1a-SiO$_2$** or **1a@NaY** (100 mg) were suspended in an aqueous solution at pH 6.7 (buffered with HEPES). Some drops of the nitrate or sodium salts of the ions (from 10^{-2} to 10^{-4} M in water) Fe^{3+}, Al^{3+}, Mg^{2+}, Br^-, HPO_4^- were then added to each suspension and then the mixture was magnetically stirred.

Films. **1a-PS 1a-SiO$_2$** and **1a@NaY** was dissolved in hot toluene (1 ml) and some drops of this solution were cast on a glass previously covered with scotch tape to define squares (1 cm^2). Alternatively, **1a-SiO$_2$** or **1a@NaY** were dispersed in acetylacetone/water (1:10) and the paste cast onto the glass slide. After drying the films, few μl of the nitrate or sodium salts (from 10^{-2} to 10^{-4} M in water or ethanol) of the ions Fe^{3+}, Al^{3+}, Mg^{2+}, Br^-, HPO_4^- were then dropped over the film.

Acknowledgements

Financial support by the Spanish Ministry of Science and Technology (MAT 2003-1226) and Generalidad Valenciana (grupos03-020) is gratefully acknowledged. Carmela Aprile thanks the Fundation Jose Royo for a postdoctoral scholarship.

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Tetrahedron

The interaction of octamethoxyresorcinarene with halogenoacetic acids

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Received 11 February 2004; revised 17 May 2004; accepted 10 June 2004

Available online 28 July 2004

Abstract—This work deals with the interaction of the crown conformer of octamethoxyresorcinarene (OMRA) with organic acids in carbon tetrachloride and benzene. The cooperative and allosterical character of these interactions was observed using UV–Vis spectroscopy. The quantitative description of the observed conformational transformations was attempted, based on the proposed triconformational allosterical model. It was found using NMR that the crown conformer of OMRA undergoes transformation to the chair and diamond conformers in the presence of an acid.

1. Introduction

Resorcinarenes are the cavity-shaped macrocycles which can be easily synthesized from resorcinol and aldehydes.[1] The reaction catalysts are mineral acids,[2] Lewis acids[3] as well as Lewis bases.[4] The reaction usually yields a mixture of several of conformers, although using the appropriate procedure one can prepare only the crown conformers of resorcarene[5] or octamethoxyresorcarene (OMRA).[6] Recent publications describe the interconversion of OMRA conformers initiated by Lewis acids,[7] as well as the conversion of cavitand isomers effected by trifluoroacetic acid.[8]

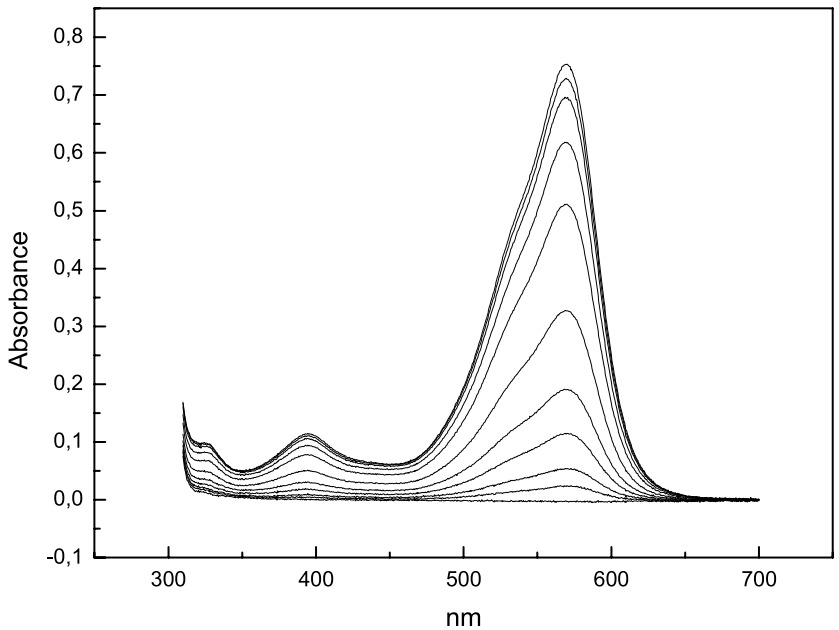

Figure 1. Changes in the absorption spectrum of benzene solution of OMRA resulting from addition of dichloroacetic acid. Concentration of OMRA is 0.0041 M, concentration of dichloroacetic acid varies from 0.002 to 0.20 M.

Keywords: Resorcinarene; Cooperativity; Allosteric effect; UV–Vis spectroscopy.
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doi:10.1016/j.tet.2004.06.054

It was observed during the studies on the synthesis of OMRA that the chloroform solution of this resorcarene turns blue in the presence of organic acid. The preliminary observations of the changes in the absorption spectra versus the concentration of an organic acid suggested the cooperative character of these interactions. This paper describes the cooperative and allosteric character of the interaction of OMRA with selected organic acids. A quantitative description of the observed conformational transformations based on the model of acetic acid dimerization and the proposed triconformational allosterical model was attempted.

2. Results and discussion

The crown conformer of OMRA readily interacts with organic acids such as trifluoroacetic, trichloroacetic, dichloroacetic and chloroacetic acid. These interactions manifest in, inter alia, formation of new intensive electronic bands in the UV–Vis spectra of chloroform, carbon tetrachloride and benzene solutions of OMRA resulting from addition of organic acids. Figure 1 shows the exemplary changes in the absorption spectra of OMRA resulting from addition of dichloroacetic acid.

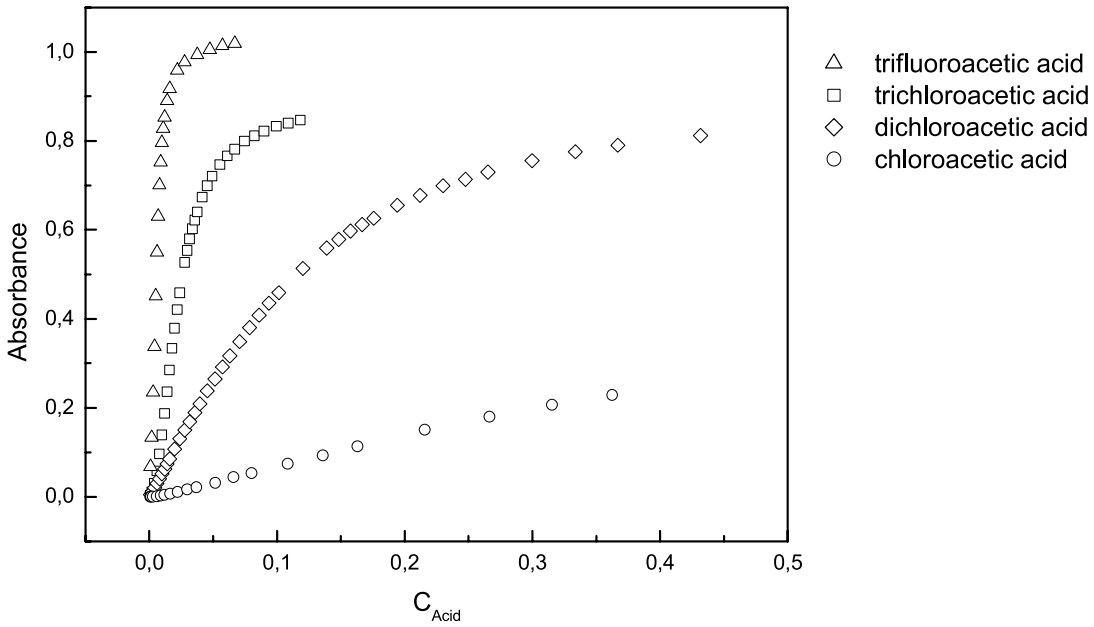


Figure 2. Changes in absorption of the electronic band of OMRA at λ_{max}=570 nm resulting from addition of organic acids in benzene.

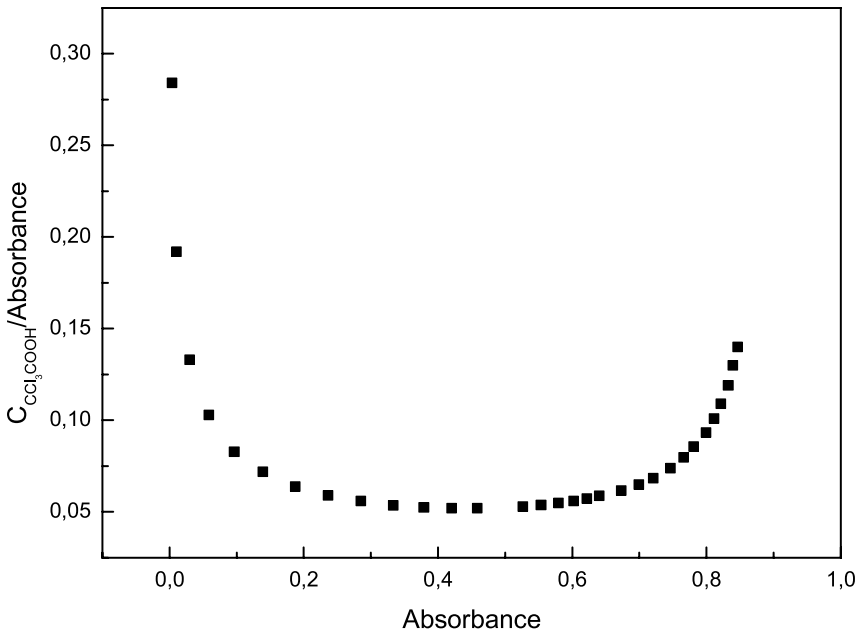


Figure 3. Changes in absorption of the electronic band of the crown conformer of OMRA at λ=567 nm resulting from addition of trichloroacetic acid shown in the Scatchard coordinates.

The sigmoidal absorption increments of the electronic bands of crown conformer OMRA resulting from the addition of acids are characteristic for all the investigated organic acids (Fig. 2).

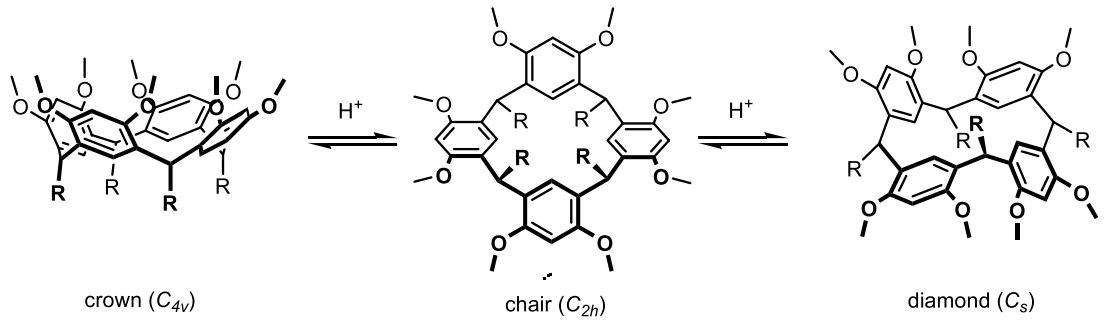
This phenomenon implicates a cooperative character to the interactions of this conformer with organic acids. This conclusion is confirmed by the plots made in Scatchard coordinates (Fig. 3).[9]

^{1}H NMR and chromatographic TLC investigations indicate that an organic acid causes isomerization of the crown conformer of OMRA, to the chair conformers and the diamond at room temperature (Scheme 1).

Figure 4 shows the aromatic region of the ^{1}H NMR spectrum of OMRA in deuterated chloroform in the presence of deuterated trifluoroacetic acid (CF_3COOD). This region is the most suitable for evaluation of the conformational transformations of OMRA and using the strongest acid means that the establishment of equilibrium is clearly visible in the spectrum. The spectrum taken immediately after preparation of the chloroform solution indicates the progress equilibration between the crown, chair, and diamond conformers of OMRA (Fig. 4).

The broadened signals of the aromatic protons of all conformers OMRA testify to the existing equilibrium. Figure 5 shows the aromatic region of the ^{1}H NMR spectrum of the above solution taken after 48 h. The sharpened signals corresponding to aromatic protons indicate the established equilibrium in the solution. Based on the integration of signals, the proportion of particular conformers in the solution can be estimated as follows: about 40% of crown conformer, 50% of diamond conformer, and about 10% of chair conformer.

The formation of chair and diamond conformers of OMRA is confirmed by chromatographic TLC investigations. The chromatogram of the carbon tetrachloride solution of crown conformer OMRA and hundredfold excess of trifluoroacetic acid developed by the 1:10 (v/v) mixture of $CHCl_3$/$CH_3COOC_2H_5$ shows the presence of colored products in addition to all three conformers. These products are probably the complexes of the crown conformer of OMRA with trifluoroacetic acid. In order to confirm this, the spectrophotometric and chromatographic measurements of chair and diamond conformer with trifluoroacetic acid were performed. Adding this acid to the chloroform solution of any of these conformers does not result in formation of new intense absorption bands in the UV–Vis spectrum. The chromatogram of these conformers in the presence of the acid does not show formation of other conformers; no colored spots are observed by TLC either.



Scheme 1.

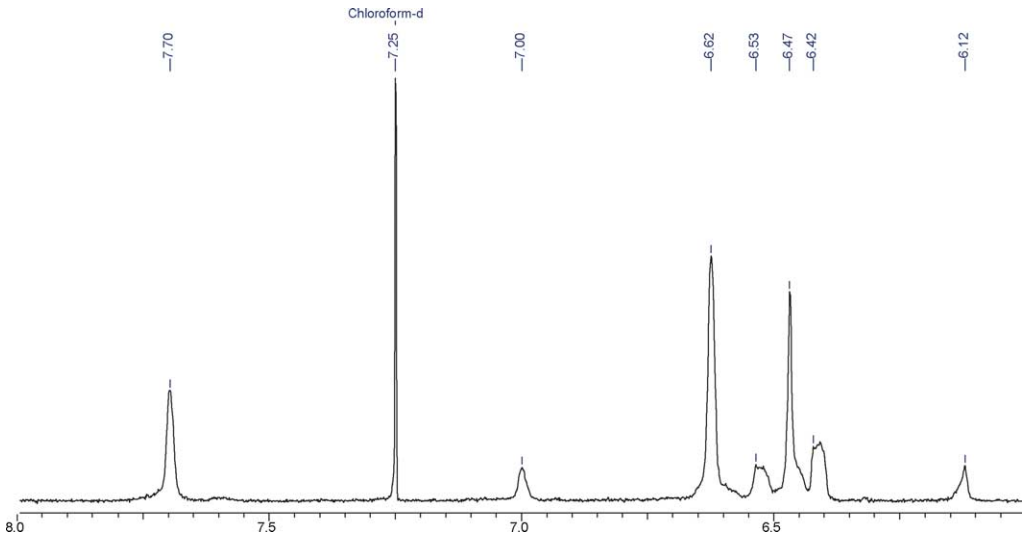


Figure 4. The ^{1}H NMR spectrum of aromatic protons of OMRA (3.96×10^{-2} M) in $CDCl_3$ freshly after addition of 50 μl CF_3COOD.

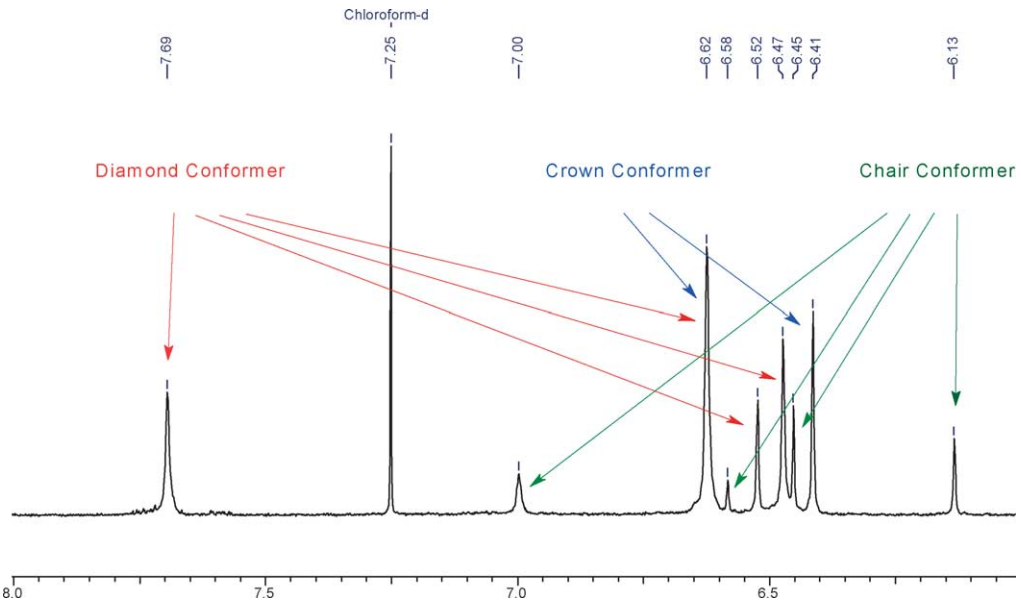


Figure 5. The ^{1}H NMR spectrum of aromatic protons of OMRA (3.96×10^{-2} M) in $CDCl_3$, 48 h after addition of 50 μl CF_3COOD).

All these observations prompted us to postulate a quantitative model which could describe the interactions of the crown conformer of OMRA with organic acids. Taking into account the literature data,[10] we assumed that: (1) the maximum number of the acid molecules which could be attached to the molecule of OMRA is 4; (2) the acid molecules form dimers in carbon tetrachloride and benzene according to Scheme 2.

$$A + A \underset{}{\overset{K_{di}=\frac{[Di]}{[A]^2}}{\rightleftharpoons}} Di$$

Scheme 2.

Table 1. The formation constants of dimers ($K_{di}[M^{-1}]$) in carbon tetrachloride and benzene from literature data

	CCL_4	C_6H_6
CCl_3COOH	526	6.7
CCl_2HCOOH	1075	27.1
$CClH_2COOH$	1613	48.4

where A and Di are molecules of organic acid and dimer, respectively; K_{di} is the formation constant of the dimer in solvent. The formation constants K_{di} for acetic acids in carbon tetrachloride and benzene according to the literature[11,12] are summarized in Table 1.

Our model is based on the allosterical model of Monod–Wyman–Changeux (M–W–C).[13] The M–W–C model describes the equilibrium between only two conformational states. In this case, the dimer formation (Scheme 2) and the equilibrium between three conformers in the presence of four acid molecules are to be modeled (Scheme 3).

where A is a molecule of organic acid; C, Ch and D are crown, chair and diamond conformers, respectively; K_C, K_{Ch} and K_D are the formation constants of complexes of the respective conformers of OMRA with acid molecules.

The general assumptions are similar to the M–W–C model, but the change of conformation of OMRA can occur only following addition of the acid molecules. Based on this model, the saturation number of crown conformer of OMRA with the acid molecules can be expressed as follows:

$$\overline{Y}=\sum_{i=1}^{4}[CA_i]/C_{anal.}=\frac{[CA]+2[CA_2]+3[CA_3]+4[CA_4]}{4\{[C]+[CA]+[CA_2]+[CA_3]+[CA_4]+[Ch]+[ChA]+[ChA_2]+[ChA_3]+[ChA_4]+[D]+[DA]+[DA_2]+[DA_3]+[DA_4]\}} \quad (1)$$

$$\begin{array}{ccccccccc}
C & + 4A \overset{K_C}{\rightleftharpoons} & CA & + 3A \overset{K_C}{\rightleftharpoons} & CA_2 & + 2A \overset{K_C}{\rightleftharpoons} & CA_3 & + A \overset{K_C}{\rightleftharpoons} & CA_4 \\
 & & \updownarrow L_1 & & \updownarrow L_1K_{Ch}/K_C & & \updownarrow L_1K_{Ch}^2/K_C^2 & & \updownarrow L_1K_{Ch}^3/K_C^3 \\
Ch & + 4A \overset{K_{Ch}}{\rightleftharpoons} & ChA & + 3A \overset{K_{Ch}}{\rightleftharpoons} & ChA_2 & + 2A \overset{K_{Ch}}{\rightleftharpoons} & ChA_3 & + A \overset{K_{Ch}}{\rightleftharpoons} & ChA_4 \\
 & & \updownarrow L_2 & & \updownarrow L_2K_D/K_{Ch} & & \updownarrow L_2K_D^2/K_{Ch}^2 & & \updownarrow L_2K_D^3/K_{Ch}^3 \\
D & + 4A \overset{K_D}{\rightleftharpoons} & DA & + 3A \overset{K_D}{\rightleftharpoons} & DA_2 & + 2A \overset{K_D}{\rightleftharpoons} & DA_3 & + A \overset{K_D}{\rightleftharpoons} & DA_4
\end{array}$$

Scheme 3.

wherein [C], [Ch], and [D] are the equilibrium concentrations of the respective conformers of OMRA; $[CA_i]$, $[ChA_i]$, and $[DA_i]$ are the equilibrium concentrations of the respective complexes of conformers of OMRA with i=1…4 molecules of the acid.

Making use of the following partial equilibria:

$$C + 4A \rightleftharpoons CA \qquad K_C[A] = \frac{[CA]}{4[C]} \qquad Ch + 4A \rightleftharpoons ChA$$

$$K_{Ch}[A] = \frac{[ChA]}{4[Ch]}$$

$$C + 3A \rightleftharpoons CA_2 \qquad K_C[A] = \frac{2[CA_2]}{3[CA]}$$

$$ChA + 3A \rightleftharpoons ChA_2 \qquad K_{Ch}[A] = \frac{2[ChA_2]}{3[ChA]}$$

$$CA_2 + 2A \rightleftharpoons CA_3 \qquad K_C[A] = \frac{3[CA_3]}{2[CA_2]}$$

$$ChA_2 + 2A \rightleftharpoons ChA_3 \qquad K_{Ch}[A] = \frac{3[ChA_3]}{2[ChA_2]}$$

$$CA_3 + A \rightleftharpoons CA_4 \qquad K_C[A] = \frac{4[CA_4]}{[CA_3]}$$

$$ChA_3 + A \rightleftharpoons ChA_4 \qquad K_{Ch}[A] = \frac{4[ChA_4]}{[ChA_3]}$$

$$D_3 + 4A \rightleftharpoons DA \qquad K_D[A] = \frac{[DA]}{4[D]}$$

$$DA_3 + 3A \rightleftharpoons DA_2 \qquad K_D[A] = \frac{2[DA_2]}{3[DA]}$$

$$DA_2 + 2A \rightleftharpoons DA_3 \qquad K_D[A] = \frac{3[DA_3]}{2[DA_2]}$$

$$DA_3 + A \rightleftharpoons DA_4 \qquad K_D[A] = \frac{4[DA_4]}{[DA_3]}$$

and introducing the symbols L_1=[ChA]/[CA] and L_2=[DA]/[ChA], one obtains the following expression for the saturation number:

$$\bar{Y} = \frac{1 + 3K_C[A] + 3K_C^2[A]^2 + K_C^3[A]^3}{(1/K_C[A] + 4 + 6K_C[A] + 4K_C^2[A]^2 + K_C^3[A]^3) + L_1(1/K_{Ch}[A] + 4 + 6K_{Ch}[A] + 4K_{Ch}^2[A]^2 + K_{Ch}^3[A]^3) + L_1L_2(1/K_D[A] + 4 + 6K_D[A] + 4K_D^2[A]^2 + K_D^3[A]^3)} \quad (2)$$

As already mentioned, the interactions of the crown conformer of OMRA with organic acids manifests by formation of new electronic bands in the presence of acids as well as the change in absorption of these bands accompanying the change of the acid concentration. In order to keep the number of parameters as low as possible, it was assumed that the molar absorption coefficients were equal for all particular complexes. This assumption was supported by the following findings: (1) an increase in the concentration of acid did not shift the new electronic bands; (2) the absorption bands standardized for various acid concentrations were identical.

The above assumption allows for making the observed absorption

$$A = \sum_{i=1}^{4} ([CA_i]\epsilon)$$

dependent on the saturation number

$$\bar{Y} = \sum_{i=1}^{4} [CA_i]/C_{anal.}$$

via the relation

$$A = 4\epsilon C_{anal.} \cdot \bar{Y}$$

As a consequence, one obtains the following expression for the absorption of newly formed electronic bands in relation to the acid concentration:

$$A = 4\epsilon C_{anal.} \frac{1 + 3K_C[A] + 3K_C^2[A]^2 + K_C^3[A]^3}{(1/K_C[A] + 4 + 6K_C[A] + 4K_C^2[A]^2 + K_C^3[A]^3) + L_1(1/K_{Ch}[A] + 4 + 6K_{Ch}[A] + 4K_{Ch}^2[A]^2 + K_{Ch}^3[A]^3) + L_1L_2(1/K_D[A] + 4 + 6K_D[A] + 4K_D^2[A]^2 + K_D^3[A]^3)} \quad (3)$$

The total concentration of acids is described by Eq. (4). This equation takes into account complexation of different conformers as well as formation of acid dimers in solvents. Similarly, the total concentration of OMRA is described by Eq. (5)

$$C_{acid} = [A] + [CA] + 2[CA_2] + 3[CA_3] + 4[CA_4] + [ChA] + 2[ChA_2] + 3[ChA_3] + 4[ChA_4] + [DA] + 2[DA_2] + 3[DA_3] + 4[DA_4] + 2[Di] \quad (4)$$

$$C_{anal.} = [C] + [CA] + [CA_2] + [CA_3] + [CA_4] + [Ch] + [ChA] + [ChA_2] + [ChA_3] + [ChA_4] + [D] + [DA] + [DA_2] + [DA_3] + [DA_4] \quad (5)$$

Making use of the partial equilibria and the symbols L_1 and L_2, one obtains the final expression for the total concentration of acids (Eq. (6)) and OMRA (Eq. (7)).

$$C_{acid} = [A] + 4K_C[A][C] + 12KC^2[A]^2[C] + 12K_C^3[A]^3[C] + 4K_C^4[A]^4[C] + 4K_{Ch}[A][Ch] + 12K_{Ch}^2[A]^2[Ch] + 12K_{Ch}^3[A]^3[Ch] + 4K_{Ch}^4[A]^4[Ch] + 4K_D[A][D] + 12K_D^2[A]^2[D] + 12K_D^3[A]^3[D] + 4K_D^4[A]^4[D] + 2K_{di}[A]^2 \quad (6)$$

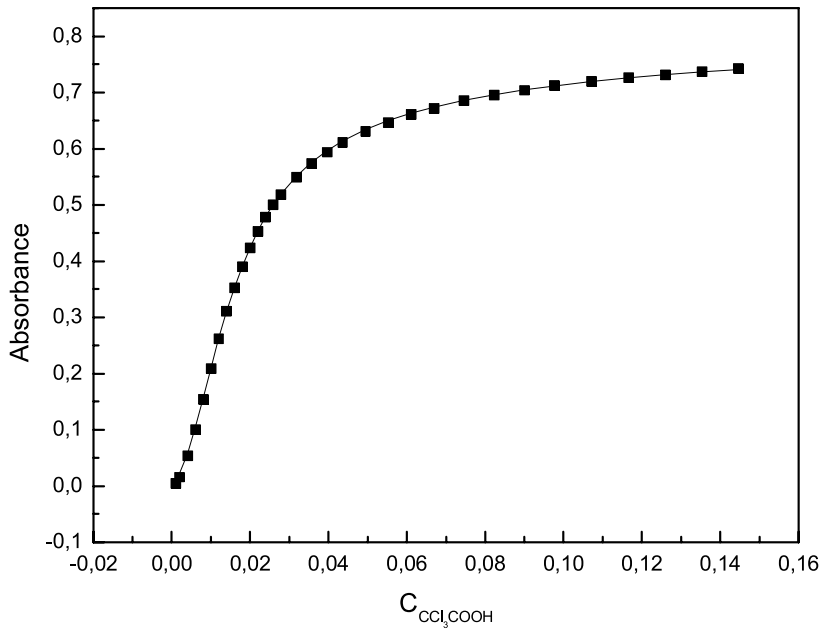


Figure 6. Fitting of Eq. (3) to the experimental data for the OMRA—trichloroacetic acid system in benzene.

$$[C]=\frac{C_{OMRA}}{(1+4K_C[A]+6K_C^2[A]^2+4K_C^3[A]^3+K_C^4[A]^4)+\frac{L_1K_C}{K_{Ch}}(1+4K_{Ch}[A]+6K_{Ch}^2[A]^2+4K_{Ch}^3[A]^3+K_{Ch}^4[A]^4)+\frac{L_1L_2K_C[C]}{K_{Ch}}(1+4K_D[A]+6K_D^2[A]^2+4K_D^3[A]^3+K_D^4[A]^4)} \quad (7)$$

First, the Eqs. (6) and (7) were solved numerically for given values of the formation constants and L_1, L_2. Then, using the equilibrium concentration of the acid for the given parameters, the theoretical absorbance was computed from Eq. (3). The values of K_C, K_D, K_{Ch}, K_{di} as well as L_1, L_2 were optimized iteratively. The goodness of fit was given by the following expression.

$$\chi^2=\frac{1}{n-p}\sum_{i=1}^{n}\frac{(A'-A)^2}{A} \quad (8)$$

wherein A is the observed absorption, A' is the computed absorption, $n-p$ is the number of degrees of freedom (n is the number of experimental data points, p is the number of fitted parameters). Figure 6 shows exemplary fitting of Eq. (3) to the experimental data for trichloroacetic acid. The values of parameters fitted for all investigated acids are summarized in Table 2.

Analyzing the data of Table 2, one can note some regularities. The increase of the protonation constants for all conformers is accompanied by an increase in the strength of acid, independently of the solvent system used. Similarly, the equilibrium constants L_2 between the crown and diamond conformers increase. Moreover, the molar absorption coefficients are almost constant (ε=58.1±16). The agreement of iteratively optimized dimer constants K_{di} and the literature data, summarized in Table 1, is remarkable. The formation constants of dimers in solvents can be slightly different[14,15] and depend on the method used.

In all cases, the ratio K_{Ch}/K_C is less than one, this indicate the low probability of converting the crown conformer into the chair conformer along with the increasing complex stoichiometry. This conclusion is substantiated by the molecular dynamics calculation performed for OMRA having a methylene bridge using the force field method MM2.[16] The complex having 1:1 stoichiometry probably will adopt the structure with the proton placed symmetrically between two methoxy groups of the benzene rings (Fig. 7a).

Calculation shows that such a complex transforms to the chair conformer much more easily than the complex having

Table 2. Parameters of Eq. (3) fitted for data of OMRA—organic acids in benzene and carbon tetrachloride at 25 °C and λ=567 nm

	K_C [M^{-1}]	K_{Ch} [M^{-1}]	K_D [M^{-1}]	L_1	L_2	α [cm^{-1} M^{-1}]	K_D [M^{-1}]	χ^2
C_6H_6								
CCl_3COOH	349.2	75.0	62.7	1.11	7.96	61.15	6.00	2.06×10^{-6}
CCl_2HCOOH	69.9	11.7	11.7	2.00	1.00	70.00	27.0	4.35×10^{-5}
$CClH_2COOH$	46.7	5.62	6.48	7.02	0.61	41.73	34.6	6.52×10^{-7}
CCl_4								
CCl_3COOH	1150.5	240.0	270.0	0.222	28.7	56.2	300.0	3.55×10^{-6}
CCl_2HCOOH	605.2	147.5	21.4	0.775	14.7	54.6	881.3	2.75×10^{-6}
$CClH_2COOH$	450.0	1.08	0.116	0.995	0.503	65.0	1050.0	8.36×10^{-5}

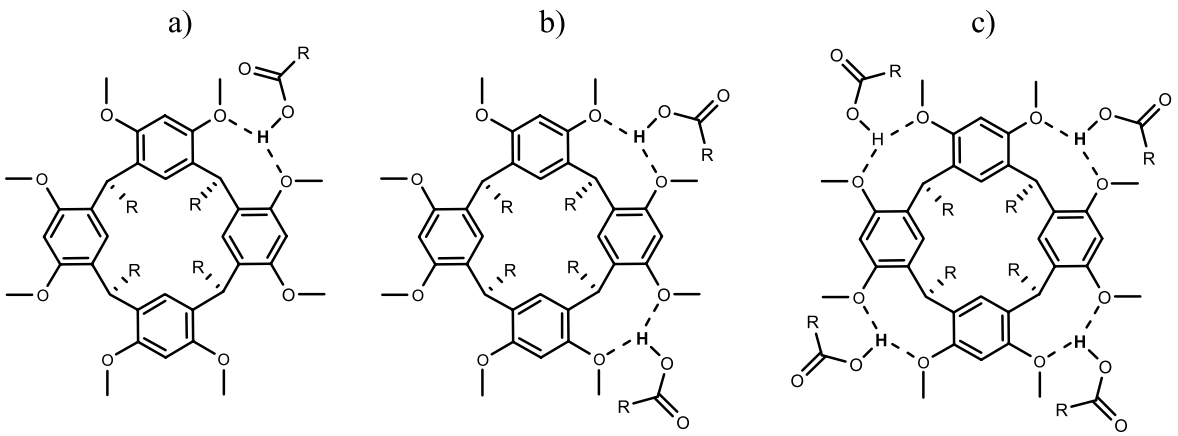
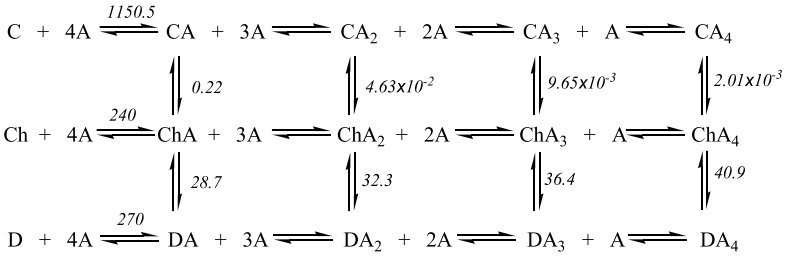


Figure 7.

the 1:2 stoichiometry (Fig. 7b), where three benzene rings are tightened by hydrogen bonds. The complex having the 1:4 stoichiometry (Fig. 7c) has a symmetrical rigid structure, which is unlikely to transform to the chair conformer. Below, we discuss quantitatively the case for trichloroacetic acid. The transformation scheme supplemented by the values of all equilibrium constants is shown in Scheme 4.

The sigmoidal dependence of the changes in absorption of the band at λ=567 nm on the concentration of acid can be explained as follows. At low acid concentration, a complex with one acid molecule is formed, which is rapidly converted to the chair conformer. Along with the rising acid concentration, the band absorption increases because of the rising proportion of complexes of higher stoichiometry, which are not so susceptible to conformational changes. At



Scheme 4.

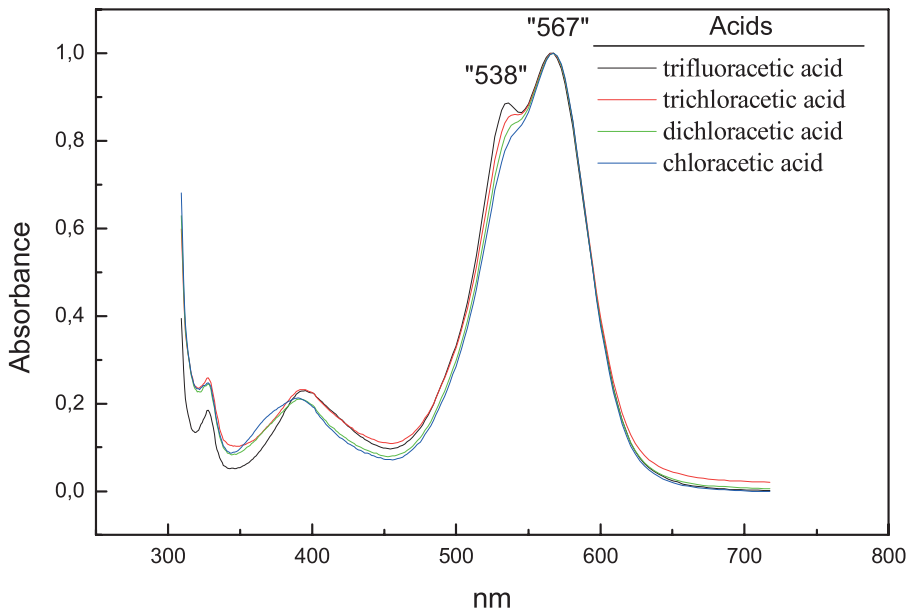
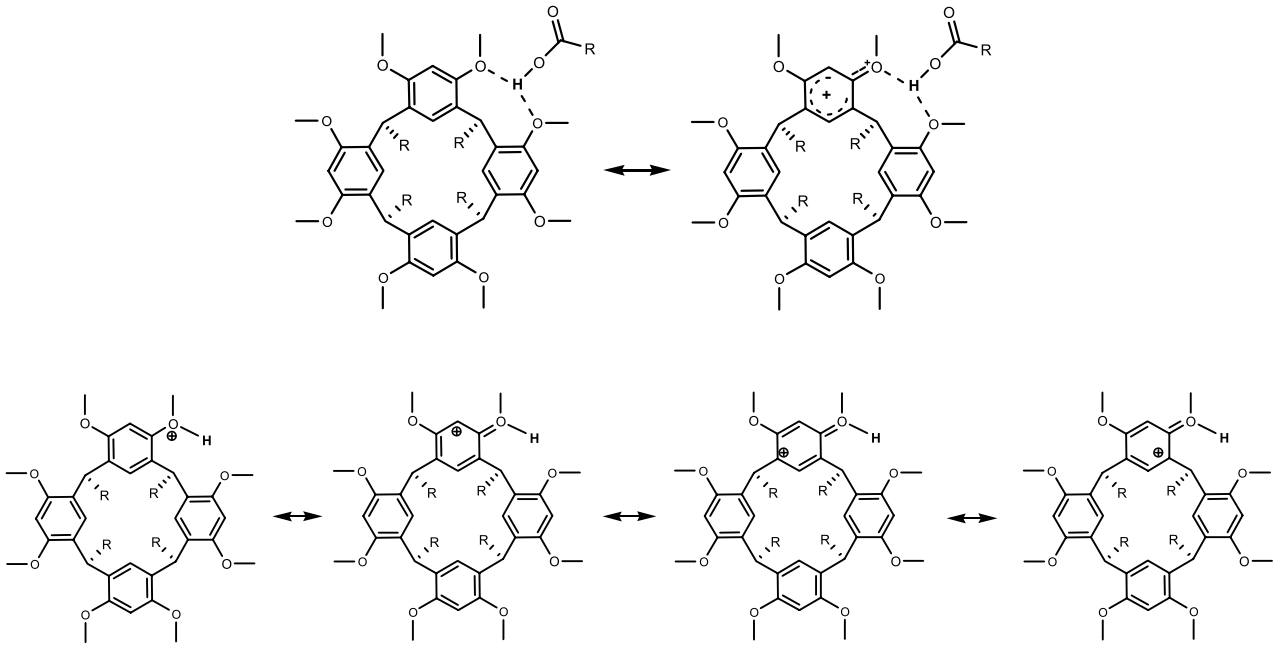


Figure 8. Standardized absorption spectra of OMRA and the investigated acids. Concentration of OMRA is 0.004 M for all measurements, concentrations of the investigated acids are 0.04 M. The spectra were taken in chloroform at 25 °C immediately after preparation of the solutions.



Scheme 5.

high acid excess, the complex having 1:4 stoichiometry predominates, since it is stabilized by four symmetrical hydrogen bonds, and its transformation to the chair conformer is very unlikely.

Along with the rising acid concentration two competitive effects show: (1) the less than one ratio K_{Ch}/K_C decreases which makes the conformation change of the crown conformer into the chair conformer difficult, (2) the ratio K_{Ch}/K_D increases which makes the conformation change of the chair conformer into the diamond conformer easier.

The values of K_C increasing along with the rising acid strength indicate that the interaction of the discussed acids with the crown conformer of OMRA rises in the same direction. Such a dependence is confirmed by the experimental data. The form of the absorption bands of the formed complexes varies along with the increasing acid strength. Figure 8 presents standardized absorption spectra of the complexes of OMRA with particular organic acids. It can be seen that the intensity of electronic band at λ=538 nm depends on the strength of used acid. It is likely that occurrence of this band results from the formation of stronger complex of the crown conformer in the series of chloroacetic acid through trifluoroacetic acid. However, no change in the maximum of the band at λ=567 nm can be observed.

Resonance structures for the complexes of OMRA with acetic (1:1) acid presented in Scheme 5 can explain the experimental results: 1) the formation of the new band at 568 nm is caused probably by a quinone structure of the complex; (2) addition of the acetic acid to the crown conformer induces a change of conformation, which is the result of bonds loosen on the alkyl bridge connecting the resorcinol units. This makes possible the change of OMRA conformation.

3. Conclusions

The interactions of crown conformer of OMRA with organic acids is manifested by formation of new absorption bands at $\lambda_{max.}$=567 nm. The change in absorption of this band versus the acid concentration has a sigmoidal course. An analysis of this change using the Scatchard equation indicates the cooperative character of these interactions. It was demonstrated using ^{1}H NMR that the crown conformer of OMRA undergoes transformation to the chair and diamond conformers in the presence of an acid. Based on experimental data, the triconformational allosterical model was proposed for quantitative description of the observed transformations.

4. Experimental

4.1. General

NMR spectra of solutions in $CDCl_3$ (internal standard: Me_4Si) were recorded with a Bruker 400 MHz spectrometer UV–Vis spectra were taken on an Specord 500 spectrophotometer.

4.2. Materials

The conformers of OMRA were synthesized according to the literature.[6] All acids were purified by distillation.

4.3. Procedure of conformers analysis

The trifluoracetic acid (2.4 mmol) were added to solution of OMRA (0.024 mmol) in 10 ml of carbon tetrachloride. The solution was stirred over 2 h at room temperature. TLC analysis (chloroform/ethyl acetate—10:1) shows that the products have following R_f values: the crown

conformer—0.72; the diamond conformer—0.93; the chair conformer—0.98, the coloured complexes of OMRA with trifluoracetic acids—from 0.07 to 0.22.

4.4. Spectroscopic measurements

For the determination of constants, a series of solutions containing OMRA (4.3×10^{-3} M) and varying concentrations of acids (1.95×10^{-2}–4.5×10^{-1} M) was prepared in a cell of 1.0 cm path length. The parameters were determined by nonlinear least-squares regression analysis using Eqs. (3) and (7).

4.5. Quantum-mechanical calculations

In order to estimate the converting ability of OMRA conformers under complexes acid molecules performed calculations for OMRA having a methylene bridge. Calculations of electronic density distributions for particular complexes with proton placed symmetrically between two methoxy groups of the benzene rings performed using AM1 method. The molecular dynamics calculations for complexes performed using the force field method (MM2, Chem3D Ultra 7.0 software). The calulations were run at 298 K temperature from 0 to 30 ps with 0.001 ps step.

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Donor–acceptor interaction-mediated arrangement of hydrogen bonded dimers

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Received 23 April 2004; revised 4 June 2004; accepted 7 June 2004

Available online 21 July 2004

Abstract—The donor–acceptor interaction-driven supramolecular arrangement of a new series of quadruply hydrogen-bonded homo- and heterodimers have been investigated in chloroform with ^{1}H NMR and UV–Vis spectroscopy. Two kinds of structurally complementary monomers have been prepared. Monomers **3** and **4** are incorporated with one ureidopyrimidone unit and one electron deficient pyromellitic diimide (PDI) or naphthalene diimide (NDI) unit, respectively, monomers **5** and **6** are incorporated with two ureidopyrimidone units and one PDI or NDI unit, respectively, whereas monomers **7** and **8** consist of one electron rich bis-*p*-phenylene[34]crown-10 unit and one or two 2,7-diamido-1,6-naphthyridine units, respectively. Compounds **3** and **4** exist exclusively as homodimers, respectively. Adding 1 equiv. of **7** to the solution of **3**·**3** and **4**·**4** induced them to partially or fully dissociate to produce heterodimers **3**·**7** and **4**·**7** due to intermolecular donor–acceptor interaction and the formation of a new binding mode between the ureidopyrimidone of **3** or **4** and the 2,7-diamido-1,6-naphthyridine unit of **7**. Both **5** and **6** exist as cyclic monomer and dimer in chloroform. Adding 1 equiv. of **8** to the solution of **5** or **6** in chloroform caused all the cyclic dimer and most of the cyclic monomer to de-cyclize to form new heterodimers **5**·**8** and **6**·**8**, respectively. ^{1}H NMR and UV–vis study revealed that heterodimer **5**·**8** has a structure in which the PDI of **5** is not threaded through the cavity of the bis-*p*-phenylene[34]crown-10 unit of **8**. In contrast, in addition to the heterodimer similar to **5**·**8**, about 40% of heterodimer **6**·**8** is generated, in which the PDI of **6** is threaded through the cavity of the bis-*p*-phenylene[3]crown-10 unit of **8** due to the increased donor–acceptor interaction between NDI and bis-*p*-phenylene[34]crown-10. Steric hindrance and mismatching of the hydrogen bonding moiety play important roles in the arrangement of the new homo- and heterodimers.

1. Introduction

Nature utilizes the cooperative interaction of discrete non-covalent forces, including hydrogen bonding, hydrophobic interaction, metal-ligand coordination, and aromatic stacking, to construct the three dimensional structures and functions of biomacromolecules.[1] One of the major aspects of supramoleulcar chemistry is to produce new well-defined unnatural assemblies in a selective and directional way.[2] In the past decade, a large number of artificial supramolecular architectures have been assembled based on single non-covalent force, such as transition metal-ligand interaction,[3] hydrogen bonding,[4] or electrostatic interaction,[5] and hydrophobic interaction.[6] Although in principle two or more different non-covalent interactions may also function well together, as shown by Nature, to generate supramolecular systems of defined structures and functions, examples of supramolecular assemblies of such kind are notably few.[7]

Since its first reported by Meijer et al. in 1998,[8] the highly stable, self-complimentary 2-ureido-4[1*H*]-pyrimidinone-based AADD-styled (A: hydrogen bonding acceptor, D: hydrogen bonding donor) quadruple hydrogen bonding motif has found extensive applications in self-assembly of discrete supramolecular systems with well-established structures.[9,10] In search of efficient methods for selective formation of heterodimeric structures from this versatile self-binding mode, we recently reported that more stable

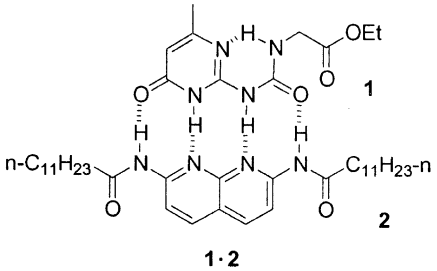

Chart 1.

Keywords: Hydrogen bonding; Donor–acceptor interaction; Self-assembly; Heterocyclic compounds; Arrangement.

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doi:10.1016/j.tet.2004.06.104

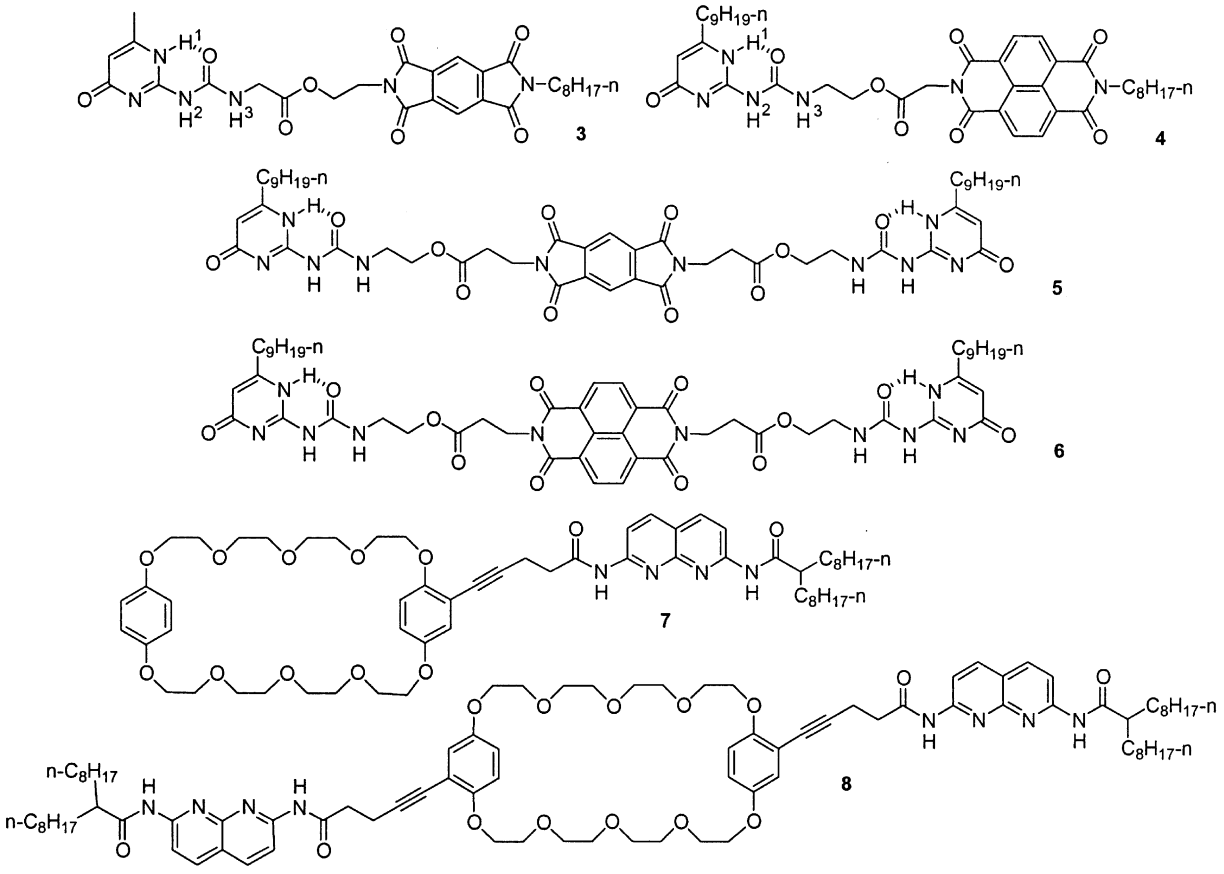


Chart 2.

ADDA–DAAD hydrogen bonded heterodimer **1**·**2** could be exclusively formed from homodimer **1**·**1** and diamide **2** in chloroform (Chart 1).[11–13] Previously, we had also found that two different homodimers could also decompose to form new quadruple hydrogen bonding heterodimers,[13,14] as a result of additional intermolecular donor–acceptor interaction between electron-rich bis-*p*-phenylene-[34]crown-10 moiety and electron-deficient pyromellitic diimide (PDI) or naphthalene diimide (NDI) unit.[5c,15] The generation of hydrogen bonded heterodimers from related homodimers driven by additional donor–acceptor interaction represents a new useful strategy for constructing novel kind of supramolecular architectures based on two different non-covalent forces. In this paper, we describe that this strategy has been utilized for the self-assembly of a novel series of structurally unique hydrogen bonded heterodimers, which are driven by intermolecular donor–acceptor interaction.

2. Results and discussion

Compounds **3**-**8** have been designed and synthesized for the present study (Chart 2). It was expected that in chloroform the identical equivalent of **3** or **4** and **7** will form heterodimers with a binding mode similar to that of **1**·**2**, which would also be facilitated by the intermolecular electrostatic interaction between the electron deficient PDI unit of **3** or NDI unit of **4** and the electron rich bis-*p*-phenylene[34]crown-10 unit, while the binding of **5** or **6** with **8** would produce a macrocyclic dimer, in which the PDI of **5** or NDI of **6** is threaded through the cavity of bis-*p*-phenylene[34]crown-10 of **8** due to the intermolecular donor–acceptor interaction (Chart 3).

The preparation of **3** and **4** has been described in a recent report.[13] Initial attempts to prepare compounds similar to **5** and **6** but with the linker of **3** or **4** did not succeed. The

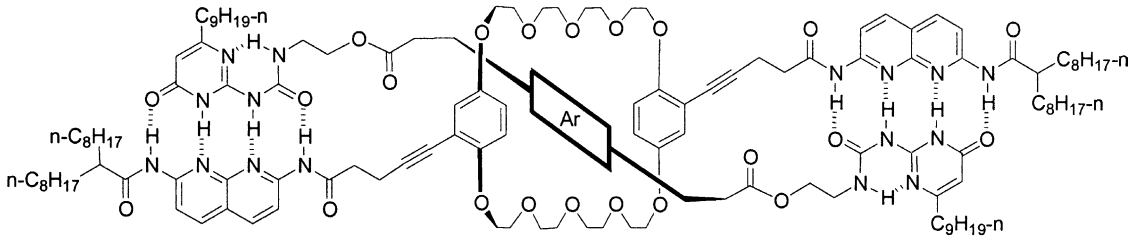
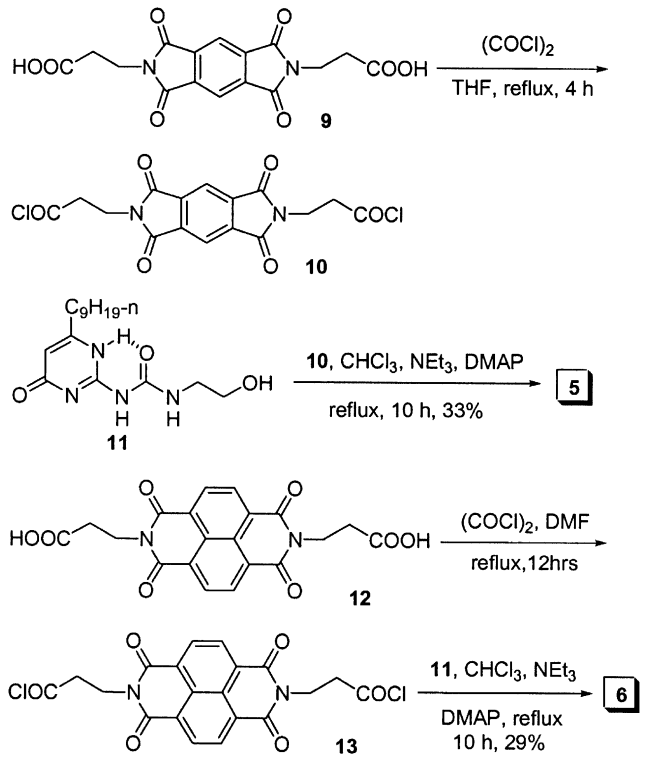
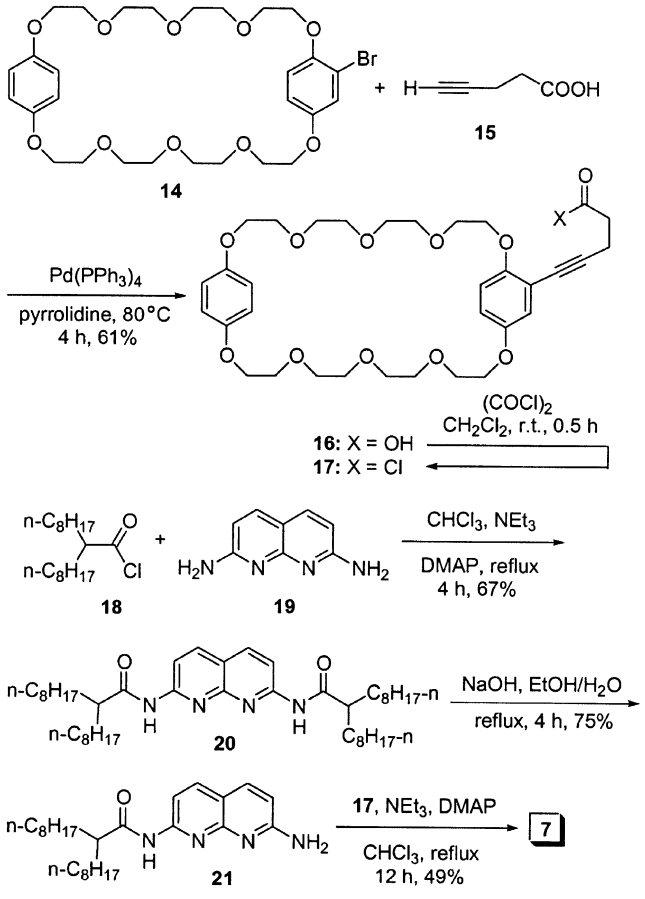


Chart 3.



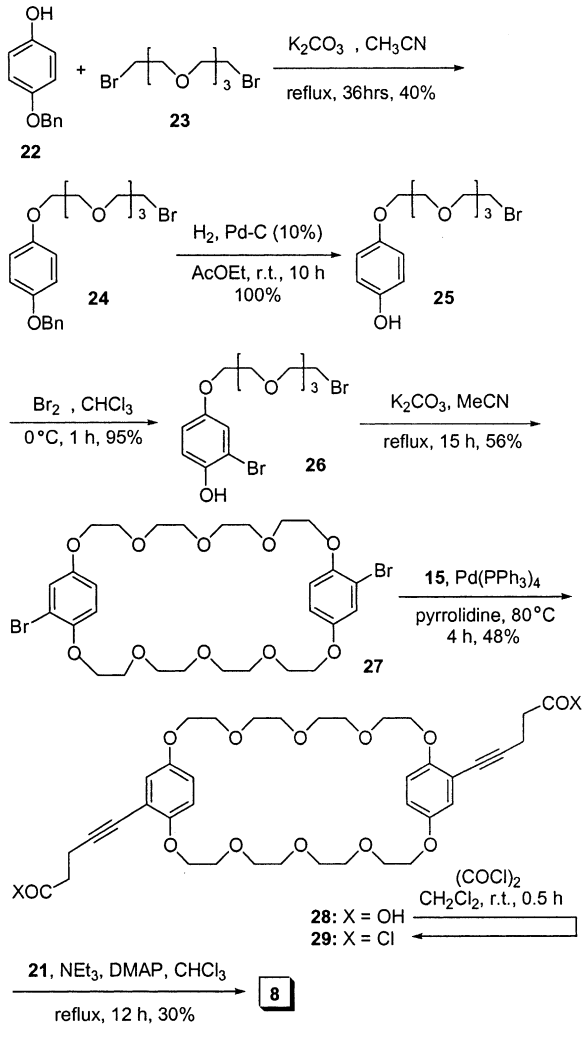
Scheme 1.



Scheme 2.

synthesis of **5** and **6** is shown in Scheme 1. Thus, diacid **9** was first produced from the reaction of pyromellitic dianhydride and 3-amino propionic acid in hot DMF and then converted into **10** with oxalyl chloride in THF. Subsequent reaction of **10** with **11**[13] in refluxing chloroform in the presence of triethylamine afforded **5** in 33% yield. For the preparation of **6**, **12** was first produced from naphthalene-1,4,5,8-tetracarboxylic dianhydride and 3-amino propionic acid in hot DMF and then transformed into **13**. The reaction of **13** with **11** in chloroform gave compound **6** in 29% yield.

For the preparation of **7** (Scheme 2), compound **16** was first prepared in 61% yield from the palladium-catalyzed reaction of **14** and **15** in hot pyrrolidine. Treatment of **16** with oxalyl chloride in dichloromethane yielded acyl chloride **17**, which was used for the next step without purification. Compound **20** was then prepared in 67% yield from the reaction of **18** and **19**[14a] in refluxing chloroform and hydrolyzed with sodium hydroxide in aqueous ethanol to **21** in 75% yield. Compound **21** could not be directly obtained from the reaction of **18** and **19** because it was converted into **20** upon being generated. Finally, the reaction of **21** with **17** in refluxing chloroform produced **7** in 49% yield.



Scheme 3.

The synthetic route for **8** is shown in Scheme 3. Phenol **22** was first treated with excessive amount of **23** in refluxing acetonitrile to give bromide **24** in 40% yield. Palladium-catalyzed hydrogenation of **24** in ethyl acetate afforded **25** quantitatively. Compound **25** was then reacted with bromine to produce **26** in 95% yield. Macrocycle **27** was obtained in 56% yield from **26** in refluxing acetonitrle in the presence of potassium carbonate and then coupled with **15** to afford **28** in 48% yield. Compound **28** was then converted into **29** with oxalyl chloride, and **29** was reacted with **21** in refluxing chloroform to afford **8** in 30% yield. The dioctylmethyl chain provides good solubility to **7** and **8** in common organic solvents such as chloroform and dichloromethane.

Previous study had revealed that both **3** and **4** exist exclusively as homodimer **3·3** and **4·4** in chloroform, respectively, and the PDI and NDI unit have no important effect on the stability of the dimers.[13] Adding 1 equiv. of **7** to the solution of **3·3** in chloroform-*d* caused the dimer to partially dissociate to form new heterodimer **3·7** (Chart 4). The evidence came from the ^{1}H NMR spectrum, which shows one set of signals for **3·7** and another set of signals

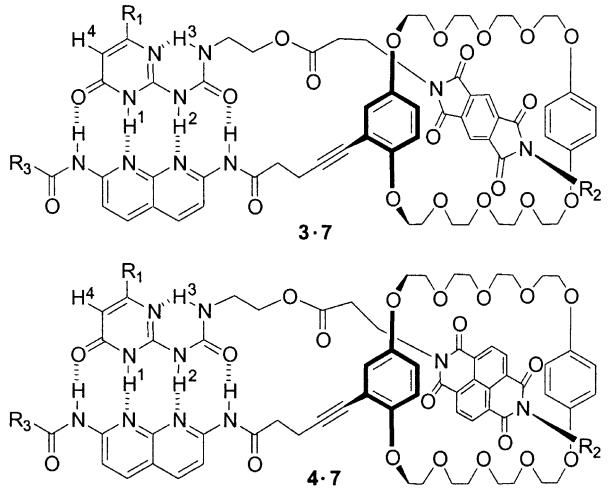


Chart 4.

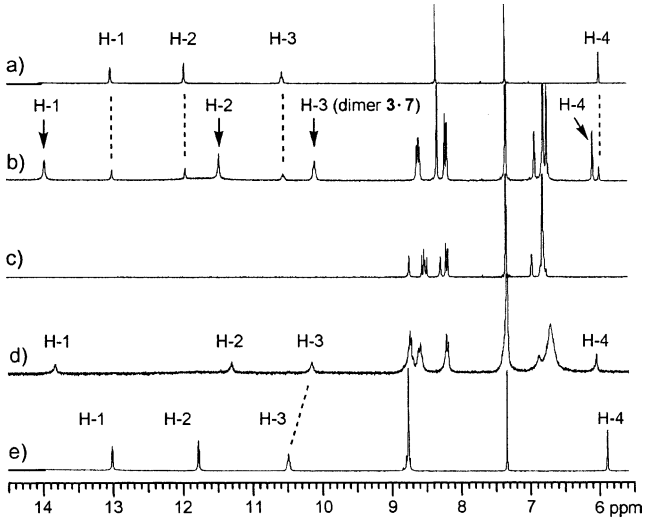


Figure 1. Partial 400 MHz ^{1}H NMR spectrum (5 mM) of (a) **3**, (b) **3**+**7** (1:1), (c) **7**, (d) **4**+**7**, and (e) **4** in $CDCl_3$ at 25 °C.

for **3·3** (Fig. 1a–c). The signals for **3·3** had been assigned by changing the ratio of **3** and **7** in the solution, while the ADDA-DAAD binding mode of **3·7** had been established by the ^{1}H NMR NOESY experiment.[11–13] Based on the relative integrating intensity of the H-1 signal of both dimers, we determined the yield of heterodimer **3·7** to be ca. 80%. The solution of the 1:1 mixture of **3** and **7** (5 mM) in chloroform also turned pale orange. The UV–vis spectrum exhibited a typical charge-transfer absorption band (λ_{max}= 465 nm, ε=45 $M^{-1}cm^{-1}$), which provides additional evidence for the formation of heterodimer **3·7**. Controlling experiment had revealed that no detectable absorption within 400–700 nm could be observed for the 1:1 mixture of a donor compound and an acceptor compound bearing no hydrogen bonding moiety in chloroform even at higher concentration.[13,16]Therefore, the charge-transfer absorption was obviously generated as a result of the donor–acceptor interaction between the PDI unit of **3** and the bis-*p*-phenylene[34]crown-10 moiety of **7** in heterodimer **3·7**. In addition, the solution of the 1:1 mixture of **3** and **7** in DMSO-d_6 is colorless, and the ^{1}H NMR spectrum reveals only the signals of **3** and **7**, due to the highly competitive interaction of the solvent. The fact that only 80% of dimer **3·3** was converted into **3·7** by 1 equiv. of **7** is quite different from the previous observation that **1·2** could be generated quantitatively from dimer **1·1** and **2**. This may be attributed to the greater steric hindrance of the dioctylmethyl group relative to the undecyl group.

Mixing 1 equiv. of **7** with 1 equiv. of **4** in chloroform-*d* caused full disruption of dimers **4·4**, exclusively affording heterodimer **4·7** (Chart 4), as indicated by the ^{1}H NMR spectrum (Fig. 1c–e). No detectable ^{1}H NMR signals of homodimer **4·4** were observed from the ^{1}H NMR spectrum within the temperature range of −10 to 55 °C. This observation clearly demonstrates that the strengthened donor–acceptor interaction between the bis-*p*-phenylene[34]crown-10 moiety of **7** and the NDI unit of **4** remarkably stabilizes the hydrogen bonded heterodimer **4·7** in chloroform.[17] A typical, but obviously stronger charge-transfer absorption band was also displayed for heterodimer **4·7** in chloroform (λ_{max}=470 nm, ε=139 M^{-1} cm^{-1}). Within the measurable concentration range of 10–0.5 mM, the ε value is concentration-independent, proving the extremely high stability of the heterodimer, which is reminiscent of that produced from intramolecular interaction.

The ^{1}H NMR spectrum of a relatively concentrated solution (75 mM) of **5** in chloroform-*d* displayed two sets of signals that are typical for the hydrogen bonded NH protons (Fig. 2a). The relatively weaker set of signals (ca. 18% based on the relative intensity of the NH signal) was decreased in magnitude upon dilution and vanished when the solution was diluted to 1.1 mM. The viscosity of the solution was almost unchanged (<20%) when diluting the solution 110–1.0 mM. This result indicates that no important amount of linear supramolecular polymers of **5** were formed in the solution, which otherwise should cause remarkable increase of viscosity at the range of high concentration. Molecular modeling revealed that compound **5** can cyclize intramolecularly. In addition, recent study by Meijer had also demonstrated that flexible linker-connected bifunctional

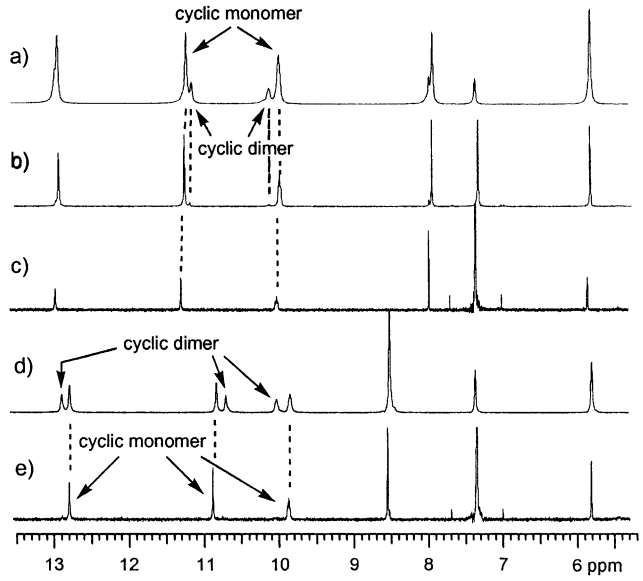


Figure 2. Partial ^{1}H NMR (400 MHz) spectrum of **5** at (a) 75 mM, (b) 25 mM, and (c) 1.1 mM and **6** at (d) 50 mM and (e) 1.5 mM in chloroform-*d*.

2-ureido-4[1*H*]-pyrimidinone derivatives preferred to form cyclic structures over linear oligomers and polymers.[18] Therefore, the two sets of signals shown in the ^{1}H NMR spectra can be reasonably assigned to those of cyclic monomer **5** (ca. in 82% yield) and cyclic dimer **5**·**5** (Chart 5), respectively, and upon dilution dimer **5**·**5** was gradually converted into the more stable cyclic monomer **5** (Fig. 2b and c). ^{1}H NMR spectroscopy revealed that **6** also existed as cyclic monomer and cyclic dimer (ca. 40% and 60%, respectively, at [**6**]=75 mM in chloroform-*d* (Fig. 2d) and

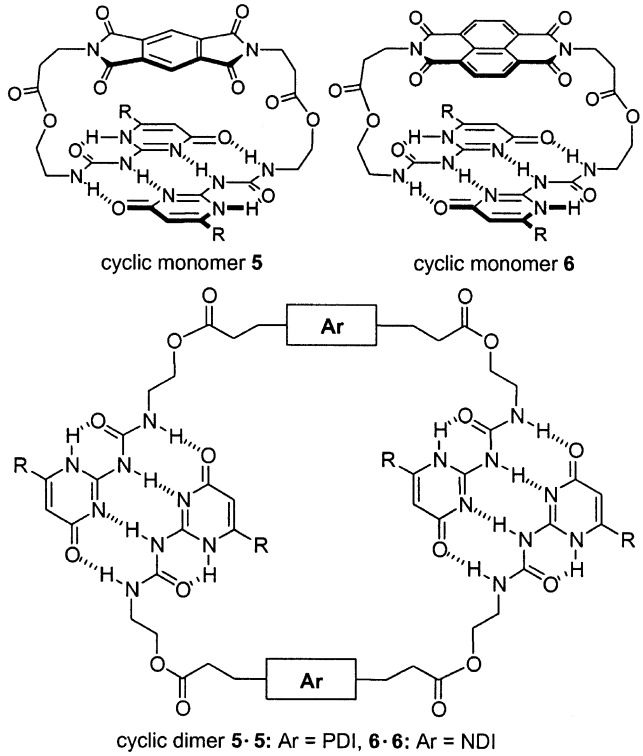


Chart 5.

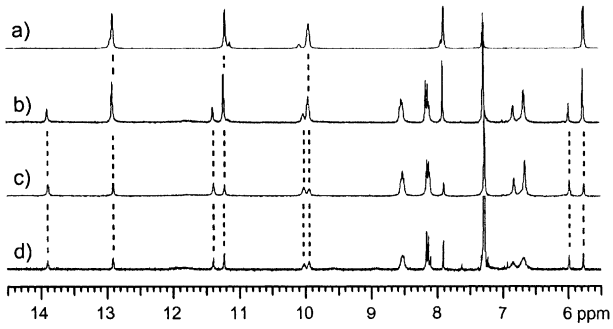


Figure 3. Partial ^{1}H NMR (400 MHz) spectrum of (a) **5** (10 mM), (b) **5** (10 mM)+**8** (5 mM), (c) **5** (10 mM)+**8** (10 mM), and (d) **5** (1.5 mM)+**8** (1.5 mM) in chloroform-*d*.

the cyclic dimer was completely converted into the cyclic monomer at [**6**]=1.9 mM (Fig. 2e).

Adding **8** to the solution of **5** in chloroform-*d* first caused the less stable cyclic dimer **5**·**5** to decompose to produce new heterodimer **5**·**8** (Fig. 3a and b). With more amount (1 equiv.) of **8** added, the more stable cyclic monomer **5** also began to de-cyclize to form **5**·**8** (in ca. 50% yield in the 1:1 mixture of **5** and **8**, Figure 3c). Dilution of the 1:1 mixture of **5** and **8** in chloroform-*d* did not have dramatic effect on the ratio of heterodimer **5**·**8** and cyclic monomer **5** (Fig. 3d). Since no detectable charge-transfer absorption band was observed in the UV–vis spectrum of the 1:1 mixture of **5** and **8** (10 mM) in chloroform and the solution is colorless, it is reasonable to propose that the new heterodimer **5**·**8** in the mixture actually possess a binding mode in which the PDI unit is not threaded through the cavity of the bis-*p*-phenylene[34]crown-10 unit of **8**, as shown in Chart 6, due to the flexibility of the linkers between the binding moieties and the weakness of the electrostatic interaction between the PDI unit of **5** and the bis-*p*-phenylene[34]crown-10 moiety of **8**.

Addition of 1 equiv. of **8** to the solution of **6** in chloroform-*d* also caused all the cyclic dimer **6**·**6** and most cyclic monomer **6** to dissociate, as indicated by the ^{1}H NMR spectra (Fig. 4a–c). Different from that observed for the mixture of **5** and **8**, the ^{1}NMR spectrum of the 1:1 mixture of **6** and **8** displayed two new sets of signals, which we attributed to the formation of two new isomeric heterodimers **6**·**8**. One is that in which the NDI unit of **6** is not threaded through the cavity of the bis-*p*-phenylene[34]-crown-10 unit of **8** (Chart 6). Another one is that in which the NDI unit of **6** is threaded through the cavity of the bis-*p*-phenylene[34]crown-10 unit of **8**, as shown in Chart 3. UV–vis spectrum recorded in chloroform provides evidence that the threaded heterodimer **6**·**8** was generated, which showed a typical charge-transfer absorption band at $\lambda_{max}=$ 470 that is not available for dimer **5**·**8**. The apparent molar absorption coefficient ε was determined to be 450 M^{-1} cm^{-1}, which was also concentration-independent within the measurable range of concentration of $\geq$0.8 mM. This result can be explained by considering the increased, intermolecular steric hindrance within heterodimer **6**·**8** and also the stacking weakening between the NDI unit of **6** and the bis-*p*-phenylene[34]-crown-10 unit of **8** due to the hydrogen bonded moiety-induced mismatching and the longer flexible

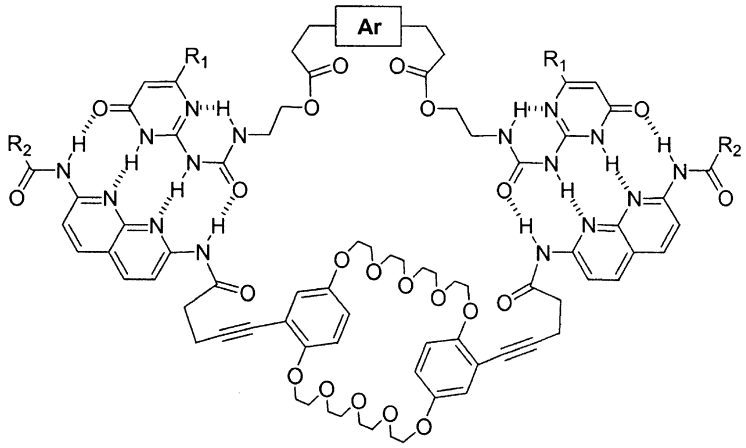


Chart 6.

linkers between the binding moiety. The formation of the threaded heterodimer **6·8** but not **5·8** is consistent with the stronger donor–acceptor interaction between NDI and bis-*p*-phenylene[34]crown-10 than that between PDI and bis-*p*-phenylene[3]crown-10.[15] The yields of the threaded and unthreaded heterodimers **6·8** are comparable, and have been estimated to be approximately 45%, based on the integrating intensity of their NH signals in the ^{1}H NMR spectrum.

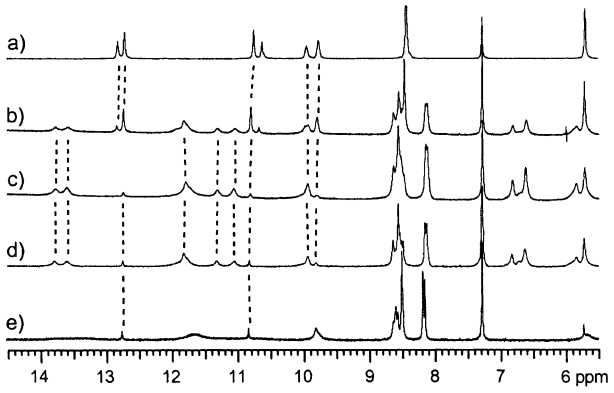
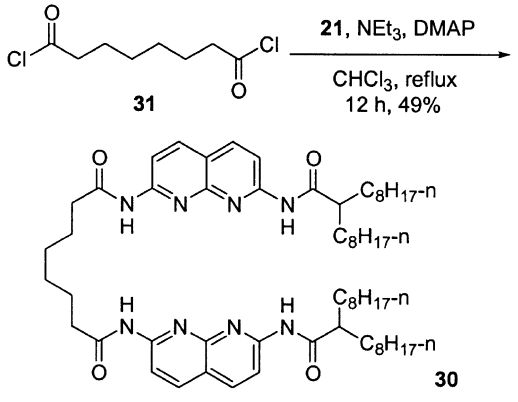


Figure 4. Partial ^{1}H NMR (400 MHz) spectrum of (a) **6** (15 mM), (b) **6** (15 mM)+**8** (7.5 mM), (c) **6** (15 mM)+**8** (15 mM), (d) **6** (2 mM)+**8** (2 mM), and (e) **6** (15 mM)+**30** (15 mM) in chloroform-*d*.



Scheme 4.

Adding 1 equiv. of compound **30**, which is prepared from **21** and **31** in refluxing chloroform (Scheme 4), to the solution of **5** or **6** in chloroform-*d* also caused similar de-cyclization of the latter's cyclic dimer and monomer. However, the new signals are quite broadened (Fig. 4e), suggesting that more cyclic or linear oligomers are formed between **30** and **5** or **6**.

3. Conclusion

We have reported the self-assembly of a new series of multiply hydrogen-bonded heterodimers based on the quadruple hydrogen bonding DAAD–ADDA mode between ureidopyrimidone and 2,7-diamino-1,6-naphthyridine diamide monomers. The assembling efficiency of the relatively complicated supramolecular structures is reduced remarkably due to the possible steric hindrance and the structural flexibility of the linkers between the hydrogen bonding and the electrostatic binding moieties. It is expected that, by rigidifying the linking groups and reducing the steric hindrance produced by the peripheral aliphatic groups in **8**, more selective self-assembly of heterodimers similar to threaded dimers **6·8** or other related supramolecular architectures might be constructed, which is being investigated in our lab.

4. Experimental

4.1. General methods

Melting points are uncorrected. All reactions were carried out under an atmosphere of nitrogen. The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Viscosity was obtained with a NPJ-S viscosimeter. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures.

4.1.1. 3,3′-(1,3,5,7-Tetraoxo-5,7-dihydro-1*H*,3*H*-pyrrolo[3,4-*f*]isoindole-2,6-diyl)-bis-propionic acid (9). A mixture of pyrromellitic dianhydride (1.50 g, 6.90 mmol) and 3-aminopropionic acid (1.40 g, 15.7 mmol) in DMF (10 mL) was stirred at 120 °C for 4 h. Upon cooling to room temperature, the resulting solid was filtered, washed with water and acetone thoroughly to afford compound **9** as a white powder (1.20 g, 48%). Mp >330 °C (Lit.[19] 329 °C). ^{1}H NMR (DMSO-d_6): δ 2.40 (t, J=6.8 Hz, 4H), 3.41 (t, J=6.8 Hz, 4H), 7.98 (s, 2H). MS (ESI): m/z 361 $[M+H]^+$. Anal. Calcd for $C_{16}H_{12}N_2O_8$: C, 53.34; H, 3.36; N, 7.78. Found: C, 52.99; H, 3.54; N, 7.77.

4.1.2. Compound 5. To a solution of **9** (0.10 g, 0.25 mmol) in THF (5 mL) was added oxalyl chloride (0.2 mL) and 1 drop of DMF. The mixture was heated under reflux for 4 h and concentrated under reduced pressure to afford crude compound **10** as an oil, which was used for next step without further purification. To a stirred solution of compound **11** (0.20 g, 0.62 mmol), NEt_3 (0.3 mL) and DMAP (10 mg) in $CHCl_3$ (15 mL) was added a solution of the above compound **10** in $CHCl_3$ (5 mL). The mixture was heated under reflux for 10 h, cooled, washed with dilute aqueous hydrochloride solution, aqueous sodium carbonate solution, water, brine and dried over (Na_2SO_4). After the solvent was removed in vacuo, the residue was subjected to flash chromatography (EtOAc/CH_2Cl_2 2:1) to afford **5** as a white solid (80 mg, 33%). Mp 232–233 °C. IR (cm^{-1}): 3310, 2929, 2856, 1776, 1725, 1656, 1583, 1253, 1182, 725. ^{1}H NMR ($CDCl_3$): δ 0.90–0.92 (m, 6H), 1.32–1.40 (m, 24H), 1.70–1.72 (m, 4H), 2.52–2.65 (m, 4H), 2.68 (d, d, J_1=4.8 Hz, J_2=8.7 Hz, 2H), 3.13–3.29 (m, 4H), 3.72–3.76 (m, 2H), 3.85–3.92 (m, 2H), 4.12–4.22 (m, 4H), 4.51–4.53 (m, 2H), 5.78 (s, 2H), 7.91 (s, 2H), 9.96 (s, 2H), 11.24 (s, 2H), 12.92 (s, 2H). MS (ESI): m/z 973 $[M+H]^+$. Anal. Calcd for $C_{48}H_{64}N_{10}O_{12}$: C, 59.25; H, 6.63; N, 14.39. Found: C, 59.44; H, 6.39; N, 14.00.

4.1.3. 3,3′-(1,3,6,8-Tetraoxo-1,3,6,8-tetrahydro-benzo[*lmn*][3,8]phenanthroline-2,7-diyl)-bis-propionic acid (12).[20] A suspension of 1,4,5,8-naphthalenetetracarboxylic dianhydride (1.00 g, 3.70 mmol) and 3-amino propionic acid (0.80 g, 9.00 mol) in DMF was heated at °C for 4 h. Upon cooling to room temperature, the mixture was poured into water (50 mL). The resulting solid was filtered, washed with water and acetone to give compound **12** as a pink powder (1.20 g, 80%). Mp >300 °C (decomp.). ^{1}H NMR (DMSO-d_6): 2.53 (t, J=6.4 Hz, 4H), 3.65 (t, J=6.4 Hz, 4H), 8.46 (s, 4H). MS (ESI): m/z 411 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_2O_8$: C, 58.54; H, 3.44; N, 6.83. Found: C, 57.95; H, 3.46; N, 6.84.

4.1.4. Compound 6. To a suspension of **12** (0.21 g, 0.50 mmol) in oxalyl chloride (10 mL) was added two drops of DMF. The mixture was heated under reflux for 12 h and concentrated in vacuo to give crude compound **13** as an oil. To a stirred solution of compound **12** (0.36 g, 1.10 mmol), NEt_3 (1.0 mL) and DMAP (10 mg) in chloroform (15 mL) was added a solution of the above **13** in chloroform (8 mL). The mixture was heated under reflux for 12 h, cooled, washed with dilute aqueous hydrochloride solution, aqueous sodium carbonate solution, water, brine and dried over (Na_2SO_4). The solvent was removed and the residue was subjected to flash chromatography (CH_2Cl_2/MeOH 200:1) to afford **6** as a yellow solid (150 mg, 29%). Mp 188–190 °C. IR (cm^{-1}): 3213, 2928, 2856, 1742, 1708, 1670, 1585, 1338, 1247, 768. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=6.0 Hz, 6H), 1.20–1.45 (m, 24H), 1.69–1.71 (m, 4H), 2.46–2.51 (m, 4H), 2.70–2.71 (m, 2H), 3.19–3.28 (m, 4H), 3.69–3.75 (m, 2H), 4.12–4.21 (m, 4H), 4.45 (t, J=7.2 Hz, 2H), 4.72 (t, J=12.6 Hz, 2H), 5.72 (s, 2H), 8.47 (s, 4H), 9.80 (s, 2H), 10.82 (s, 2H), 12.74 (s, 2H). MS (ESI): m/z $[M+H]^+$. Anal. Calcd for $C_{52}H_{66}N_{10}O_{12}$: C, 61.04; H, 6.50; N, 13.69. Found: C, 61.07; H, 6.74; N, 13.22.

4.1.5. 1,4,7,13,20,23,26,29,32-Decaoxa-15-(4-carboxy-but-1-ynyl)[13,13]paracyclophane (16). To a stirred solution of pyrrolidine (4 mL) were added compounds **14**[13] (0.40 g, 0.65 mmol), $Pd(PPh_3)_4$ (80.0 mg, 0.07 mmol, 10%) and **15** (170.0 mg, 1.73 mmol). The reaction mixture was stirred at 80 °C for 4 h and then cooled to room temperature. The solvent was evaporated in vacuo and the residue was triturated with dichloromethane (50 mL). The organic phase was washed with 1 N hydrochloride (20 mL), water (20 mL), brine (20 mL), and dried over sodium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (CH_2Cl_2/CH_3OH 50:1). Compound **16** was obtained as a yellow solid (0.25 g, 61%). Mp 65–67 °C. IR (cm^{-1}): 3553, 3471, 2882, 2233, 1724, 1604, 1510, 1455, 1234, 839. ^{1}H NMR ($CDCl_3$): δ 2.58 (t, J=6.0 Hz, 2H), 2.73 (t, J=6.0 Hz, 2H), 3.71–4.75 (m, 16H), 3.81–3.85 (m, 8H), 3.94–3.97 (m, 8H), 6.55 (d, J=6.0 Hz, 1H), 6.70–6.75 (m, 5H), 6.89 (d, J=3 Hz, 1H). MS (ESI): m/z 633 $[M+H]^+$. Anal. Calcd for $C_{33}H_{44}O_{12}$: C, 62.65; H, 7.01. Found: C, 62.54; H, 6.68.

4.1.6. (Dioctyl)acetyl(7-(dioctyl)acetylamino[1,8]naphthyri-din-2-yl)amide (20). A suspension of **18** (0.75 g, 2.50 mmol) and **19** (0.16 g, 1.00 mmol), NEt_3 (1.00 mL), and DMAP (20 mg) in chloroform (100 mL) was heated under reflux for 10 h. Upon cooling to room temperature, the insoluble material was filtered off and the filtrate was washed with water, brine, and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was purified by column chromatography (hexane/CH_2Cl_2 5:1 to 1:2) to afford **20** as a yellowish oil (67%). ^{1}H NMR ($CDCl_3$): δ 0.82–0.86 (m, 12H), 1.23–1.28 (m, 48H), 1.46–1.55 (m, 4H), 1.64–1.74 (m, 4H), 2.29–2.35 (m, 2H), 8.13 (d, J=9.0 Hz, 2H), 8.48 (d, J=8.7 Hz, 2H), 8.70 (s, 2H). HRMS (MALDI): m/z 693.6020. Calcd for $C_{44}H_{77}N_4O_2$ $[M+H]^+$: 693.6047.

4.1.7. *N*-(7-Amino-1,8-naphthyridin-2-yl)-2-octyldecoic amide (21). A solution of **20** (1.25 g, 1.80 mmol) and NaOH (0.30 g) in ethanol (20 mL) and water (4 mL) was heated under reflux for 4 h. After work-up as described for **8**, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 20:1) to obtain **21** as a white solid (0.57 g, 75%). Mp 197–198 °C. ^{1}H NMR ($CDCl_3$): δ 0.82–0.89 (m, 6H), 1.28–1.39 (m, 24H), 1.43–1.56 (m, 2H), 1.64–1.73 (m, 2H), 2.26–2.32 (m, 1H), 5.45 (s, 2H), 6.66 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.7 Hz, 1H), 7.94 (d, J=9.0 Hz, 1H), 8.27 (d, J=9.0 Hz, 1H), 8.57 (s, 1H). MS (MALDI): m/z 427 $[M+H]^+$. Anal. Calcd for $C_{26}H_{42}N_4O$: C, 73.20; H, 9.92; N, 13.13. Found: C, 73.30; H, 9.97; N, 13.04.

4.1.8. Compound 7. To a solution of **16** (0.15 g, 0.39 mmol) in dichloromethane (5 mL) was added oxalyl chloride (0.2 mL). The solution was stirred for 0.5 h at room temperature and then concentrated to give crude **17** as an oil, which was used directly for next step. To a stirred solution of **21** (0.17 g, 0.39 mmol), NEt_3 (0.5 mL) and DMAP (10 mg) in chloroform (15 mL) was added a solution of the above **17** in chloroform (5 mL). The mixture was heated under reflux for 12 h, cooled, washed with water, brine, and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was subjected to flash chromatography (EtOAc/CH_2Cl_2 2:1) to afford **7** as a yellowish oil (0.20 g, 49%). IR (cm^{-1}): 3190, 2926, 2856, 2230, 1703, 1609, 1506, 1287, 1137, 855, 804. ^1H NMR ($CDCl_3$): δ 0.85 (t, $J=6.9$ Hz, 6H), 1.20–1.29 (m, 24H), 1.50–1.56 (m, 2H), 1.66–1.73 (m, 2H), 2.24–2.30 (m, 1H), 2.83 (s, 4H), 3.68–3.72 (m, 16H), 3.77–3.87 (m, 8H), 3.94–4.06 (m, 8H), 6.71–6.73 (m, 6H), 6.88 (d, $J=2.4$ Hz, 1H), 8.12 (d, d, $J_1=1.5$ Hz, $J_2=9.0$ Hz, 2H), 8.22 (s, 1H), 8.45 (d, d, $J_1=9.0$ Hz, $J_2=13.2$ Hz, 2H), 8.67 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 15.6, 22.7, 27.6, 29.3, 29.5, 29.7, 31.8, 33.1, 36.6, 49.3, 68.1, 68.1, 68.2, 69.7, 69.7, 69.8, 69.8, 70.7, 70.7, 70.8, 70.8, 70.9, 92.3, 113.6, 114.1, 114.6, 115.5, 115.6, 116.1, 118.4, 118.7, 139.0, 139.1, 152.8, 153.0, 153.0, 153.7, 154.0, 154.0, 154.0, 170.9, 175.8. MS (MALDI): *m/z* 1041.6153 $[M+H]^+$. Calcd for $C_{59}H_{85}N_4O_{12}$: 1041.6158.

4.1.9. 4-[2-[2-[2-(2-Bromo-ethoxy)-ethoxy]-ethoxy]-ethoxy]-phenyl benzyl ether (24). A mixture of **22** (5.70 g, 28.0 mmol), **23**[21] (45.0 g, 0.14 mol), and potassium carbonate (7.00 g, 70.0 mmol) in dry acetone (200 mL) was stirred at room temperature for 1 h and then under reflux for another 36 h. Upon cooling to room temperature, the solid was filtered and washed with chloroform. The filtrate was concentrated under reduced pressure and the resulting residue was triturated with ether (300 mL). The organic phase was washed with dilute Na_2CO_3 solution (1 N), water, brine, and dried over sodium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (petroleum ether/AcOEt 6:1) to afford the desired product as a white solid (5.00 g, 40%). ^1H NMR ($CDCl_3$): δ 7.45–7.32 (m, 5H), 6.92–6.83 (m, 4H), 5.01 (s, 2H), 4.10–4.07 (m, 2H), 3.85–3.68 (m, 12H), 3.47 (t, $J=6.0$ Hz, 2H). MS (EI): *m/z* 438 $[M]^+$. Anal. Calcd for $C_{21}H_{27}BrO_5$: C, 57.41; H, 6.19. Found: C, 57.64; H, 6.15.

4.1.10. 4-[2-[2-(2-Propoxyethoxy)-ethoxy]-ethoxy]phenol (25). A suspension of compound **24** (2.30 g, 4.40 mmol) and Pd–C (10%, 0.20 g) in ethyl acetate (100 mL) was stirred at room temperature under 1 atom of hydrogen gas for 8 h. The solid was then removed by filtration through celite and washed with dichloromethane. The combined filtrate was evaporated under reduced pressure and the resulting residue was purified by column chromatography (CH_2Cl_2/AcOEt 30:1) to afford compound **25** as a colorless oil (15.0 g, 98%). ^1H NMR ($CDCl_3$, 300 Hz): δ 6.74 (d, $J=1.2$ Hz, 4H), 5.58 (s, 1H), 4.03–4.00 (m, 2H), 3.83–3.77 (m, 4H), 3.75–3.67 (m, 8H), 3.44 (t, $J=6.0$ Hz, 2H). MS (EI): *m/z* 348 $[M]^+$. Anal. Calcd for $C_{14}H_{21}BrO_5$: C, 48.15; H, 6.06. Found: C, 48.02; H, 5.92.

4.1.11. 2-Bromo-4-[2-[2-[2-(2-bromo-ethoxy)-ethoxy]-ethoxy]-ethoxy]phenol (26). To a solution of **25** (10.8 g, 31.0 mmol) in dichloromethane (100 mL) in an ice bath was added dropwise a solution of bromine (1.7 mL, 31.0 mmol) in dichloromethane (50 mL) within 30 min. The mixture was stirred at 0 °C for 1 h. Then, aqueous $NaHSO_3$ solution (5%, 100 mL) was added. Stirring was continued until the mixture became colorless. The organic phase was washed with water, brine, and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude produce was purified by flash chromatography (AcOEt/petroleum ether 1:4) to afford compound **26** as a colorless oil (13.0 g, 100%). ^1H NMR ($CDCl_3$): δ 7.03 (d, $J=3.0$ Hz, 1H), 6.92 (d, $J=9.0$ Hz, 1H), 6.92 (d, d, $J_1=3.0$ Hz, $J_2=9.0$ Hz, 1H), 5.44 (s, 1H), 4.06–4.03 (m, 2H), 3.84–3.78 (m, 4H), 3.74–3.68 (m, 8H), 3.46 (t, $J=6.0$ Hz, 2H). HRMS (EI): Calcd for $C_{14}H_{20}Br_2O_5Na$ $[M+Na]^+$: 425.9676. Found: 448.9576.

4.1.12. 1,4,7,13,20,23,26,29,32-Decaoxa-15,34-dibromo-[13,13]paracyclophane (27). A suspension of phenol **26** (0.85 g, 2.00 mmol) and potassium carbonate (1.40 g, 10.0 mmol) in acetonitrile (80 mL) was heated under reflux for 24 h and then cooled to room temperature. The solid was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was triturated with dichloromethane (100 mL) and the organic phase was washed with dilute sodium carbonate solution, water, brine, and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude produce was purified by column chromatography (CH_2Cl_2/AcOEt 2:1) to afford **27** as a white solid (0.38 g, 56%). Mp 104–106 °C. ^1H NMR ($CDCl_3$): δ 7.08 (d, $J=3.0$ Hz, 2H), 6.78 (d, $J=9.0$ Hz, 2H), 6.73 (d, d, $J_1=9.0$ Hz, $J_2=3.0$ Hz, 2H), 4.04–4.07 (m, 4H), 3.99–3.96 (m, 4H), 3.88–3.85 (m, 4H), 3.83–3.80 (m, 4H), 3.78–3.75 (m, 4H), 3.70–3.64 (m, 12H). MS (EI): *m/z* 694 $[M]^+$. Anal. Calcd for $C_{28}H_{38}Br_2O_{10}$: C, 48.43; H, 5.52. Found: C, 48.44; H, 5.51.

4.1.13. 1,4,7,13,20,23,26,29,32-Decaoxa-15,34-di(4-carboxy-but-1-ynyl)[13,13]paracyclophane (28). To a stirred solution of pyrrolidine (4 mL) were added compound **27** (0.30 g, 0.43 mmol), $Pd(PPh_3)_4$ (80.0 mg, 0.070 mmol, 10%) and **15** (0.30 g, 3.00 mmol). The reaction mixture was stirred at 80 °C for 4 h and then cooled to room temperature. The solvent was evaporated in vacuo and the residue was triturated with dichloromethane (50 mL). The organic phase was washed with 1 N hydrochloride, water, brine, and dried over sodium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (CH_2Cl_2–CH_3OH (50:1). Compound **28** was obtained as a yellow solid (0.15 g, 48%). Mp 108–110 °C. IR (cm^{-1}): 3110, 3045, 2912, 2868, 2233, 1729, 1604, 1505, 1236, 842, 802. ^1H NMR ($CDCl_3$): δ 2.61 (t, $J=6.9$ Hz, 4H), 2.76 (t, $J=6.6$ Hz, 4H), 3.71–4.73 (m, 12H), 3.79–3.83 (m, 8H), 3.90 (s, 12H), 6.56 (d, $J=9.0$ Hz, 2H), 6.72 (d, d, $J_1=3$ Hz, $J_2=9.3$ Hz, 2H), 6.88 (d, $J=3$ Hz, 2H). MS (ESI): *m/z* 752 $[M+Na]^+$. Anal. Calcd for $C_{38}H_{48}O_{14}$: C, 62.63; H, 6.64. Found: C, 62.27; H, 6.38.

4.1.14. Compound 8. To a solution of **28** (0.17 g, 0.23 mmol) in dichloromethane (5 mL) was added oxalyl chloride (0.2 mL). After stirring for 0.5 h at room temperature, the solution was concentrated in vacuo to afford **29** as an oil, which was used directly for next step. To

a stirred solution of **21** (0.21 g, 0.49 mmol), NEt_3 (0.5 mL) and DMAP (10 mg) in chloroform (10 mL) was added a solution of the above **29** in chloroform (5 mL). The mixture was heated under reflux for 12 h. After work-up, the crude product was subjected to flash chromatography (EtOAc/CH_2Cl_2 1:1) to afford **8** as a yellowish oil (0.10 g, 30%). IR (cm^{-1}): 3304, 2926, 2855, 2228, 1706, 1610, 1503, 1389, 1286, 1136, 855, 803. ^1H NMR ($CDCl_3$): δ 0.85 (t, J= 7.2 Hz, 12H), 1.14–1.25 (m, 48H), 1.41–1.51 (m, 4H), 1.61–1.70 (m, 4H), 2.25–2.28 (m, 2H), 2.78 (s, 8H), 3.69–3.72 (m, 16H), 3.79–3.82 (m, 8H), 3.95–3.98 (m, 4H), 4.05–4.09 (m, 4H), 6.71 (s, 4H), 6.87 (s, 2H), 8.13 (d, d, J_1=3.6 Hz, J_2=8.7 Hz, 4H), 8.46–8.51 (m, 4H), 8.99 (s, 2H), 9.63 (s, 2H). MS (ESI): m/z 1545 $[M+H]^+$. Anal. Calcd for $C_{90}H_{128}N_8O_{14}$: C, 69.92; H, 8.34; N, 7.25. Found: C, 69.49; H, 8.38; N, 6.94.

4.1.15. Compound 30. This compound was prepared from **21** and **31** by a method analogous to **20**. The crude product was chromatographed (CH_2Cl_2/MeOH 50:1) to give **30** as a yellow solid (49%). Mp 156–158 °C. ^1H NMR ($CDCl_3$): δ 0.84 (t, J=6.9 Hz, 12H), 1.22–1.54 (m, 52H), 1.63–1.75 (m, 12H), 2.27–2.30 (m, 2H), 2.46 (t, J=7.2 Hz, 4H), 8.11 (d, J=9.0 Hz, 4H), 8.44 (t, J=8.4 Hz, 4H), 8.65 (s, 4H). HRMS (MALDI): m/z 991.7435. Calcd for $C_{60}H_{95}N_8O_4$ $[M+H]^+$: 991.7476.

Acknowledgements

We thank the Ministry of Science and Technology (No. G2000078101), the National Natural Science Foundation (20321202, 20332040, 20372080), and the State Laboratory of Bioorganic and Natural Products Chemistry of China for financial support.

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Corrigendum

Corrigendum to: "Studies on organolithium-induced alkylative desymmetrisation of epoxides: synthesis of enantioenriched β-amino cycloheptenols from 6,7-epoxy-8-azabicyclo[3.2.1]octanes" [Tetrahedron 60 (2004) 5185]

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Available online 21 July 2004

6,7-Epoxy-8-azabicyclo[3.2.1]octanes **7** and **8**, differing only in the *N*-protecting group (benzyloxycarbonyl instead of Boc), have been previously synthesized (by a very different route to that we described).[1] This previous work should have been cited to put our substrate syntheses in proper perspective. We thank Dr. Malpass for bringing this paper to our attention.

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doi of original article 10.1016/j.tet.2004.04.047
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doi:10.1016/j.tet.2004.06.091