University of Southampton

School of Chemistry

The investigation of group selective intramolecular Diels-Alder reactions towards hydrindene moieties

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Thesis for the degree of Doctor of Philosophy

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Preface

The research described in this thesis was carried out by Nadia Azzi under the supervision of Dr Bruno Linclau at the University of Southampton between October 2002 and August 2005. No part of this thesis has been previously submitted at this university or any other university.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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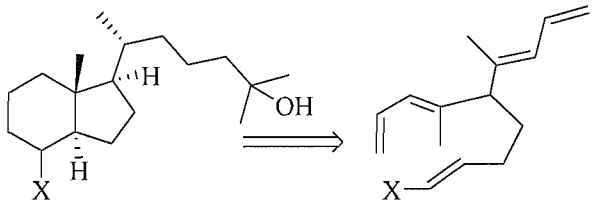
Doctor of Philosophy

THE INVESTIGATION GROUP SELECTIVE INTRAMOLECULAR DIELS-ALDER REACTION TOWARDS THE SYNTHESIS OF HYDRINDENES MOIETIES

By Nadia Azzi

We report the combination of an intramolecular Diels-Alder (IMDA) reaction and a desymmetrisation processes to build enantioselectively the steroid CD-ring moiety starting from an achiral precursor. This novel methodology would be applied in vitamin D total synthesis.



Apparent symmetry in CD-ring / side chain **Achiral precursor**

We describe the synthesis of 5-substituted-nona-1,3,6,8-tetraene, a simplified precursor, and its use in group selective IMDA reaction. We also describe our progress toward the synthesis of 4,6-dimethyl-5-substituted-nona-1,3,6,8-tetraene, the desired IMDA precursor. We report the attempts to form a skipped bis(diene) from a skipped bis(acetylene) system. We also described another attempt for the bis(diene) synthesis based on a double Wittig-Horner reaction which appeared to be unsuccessful. Eventually, the bis(diene) was prepared in 8 steps from ethyl sorbate. The second part of the project concerns the survey on the IMDA reaction. The reaction was studied with an achiral auxiliary and Lewis acid (chiral or achiral). The reaction was also carried out with chiral auxiliary and a Lewis acid. A wide range of Lewis acids were screened. It was found that the IMDA reaction proceeded in moderate yield with a good diastereoselectivity and excellent enantioselectivity.

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RESUME

FACULTY OF SCIENCE

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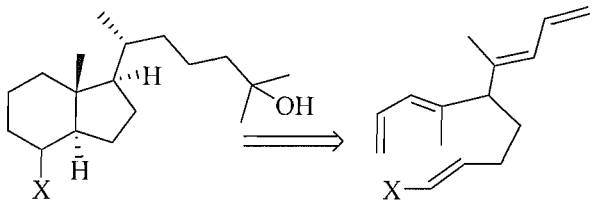
L'ETUDE D'UNE SELECTION DE GROUPE PAR UNE REACTION INTRAMOLECULAIRE DE DIELS-ALDER POUR LA SYNTHESE DE NOYAUX HYDRINDENES

Par Nadia Azzi

Le travail effectué au cours de mon Ph D concerne la synthèse des cycles CD de la vitamine D à partir d'un précurseur achiral. L'étape clés est une réaction de déssymétrisation d'un bis(diene) à l'aide d'une réaction intramoléculaire de Diels-Alder (IMDA).



Apparent symmetry in CD-ring / side chain **Achiral precursor**

Pour commencer l'étude de déssymétrisation, un précurseur simplifié sans les méthyles a été préparé. Plusieurs stratégies ont été envisagées pour former ce type de système. La formation de bis(diene) à partir de 1,4-diyne a été infructueuse. L'utilisation d'une double réaction de Wittig-Horner a aussi échouée. La préparation de bis(diene) a finalement été effectué en 8 étapes à partir du sorbate d'éthyle. La deuxième partie du projet concerne l'étude de la réaction d'IMDA avec un auxiliaire achiral et un acide de Lewis (chiral ou achiral). La réaction a également été étudiée avec un auxiliaire chiral et un acide Lewis. Une large variété d'acide de Lewis a été utilisée au cours de cette étude. Il a été observé que la réaction d'IMDA s'effectue avec des rendements modérés mais avec une bonne diastereoselectivité et une excellente enantioselectivité.

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Pour ma mère

« Quand on ne sait pas, on ne se pose pas trop de questions, mais quand on commence à disposer d'un début d'explication, on veut à tout prix tout savoir, tout comprendre. »

- Bernard Werber

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I am also grateful to Julie Herniman and John Langley who kept the MS running as well as Joan Street and Neil Wells who kept the NMR running. I want to thank Mark Light for the X-ray elucidation of **130a**.

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I also want to thank Mathieu who support me during those three years and never complained when I had to spend my week end working. You always encouraged me in my difficult moments.

Then I really want to thank my mum who always was behind me and supported me during all those years. However, surely the PhD it's not that easy !

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Je veux aussi remercier Mathieu qui m'a soutenu pendant ces trois années et qui ne s'est jamais plaint quand je devais passer mes week end à travailler. Tu m'as toujours encouragé dans les moments difficiles.

Enfin je veux vraiment remercier ma mère qui a toujours été derrière moi et qui m'a soutenu pendant toutes ces années. Par contre, ce qui est sûr, c'est que le PhD n'est pas si facile !

Abbreviations

Bn	benzyl
BHT	2,6-di-*tert*-butyl-4-methylphenol
BLA	Brønsted Lewis acid
CAB	chiral acyloxyborane
calc	calculated
CIMS	chemical ionisation mass spectrometry
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-diacyano-*p*-benzoquinone
DIAD	diisopropyl azodicarboxylate
Dibal-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMA	dimethyl acetamide
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin's periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DTBH	2,5-di-*tert*-butylhydroquinone
ee	enantiomeric excess
EIMS	electron ionisation mass spectrometry
equiv	equivalent
EDG	electron donating group
EWG	electron withdrawing group
FMO	frontier molecular orbital
HDA	hetero Diels-Alder
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HOMO	Highest Occupied Molecular Orbital
IMDA	intramolecular Diels-Alder
IR	infrared

LAC	Lewis acid catalysed Diels-Alder
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2,6,6-tetramethyl piperidine
LUMO	Lowest Unoccupied Molecular Orbital
m-CPBA	*m*-chloroperoxybenzoic acid
MPM	*p*-methoxyphenylmethyl
Na_2EDTA	disodium ethylenediamine tetraacetic acid
NaHMDS	sodium hexamethyldisilazane
NMR	nuclear magnetic resonance
PMB	*p*-methoxybenzyl
PTH	parathyroid hormone
PTSA	p-toluene sulfonic acid
pyr	pyridine
rt	room temperature
RP-HPLC	reverse-phase high performance liquid chromatography
TADA	trans annular Diels-Alder
TBA	*tris*(*p*-bromophehyl)aminium hexachloroantimonate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	triflluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl

Chapter 1: Introduction

1.1 Vitamin D

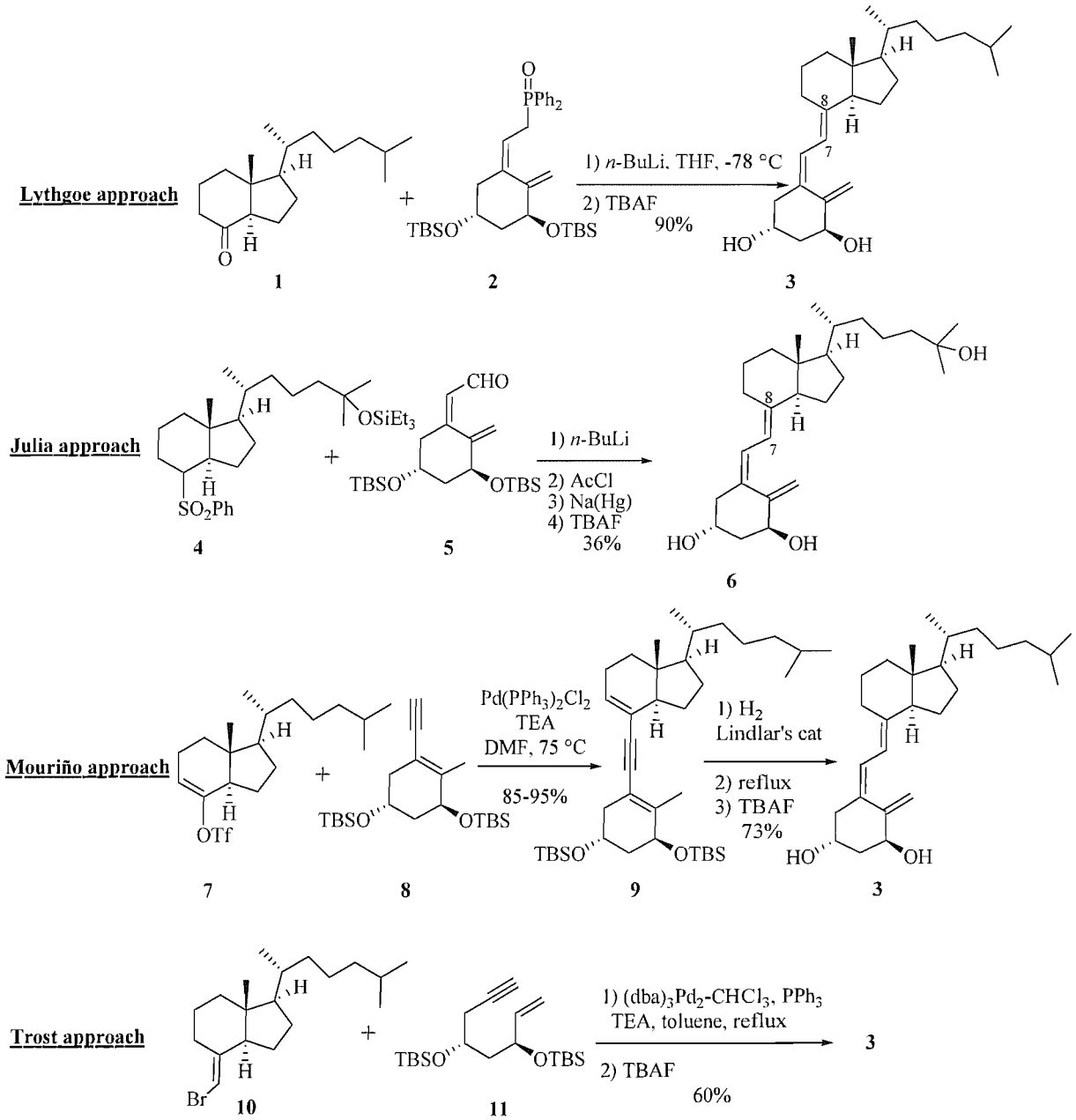
1.1.1 Biological activity

It was found that 1α,25-dihydroxyvitamin D_3 (also called calcitriol or 1α,25-$(OH)_2$-D_3) exhibits a much broader spectrum of biological activities beyond its classical calcium and phosphate regulation. It appeared that 1α,25-dihydroxyvitamin D_3 can be used to treat a wide range of human diseases such as cancer, bone diseases, skin diseases and diseases associated with aberrant immunological responses.[1] Calcitriol and its metabolites reduce the proliferation of malignant cells. It was shown that 1α,25-dihydroxyvitamin D_3 target cells have their own enzyme machinery for the local regulation of 1α,25-dihydroxyvitamin D_3 concentration that enables to separate regulation of mineral homeostasis and other actions of 1α,25-dihydroxyvitamin D_3.[2] However the synthesis of 1α,25-dihydroxyvitamin D_3 analogues able to separate the anticancer activity and the calcium regulation was necessary in order to reduce side effects occurring when 1α,25-dihydroxyvitamin D_3 level in the blood is too high.[3,4]

1.1.2 Synthesis of 1α,25-dihydroxyvitamin D_3

1α,25-Dihydroxyvitamin D_3 contains a *trans*-hydrindane moiety and 8 stereocenters (including the two trisubstituted double bonds). The 1α,25-dihydroxyvitamin D_3 total synthesis is usually achieved by a convergent strategy where the CD-ring system and the A ring are prepared separately and assembled in the final stages. A number of general procedures to synthesize the vitamin D skeleton have been reported.[5-7]

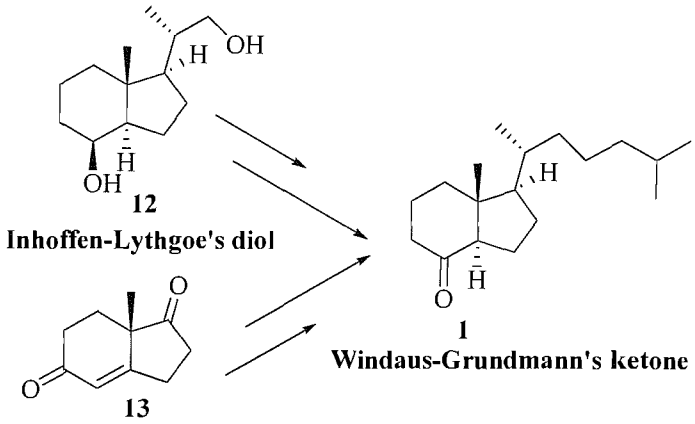
The most important strategy for vitamin D total synthesis is based on Lythgoe's method with a disconnection between the carbon C-7 and C-8 (Scheme 1-1). The Windaus-Grundmann's ketone **1** and the phosphine oxide **2** are coupled *via* a Wittig-Horner reaction, typically with high stereoselectivity to afford 1α-hydroxyvitamin D_3 **3**. The ketone **1** has been used as a key building block by many groups for 1α-hydroxyvitamin D_3 total synthesis.[8-17] Lythgoe also reported the synthesis of calcitriol by using a Julia olefination for the coupling step. The sulfone **4** was deprotonated with *n*-BuLi and was reacted with the A-ring **5**. After the acylation of the alcohol, sodium-amalgam reduction and deprotection of the silyl groups afforded 1α,25-dihydroxyvitamin D_3 **6** in 45% yield.[18,19]



Scheme 1-1

Mouriño *et al.*,[20,21] prepared vitamin D using a Stille coupling reaction. The dienyne **8** and the enol triflate **7**, prepared from the corresponding ketone **1**, were coupled using $Pd(PPh_3)_2Cl_2$ to afford **9** in high yield. The dienyne **9** was then semi-hydrogenated with Lindlar's catalyst giving a triene which then isomerised under thermal conditions followed by silyl deprotection to obtain 1α-hydroxyvitamin D_3 **3**. More recently, Trost *et al.*,[22] developed an approach based on a tandem coupling reaction using vinyl bromide **10** and enyne **11**. The formation of the A-ring and the coupling occurs in a single step to give, after silyl deprotection, 1α-hydroxyvitamin D_3 **3** in 60% yield.

Hence, all the coupling steps involved the Windaus-Grundmann's ketone **1** or a derivative. The CD-ring system **1** is usually prepared from the Inhoffen-Lythgoe diol[23,24] **12** or from the Hajos-Wiechert ketone[18,19,25] **13** (Scheme 1-2). It can also be prepared by an intramolecular Diels-Alder (IMDA) reaction (see section 1.3.4).

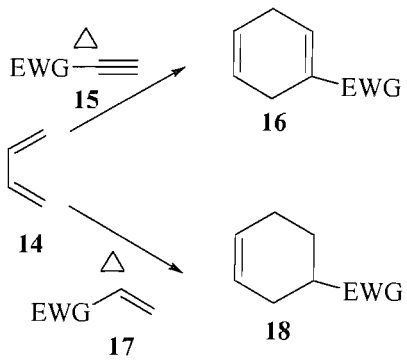


Scheme 1-2

1.2 The Diels-Alder reaction

1.2.1 Introduction

The Diels-Alder reaction is widely used to form six-membered rings in natural product total synthesis.[26] This pericyclic reaction is classified as a [4+2] cycloaddition reaction where the 4 and the 2 represents the number of π electrons engaged in the process. The cycloaddition involves a dienophile, which has at least one π bond such as **15** or **17**, typically electron deficient and a conjugated diene **14**, typically electron rich. The two components are heated in an apolar solvent to afford a cyclohexadiene **16** or a cyclohexene **18** (Scheme 1-3). The Diels-Alder reaction usually proceeds in high yield with a high regioselectivity and diastereoselectivity. The stereochemistry is controlled by a six-membered boat transition state.



Scheme 1-3

In the last decades, different variants of the Diels-Alder reaction have been developed: hetero Diels-Alder (HDA),[27,28] Lewis acid catalysed Diels-Alder (LAC),[29-31] intramolecular Diels-Alder (IMDA),[32-34] transannular Diels-Alder (TADA),[32] biosynthetic Diels-Alder.[35] In this thesis, discussion will be focused on the IMDA reaction.

1.2.2 The FMO theory

1.2.2.1 HOMO-LUMO interactions

The Frontier Molecular Orbital (FMO) theory states that the course of reaction is directed by the most favourable interaction between the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) of the two reactants.

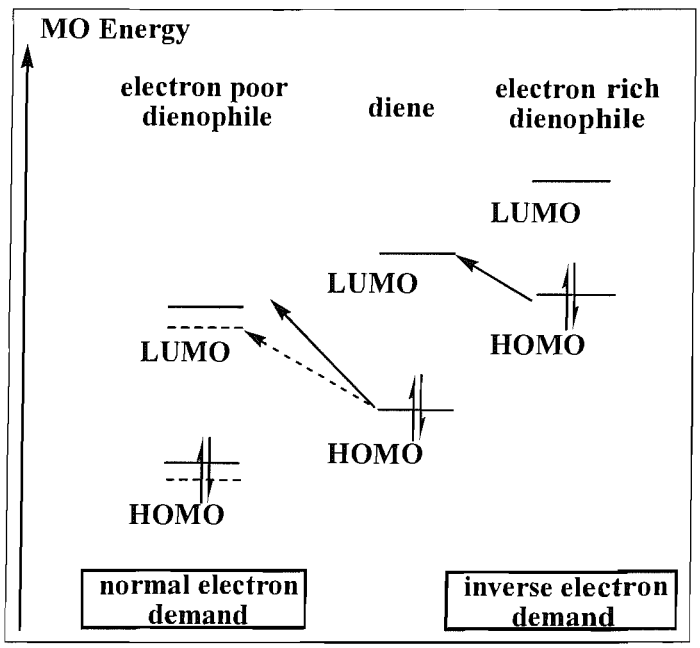


Figure 1-1

The normal electron demand Diels-Alder reaction is a $HOMO_{diene}$-$LUMO_{dienophile}$ Diels-Alder reaction which occurs between electron rich dienes and electron deficient dienophiles (Figure 1-1, left). The inverse electron demand Diels-Alder reaction is a $LUMO_{diene}$-$HOMO_{dienophile}$ Diels-Alder reaction which occurs between electron deficient dienes and electron rich dienophiles (Figure 1-1, right).

The normal electron demand cycloaddition can be activated by lowering the energy gap between the $HOMO_{diene}$ and the $LUMO_{dienophile}$ which allows the reaction to occur under milder conditions. The $HOMO_{diene}$ energy can be raised by introducing electron donating groups (EDG). On the other hand, the $LUMO_{dienophile}$ energy can be lowered by introducing electron withdrawing groups (EWG) and/or by Lewis acid coordination. The coordination to a Lewis acid reduces the electron density of the C=O double bond.

The orbital coefficient of the termini in the HOMO of a $(4n + 2)\pi$ electron alkene or polyene have the same sign, but have opposite signs in the LUMO. On the other hand, the orbital coefficient of the termini in the HOMO of a $(4n)\pi$ electron polyene have the opposite signs, but have the same sign in the LUMO (Figure 1-2).[36]

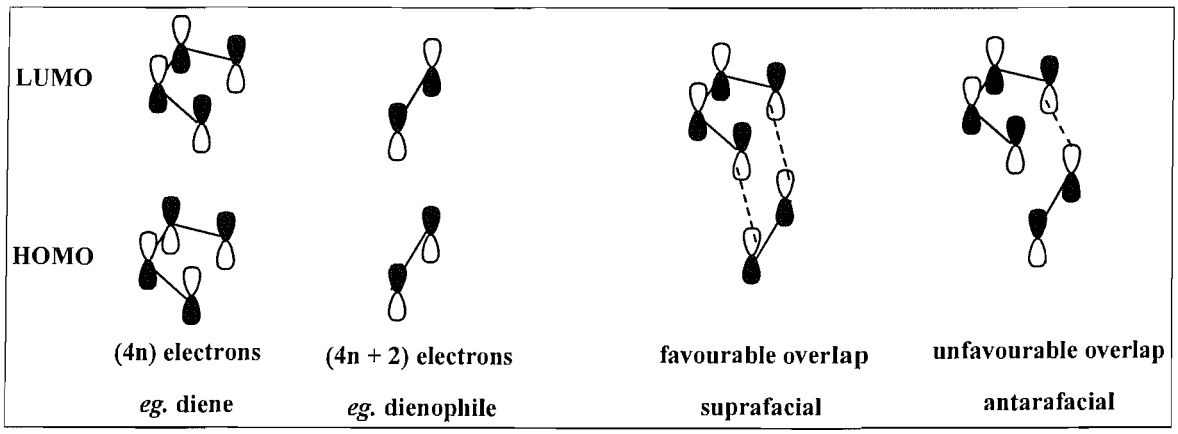
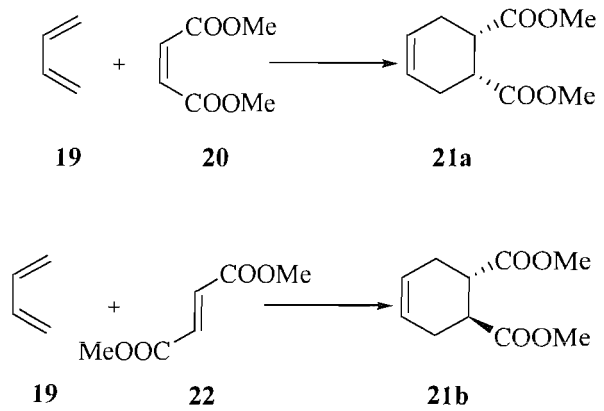


Figure 1-2

A bond can only be formed when the orbital of the termini in the HOMO and in the LUMO, having the same sign, overlap. When the reaction occurs between a molecule with $(4n + 2)\pi$ electrons and a molecule with $(4n)\pi$ electrons, the bonds are formed on the same side of a π-system, the process is then called suprafacial. On the other hand, when the reaction involves two molecules with $(4n + 2)\pi$ electrons or $(4n)\pi$ electrons, the two new bonds are formed on the opposite sides of a π-bond. The process is then called antarafacial. The Diels-Alder reaction occurs with a suprafacial mode, leading to a boat type transition state (Figure 1-2).

1.2.2.2 Stereochemistry

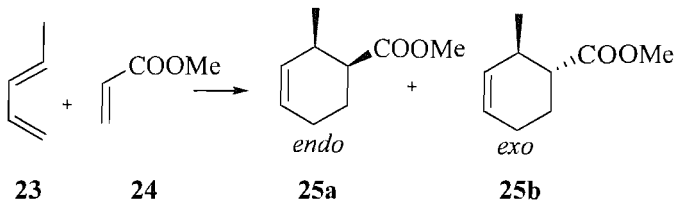
The *E* or *Z* stereochemistry in the diene or in the dienophile is reproduced in the Diels-Alder product as illustrated on Scheme 1-4. This is a direct consequence of the suprafacial approach. The *Z* dienophile **20** affords cycloadduct **21a** with *cis* substituents while the *E* dienophile **22** affords cycloadducts **21b** with *trans* substituents.



Scheme 1-4

1.2.2.3 The *endo/exo* selectivity

The Diels-Alder reaction can give two different cycloadducts, the *endo* **25a** or the *exo* **25b** as depicted on Scheme 1-5.



Scheme 1-5

When the dienophile approaches the diene in the *endo* transition state (Figure 1-3), secondary interactions can take place leading to additional stabilisation compared to the *exo* approach. Hence, the *endo* adduct is kinetically favoured which gives rise to the so called *endo/exo* selectivity. The *endo/exo* selectivity can be influenced by the nature of the Lewis acid employed, by the electronic nature of the groups present on the dienophile or by the introduction of bulky groups which introduced steric hindrance.

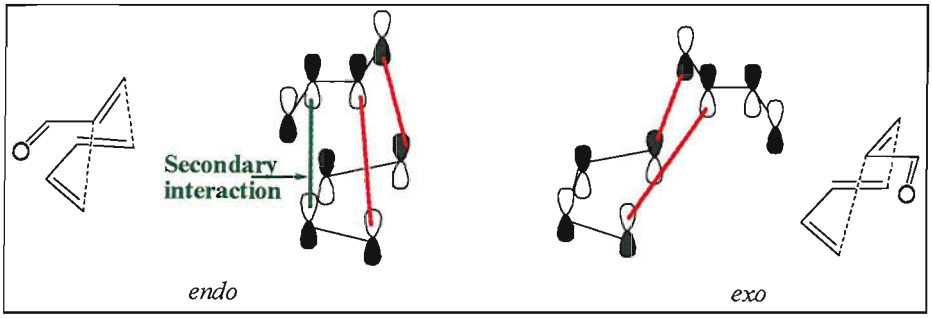
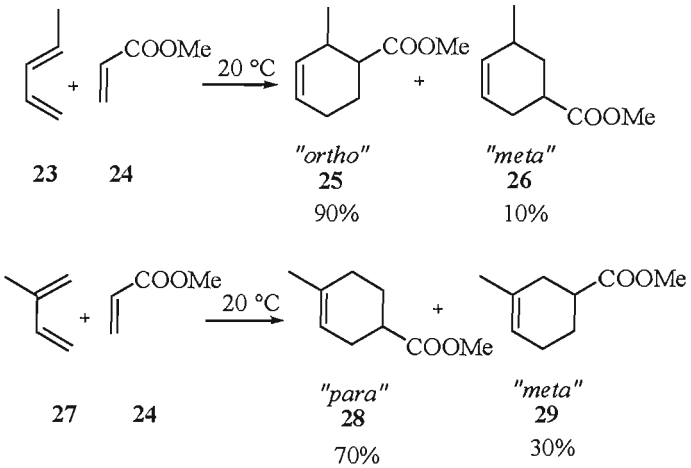


Figure 1-3

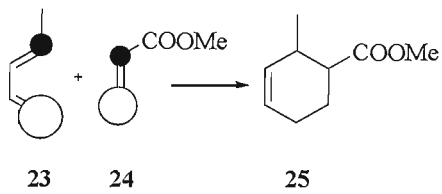
1.2.2.4 Regioselectivity

When the Diels-Alder reaction occurs between an unsymmetrical diene and an unsymmetrical dienophile, two regioisomers can be formed. The relative position of the substituents on the cycloadduct is indicated such as in disubstituted benzene nomenclature (*ortho*, *meta*, *para*). Usually, "*ortho*" **25** and "*para*" **28** regioisomers are favoured over the "*meta*" **26** or **29** regioisomer (Scheme 1-6).[37]



Scheme 1-6

The *ortho-para* regioselectivity is explained by the orbital coefficient. The strongest interaction occurs between the orbital on each molecule with the largest coefficient (Scheme 1-7).

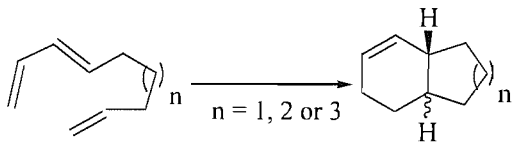


Scheme 1-7

1.2.3 The IMDA reaction

The IMDA occurs when the substrate incorporates both a diene and a dienophile unit separated by a tether of at least 3 atoms. The intramolecular reaction is faster than the intermolecular reaction. However IMDA reactions are usually performed in dilute solution to avoid the bimolecular Diels-Alder process.

The IMDA reaction is often used to form a cyclohexene ring fused with a five, six or seven-membered ring (Scheme 1-9). The presence of the tether has a dramatic influence on the stereochemical outcome of the Diels-Alder reaction.

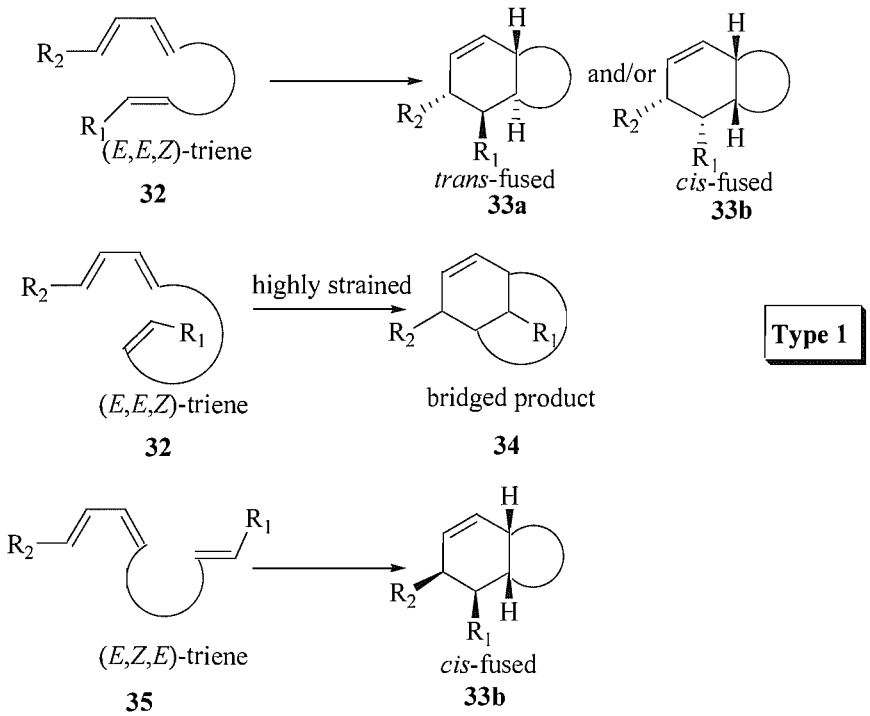


30 **31**

Scheme 1-8

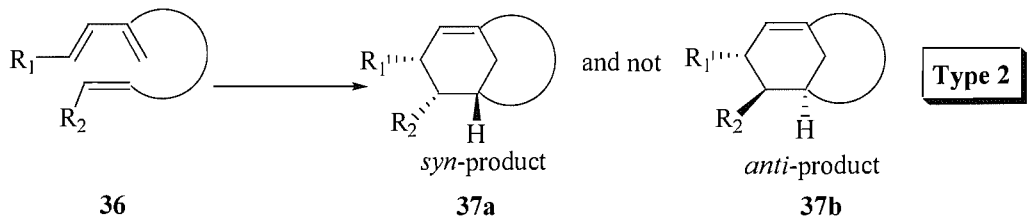
1.2.3.1 Regioselectivity

Unlike in the intermolecular Diels-Alder case, regioselectivity is controlled by the length of the tether as well as the conformation of the triene system. There are two different types of IMDA reactions: the type 1 and the type 2. In the type 1, the diene and the dienophile are linked from the terminal carbon atom of the diene (Scheme 1-9). The resulting IMDA product is a fused bicyclic adduct **33a** and/or **33b**. The formation of the bridged bicyclic product **34** is highly strained for short tether but few examples have been reported for a tether greater than 10 atoms.[38] The (*E*,*E*)-dienes **32** usually affords the *trans*-fused **33a** (*endo* adduct) and/or the *cis*-fused **33b** (*exo* adduct) products. On the other hand, the (*E*,*Z*)-dienes **35** affords preferentially *cis*-fused product. (*E*,*Z*)-dienes are less reactive than (*E*,*E*)-dienes and the use of stronger Lewis acid such as $MeAlCl_2$ is required. For this reason, (*Z*,*E*,*E*)-trienes and (*E*,*Z*,*E*)-trienes have been less employed than (*E*,*E*,*E*)-trienes.[33,39]



Scheme 1-9

In the type 2 IMDA,[39] the diene and the dienophile are linked from the non terminal carbon of the diene such as **36** In this case, the IMDA product **37a** is a bridgehead alkene bicycle adduct (Scheme 1-10).[40] The strain in the bridgehead alkene requires high temperature under thermolytic conditions. Lewis acid catalysed type 2 IMDA reaction allows to perform the cyclisation in mild conditions (lower temperature).[40]



Scheme 1-10

In this thesis, discussion will be focused on the study of type 1 IMDA reaction.

1.2.3.2 Polymerisation side processes

The IMDA gives in some cases low yield due to competitive reactions. The polymerisation of trienes competes with the IMDA reaction especially under Lewis acid catalysis conditions. Evans et *al.*[41] showed that under the IMDA conditions, (*E*,*E*)-2,8,10-

undecatrienoate ester polymerised in presence of any Lewis acid while the thermal conditions afford a 1:1 mixture of diastereoisomers. Roush *et al.*,[42] observed that the (*E*,*E*)-2,7,9-decatrienoate ester polymerised very easily under Lewis acid catalysis. It also appears that monosubstituted dienes are more likely to polymerise than 1,4-disubstituted dienes. The polymerisation reaction explains the low yield observed for the IMDA product under Lewis acid catalysis.

The polymerisation is limited by reducing the amount of Lewis acid employed and/or by using a catalytic amount of a radical inhibitor such as BHT or DTBH.[43] The use of milder Lewis acid such as alkyl aluminium chloride or alkyl aluminium is also beneficial to limit the polymerisation.

1.3 The IMDA reaction toward hydrindane moieties

1.3.1 The hydrindane moiety

The hydrindane, also called bicyclo[4.3.0]nonane, is a C6-C5 ring fused moiety and the hydrindene is the name given to the moiety containing a double bond (Figure 1-4). The hydrindene system numbering is depicted on Figure 1-4. In this section, the hydrindene numbering will be used to describe the position of the substituents on the hydrindene moiety (as opposed to steroid numbering).

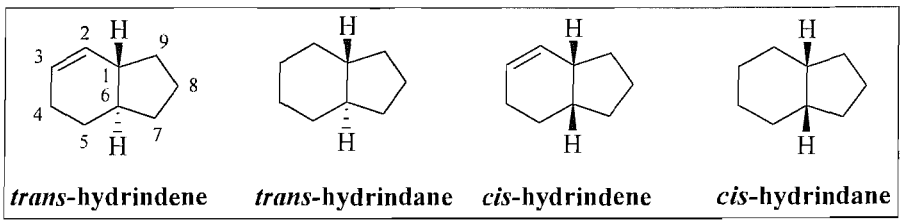


Figure 1-4

The *trans*-hydrindane skeleton is present in a large number of natural product among steroids, vitamin D[44] or antibiotics.[35,45-47] Recently other natural compounds with interesting biological activities and containing the *trans*-hydrindane moiety were characterised (Figure 1-5).[48-50]

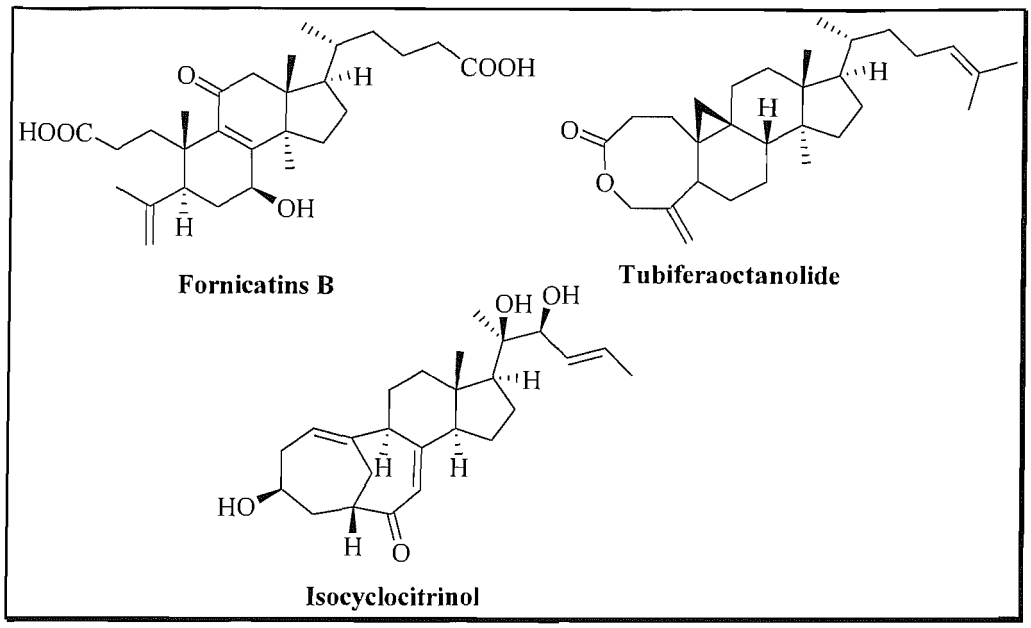
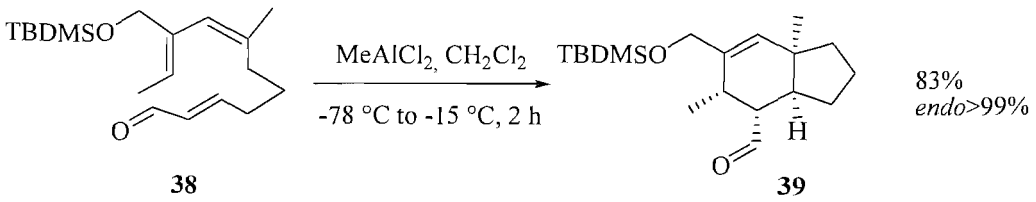


Figure 1-5

1.3.2 Achiral tether

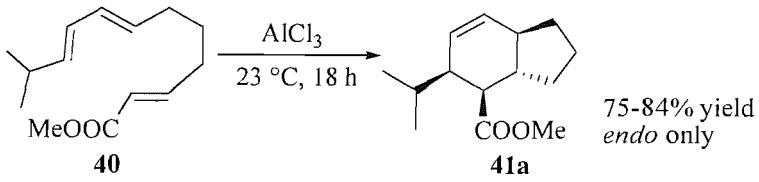
The tether is a spacer which can be used permanently or temporarily to join the diene and the dienophile. The tether is an alkane chain with or without heteroatoms such as O, N, S or Si to afford, after the cycloaddition, a cyclohexene fused with a heterocyclic ring. The nature of the heteroatom does not affect the diastereoselectivity, with simple trienes. Some functionality present in the final product can be present on the tether such as an ester, an amide or a ketone.

Previous studies on IMDA reaction show that a reaction occurring between a (*E*)-dienophile and a (*E,E*)-diene affords a *trans*-fused ring system[26] proving an *endo* transition state. The IMDA reaction between a (*E*)-dienophile and an (*E,Z*)-diene affords a *cis*-fused ring system. The ratio of *trans*/*cis*-fused product depends on the reaction conditions and on the nature of the substituents present on the tether and on the diene. Recently, Roush *et al.*,[51,52] reported that Lewis acid catalysed IMDA of (*E,Z,E*)-1,6,8-nonatrienes **38** gave preferentially the *cis*-fused hydrindene moiety **39** by Lewis acid catalysis or by thermal conditions (Scheme 1-11). Munakata *et al.*,[53] compared the thermolytic IMDA reaction of (*E,Z,E*)-1,6,8-nonatrienes and (*E,E,Z*)-1,6,8-nonatrienes. The IMDA reaction of (*E,Z,E*)-1,6,8-nonatrienes afforded the *cis*-fused hydrindene as a single diastereoisomer. On the other hand, (*E,E,Z*)-1,6,8-nonatrienes gave a mixture of 4 diastereoisomers along with two others diastereoisomers resulting from diene isomerization.



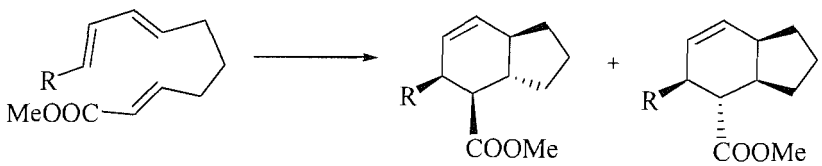
Scheme 1-11

Many examples in the literature show a total *endo* selectivity either by Lewis acid catalysis[54-56] or even by silica gel catalysis.[57] The Lewis acid employed is usually an aluminium (Scheme 1-12) or borane catalyst.[55]



Scheme 1-12

The selectivity of the IMDA reaction is also influenced by the nature of substituents on the diene. The presence of an iPr group on the terminal position of the diene slightly improved the *endo* selectivity for (*E*,*E*,*E*)-nonatrienes while no difference was observed for (*E*,*E*,*Z*)-nonatrienes.[42] The presence of alkyl groups on C-4 increases the orbital coefficient of the HOMO of the diene.

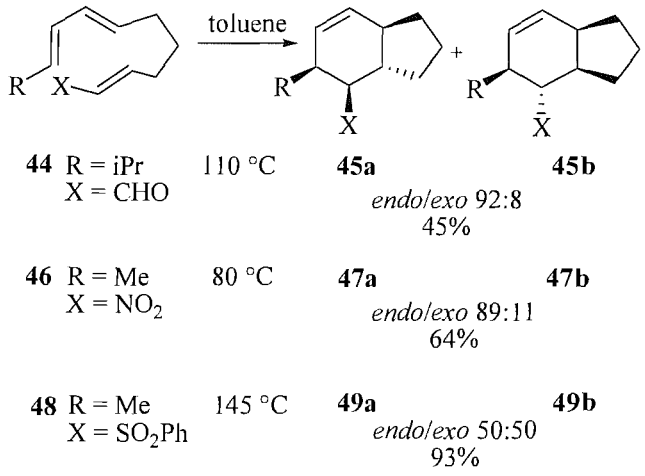


42		**43a**		**43b**
R = H	150 °C, 24 h	60	: 65%	40
40		**41a**		**41b**
R = iPr	150 °C, 40 h	72	: 72%	28

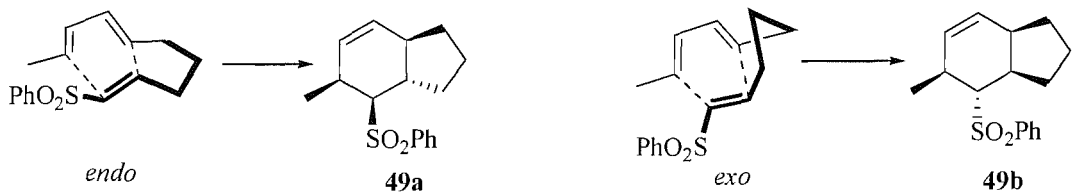
Scheme 1-13

Roush *et al.*,[58] showed that the *endo* selectivity obtained with (*E*,*E*,*E*)-nonatrienes is increased under thermal conditions as the EWG of the dienophile is changed along the series $CONR_2<CO_2Me<COMe<CHO$. However, the (*E*,*E*,*E*)-nonatrienal **44** gave the cycloadduct in moderate yield surely due to polymerisation (Scheme 1-14). Kurth *et al.*,[59] studied the thermal IMDA reaction with a dienophile activated by a nitro group. The (*E*,*E*,*E*)-nitrotrienes **46**

afforded the *trans*-hydrindene moiety with a slightly lower selectivity than when aldehyde **44**[58] was used. Craig *et al.*[60] studied the behaviour of sulphonyl-trienes **48** in the IMDA reaction. Contrarily to the other groups described above, the sulphonyl group tend to favour the *cis*-fused adduct **49b** resulting from the *exo* transition state. The *endo/exo* ratio was improved from 50:50 to 1:99 respectively from (*E,E,E*)-nonatrienes to (*E,E,Z*)-nonatrienes. The lack of *endo* selectivity was attributed to the steric interactions between the sulphonyl group and the diene in the *endo* transition state (Scheme 1-15).

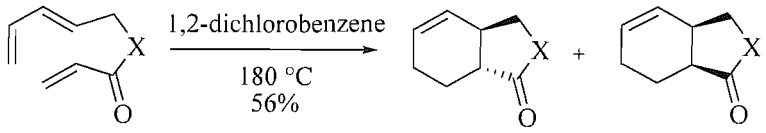


Scheme 1-14



Scheme 1-15

The IMDA reaction of internally activated nonatrienone afforded mainly the *cis*-fused hydrindene. The IMDA stereoselectivity depends on the nature of the EWG which internally activates the dienophile. The *cis*-fused **52** hydrindene is preferentially formed over the *trans*-fused **51**, with a ketone[61] or an ester[62] tether, at least with non substituted trienes (Scheme 1-16).

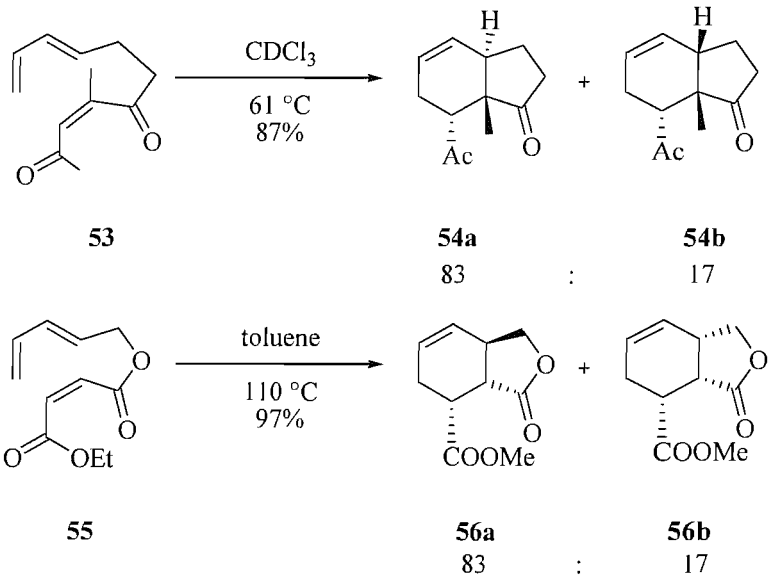


50a X = O **51a** 30 : **52a** 70 — 56%

50b X = CH_2 **51b** 13 : **52b** 87 — 51%

Scheme 1-16

On the other hand, the introduction of substituents on the tether or the activation of the terminal position of the dienophile tend to favour the formation of *trans*-fused hydrindene **54a** and **56a**, respectively with a ketone tether and an ester tether (Scheme 1-17).[63,64] The tether limits the flexibility and makes the transition state more rigid therefore a better regioselectivity and stereoselectivity are usually obtained .

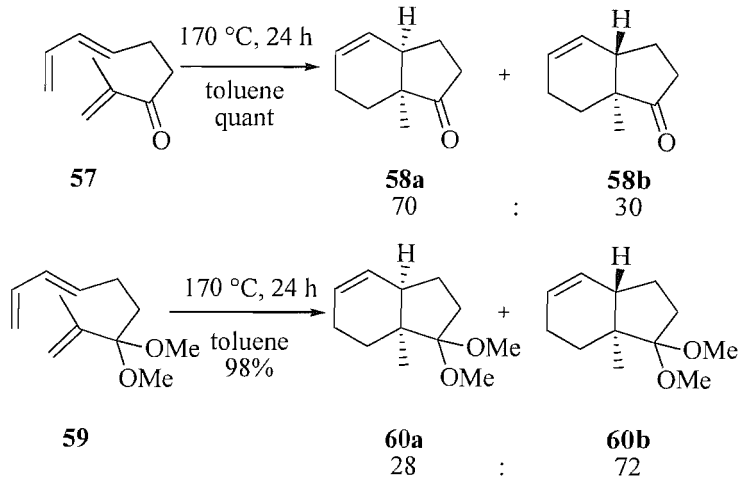


53 **54a** 83 : **54b** 17

55 **56a** 83 : **56b** 17

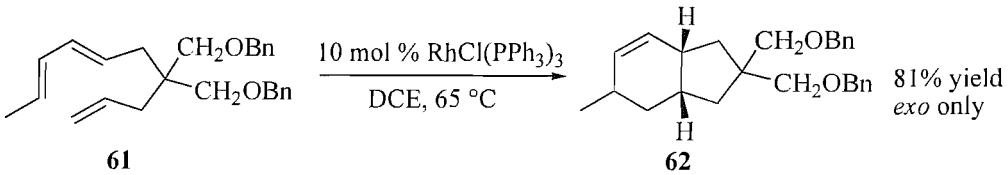
Scheme 1-17

The IMDA reaction of internally activated nonatrienone **57** afforded mainly the *cis*-fused hydrindene. The major adduct **58a** is consistent with the *endo* transition state. When the EWG is attached to C-6, the orbital coefficient of the LUMO is reversed compared with the IMDA precursor with the EWG on C-5. On the other hand, when the ketone was replaced by an acetal, the *trans*-fused hydrindene **60b** was isolated as the major cycloadduct (Scheme 1-18). The steric interaction, between the geminal methoxy groups and the diene, favoured the *trans*-hydrindene moiety.



Scheme 1-18

The total *exo* selectivity can be obtained by using Rh(I) catalyst as shown on Scheme 1-19. Mori[65] and Livinghouse[66] reported independently the use of Rh(I) catalyst for *exo* selectivity. However the cycloaddition reaction competes with the cycloisomerisation. The success of the cycloaddition depends on the nature of the ligands present on Rh complex and on the nature of the tether.[65,66] The *exo* selectivity is obtained if the (*E,E*)-nonatrienes is substituted in C-5 or C-6 as in **61** to afford **62** as a single isomer.



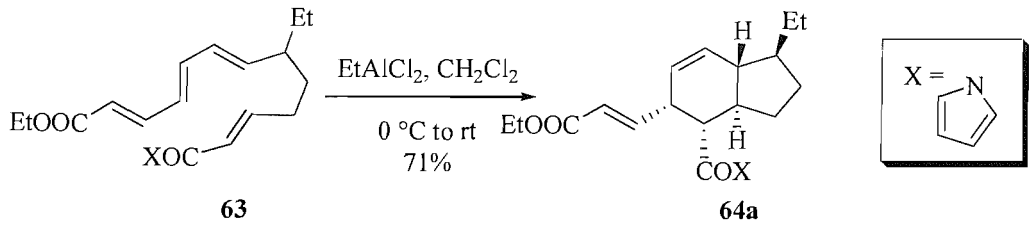
Scheme 1-19

1.3.3 Chiral tether

1.3.3.1 α-diene substitution

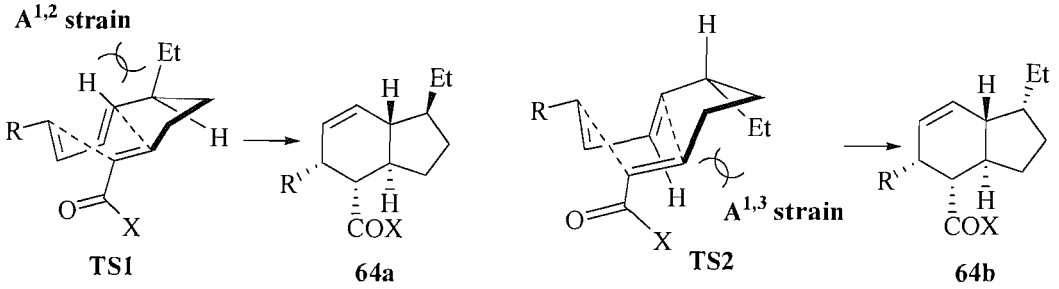
The introduction of bulky groups on the α-position of the diene influences the selectivity observed for the IMDA reaction. In that case, the *endo* adduct is usually isolated in higher yield than the *exo* adduct.

The racemic trienes **63** substituted on C-9 afford the cycloadduct **64a** as a single isomer (Scheme 1-20). The ethyl group on C-9 interacts with the hydrogen of the diene. The outcome of the IMDA reaction shows that the $A^{1,3}$ strain in **TS2** is less favourable than the $A^{1,2}$ strain in **TS1** (Scheme 1-21).[67,68]



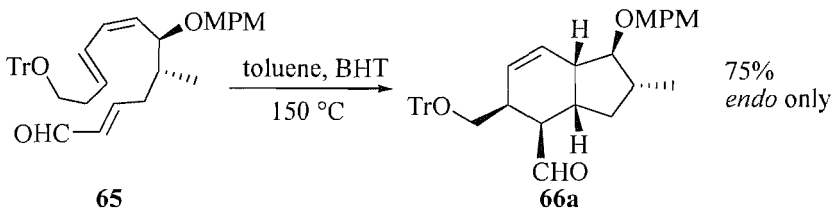
63 64a

Scheme 1-20



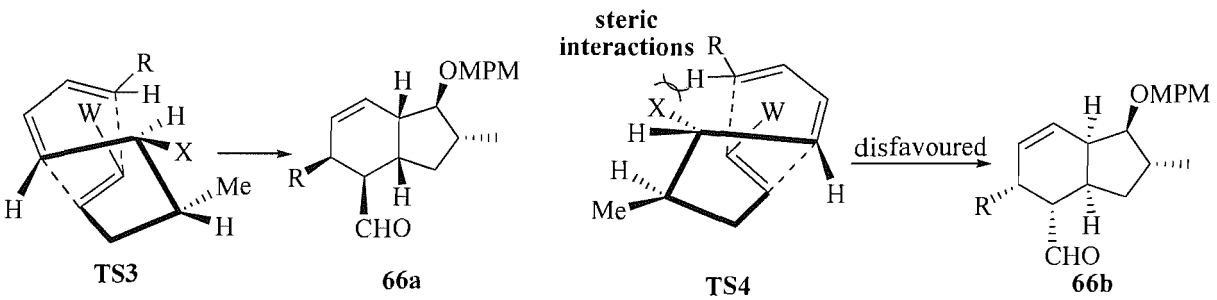
Scheme 1-21

In the example shown on Scheme 1-22, the (*E*,*Z*,*E*)-trienes substituted on C-9 affords the *cis*-fused cycloadduct **66a** as a single product. The *exo* transition state is sterically unfavourable.[52] Severe steric interactions between the MPM group and the vinylic hydrogen in **TS4** shows that the reaction occurs *via* a single transition state **TS3** leading to the cycloadduct **66a** (Scheme 1-23).



65 66a

Scheme 1-22

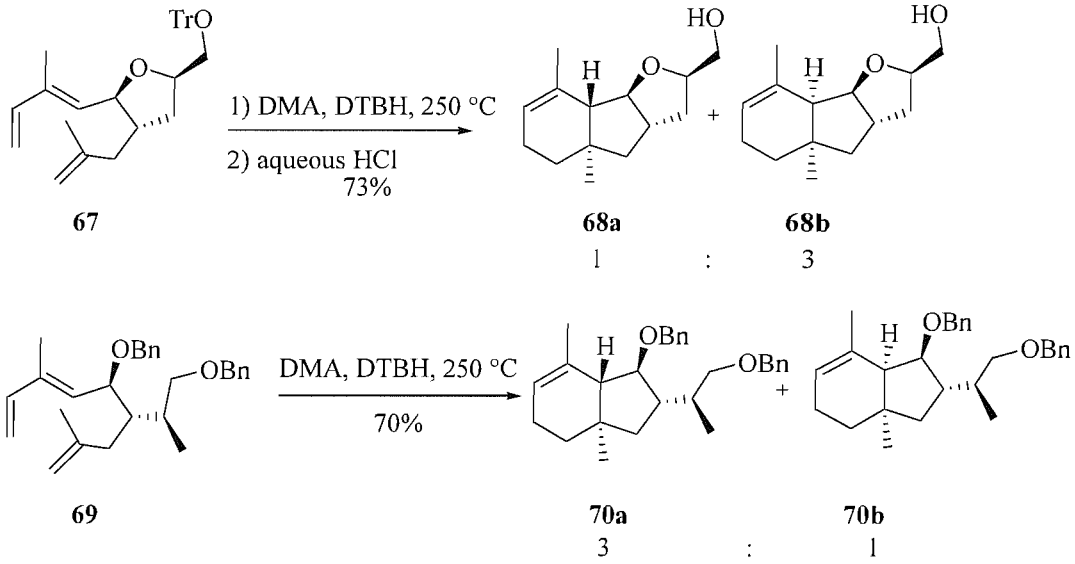


TS3 66a TS4 66b

Scheme 1-23

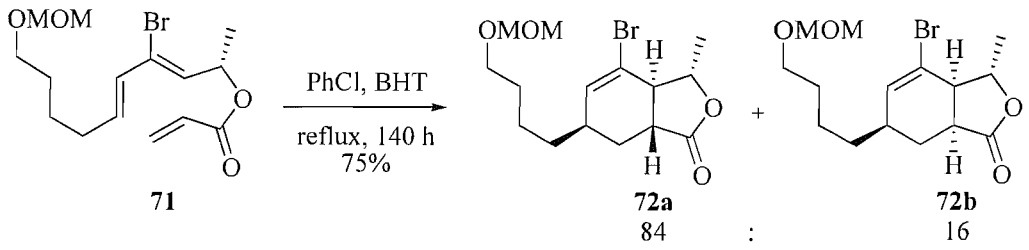
The IMDA can be achieved with unactivated dienophiles but the thermal conditions requires temperatures greater than 250 °C.[43] Taber *et al.*, observed that unactivated

nonatrienes **67** with rigid structure gave predominantly *cis*-fused hydrindene **68b** (Scheme 1-24). On the other hand, the cyclisation of **69**, with a less rigid structure than **70**, gave predominantly the *trans*-fused hydrindene **70a**. The selectivity is controlled by steric interactions.

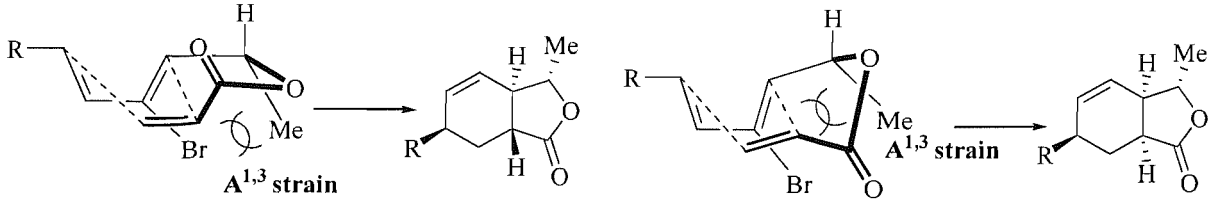


Scheme 1-24

The introduction of bulky substituents on the tether usually improves the selectivity. The presence of the methyl substituent on C-5 and the bromine on C-3 favoured the *exo* transition state to give predominately the *trans*-fused adduct **72a** (Scheme 1-25). The π facial differentiation is due to the destabilizing $A^{1,3}$ strain between the methyl on C-5 and the bromine on C-3 in the *endo* transition state (Scheme 1-25).[62]



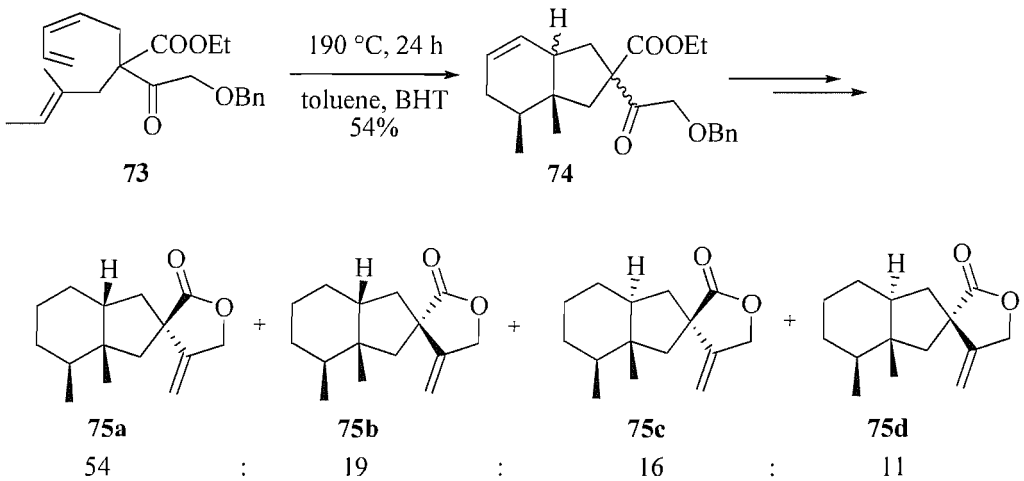
Scheme 1-25



Scheme 1-26

1.3.3.2 β and γ-diene substitution

Back *et al.*, studied the IMDA reaction of the (*E,Z,E*)-nonatrienes **73** substituted on the tether (β position of the diene).[69] A mixture of four diastereoisomers **75a/75b/75c/75d** was isolated in the 54:19:16:11 ratio (Scheme 1-27). The *endo* transition state is preferred over the *exo* transition state. However, when the IMDA reaction was carried out with (*E,E,E*)-nonatrienes, the same mixture of diastereoisomers **75a/75b/75c/75d** was isolated in the very different ratio 24:10:34:32. The origin of the selectivity observed on the spiro configuration is unclear.



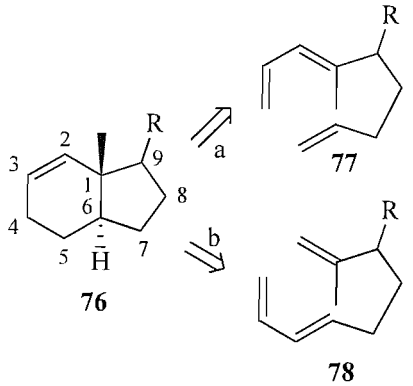
Scheme 1-27

1.3.4 Synthesis of vitamin D CD-ring system by IMDA reaction

1.3.4.1 Disconnection

The syntheses of *trans*-hydrindane moiety of steroids and vitamin D has been achieved by various methods.[44] In this section discussion will be focused on the synthesis of CD-ring system using the IMDA reaction. A few examples have been reported. In all the

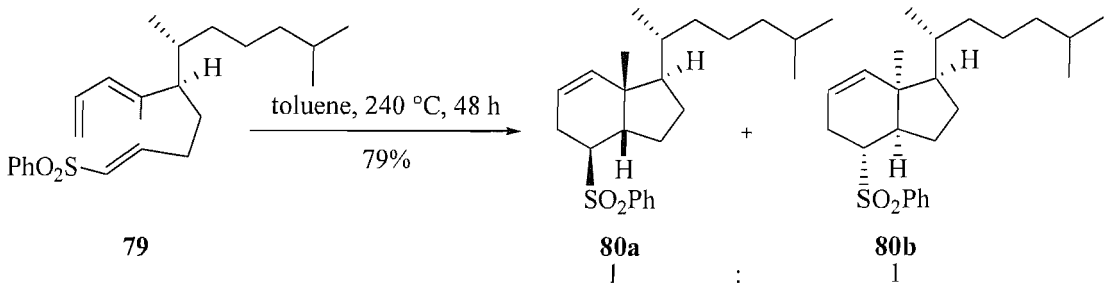
synthesis reported, the stereochemistry at C-9 was introduced before the IMDA step. The C-9 stereochemistry influences the IMDA selectivity. There are two different possible disconnections for the formation of hydrindene moiety **76** by IMDA reaction (Scheme 1-28). The first disconnection (path a) between C-1 C-6 and C-4 C-5 leads to the nonatrienes **77** where the R group is in allylic position of the diene. The second disconnection (path b) between C-1 C-6 and C-2 C-3 leads to the formation of the nonatrienes **78** where the R group is in allylic position of the dienophile.



Scheme 1-28

1.3.4.2 Formation of C1-C6 and C4-C5

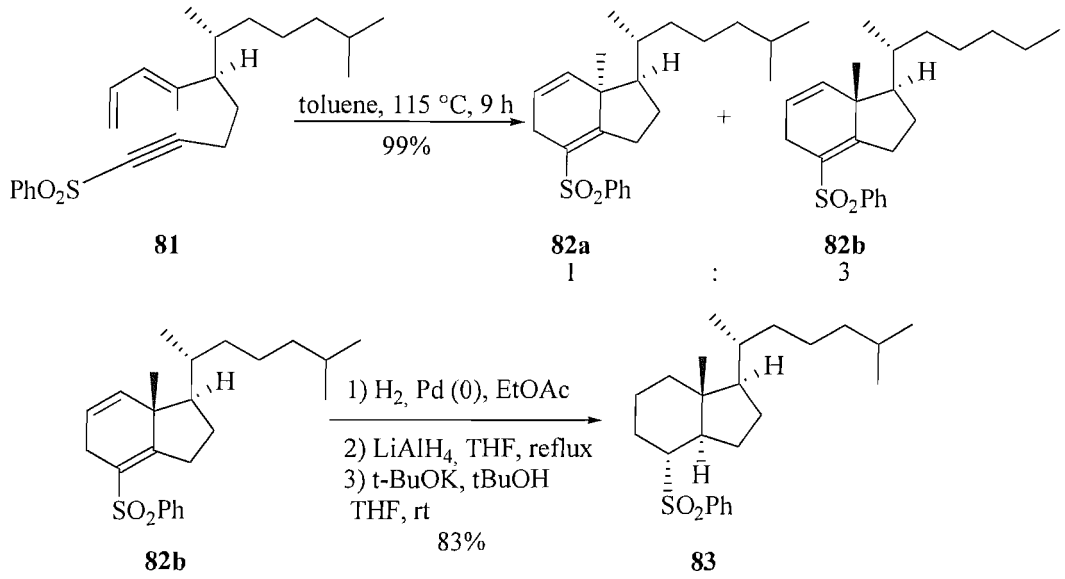
Craig *et al.*,[70] studied the IMDA reaction of triene **79**. The cyclisation of **79** did not afford the desired *trans*-fused junction because of unfavourable steric interactions between the methyl group at C-1 and the side chain at C-9 (Scheme 1-29). In addition, the bulky sulfonate group probably destabilised the *endo* transition state. The IMDA reaction occurred with an *exo* selectivity. No diastereoselectivity was observed since the two isomers **80a** and **80b** were obtained in an equimolar ratio.



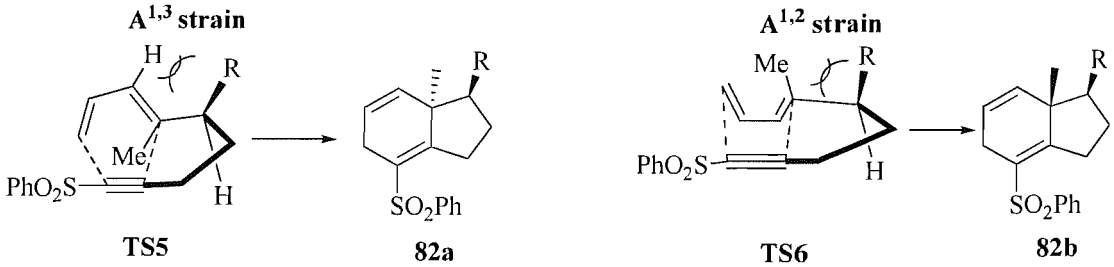
Scheme 1-29

Eventually, the *trans*-fused junction was obtained by using IMDA reaction between the diene and the alkyne in **81** to afford a mixture of two diastereoisomers **82a** and **82b** which

were separated by HPLC (Scheme 1-30). The sulfone **82b** was reduced to give the *trans*-fused hydrindene **83**. The main difference with the previous method is the linear alkyne which obviates any *endo/exo* selectivity. The stereochemistry obtained at C-1 can be explained by the difference in energy between the $A^{1,3}$ strain and the $A^{1,2}$ strain. In the transition state **TS6** leading to **82a**, the destabilising $A^{1,3}$ strain occurs between the hydrogen on C-2 and the R group on C-9. On the other hand, in the transition state **TS5** leading to **82b**, the destabilising $A^{1,2}$ strain occurs between the methyl at C-1 and the R group at C-9. The outcome of the IMDA reaction suggested that the $A^{1,3}$ strain in **TS5** is greater than the $A^{1,2}$ strain in **TS6**.



Scheme 1-30

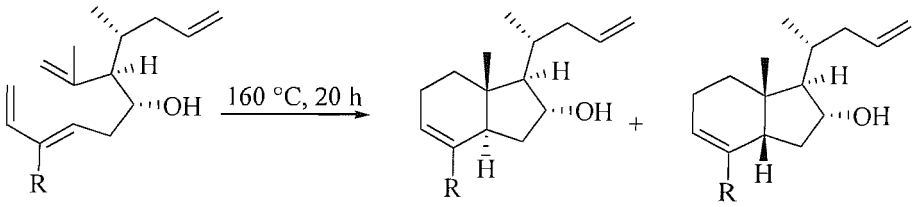


Scheme 1-31

1.3.4.3 Formation of C1-C6 and C2-C3

Wilson *et al.*,[71,72] used the IMDA reaction to build the vitamin D CD-ring system. The steric effects in C-5 increase the selectivity observed (Scheme 1-32). Indeed, when R = H, as in **84a**, the cycloadducts **85a** and **86a** were isolated in a 1:1 *trans/cis* ratio while when R = CH_3, as in **84b**, the ratio of **85b** and **86b** increased to 3:1. The *trans/cis* selectivity increased

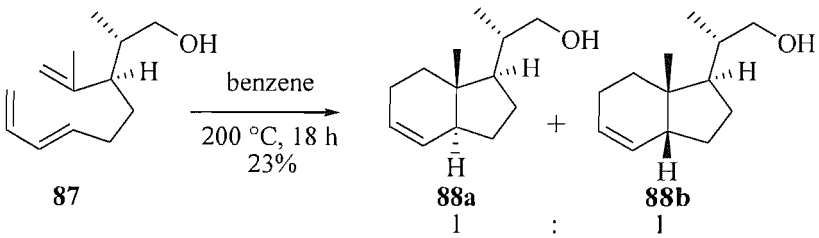
to 4:1 when R = $(CH_2)_2$-OH or $(CH_2)_2$-Ar. This survey shows that the substituent at C-5 influences the outcome of the IMDA reaction.



84a	R = H	**85a**		**86a**
		1	:	1
			np	
84b	R = CH_3	**85b**		**86b**
		3	:	1
			78%	
84c	R = $(CH_2)_2$-OH	**85c**		**86c**
		4	:	1
			89%	
84d	R = $(CH_2)_2$-Ar	**85d**		**86d**
		4	:	1
			68%	

Scheme 1-32

Parker *et al.*,[73] showed that a substituent at C-1 influences the IMDA product stereochemistry (Scheme 1-33). The stereochemistry was fixed at C-9. The cyclisation of **87** by thermocatalysis affords only two diastereoisomers **88a** and **88b** in a 1:1 ratio. The two isolated compounds **88a** and **88b** have *syn* substituents at C-1 and C-9. The dienophile was not activated by an electron withdrawing group which means the steric effects determined the outcome of the cyclisation in particular the $A^{1,2}$ and $A^{1,3}$ strain.

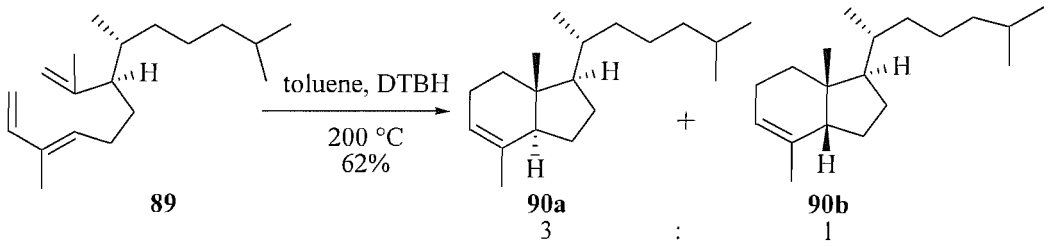


87 → **88a** : **88b** = 1 : 1

Scheme 1-33

Parker *et al.*,[74] applied those surveys in order to study the IMDA selectivity with trienes substituted at both position C-5 and C-1.[71,72] The IMDA of **89** under thermocatalysis affords a 3:1 mixture of cycloadducts **90a/90b**. The fixed stereochemistry at C-9 controls the

stereochemistry at C-1 while the C-5 substituent controls the stereochemistry at C-6 leading mainly to the formation of *trans*-hydrindene ring.



Scheme 1-34

Those studies show that the C-1 and the C-5 are strategic positions to control the stereochemistry in the final product. The use of chiral centres might improve the diastereodifferentiation.

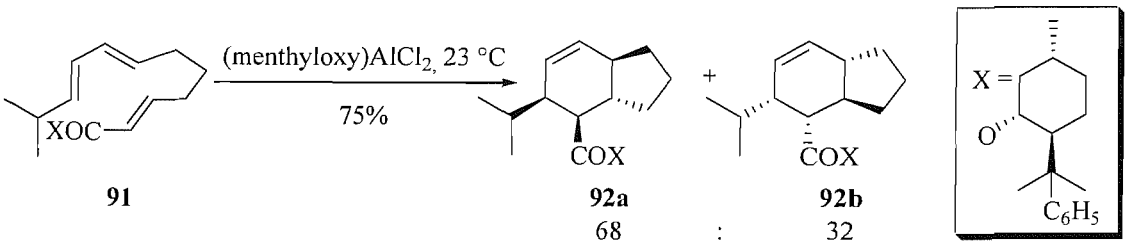
1.3.5 Enantioselective approach to hydrindene ring moiety

Two different approaches involving IMDA reactions have been reported to form enantio enriched *trans*-hydrindene systems. The first method involved the introduction of a chiral auxiliary attached to the dienophile unit. The second method involved the use of a chiral catalyst. Both chiral Lewis acids and organocatalysts have been described in the literature. The cyclisation can be achieved in mild conditions with a temperature generally ranging between -78 °C to 23 °C. The advantage of this method is that the Lewis acid or the organocatalyst can be used in catalytic amount while the chiral auxiliary has to be used in stoichiometric amount. The limitation of this approach is that no chiral center can be present on the tether since it would induce a matched versus mismatched cycloaddition behaviour.

1.3.5.1 The use of chiral auxiliaries to form hydrindene moieties

Although a wide range of chiral auxiliaries have been reported for the intermolecular Diels-Alder, only seven of them have been applied for the IMDA reaction.

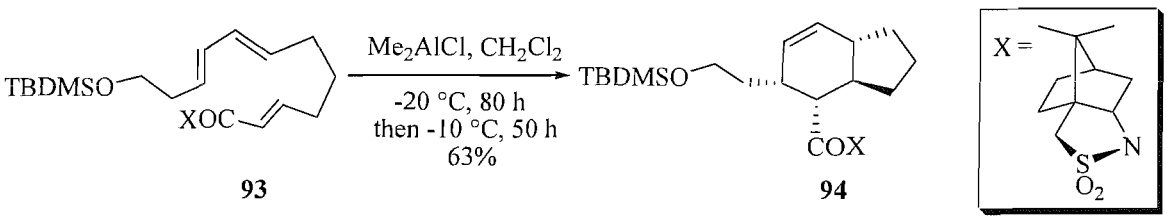
Roush *et al.*,[42] reported the first example of asymmetric IMDA reaction. Phenylmenthol was used as a chiral auxiliary. The cycloadduct adduct **92** was isolated in 75% yield with a moderate selectivity (Scheme 1-35). The lack of selectivity was explained by unfavourable steric interactions between the isopropyl group and the phenylmenthyl group.



91 **92a** 68 : **92b** 32

Scheme 1-35

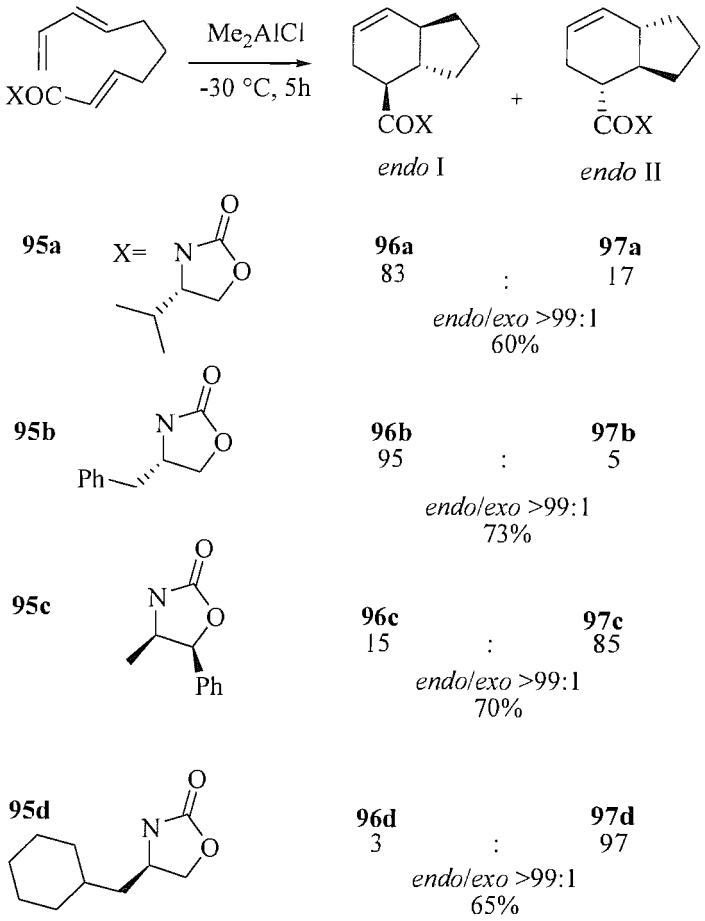
The chiral camphor-sultam derivate was used for the IMDA reaction of **93** to form *trans*-hydrindene **94** in 63% yield and 100% de, with the *endo* product formed exclusively (Scheme 1-36).[75,76] The cycloadduct **94** was an intermediate in the total synthesis of (-)-pulo'upone.



93 **94**

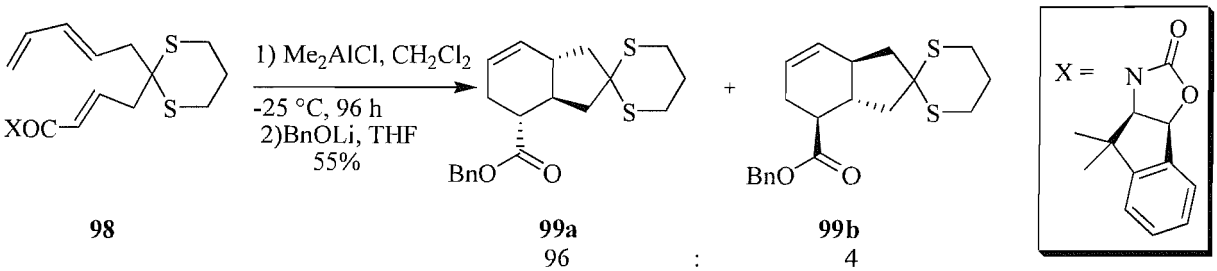
Scheme 1-36

The IMDA reaction towards hydrindenes has also been achieved using an Evans oxazolidinone auxiliary.[41,77] The reaction was performed in presence of a mild Lewis acid which forms a bidentate complex with the carbonyl of the imide and the carbonyl of the oxazolidinone to give a rigid transition state. Interestingly, although all examples showed excellent *endo*/*exo* selectivity, the facial selectivity of the reaction was much more pronounced with the oxazolidinone derived from (*S*)-phenylalaninol **95b** or (*R*)-cyclohexylalaninol **95d** compared to the other two (**95a** and **95c**) (Scheme 1-37).



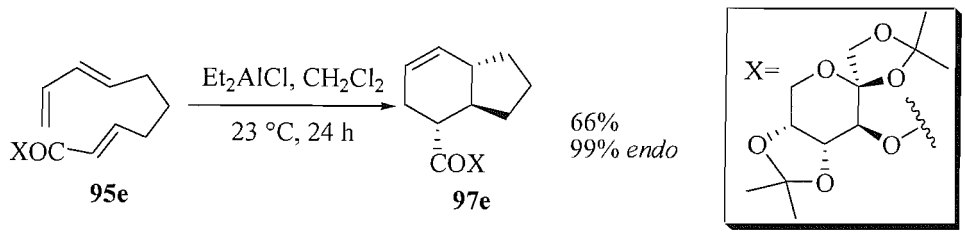
Scheme 1-37

Hoshino *et al.*,[78] have studied the IMDA reactions of dithiane trienimide **98** as intermediates towards the synthesis of plakotenin. The reaction was carried out with various chiral auxiliaries such as oxazolidinone and camphor-sultam. The best enantioselectivity (96% ee) and diastereoselectivity were observed with Saigo's oxazolidinone[79] outlined on Scheme 1-38.



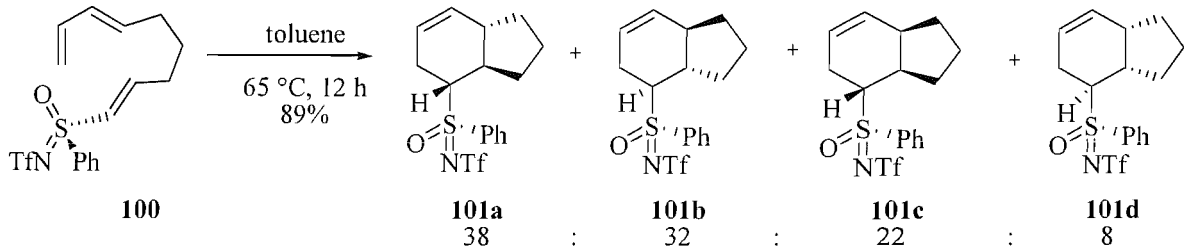
Scheme 1-38

Another type of auxiliary reported in the literature was derived from carbohydrates (Scheme 1-39).[80] Using the protected fructose, the *trans*-fused cycloadduct **97e** was isolated in moderate yield with excellent *endo* selectivity (*endo*/*exo* 99:1).



Scheme 1-39

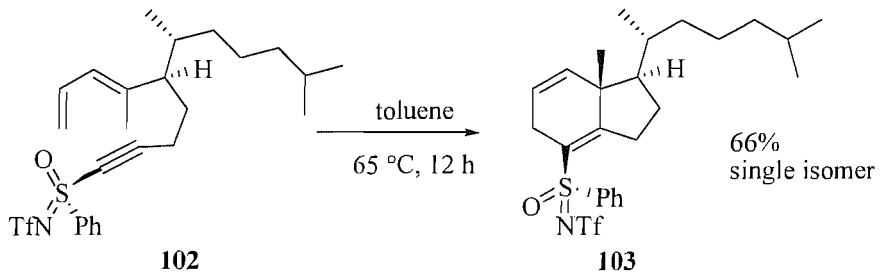
Craig *et al.*, proved that a good selectivity was obtained by using homochiral sulfoximine **100**.[81] Preliminary studies with simple trienes activated by a *N*-triflylsulfoximidoyl group gave a mixture of four diastereoisomers **101** (Scheme 1-40).[82]



100 → **101a** : **101b** : **101c** : **101d**
38 : 32 : 22 : 8

Scheme 1-40

On the other hand, the presence of a stereocenter at C-9 and the chiral alkynylsulfoximine dienophiles showed matched and mismatched cycloaddition behaviour resulting from cooperative and competing directing effects of the sulphur and carbon stereocenters (Scheme 1-41). The cycloadduct **103** was isolated as a single isomer in 66% yield.

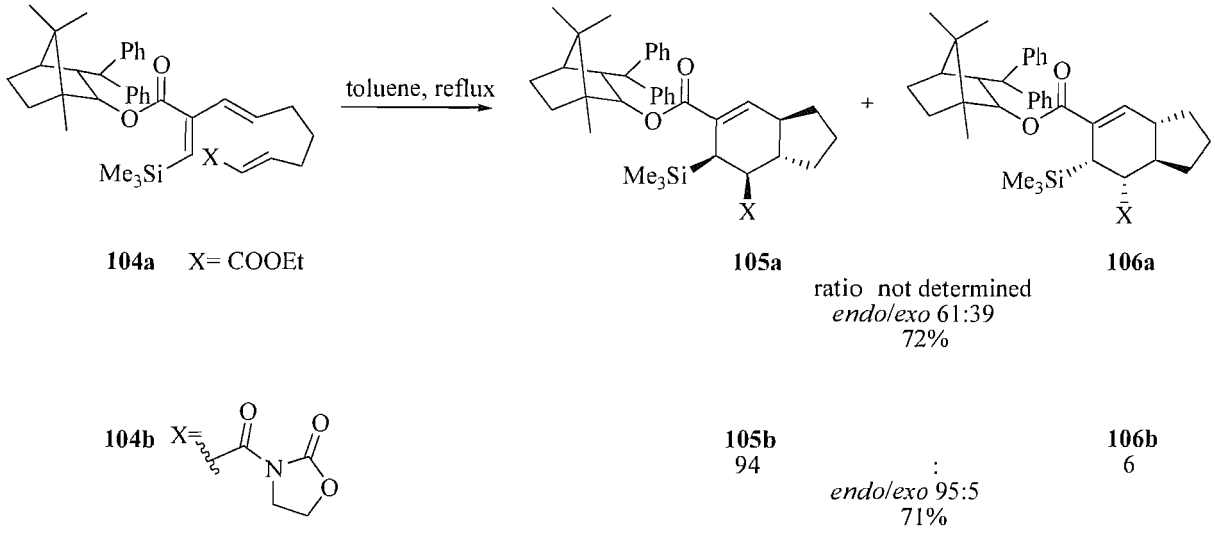


102 **103**

Scheme 1-41

The last auxiliary reported in the literature is a (diphenylmethyl)isoborneol based auxiliary (Scheme 1-42).[83] The thermal IMDA of **104a** gave a mixture *endo*/*exo* 61:39 while Lewis acid catalysis afforded only the *endo* isomer albeit at a lower yield. The Lewis acid catalysis gave a mixture of two diastereoisomers **105a** and **106a**. The cyclisation was also performed with a dienophile activated by an oxazolidinone instead of an ester. The thermal

IMDA with **104b** provided the *trans*-fused hydrindene **105b/106b** with a good *endo* selectivity and diastereoselectivity.



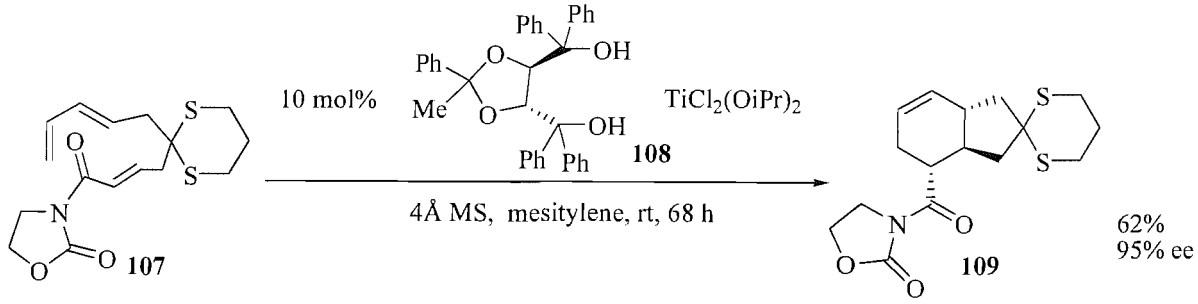
Scheme 1-42

1.3.5.2 The use of chiral catalysts to form hydrindene moieties

The use of chiral Lewis acid catalysts in Diels-Alder reactions was developed only in the past decade.[29-31,84] The dienophile is activated by coordination of the carbonyl group to the chiral Lewis acid. The Lewis acid withdraws the electrons from the dienophile, causing a polarization of the dienophile and increasing the reaction rate. The chiral environment affects the π facial selectivity.

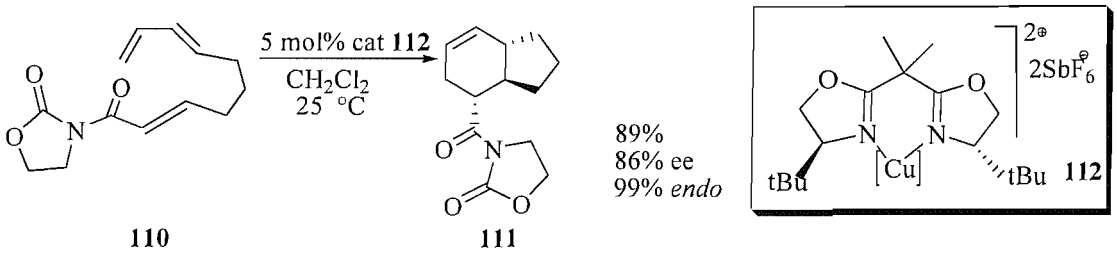
Four different chiral Lewis acid catalysts have been successfully used for the IMDA reaction.

The Ti(Taddol) is the first chiral catalyst described in the literature for asymmetric IMDA reaction to form *trans*-hydrindene system **109**. This reaction proceeds with a high enantioselectivity by using a catalytic amount of catalyst (Scheme 1-43). The catalyst was prepared *in situ* by reaction of a chiral diol **108** derived from (+)-tartaric acid and $TiCl_2(OiPr)_2$. Molecular sieves (4Å MS) were required to keep the reaction catalytic in titanium reagent.[85,86] This example is one of the few enantioselective IMDA reactions performed with substitution on the tether.



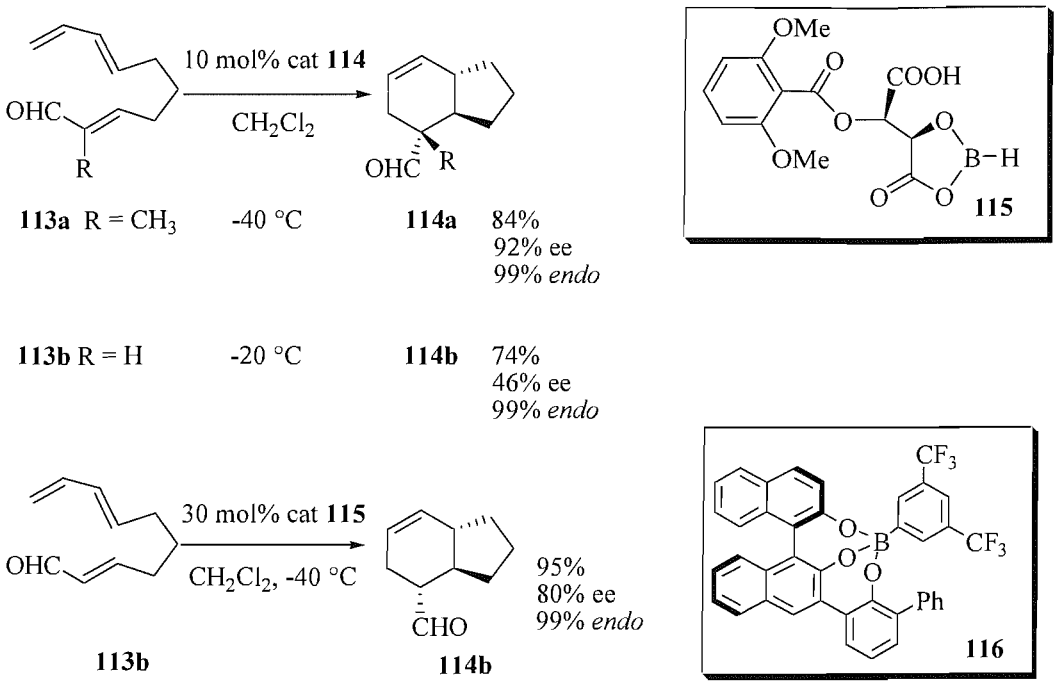
Scheme 1-43

Evans *et al.*,[87,88] developed Cu(II)bis(oxazoline) catalyst **112** for IMDA reaction. This catalyst requires two carbonyl groups in the substrate for effective coordination. The methodology was applied on trienimides possessing a three or a four-carbon tether. The *endo* adduct was isolated with high enantioselectivity (Scheme 1-44).[87,89] However, it was observed that some of the IMDA precursors with the four-carbon tether did not undergo cycloaddition with the Cu(II)bis(oxazoline) catalyst **112**. It also appeared that the nature of the counter cation of the catalyst **112** was really important. Better selectivity was observed with SbF_6^- than when TfO^- was used.



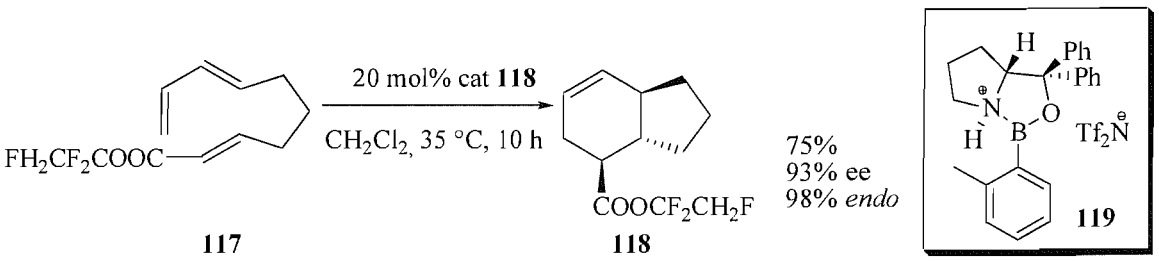
Scheme 1-44

Yamamoto *et al.*, developed chiral acyloxyborane complex **115** (CAB) prepared from (*S*)-mono(2,6-dimethoxybenzoyl)tartaric acid.[56] The CAB complex was successfully applied to enantioselective IMDA. The selectivity observed is higher with the trisubstituted dienophile precursor **113a** than with the disubstituted dienophile **113b**. The IMDA precursor devoid of methyl group in α-position of the aldehyde afford the adduct **114b** in 74% yield with only 46% ee. On the other hand, the precursor **113a** with methyl substituent on C-5 gave the cycloadduct in 84% yield with a 92% ee. A few years later, Yamamoto *et al.*, proved that the enantioselectivity could be improved using a chiral Brønsted-Lewis acid boron based catalyst **116** (BLA).[90] The cycloadduct **114b** was isolated in 95% yield with 80% ee as shown on Scheme 1-45. The *endo* selectivity observed depends also on the dienophile reactivity.[58]



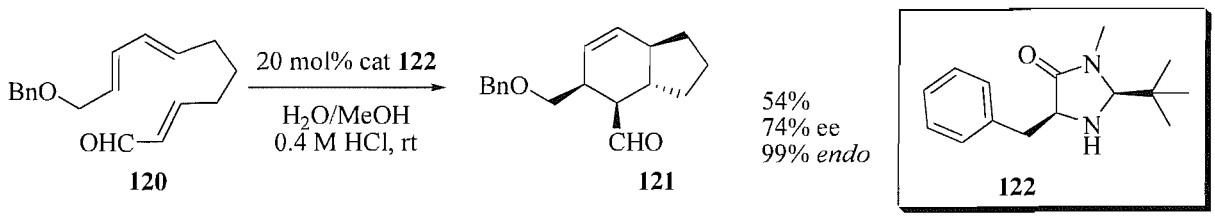
Scheme 1-45

Recently, Corey *et al.*, used an *N*-protonated chiral oxazaborolidine **119** in enantioselective IMDA. The dienophile was activated by an ester which represents the first example of asymmetric IMDA with a trienoate ester. The cycloadduct **118** was isolated in 75% yield with 93% ee (Scheme 1-46).[91]



Scheme 1-46

In the past few years, MacMillan developed the use of organocatalysts in intermolecular Diels-Alder.[92,93] Koskinen demonstrated the use of this methodology for IMDA reaction.[93] Aldehydes were reacted with **122** under acid catalysis to form an iminium salt, which activated the dienophile. The cycloadduct was then isolated with a high *endo* selectivity and moderate to good ee. The cycloadduct **121** was isolated in good to moderate yield depending on the conditions. The best *endo* selectivity and enantioselectivity were obtained with the organocatalyst **122** outlined in Scheme 1-47.



120 121 122

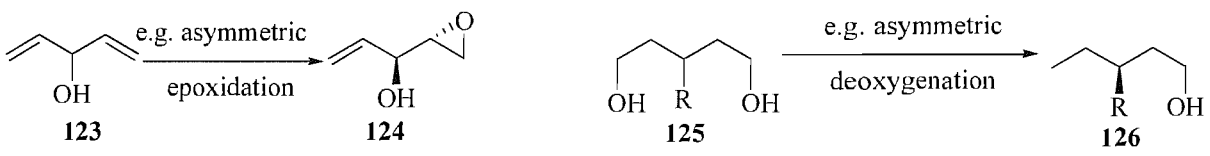
Scheme 1-47

1.4 Group selective desymmetrisation reactions

A desymmetrisation approach is attractive for organic synthesis.[94-97] It can reduce the number of steps in total synthesis. Symmetric acyclic precursors are usually prepared by two-directional synthesis.[95,97-99] This strategy involves the homologation of both ends of the chain either sequentially or simultaneously. Sequential homologation is no more efficient than one directional synthesis (linear or convergent). The simultaneous homologation is more efficient and presents the advantage to dramatically reduce the number of steps compare to the sequential homologation.

The desymmetrisation itself can be defined as a reaction which breaks the symmetry of an achiral, *meso* (mirror plane, inversion centre), C_2-symmetric, or pseudo C_2-symmetric substrate. For achiral and *meso* compounds, a desymmetrisation reaction can be achieved using enzymatic[96] or non enzymatic[94,97,98] transformation.

In this thesis, discussion will be focused on achiral chain desymmetrisation.[97,100] The desymmetrisation is accomplished by differentiation of two enantiotopic faces[101,102] or enantiotopic groups[103,104] (Scheme 1-48). The reaction has to be carried out with a chiral reagent or catalyst to form a chiral molecule. When the reaction is performed on an achiral or a *meso* compound, the reaction leads to the formation of an enantiomerically pure product with multiple stereocenters. Desymmetrisation of achiral and *meso* compounds are the most studied ones. To the best of our knowledge, the desymmetrisation of a bis(diene) with an IMDA reaction has not yet been reported.



123 124 125 126

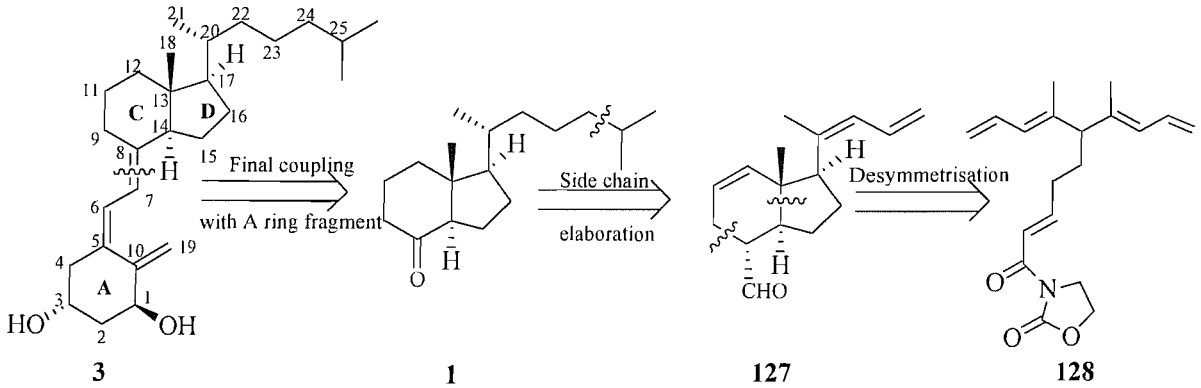
Differentiation of enantiotopic faces ***Differentiation of enantiotopic groups***

Scheme 1-48

1.5 Aim: a group selective IMDA for the synthesis of the steroid CD-ring /side chain

1.5.1 Retrosynthesis

The aim of this project was to investigate a desymmetrisation strategy of achiral substrates by using enantioselective and diastereoselective IMDA reaction. This methodology would be applied on the development of an asymmetric strategy to build steroid CD-ring systems. Although the methodology would be appropriate to the synthesis of a range of steroids, we chose 1α-hydroxyvitamin D_3 **3** as a biologically relevant target (Scheme 1-49). In this section, steroid numbering will be used for the hydrindene moiety.



Scheme 1-49

The Windaus-Grundmann's ketone **1** is a well known intermediate in total synthesis of 1α,25-dihydroxyvitamin D_3. The ketone **1** might be derived from the aldehyde **127**, after removal of one carbon, elaboration of the side chain and eventually hydrogenation of the remaining double bonds. Hence, when **127** is considered, a hidden symmetry can be discovered when an IMDA disconnection is applied, leading to an achiral substrate **128**. We are aiming to control the selectivity in C-8, C-13, C-14 and C-17 in a single step.

It was decided to investigate **129a** as a model compound to study the group selective IMDA process (Figure 1-6). The absence of the methyl groups simplifies the synthesis of the precursor and should give us a good understanding about the selectivity obtained for the IMDA reaction.

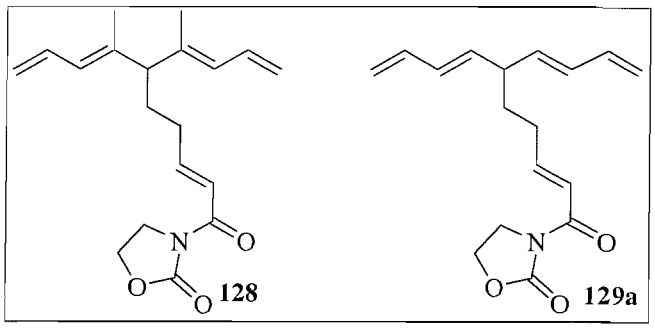
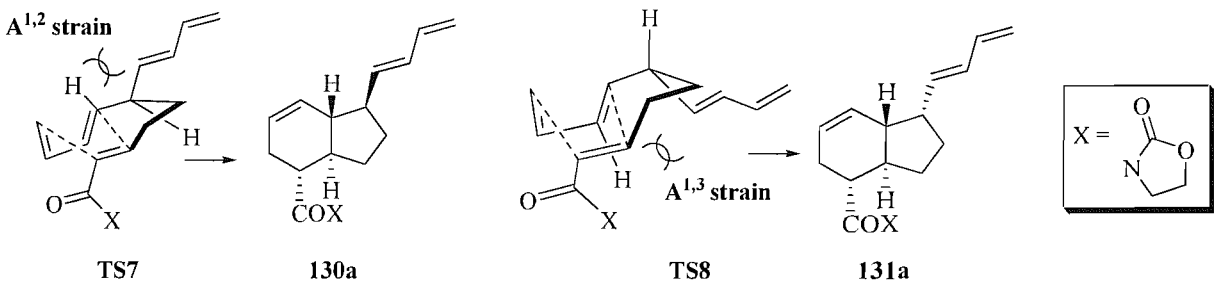


Figure 1-6

The use of a chiral auxiliary or a chiral Lewis-acid catalyst would enable the enantioselective synthesis of **127**. Interestingly, this desymmetrisation approach allows us to have a substituent present on the tether, the future C-17 side chain. On the other hand, in all previous examples, this was not possible, as a chiral centre would then be present (see section 1.3.5). In our approach, the substitution on the spacer only becomes chiral after the IMDA, even though it does not participate in the reaction. It was anticipated that the *endo* transition state was favoured over the *exo* transition state. All the mechanisms discussed below concern the *endo* transition states.

1.5.2 The C-17 selectivity

The stereochemistry at C-17 depends on the group selection *ie* which of the two dienes reacts with the dienophile. The two dienes present in the IMDA precursor can potentially react with the dienophile *via* **TS7** or **TS8** (Scheme 1-50). The C-17 diastereoselectivity will be controlled by the difference in $A^{1,2}$ and $A^{1,3}$ strain of the transition state. In the **TS7**, the $A^{1,2}$ strain occurs between the H of the reacting diene and the second diene. In the **TS8**, the $A^{1,3}$ strain occurs between the H of the reacting diene and the second diene. The major product will depend on the more favourable of the $A^{1,2}$ strain or the $A^{1,3}$ strain. Based on literature precedent, we anticipated that the **TS7** could be more favourable than **TS8**.



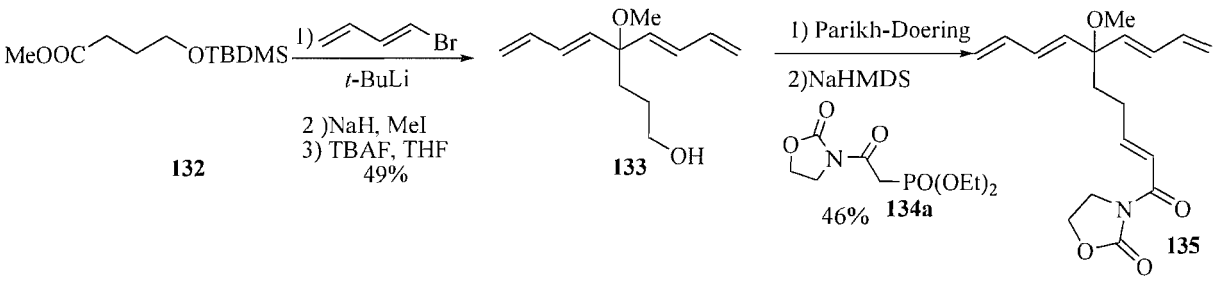
TS7 **130a** **TS8** **131a**

Scheme 1-50

Obviously, the C-19 and C-21 methyl groups are not present in the model substrate, and the $A^{1,2}$ strain undoubtedly will be much greater for the real substrate. However, work reported by Craig *et al.*, does suggest that the $A^{1,3}$ strain between the hydrogen at C-12 and the chain at C-17 is greater than the $A^{1,2}$ strain between the methyl on C-13 and the chain at C-17 (see section1.3.4.2).[105] In Craig's IMDA, the $A^{1,2}$ strain was due to the sp^3 centre on C-20 but in our case it will be replaced by an sp^2 centre at C-20 which should reduce the $A^{1,2}$ strain.

1.5.3 Previous work

Previous work has been attempted in our laboratory to prepare a bis(diene) precursor **135** with a methoxy substituent at C-13 in 6 steps and 17% overall yield (Scheme 1-51).[106]



Scheme 1-51

The bis(diene) **135** is more stable than **129a** that we are aiming to prepare since the quaternary centre between the two dienes prevent any isomerisation to the corresponding tetraene. However, IMDA precursor **135** was heated in toluene for 48h to afford a complex mixture of four different diastereoisomers in 24:66:7:3 ratio. Unfortunately, the diastereoisomers could not be separated by HPLC and therefore the structure of the major isomer could not be determined.

1.6 Structure of the results and discussion

The results of this thesis are described in three chapters organised as follows:

Chapter two discusses the preparation of a simplified skipped bis(diene).

Chapter three investigates the IMDA reaction with a simplified model compound and formation of the side chain.

Chapter four examines the progress toward the synthesis of 1α,25-dihydroxyvitamin D_3 CD-ring system precursor.

Chapter 2: Synthesis of the simplified bis(diene) model compound

2.1 Introduction

In order to study the IMDA reaction, it was decided to prepare the simplified bis(diene) **129a** and use it as model compound for the IMDA survey. The absence of the methyl groups compared to **128** would considerably simplify the synthesis of the bis(diene). The bis(diene) **129a** is suspected to be more stable than **128** which would be more prone to isomerisation (Figure 2-1).

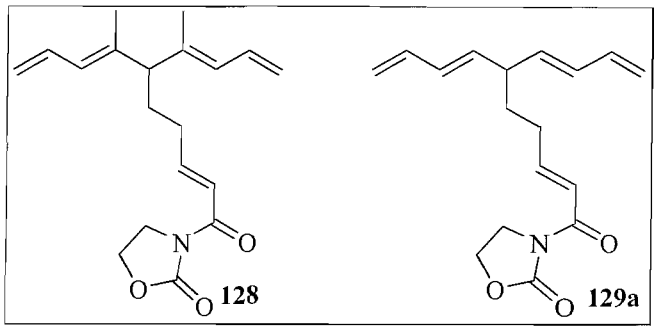
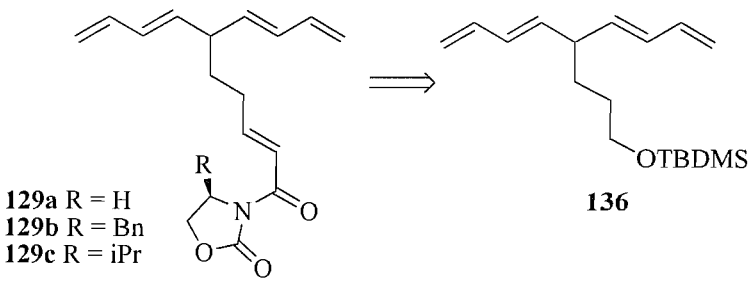


Figure 2-1

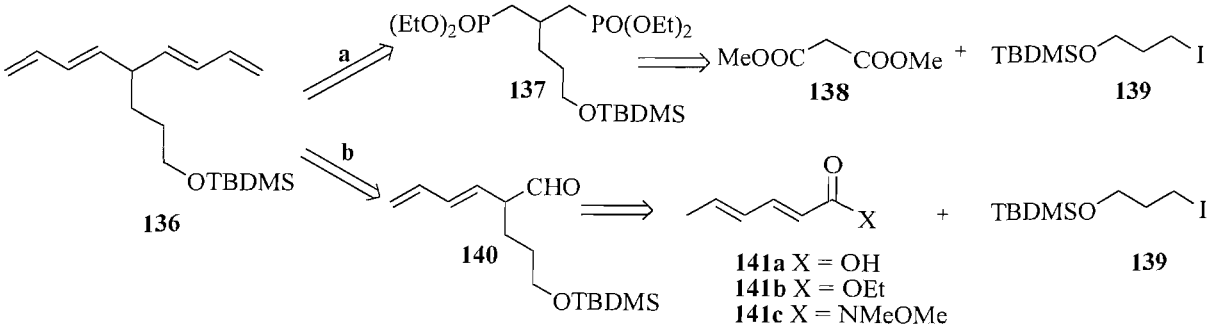
2.2 Retrosynthetic analysis

The bis(diene) **136** was considered as a key intermediate for the synthesis of the desired symmetric IMDA precursor **129a-c** (Scheme 2-1). The introduction of the auxiliary would be performed by deprotection of **136**, followed by oxidation and Horner-Wadsworth-Emmons reaction to lead to **129**.



Scheme 2-1

Two retrosynthetic analyses were envisaged to prepare **136**. A double disconnection involving both dienes through path a (Scheme 2-2) leads to the 1,3-diphosphonate **137**. On the other hand, a single disconnection involving one diene through path b (Scheme 2-2) leads to the aldehyde **140** which can be prepared from sorbic acid derivatives **141a-c**.

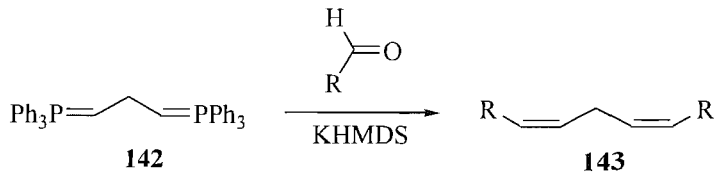


Scheme 2-2

2.3 Synthesis of the central bis(diene) intermediate 136

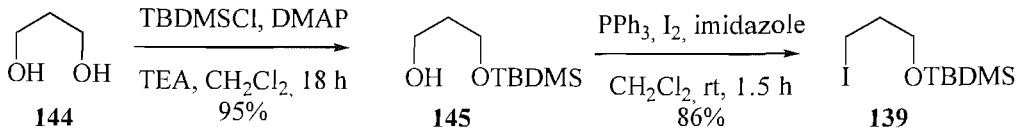
2.3.1 The double Horner-Wadsworth-Emmons approach

The first approach to form **136** is based on a double Horner-Wadsworth-Emmons as shown in the retrosynthetic analysis (Scheme 2-2). Pohnert *et al.*, described a double Wittig reaction with bis(ylide) **142** to form a (*Z*,*Z*)-1,4-diene **143** (Scheme 2-3).[107] It was envisioned that by replacing the bis(ylide) units by the bis(phosphonate) groups, *E* selectivity would be obtained for the double bond formation.



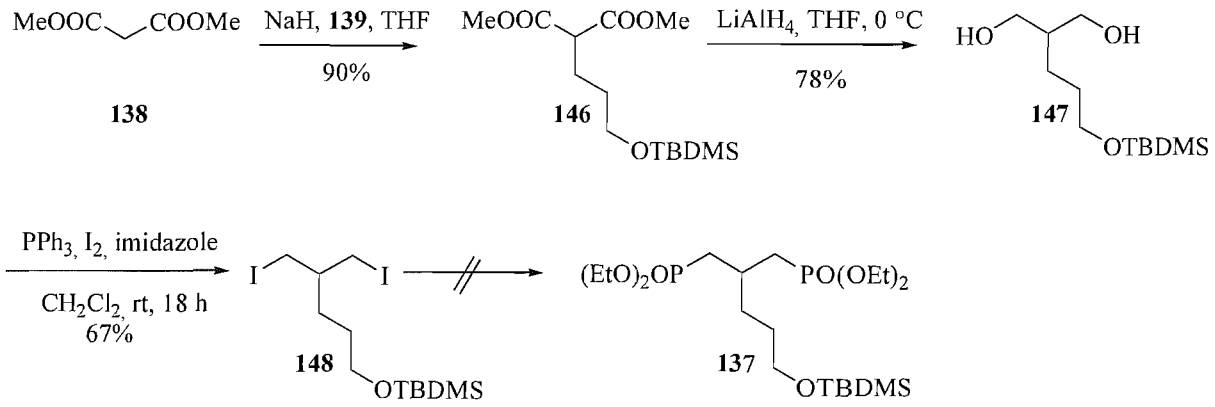
Scheme 2-3

The formation of bis(phosphonate) **137** was envisioned starting from malonic ester and iodide **139**. The primary iodide **139** was prepared according to literature procedure.[108] Monosilylation of 1,3-propanediol **144** afforded **145**[109] in 95% yield, which was subsequently reacted with iodine, PPh_3 and imidazole to give 1-iodo-3-[*tert*-butyldimethylsilyloxy]-propane **139** in 86% yield (Scheme 2-4).



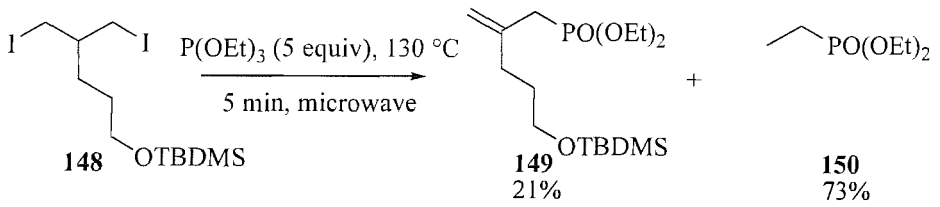
Scheme 2-4

Dimethyl malonate **138** was treated with NaH and the resulting anion was reacted with the primary iodide **139** to give diester **146** in 90% yield.[110] Diester **146** was reduced with $LiAlH_4$ to give diol **147** in 78% yield.[111,112] Diol **147** was iodinated[107] by using iodine, PPh_3 and imidazole to afford diiodide **148** in 47% yield overall from **138**. The next step was the formation of bis(phosphonate) **137** followed by the Horner-Wadsworth-Emmons reaction with acrolein to form bis(diene) **136**.



Scheme 2-5

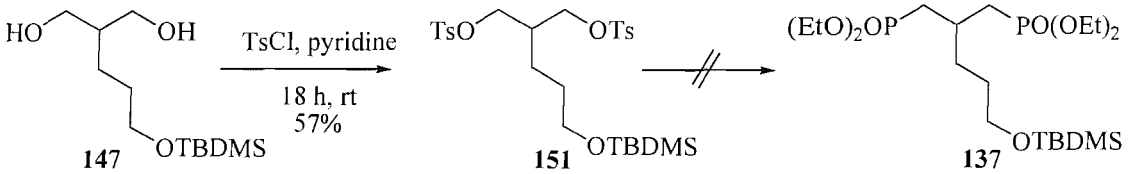
The synthesis of bis(phosphonate) **137** appeared problematic. Diiodide **148** was heated for 18 h at 130 °C with an excess of triethyl phosphite. After 18 h, TLC analysis showed that the reaction was completed. The excess of triethyl phosphite was removed by distillation.[113] However, the elimination product **149** was isolated in 10% yield along with 60% of diethyl ethyl phosphonate **150** (Scheme 2-6). The side product **150** was obtained by a Michaelis-Arbuzov isomerization of triethyl phosphite catalysed by the ethyl iodide released during the reaction.[114] In order to avoid the formation of **150**, ethyl iodide was removed continuously from the reaction mixture by distillation. However, the reaction was unsuccessful. Some microwave experiments were also performed with 1 and 5 equivalents of triethyl phosphite respectively for 10 and 5 min at 130 °C. Toluene was used as a solvent for the reaction performed with 1 equivalent of triethyl phosphite. In both cases, the same elimination product **149** was isolated with a yield ranging between 11 and 21%. Nevertheless, the phosphonate **150** was only isolated when an excess of triethyl phosphite was used. We have not been able to explain the formation of **149**.



Scheme 2-6

It was reported that bis(phosphonate) can be prepared from the corresponding bis(tosylate) by reaction with diethyl phosphite.[115] The main advantage of this method is that when a tosylate reacts with diethyl phosphite, sodium tosylate is formed. The salt can easily be removed by washing with water during the work up.

The bis(tosylate) **151** was prepared in moderate unoptimized yield by reacting the diol **147** with tosyl chloride in pyridine (Scheme 2-7). Diethyl phosphite was deprotonated with NaH in a THF and dioxane co-solvent mixture. The anion was then reacted with bis(tosylate) **151**. The reaction mixture was refluxed with diethyl phosphite, with a reaction time ranging between 18 h and 48 h. However, the starting material **151** was recovered along with a small amount of monophosphonate product.



Scheme 2-7

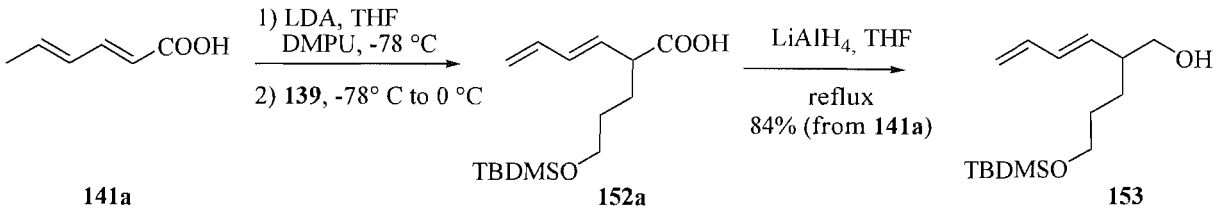
2.3.2 The sorbic acid approach

The following strategy involved the formation of the bis(diene) using a starting material which already contains another diene such as sorbic acid derivatives **141a-c**.

2.3.2.1 Alkylation of sorbic acid and sorbic acid derivatives

Sato *et al.*,[112] reported the synthesis of the alcohol **153** from sorbic acid. The sorbic acid was alkylated with **139** in presence of HMPA. The carboxylic acid **152a** was reacted with diazomethane to form the corresponding methyl ester which was then reduced to give the alcohol **153** in 56% over 2 steps. The main drawback of this synthesis is the use of diazomethane to form the methyl ester. Because of diazomethane toxicity (highly carcinogen) and its explosive nature, it was decided to prepare the alcohol **153** using a slightly modified literature procedure.

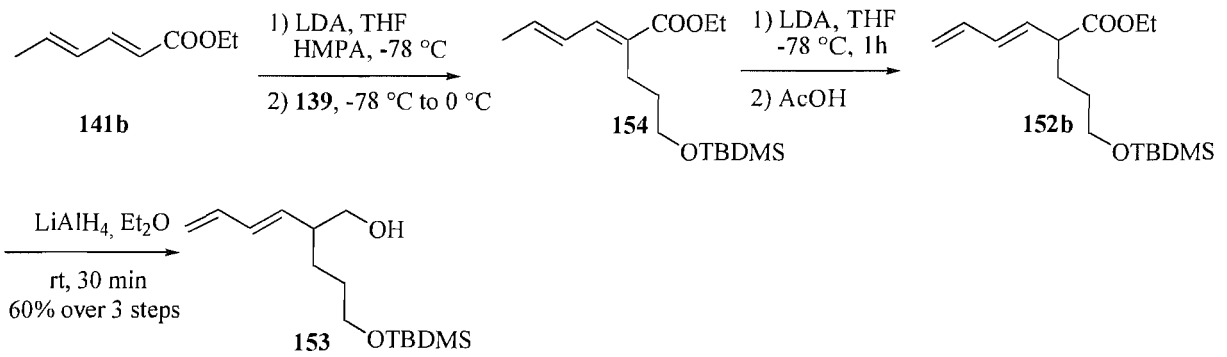
The sorbic acid **141a** was deprotonated using 2.2 equivalents of LDA to generate the dianion[116] which was reacted with 1-iodo-3-[*tert*-butyldimethylsilyloxy]-propane **139** to afford the carboxylic acid **152a**. The crude acid **152a** was immediately reduced with $LiAlH_4$ at reflux to afford the alcohol **153** in 84% yield over 2 steps (Scheme 2-8).[117] The alkylation of sorbic acid **141a** was performed with an excess of HMPA. However, the overall yield of this two steps process was improved from 69 to 84% when DMPU was used instead of HMPA.



Scheme 2-8

It was reported that methyl sorbate could be deprotonated with LDA.[118] The anion is then reacted with a bromide to give an adduct containing a diene conjugated with the ester group.

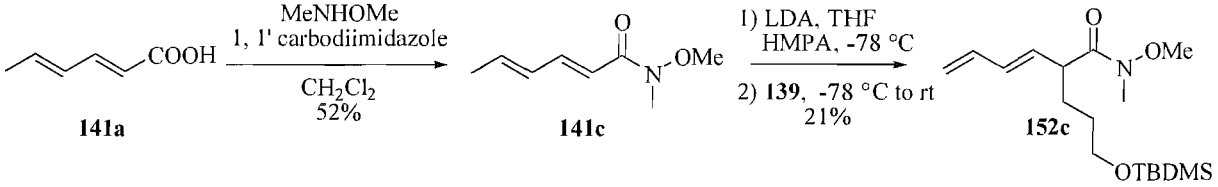
Hence, ethyl sorbate **141b** was deprotonated using 1.2 equivalents of LDA and the anion was reacted with 1-iodo-3-[*tert*-butyldimethylsilyloxy]-propane **139** to afford the fully conjugated ester **154** (Scheme 2-9). The ester **154** was easily deconjugated[119] under kinetic conditions by deprotonation at -78 °C with LDA followed, after 1 h, by quenching with AcOH, to give the unconjugated ester **152b**. The ester **152b** was then reduced with $LiAlH_4$ at room temperature to afford the corresponding alcohol **153** in 60% yield over 3 steps. The overall yield dropped to 45% when HMPA was replaced by DMPU in the alkylation step. However, DMPU was preferred over HMPA since it is a less toxic reagent.



Scheme 2-9

The alkylation of sorbic Weinreb amide **141c** was also considered, as subsequent transformation to the required key aldehyde **140** would then easily be achieved.[120]

The sorbic Weinreb amide **141c** (Scheme 2-10) was prepared from sorbic acid **141a** according to literature procedure.[121] To the best of our knowledge, alkylation of sorbic Weinreb amide **141c** has never been investigated. The Weinreb amide **141c** was deprotonated with LDA and the anion was reacted with the 1-iodo-3-[*tert*-butyldimethylsilyloxy]-propane **139** to form **152c** in low yield. No deprotonation was observed at 0 °C. Hence, the deprotonation of **141c** has to be carried out at -78 °C. The reaction mixture was warmed up from -78 °C to 0 °C and after few hours at 0 °C the reaction was quenched to afford **152c** in 8% yield. It was then attempted to warm up the reaction mixture from -78 °C to room temperature and after 2.5 h at room temperature, **152c** was isolated in 21% yield. On the other hand, the yield dropped to 6% when the reaction mixture was stirred for a longer time at room temperature.



141a **141c** **152c**

Scheme 2-10

Alkylation of sorbic acid **141a** and ethyl sorbate **141b** occurs in high yield while alkylation of sorbic Weinreb amide **141c** appeared more difficult. It was suspected that the formation of a stable lithium-chelated indermediate prevents the alkylation (Figure 2-2). The use of a different base or a larger amount of HMPA has not been investigated and may help to improve the yield.

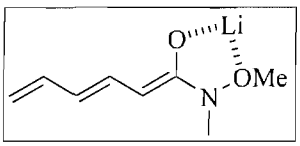


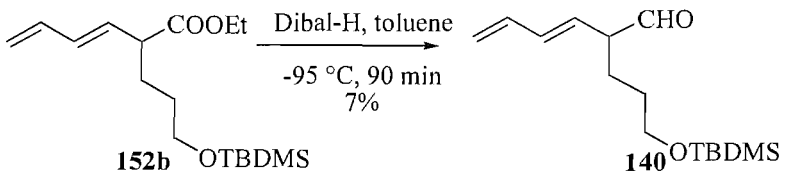
Figure 2-2

Both the ethyl sorbate and the sorbic acid methods afforded the alcohol **153**. Although the sorbic acid approach gave the alcohol **153** with a better yield, the method was not always reproducible compared to the ethyl sorbate one. Hence, the ethyl sorbate based synthesis was chosen as the preferred route.

2.3.2.2 Synthesis of the key aldehyde

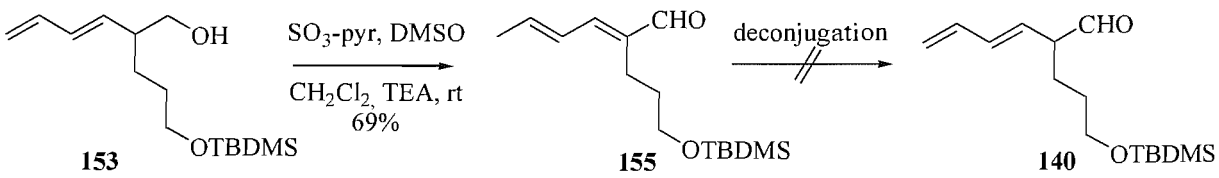
Three different approaches were considered to prepare the key aldehyde. The first involves the reduction of an ester, the second involves the oxidation of an alcohol, and the last involves the reduction of a Weinreb amide.

The ester **152b** was considered as a good intermediate to prepare the aldehyde **140**. Unfortunately, reduction of the ester **152b** with Dibal-H at -95 °C (Scheme 2-11) affords the desired aldehyde **140** in 7% yield along with a mixture of conjugated aldehyde **155** and alcohol **153**.



Scheme 2-11

The oxidation of the alcohol **153** to the corresponding aldehyde **140** was investigated. The attempts to oxidise the alcohol **153** using the Parikh-Doering conditions gave the conjugated aldehyde **155** in 69% yield (Scheme 2-12). The oxidation was also attempted using Swern's conditions. However, after 6 h at -78 °C, the same conjugated aldehyde **155** was isolated in 38% yield.

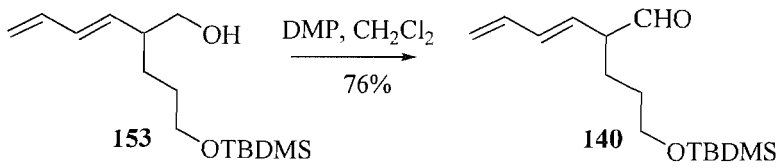


Scheme 2-12

A few examples in the literature report the kinetic deconjugation of 2,4-hexadienoic acid[116] or 2,4-hexadienoic ester.[119,122,123] However, the deconjugation of 2,4-hexadienal has never been reported. The isomerisation was attempted on aldehyde **140** with LDA[119,122] or LiHMDS[123] in THF, with a reaction time ranging between 30 and 60 min. Unfortunately, the starting material was fully recovered in all cases.

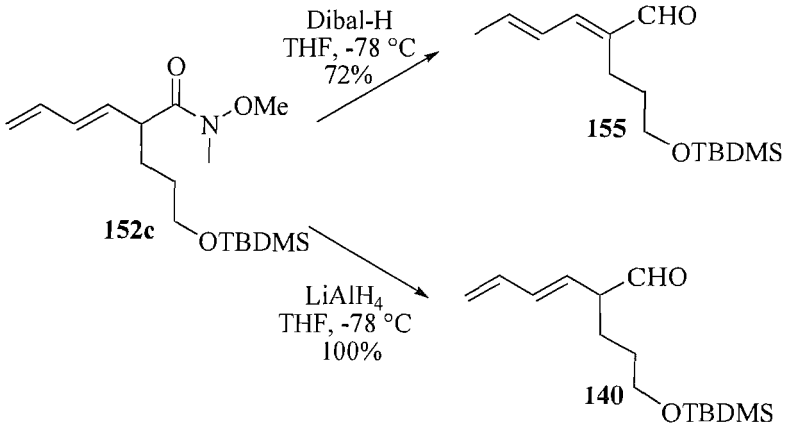
The oxidation was also attempted with a wide range of oxidant (PCC, IBX, TPAP, $AgCO_3$, trichloroisocyanuric) without avail. The starting material **153** and/or the conjugated aldehyde **155** were isolated.

Fortunately, the aldehyde **140** could be obtained from **153** by oxidation with DMP (Dess-Martin's periodinane) (Scheme 2-13).[124,125] It appeared that freshly prepared DMP gave irreproducible yields ranging between 5 to 47%.[126-128] However, the aldehyde **140** was isolated in 76% yield when commercially available DMP was used. A wide range of oxidation methods were attempted to oxidise the alcohol **153** but only the DMP led to the desired aldehyde **140**.



Scheme 2-13

The Weinreb amide **152c** was reduced with Dibal-H to afford the conjugated aldehyde **155** in 72% yield.[120] On the other hand, reduction of the Weinreb amide **152c** with $LiAlH_4$ affords the desired aldehyde **140** in quantitative yield (Scheme 2-14).[120,129] Although the aldehyde **140** was isolated in good yield, the alkylation step could not be improved.



Scheme 2-14

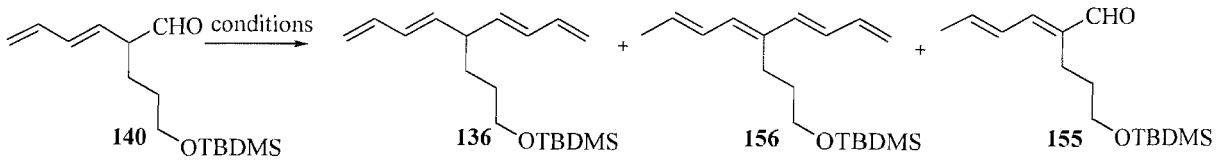
The oxidation of the alcohol **153** with DMP was the preferred method to access the key aldehyde **140**.

2.3.2.3 Olefination towards the bis(diene)

2.3.2.3.1 The Wittig-Horner olefination

The aldehyde **140** was prone to oligomerisation and was used directly in the next step within the same day. The Wittig-Horner type olefination of **140** with the anion of allyl diphenylphosphine oxide[130] gave the skipped bis(diene) **136** in low to moderate yield along with

the conjugated aldehyde **155** (Table 2-1, Scheme 2-15). In certain conditions, the conjugated tetraene **156** was also isolated.



Scheme 2-15

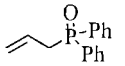
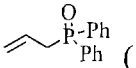
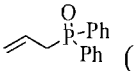
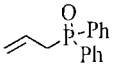
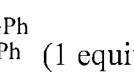
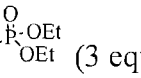
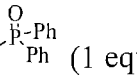
entry	*conditions*	*yield of **136** on small scale (<500 mg of **136**)*	*yield of **136** on large scale (>3 g of **136**)*
1	*n*-BuLi, HMPA,  (3 equiv) -78 °C to rt, 18 h	52%	0%
2	*n*-BuLi, HMPA,  (1 equiv) -78 °C to rt, 18 h	40%	40%
3	*n*-BuLi, DMPU,  (1 equiv) -78 °C to rt, 18 h	3%	nd
4	*n*-BuLi, TMEDA, BHT,  (1 equiv) -78 °C to rt, 18 h	23%	6%
5	NaHMDS,  (1 equiv) -78 °C to rt, 18 h	25%	15%
6	*n*-BuLi, HMPA,  (3 equiv) -78 °C to rt, 18 h	5%	nd
7	*n*-BuLi, HMPA,  (1 equiv) -78 °C for 45 min then 0 °C for 45 min	25%	25%

Table 2-1

The (*E*-*E*)-bis(diene) configuration of **136** was confirmed by the coupling constant $J_{H3\text{-}H4}$ = 15.2 Hz. The ^{1}H NMR spectrum of **136** proved that the skipped bis(diene) was isolated (Figure 2-3).

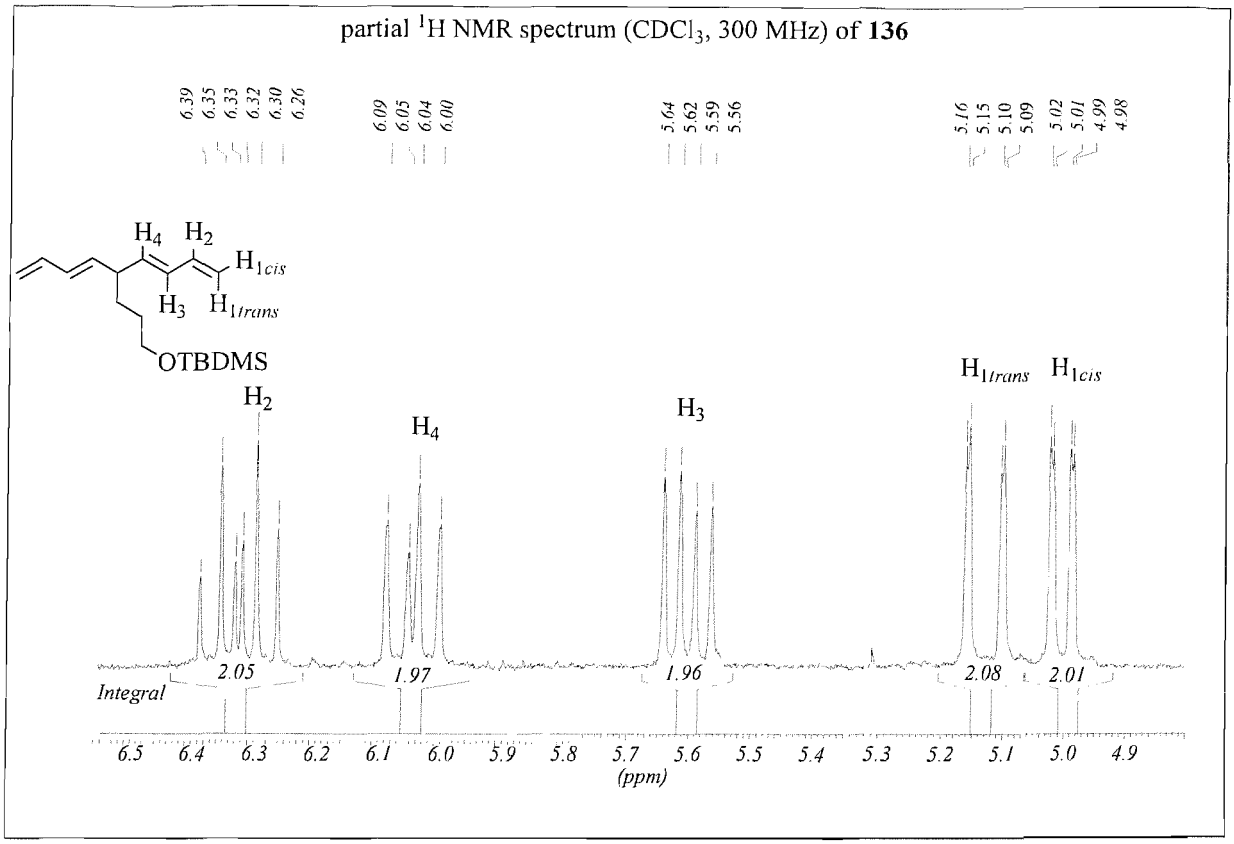


Figure 2-3

The low yield observed for **136** was probably due to oligomerisation of the starting material **140**. The aldehyde **140** was suspected to be light sensitive. The reaction was carried out in the dark but the yield did not improve.

It was observed that the outcome of the olefination dramatically changed depending on the scale used for the reaction. The olefination competes with a proton exchange process between the anion of allyl diphenylphosphine oxide and the aldehyde **140** leading to the formation of aldehyde **155**. The olefination and the proton exchange competition needed further survey in order to favoured the formation of the desired bis(diene) **136** over the conjugated tetraene **156** or the conjugated aldehyde **155**.

Initially, the bis(diene) **136** was isolated in 52% yield by using a 3 fold excess of allyl diphenylphosphine oxide on small scale (entry 1). However, on a larger scale only the fully conjugated tetraene **156** was isolated in 16% yield. Then, the reaction mixture was carried out with 1 equivalent of allyl diphenylphosphine oxide. The reaction mixture was slowly warmed up from -78 °C to room temperature over 18 h to get the bis(diene) **136** in 40% yield along with 20% of conjugated aldehyde **155** (entry 2). The same yield was obtained on a larger scale. However, it appeared difficult to control the rate of the warming up. In certain cases, an inseparable mixture of bis(diene) **136** and the conjugated tetraene **156** was isolated. The

separation on silica gel was of no avail since the bis(diene) **136** tend to decompose on silica (even on neutralised silica). On the other hand, bis(diene) **136** is stable on neutral alumina but no separation was obtained. It appeared very difficult to control fully all the parameters of the Wittig-Horner to avoid those side reactions.

The bis(diene) **136** was prepared in four steps. Nevertheless, the synthesis involves the use of carcinogenic HMPA. Some investigations were carried out to replace HMPA by a less toxic reagent in order to allow the synthesis of **136** during a placement at Astra Zeneca. HMPA is usually used as a co-solvent in reaction with a base such as *n*-BuLi, *sec*-BuLi or *t*-BuLi. HMPA chelates the lithium cation and increases the amount of deprotonated compound and is often replaced by DMPU or TMEDA.

When the reaction was performed with DMPU, the bis(diene) **136** was isolated in 3% yield (entry 3) and TMEDA/BHT afforded the bis(diene) **136** in 23% yield (entry 4). Unfortunately, the yield dropped to 6% when the reaction was scaled up. A catalytic amount of BHT was used as a radical inhibitor to stabilize the starting material **140**. TMEDA alone failed to replace HMPA.

Another alternative was to change the base used in the Wittig-Horner reaction. NaH and DBU were not strong enough to deprotonate the allyl diphenylphosphine oxide. Treatment of allyl diphenylphosphine oxide with LiHMDS or NaHMDS in THF gave a red solution characteristic of the deprotonation. Unfortunately, only the starting material was recovered when LiHMDS was used. On the other hand, the bis(diene) **136** was isolated in 25% with NaHMDS (entry 5) but the yield dropped to 15% when the reaction was scaled up.

The Horner-Wadsworth-Emmons reaction was also attempted with the allyl diethylphosphonate (entry 6) but only the conjugated aldehyde **155** was recovered in 45% yield along with 5% of a mixture of bis(diene) **136** and conjugated tetraene **156**.

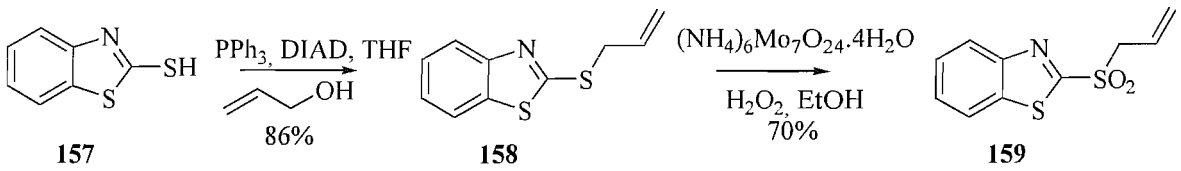
The formation of the conjugated aldehyde **155** in the Wittig-Horner olefination results from the proton exchange between the anion of allyl diphenylphosphine oxide and the aldehyde **140**. It was observed that aldehyde **140** was more reactive than aldehyde **155**. However, when the aldehyde **155** and the anion of allyl diphenylphosphine oxide are present in reaction mixture, then the fully conjugated tetraene **156** is formed.

It was then decided to stop the reaction before the formation of the conjugated tetraene **156**. The reaction mixture was stirred for 45 min at -78 °C followed by 45 min at 0 °C. In that case, the bis(diene) **136** was isolated in 25% yield along with 40% of conjugated aldehyde **155** (entry 7). The formation of the conjugated tetraene **156** was not observed in those conditions.

Although, the last method (entry 7) afforded the bis(diene) **136** in only 25% yield, it appeared to be more reproducible than all the others conditions attempted. The reaction was successfully performed on 3-4 g of aldehyde **140**.

2.3.2.3.2 The Julia-Kocienski olefination

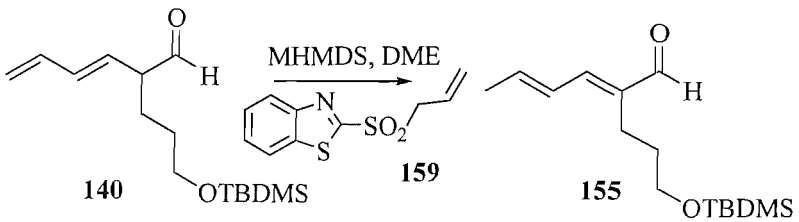
For all the reasons described above, it was decided to investigate the Julia-Kocienski olefination to improve the synthesis of the bis(diene) **136**.[131,132] The allylbenzothiazole-sulfone **159** (BT-sulfone) was prepared in two steps (Scheme 2-16). The mercaptobenzothiazole **157** was reacted with allyl alcohol using the Mistsunobu variant to afford **158** in 86% yield. The sulphide **158** was then oxidised with peroxymolybdate (VI) reagent[133] to give the sulfone **159** in 70% yield.



157 **158** **159**

Scheme 2-16

The allylbenzothiazole-sulfone **159** was reacted with aldehyde **140**. The olefination reaction was first of all attempted with 1.2 equivalents MHMDS at -78 °C for 3 h in DME. Unfortunately, only the conjugated aldehyde **155** was isolated in yields ranging between 27% to 53% (Scheme 2-17, Table 2-2).



140 **159** **155**

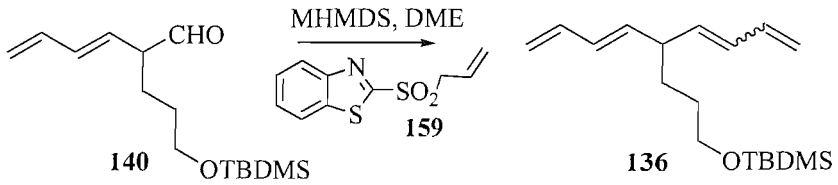
Scheme 2-17

entry	*base (equiv)*	*conditions*	*yield of **155***
1	LiHMDS (1.2)	-78 °C, 3 h	53%
2	NaHMDS (1.2)	-78 °C, 3 h	27%

Table 2-2

The olefination was attempted by stirring the reaction mixture at -78 °C for 15 min or 30 min and the solution was then warmed up at 0 °C or room temperature (Scheme 2-18, Table 2-3).

The reaction appeared to be slower at 0 °C than at room temperature. The bis(diene) **136** was isolated in yield ranging between 10% to 83%, as an *E/Z* mixture. In order to improve the *E/Z* ratio, different reaction conditions were screened. However, all the conditions tried met with failure to improve the *E/Z* ratio. On the other hand, the yield dramatically changed with the reaction conditions. It was observed that the yield increased when the reaction was performed at room temperature (entry 3-4). Furthermore it was attempted to stir the reaction mixture for 15 min at -78 °C (entry 3) to limit the aldehyde isomerisation before warming to room temperature. The yield was lower than when the reaction mixture was stirred for 30 min at -78 °C (entry 4). It was also observed that by using a 1.2 fold excess of NaHMDS improved the yield from 13% to 83% (entry 5). In those conditions the reaction has to be carried out at 0 °C to limit the aldehyde isomerisation.



Scheme 2-18

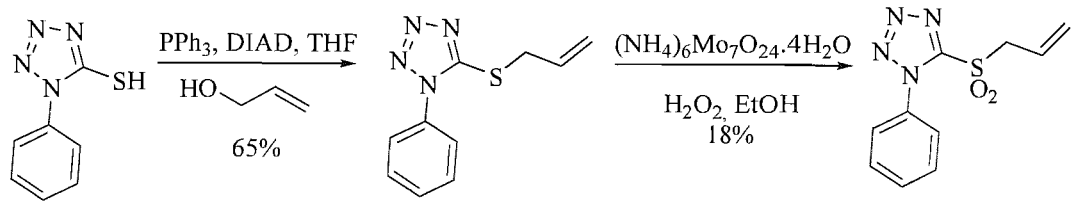
entry	*base (equiv)*	*conditions*	*E/Z ratio*[a]	*yield of* ***136***
1	LiHMDS (1.1)	-78 °C, 30 min then rt, 50 min	75:25	27%
2	NaHMDS (1)	-78 °C, 30 min then 0 °C, 50 min	73:27	13%
3	NaHMDS (1)	-78 °C, 15 min then rt, 45 min	73:27	22%
4	NaHMDS (1)	-78 °C, 30 min then rt, 30 min	73:27	45%
5	NaHMDS (1.2)	-78 °C, 30 min then 0 °C, 45 min	77:23	83%

Table 2-3

The *E/Z* mixture could not be separated even after TBDMS deprotection. As the IMDA has to be performed with pure (*E,E*)-bis(diene), further investigation was undertaken. The olefination involving 1-phenyl-1*H*-tetrazole-sulfone (PT-sulfone) is known to provide a high level of *E* double bond compared to the benzothiazole-sulfone (BT-sulfone).[132,134] It was then decided to prepare the 5-(allylsulfonyl)-1-phenyl-1*H*-tetrazole **162** (Scheme 2-19). The 1-phenyl-1*H*-tetrazole-5-thiol **160** was reacted with allyl alcohol using the Mitsunobu variant to afford **161**

[a] Ratio determined by ^{1}H NMR in $CDCl_3$

in 65% yield. The sulphide **161** was then oxidised with peroxymolybdate (VI) reagent[133] to give the PT-sulfone **162** in 18% yield which was not further optimised.



160 **161** **162**

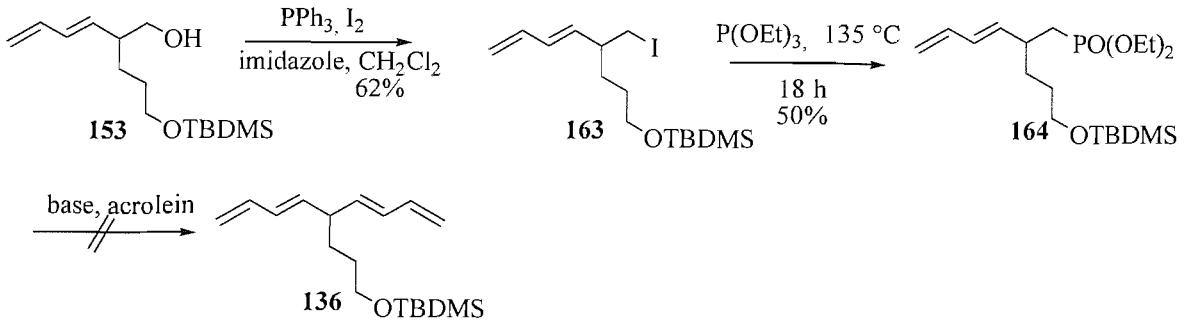
Scheme 2-19

The PT-sulfone **162** was then reacted with the aldehyde **140** using the standard conditions described in the literature.[134] The reaction was attempted with KHMDS or NaHMDS unfortunately, a mixture of conjugated tetraene **156** and *E/Z* bis(diene) **136** was isolated. The conjugated aldehyde **155** was also isolated in yield ranging between 18% to 54%.

2.3.2.4 Formation of the bis(diene) with Horner-Wadsworth-Emmons approach

Another strategy was considered to prepare the bis(diene) **136**. The key step is a Horner-Wadworth-Emmons reaction between the commercially available acrolein and the phosphonate **164** (Scheme 2-20).

The alcohol **153** was iodinated using PPh_3, imidazole and iodine to afford the iodide **163** in 62% yield. The phosphonate **164** was formed in moderate yield by heating the iodide **163** in neat triethyl phosphite at 135 °C. The phosphonate **164** was then deprotonated with NaHMDS, LiHMDS, LDA or *n*-BuLi to get an orange-red solution characteristic of the anion formation. Unfortunately, the Horner-Wadworth-Emmons reaction between the phosphonate **164** and acrolein was fruitless since only the starting material **164** was recovered (Scheme 2-20).



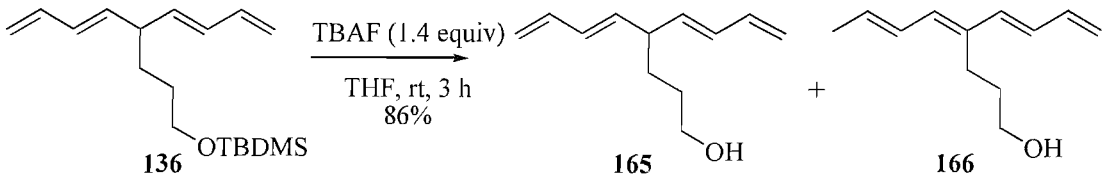
Scheme 2-20

2.3.3 Conclusion for the synthesis of the bis(diene) 136

Different approaches were considered for the preparation of the bis(diene) **136**. Direct olefination of the aldehyde **140** using the Julia-Kocienski olefination gave a mixture of *E/Z* bis(diene) **136**. Attempts to improve the *E/Z* ratio met with failure. The formation of the bis(diene) from the phosphonate **164** was also unsuccessful. Eventually, the Wittig-Horner reaction of aldehyde **140** with allyl diphenylphosphine oxide afforded the desired bis(diene) **136** in low yield. The reaction conditions described above are aimed to first get some of the pure bis(diene) and then to have a good reproducibility.

2.4 Final steps to the IMDA precursor

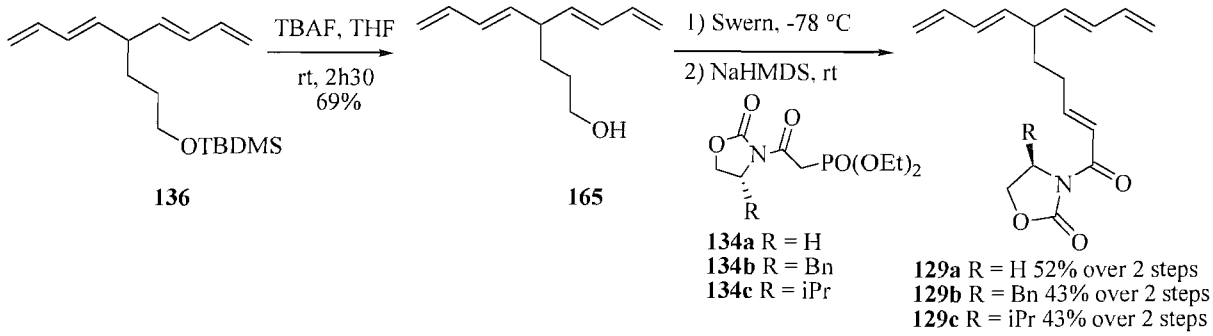
The alcohol deprotection was performed with 1.4 equivalents of TBAF. However, the deprotected bis(diene) was isolated in 86% yield as a 1.5:1 mixture of bis(diene) **165** and tetraene **166** (Scheme 2-21).



Scheme 2-21

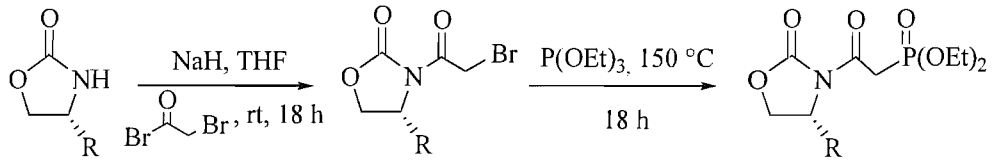
The alcohol was successfully deprotected with $LiBF_4$ to give the alcohol **165** in 68% yield.[135] The TBDMS group was also removed by using 1 equivalent of TBAF to afford to alcohol **165** in 69% yield (Scheme 2-22). Although both deprotections gave the same yield, TBAF was preferred since the deprotection occurred faster than with $LiBF_4$. The bis(diene) **136**

remained intact after 2 months of storage neat at -20 °C while the neat alcohol **165** tended to polymerise after few days at -20 °C.



Scheme 2-22

The incorporation of the auxiliary in our IMDA precursor was envisioned *via* a Horner-Wadworth-Emmons reaction using the known reagents **134a-c**. The phosphonates were prepared in two steps from the corresponding oxazolidinones **167a-c**. The oxazolidinones **167a-c** were deprotonated with 1.2 equivalents of NaH and reacted with bromoacetyl bromide to afford **168a-c** in yield ranging between 53% and 82%.[136-138] The bromides **168a-c** were then reacted with an excess of triethyl phosphite to afford the phosphonates **134a-c** in yields ranging between 59% and 95%.[139-141]



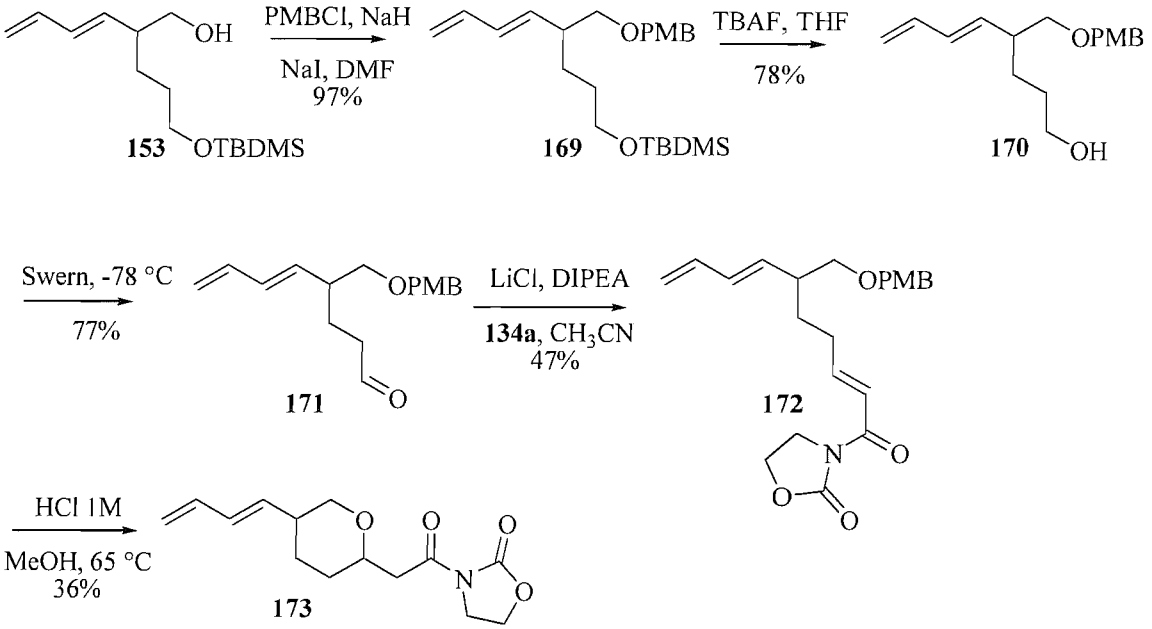
Scheme 2-23

The alcohol **165** was then oxidised under Swern's conditions to the corresponding aldehyde which was immediately treated with the phosphonates **134a-c** to afford the IMDA precursors **129a-c** in yields ranging between 43% and 52% over 2 steps (Scheme 2-22).[142] The nature of the counter cation of the base used in the Horner-Wadsworth-Emmons reaction seemed really important. By replacing NaHMDS by LiHMDS, the IMDA precursor **129a** was isolated in 10% yield over 2 steps (oxidation, Horner-Wadsworth-Emmons). The Horner-Wadsworth-Emmons step was also performed using the soft conditions established by Roush *et al.*, for base sensitive compounds (LiCl, DIPEA),[143] which afforded the IMDA precursor **129a** in 20% yield

over 2 steps. No formation of the conjugated tetraene was observed after the oxidation-olefination processes.

2.5 A modified approach

Bis(diene) moieties are very sensitive. Those compounds are prone to polymerise and to decompose on silica. It was decided to consider a strategy where the bis(diene) moiety is only introduced at the very last stage of the synthesis (Scheme 2-24).



Scheme 2-24

The alcohol **153** was protected using PMBCl, NaI in DMF to afford the PMB ether **169** in 97% yield. The PMB ether **169** was isolated with a lower yield (72%) when *para*-methoxybenzyl-trichloroacetimidate was used.

The TBDMS group was removed using a 1.5 fold excess of TBAF to give the alcohol **170** in 78% yield. Alcohol **170** was subjected to Swern's oxidation conditions to afford the aldehyde **171** in 77% yield. The auxiliary was introduced using the Horner-Wadworth-Emmons reaction conditions. The trienimide **172** was isolated in 20% yield when the standard conditions were utilized (NaHMDS, THF). The yield was improved to 47% when milder conditions were used (LiCl, DIPEA, CH_3CN).[143]

The PMB removal was attempted with DDQ.[124] A mixture of unidentified product was isolated at room temperature while no reaction was observed at 0 °C. The deprotection was then

performed with HCl 1M in MeOH at 65 °C[144] to give the tetrahydropyran derivative **173** in 36% yield along with an other unidentified product.

The formation of the pyrane ring could be explained as follows. The PMB group was removed to get the corresponding alcohol which reacted instantaneously *via* an intramolecular 1,4-addition on the α,β-unsaturated imide to afford the pyrane moiety **173**. It was anticipated that deprotection with CAN would also give side reactions since cerium can act as a Lewis acid and promoted IMDA reaction.

2.6 Conclusion

Different strategies were considered for the synthesis of 5-subsituted-1,3,6,8-nonatetraene. The double Horner-Wadworth-Emmons met with failure since the bis(phosphonate) **137** was not isolated. However, it was observed that the bis(diene) **136** could not be formed from the monophosphonate **164** which strongly compromised the double Horner-Wadworth-Emmons strategy.

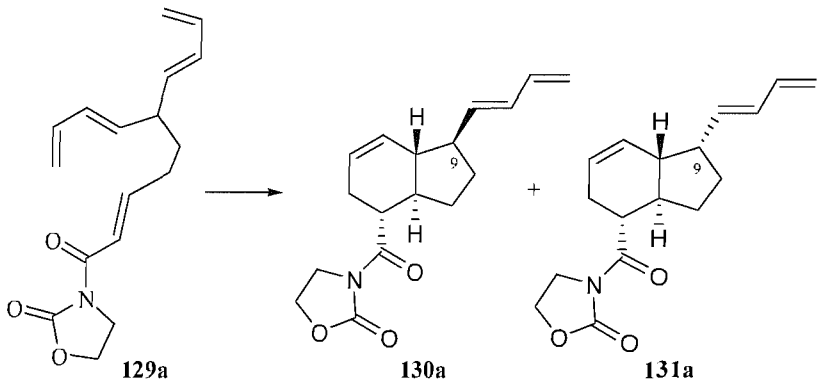
The sorbic acid approach appeared as a quick and simple method to access to 5-substituted-1,3,6,8-nonatetraene. We managed to find the right conditions to avoid the isomerisation of the bis(diene) **136** to the fully conjugated tetraene **157**. However, the formation of bis(diene) moiety through a Wittig-Horner reaction remains low yielding. Attempts to improve the yield of this step met with failure.

Chapter 3: The IMDA reaction

3.1 Study of the diastereoselectivity

3.1.1 Introduction

With the bis(diene) **129a** in hand, we were able to start the IMDA study with this model compound (Scheme 3-1). A wide range of auxiliaries, described in the literature, were shown to be efficient in IMDA reaction (see section 1.3.5.2). Oxazolidinone has the advantage to have a simple structure in comparison to camphorsultam or carbohydrate derivatives. Therefore the NMR spectrum of oxazolidinone is simplified compared to the other auxiliaries. Using achiral oxazolidinone, the diastereoselectivity (C-9 selectivity) was first studied under thermal conditions and by using achiral Lewis acids. It was also planned to investigate the use of chiral Lewis acids in order to make the process enantioselective. The group selective IMDA reaction was also investigated using chiral oxazolidinone auxiliaries.



Scheme 3-1

3.1.2 Investigation of the process by thermal Diels-Alder

The IMDA reaction was performed under thermal conditions with a catalytic amount of BHT, which was used as a radical inhibitor to limit the polymerisation. The results of the cyclisation are summarised in Table 3-1. A solution of **129a** was heated in a sealed tube in toluene at 150 °C for 24 h (entry 1). A mixture of two diastereoisomers **130a/131a** was isolated as a 70:30 ratio and in 80% yield. The reaction was also carried out using microwave irradiation. The reaction was performed in toluene at 150 °C for 3 h (entry 2). A mixture of **130a/131a** was isolated with lower yield and selectivity than when the conventional heating was used. However, a similar selectivity was obtained when toluene was replaced by *o*-dichlorobenzene (entry 3) albeit with a lower yield than when conventional heating was used.

entry	*conditions*	*solvent*	*ratio (**130a**:**131a**)*[b]	*yield of **130a/131a***
1	150 °C, 24 h	toluene	70:30	80%
2	150 °C, microwave, 3 h	toluene	60:40	62%
3	150 °C, microwave, 4 h	*o*-dichlorobenzene	72:28	42%

Table 3-1

The cycloadducts were purified by column chromatography and were analysed by ^{1}H NMR. The reaction mixture was quite clean with only two diastereoisomers **130a** and **131a** observed (C-9 epimers). Unfortunately, the isomers could not be separated by normal phase HPLC. Separation by RP-HPLC gave milligram quantities of isomerically pure cycloadduct **130a**. The partial NMR spectrum depicted on Figure 3-1 showed on the left the two isomers detected **130a/131a** and on the right the pure cycloadduct **130a**.

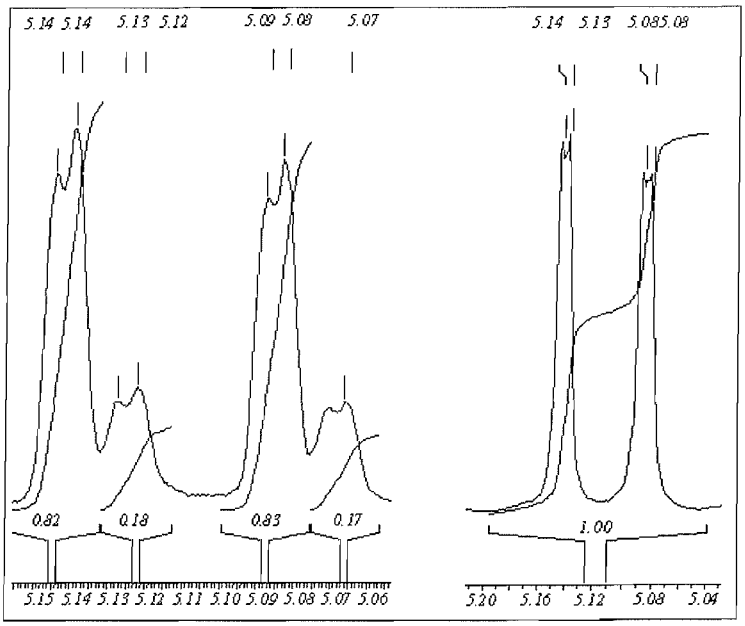


Figure 3-1

The X-ray crystal structure of **130a** is depicted in Figure 3-2. The compound analysed was racemic. The X-ray study showed that the major compound is the *trans*-hydrindene with the desired relative stereochemistry at C-9. However, the minor isomer **131a** has not been isolated in enough quantity to confirm the stereochemistry by X-ray crystallography.

[b] Ratio determined by ^{1}H NMR in $CDCl_3$

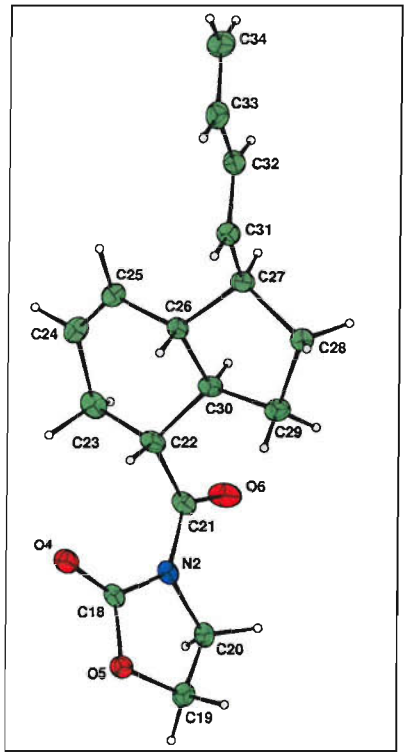


Figure 3-2

We wanted to establish the stereochemistry of the minor isomer and determine whether we had the cycloadduct **174** resulting from an *exo* transition state or **131a** (C-9 epimer of the major isomer **130a**) resulting from an *endo* transition state.

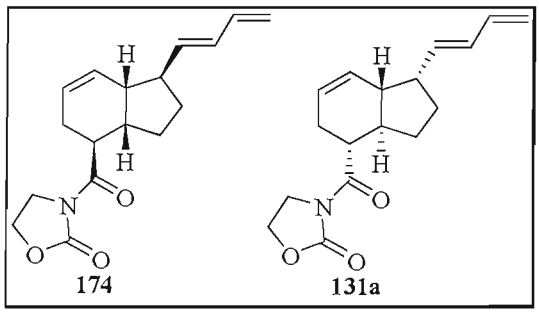


Figure 3-3

It was previously reported that the stereochemistry of the fused junction can be predicted by the value of the coupling constant of H-5 determined by ^{1}H NMR.[59] The NMR analysis allowed us to confirm the structure of **130a** but not the stereochemistry. However, the ^{1}H NMR spectroscopic data of **130a** ($J_{6\text{-}5} = J_{4ax\text{-}5} = 10.2$ Hz and $J_{4eq\text{-}5} = 6.0$ Hz) strongly suggested the indicated stereochemistry for the fused junction, in agreement with Evans's results (Figure 3-4,

Table 3-2).[142] The coupling constant suggested that H-5 and H-6 are axial confirming the *trans*-fused junction.

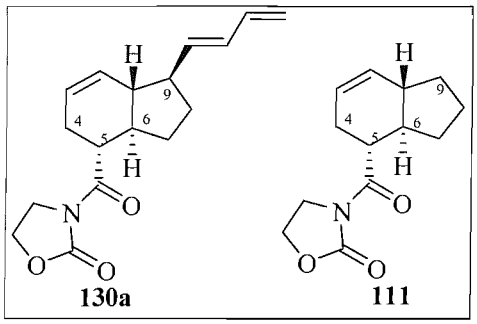


Figure 3-4

entry	*cycloadduct*	*^{1}H NMR of H-5 in $CDCl_3$*
1	**130a**	δ 3.92, td, J = 10.2, 6.0 Hz
2	**111**	δ 3.91, td, J = 10.8, 6.8 Hz

Table 3-2

The ^{1}H NMR data obtained for **131a** were then compared to the NMR data obtained for **130a**. The NMR was run in C_6D_6 in order to limit the overlap between the major **130a** and the minor **131a** isomers. The presence of *trans*-fused junction in the minor isomer **131a** was confirmed by the similar chemical shift for **130a** and **131a** (0.03 ppm) and by the presence of a td for H-5. Once again, the coupling constant for H-5 ($J_{6\text{-}5}$ = $J_{4ax\text{-}5}$ = 9.5 Hz and $J_{4eq\text{-}5}$ = 6.5 Hz) strongly suggested the indicated stereochemistry indicated at **131a** for the fused junction (entry 2). The data were then compared to the ^{1}H NMR reported for **101a** (*trans*-fused) and **101b** (*cis*-fused). The H-5 for **101a** appears as a td while the H-5 of **101b** appears as a q (Table 3-3).[82] A careful NMR analysis of the mixture **130a/131a** showed a shift ranging between 0.079 ppm and 0.024 ppm for the diene signals (H-10, H-11, H-12 and H-13). Those observations make us believe that **131a** is the C-9 epimer of **130a** (**Figure 3-5**).

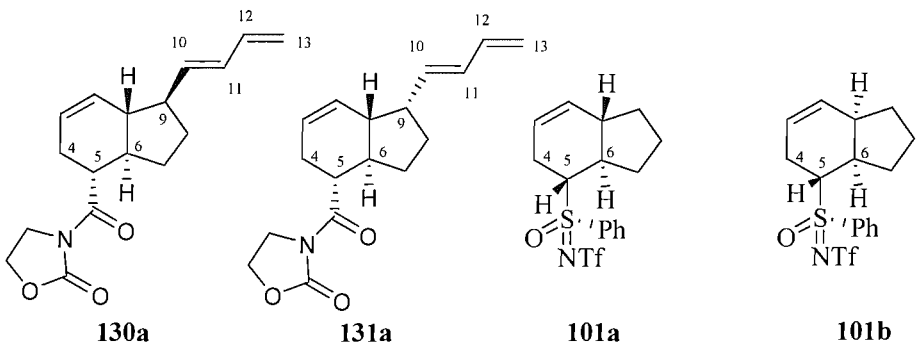
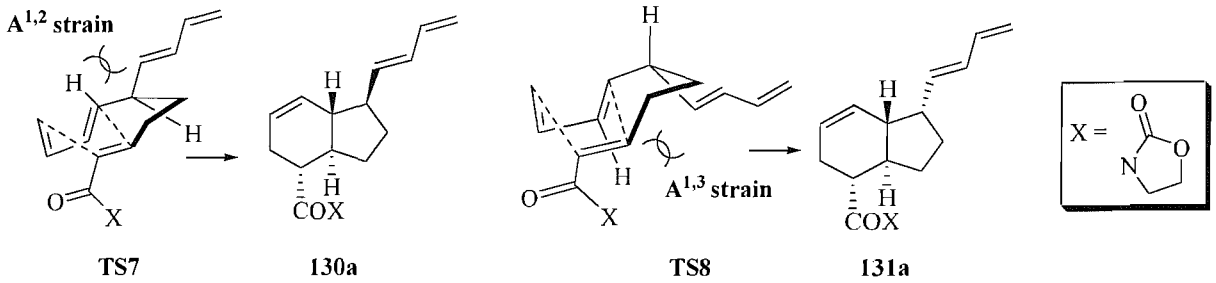


Figure 3-5

entry	*cycloadduct*	*^{1}H NMR of H-5*	*NMR solvent*
1	**130a**	δ 4.20, td, J = 10.2, 6.0 Hz	C_6D_6
2	**131a**	δ 4.17, td, J = 9.5, 6.5 Hz	C_6D_6
3	**101a**	δ 3.82, td, J = 11.0, 6.0 Hz	$CDCl_3$
4	**101b**	δ 3.69, q, J = 6.5 Hz	$CDCl_3$

Table 3-3

The outcome of the C-9 selectivity confirms that the selectivity observed depends on the difference in energy between the $A^{1,2}$ and $A^{1,3}$ allylic strains (Scheme 3-2). Both, $A^{1,2}$ and $A^{1,3}$ strain occur between the non reacting diene and the H on the reacting diene. The $A^{1,3}$ strain is minimized in **TS7** compare to **TS8** while $A^{1,2}$ strain is minimized in **TS8** compare to **TS7**. In our case, the experiment suggested that the $A^{1,2}$ strain is more favourable than the $A^{1,3}$ strain. Therefore, **TS7** is more favourable than **TS8**.



Scheme 3-2

3.1.3 Investigation of the process with Lewis acid catalysis

3.1.3.1 Lewis acid catalysis at low temperature

The Lewis acid catalysed IMDA reactions were performed in CH_2Cl_2 with 1.4 equivalents of Lewis acid. A concentration of 0.03 M of IMDA precursor **129a** in CH_2Cl_2 was used to avoid the intermolecular Diels-Alder reaction. The reaction was carried with aluminium based Lewis acid: $MeAlCl_2$, Me_2AlCl, Me_3Al (the weakest Lewis acid in the series), $EtAlCl_2$ and Et_2AlCl.

The reaction was first of all performed at -78 °C to limit the polymerisation (Table 3-4). After a few hours at this temperature, the reaction mixture was directly purified by column chromatography without prior work-up. NMR analysis showed only traces of compound when $MeAlCl_2$ was used (entry 1). On the other hand, a mixture of cycloadducts **130a/131a** was isolated in 54% yield as a 79:21 ratio, when $EtAlCl_2$ was used (entry 2).

entry	*Lewis acid (equiv)*	*conditions*	*ratio (**130a/131a**)*[c]	*yield of **130a/131a***
1	$MeAlCl_2$ (1.4)	-78 °C, 4.5 h	-	traces of compound
2	$EtAlCl_2$ (1.4)	-78 °C, 5 h	79:21	54%

Table 3-4

The reaction was then performed at -30 °C with different Lewis acids. After a few hours at -30 °C, TLC analysis showed that the reaction was complete. The crude was purified by column chromatography without prior work-up. The IMDA adduct was isolated in moderate yield as a mixture of two compounds **130a/131a**. The results of the cyclisation are summarized in Table 3-7. A better selectivity was obtained with Me_3Al (entry 3) than with any other Lewis acid. No major difference in terms of selectivity was observed between $MeAlCl_2$, Me_2AlCl or Et_2AlCl (entry 1, 2, 4). However, a better yield was obtained with Me_2AlCl and Me_3Al (entry 2, 3) than when $MeAlCl_2$ and Et_2AlCl (entry 1, 4) were used. It was then anticipated that $AlCl_3$ was too strong a Lewis acid and would favour the oligomerisation of the starting material **129a** rather than the IMDA reaction.

entry	*Lewis acid (equiv)*	*conditions*	*ratio (**130a/130b**)*[c]	*yield of **130a/131a***
1	$MeAlCl_2$ (1.4)	-30 °C, 4 h	73:27	47%
2	Me_2AlCl (1.4)	-30 °C, 4 h	69:31	59%
3	Me_3Al (1.4)	-30 °C, 2 h	77:23	55%
4	Et_2AlCl (1.4)	-30 °C, 4.5 h	70:30	47%

Table 3-5

Roush reported Lewis acid catalysed IMDA reaction in CCl_4 or CH_2Cl_2.[42] The IMDA reaction was performed with 1.4 equivalents of $AlMe_3$ at -30 °C in different solvents (Table 3-6). No reaction was observed in CCl_4 (entry 1). The temperature of the reaction mixture was probably too close to the melting point of CCl_4 which did not solvate well enough the Lewis acid and the IMDA precursor **129a**. A mixture of cycloadducts **130a/131a** was isolated in good yield when $CHCl_3$ was used (entry 2). However, the C-9 selectivity was similar in $CHCl_3$ (entry 2) and in CH_2Cl_2 (entry 3).

[c] Ratio determined by ^1H NMR in C_6D_6

entry	*solvent*	*conditions*	*ratio (**130a/131a**)*[d]	*yield of **130a/131a***
1	CCl_4	-20 °C, 3 h	-	traces of compound
2	$CHCl_3$	-30 °C, 3.5 h	75:25	73%
3	CH_2Cl_2	-30 °C, 2 h	77:23	55%

Table 3-6

The Lewis acid catalysed IMDA reaction afforded the cycloadduct in yield ranging between 47% to 73%. The best yield (73%) was observed at -30 °C in $CHCl_3$ while the best selectivity (79:21) was obtained with $EtAlCl_2$ at -78 °C.

3.1.3.2 Lewis acid catalysis at room temperature

The IMDA reaction was also performed at room temperature. The data are summarized in Table 3-7. The IMDA reaction was carried out with $TiCl_4$ or $ZnCl_2$. The Lewis acid was used in limited amount (0.7 equivalent) in order to avoid the oligomerisation.[42] However, only the starting material was recovered along with a large amount of polymer.

Lewis acid catalysed IMDA was performed with aluminium based Lewis acids (Et_2AlCl, $MeAlCl_2$, Me_2AlCl, Me_3Al) and all of them promoted the IMDA reaction. A similar selectivity was observed when the IMDA reaction was carried out at room temperature compared to the reaction performed at low temperature.

In the thermal IMDA reactions, BHT was used as radical inhibitor to limit the oligomerisation. It was decided to perform the Lewis acid catalysed IMDA with BHT in order to improve the yield. The reaction was performed with $MeAlCl_2$ and catalytic amount of BHT (entry 4). The reaction was also carried out with $MeAlCl_2$ and a stoichiometric amount of BHT (entry 5). In both cases, a mixture of cycloadducts **130a/131a** was isolated with a lower yield albeit with a slightly better selectivity than when the reaction was performed without BHT (entry 3). The same observation was made when the reaction was performed with Me_2AlCl and a catalytic amount of BHT (entry 7). On the other hand, only the starting material was recovered when Me_3Al and BHT were used. It was believed that BHT coordinates to Me_3Al preventing the formation of bidentate complex between the Lewis acid and the carbonyl groups of the auxiliary.

The reaction was also performed with Et_3Al and iBu_3Al but in both cases mixtures of unidentified compounds were isolated.

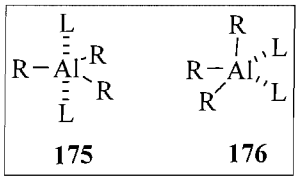
[d] Ratio determined by ^1H NMR in C_6D_6

entry	*Lewis acid (equiv)*	*conditions*	*ratio (130a/131a)*[e]	*yield of 130a/131a*
1	Et_2AlCl (1.4)	23 °C, 21 h	68:32	41%
2	Et_2AlCl (2)	23 °C, 21 h	67:33	27%
3	$MeAlCl_2$ (1.4)	23 °C, 2.5 h	66:34	42%
4	$MeAlCl_2$ (1.4) + BHT (cat)	23 °C, 3 h	67:33	28%
5	$MeAlCl_2$ (1.4) + BHT (1.4)	23 °C, 3 h	70:30	26%
6	Me_2AlCl (1.4)	23 °C, 19 h	63:37	53%
7	Me_2AlCl (1.4) + BHT (cat)	23 °C, 16 h	73:27	42%
8	Me_3Al (1.4)	23 °C, 3.5 h	68:32	50%

Table 3-7

3.1.3.3 $AlMe_3$ as a bidentate complex

Evans et *al.*[41] proved that the diastereoselectivity depends on the auxiliary and on the ability of the Lewis acid to form a bidentate complex. An intensive study on Lewis acid catalysed IMDA reaction was made by Roush.[42,51] Trialkylaluminium and alkylaluminium halides were found to be more effective than any other Lewis acids. It is also well documented that alkylaluminium halides and trialkylaluminium Lewis acids can form bidentate complexes *via* a pentacoordinate complex due to the high affinity of aluminium toward oxygen (Al-O = 511 ± 3. $kJ.mol^{-1}$) (Figure 3-6).[145,146]



175 **176**

Figure 3-6

Me_3Al promoted the IMDA reaction in moderate yield and selectivity. Although the hypothetical existence of pentacoordinate trialkylaluminium complexes with the two carbonyls is emphasized by the IMDA reaction (Table 3-7, entry 4), more direct evidence was obtained by ^{13}C NMR study. To a solution of IMDA precursor **129a** in CD_2Cl_2 at -78 °C was added 1.1 equivalents of Me_3Al. The ^{13}C NMR of **177** was run at 300 °K. An upfield shift was observed for the two carbonyls C-1 and C-2 which confirms that these were both chelated to the aluminium.

[e] Ratio determined by ^1H NMR in C_6D_6

Besides, an upfield shift was also observed for C-4 (Table 3-8). The chelation of the carbonyl C-2 reduces the electron density on C-4 and activates the dienophile for the IMDA reaction (Figure 3-7).

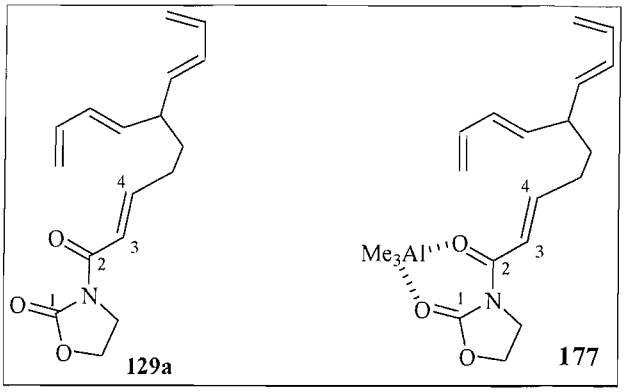


Figure 3-7

^{13}C NMR data	*C-1*	*C-2*	*C-3*	*C-4*
free **129a**	δ 153.8	δ 165.3	δ 120.7	δ 150.6
complex **177**	δ 157.7	δ 168.1	δ 119.3	δ 153.5

Table 3-8

3.1.4 Conclusion

The thermal IMDA reaction led to the same mixture of diastereoisomers as the Lewis acid catalysed IMDA reaction. The selectivities observed are similar in both cases. However the yield was better under thermal conditions since the Lewis acid also promoted oligomerisation.

3.2 Study of the enantioselectivity

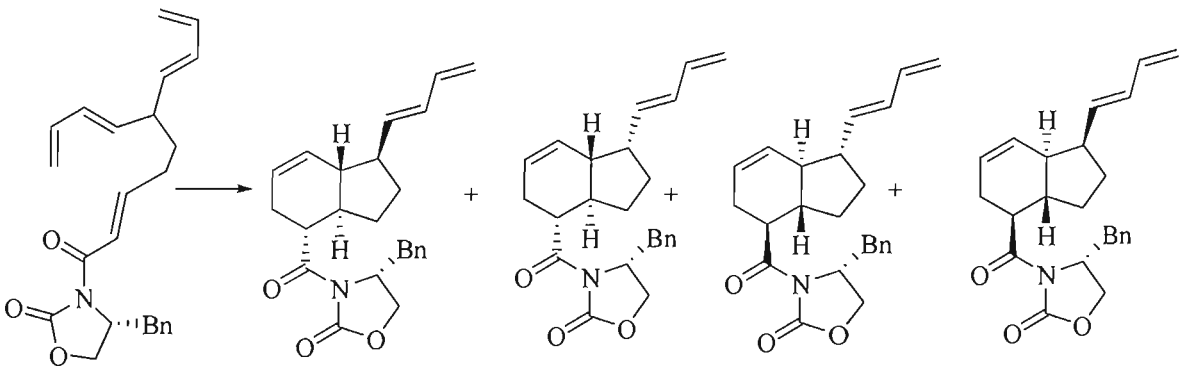
3.2.1 Chiral auxiliary

Following the studies with achiral IMDA precursor **129a** leading to the racemic hydrindene system, a chiral auxiliary approach was investigated to determine the absolute stereochemistry of the hydrindene system. Chiral oxazolidinone derivatives have been used in the IMDA reaction for a wide variety of substrates. We have selected a chiral (*R*)-4-benzyl-2-oxazolidinone and (*R*)-4-isopropyl-2-oxazolidinone auxiliaries.[41,77]

3.2.2.1 Thermal conditions

When a chiral auxiliary is used four different diastereoisomers are expected under thermal conditions because of the free rotation of the auxiliary. On the other hand, only two diastereoisomers (the C-9 epimers) are expected under Lewis acid catalysis. Indeed, the Lewis acid coordinates the two carbonyls of the auxiliary which block the dienophile in a certain configuration to give the diastereofacial differentiation.

Hence, as a control experiment, the IMDA reaction was performed under thermal conditions. This experiment allowed seeing if the four isomers were detectable by RP-HPLC. The IMDA precursor **129b** was heated in a sealed tube in toluene at 180 °C for 24 h. A mixture of 4 diastereoisomers (Figure 3-8) was isolated in 41% yield as a 22:63:9:6 ratio (Scheme 3-3). The ratio was determined by analytical RP-HPLC. Only three diastereoisomers could be detected by ^{1}H NMR in $CDCl_3$.



129b **130b** **131b** **178** **179**

Scheme 3-3

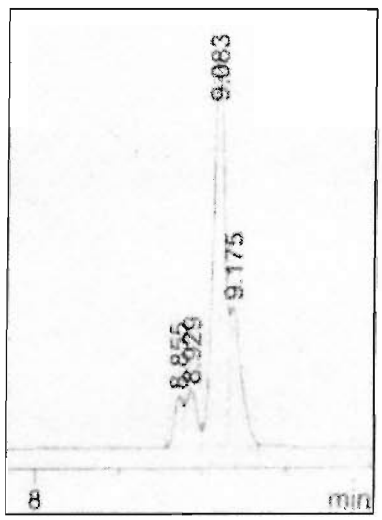
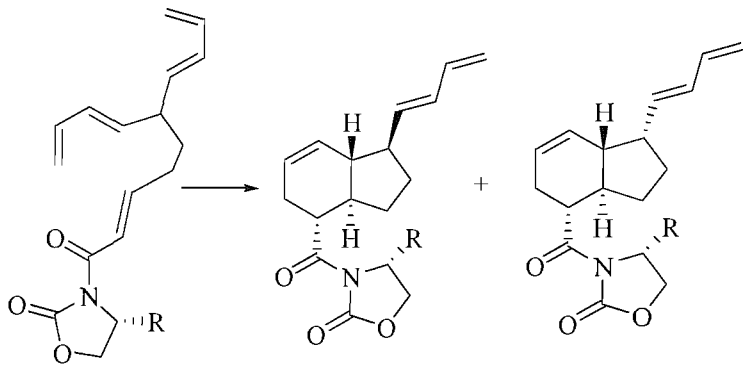


Figure 3-8

3.2.2.2 Lewis acid catalysis at low temperature

The bis(diene) **129b** was reacted with four different Lewis acids to afford a mixture of cycloadducts **130b/131b** (Scheme 3-5). After a few hours at -30 °C, the reaction mixture was directly purified by column chromatography without prior work-up. The data are summarized in Table 3-9. The mildest Lewis acid in the series ($AlMe_3$) failed to promote the cyclisation (entry 1). On the other hand, with Me_2AlCl, Et_2AlCl and $EtAlCl_2$, a mixture of cycloadducts **130b/131b** was isolated in low yield, ranging between 12 to 35%, along with some starting material **129b**. The C-9 selectivity obtained was not as good as the one obtained with an achiral auxiliary in similar conditions.



129b R = Bn
129c R = iPr

130b R =Bn
130c R = iPr

131b R = Bn
131c R = iPr

Scheme 3-4

entry	*Lewis acid (equiv)*	*conditions*	*ratio (130b/131b)*[f]	*yield of (130b/131b)*
1	Me_3Al (1.4)	-30 °C, 3 h	-	0%
2	Me_2AlCl (1.4)	-30 °C, 5.5 h	77:23	28%
3	Et_2AlCl (1.4)	-30 °C, 5 h	62:38	35%
4	$EtAlCl_2$ (1.4)	-30 °C, 6 h	70:30	12%

Table 3-9

3.2.2.3 Lewis acid catalysis at room temperature

The cyclisation proceeded slowly at room temperature (Table 3-10). Only two diastereoisomers were detected by RP-HPLC (Figure 3-9). After 45 to 66 h at room temperature,

[f] Ratio determined by ^1H NMR in C_6D_6

the cycloadduct was isolated in yields ranging between 13 to 49 %. Only two diastereoisomers **130b** and **131b** were detected by ^{1}H NMR and analytical RP-HPLC (Figure 3-9). Me_2AlCl (entry 2) afforded a mixture of cycloadducts **130b/131b** with a better selectivity than when the reaction was performed with an achiral auxiliary. Besides, Me_3Al now gave the cycloadduct with a good selectivity (entry 3). In comparison, $MeAlCl_2$ (entry 1) and Et_2AlCl (entry 4) afforded the mixture of cycloadducts **130b/131b** with a better C-9 selectivity than when Me_2AlCl (entry 2) was used. Hence, the reaction at room temperature did not improve the yield or the selectivity. The use of other Lewis acids (BEt_3, $ZnEt_2$, $InBr_3$, $B(C_6F_5)_3$, $MgBr_2$) promoted substrate decomposition.

entry	*Lewis acid (equiv)*	*conditions*	*ratio (**130b/131b**)*[g]	*yield of **130b/131b***
1	$MeAlCl_2$ (1.0)	23° C, 66 h	89:11	13%
2	Me_2AlCl (1.4)	23 °C, 45 h	79:21	49%
3	Me_3Al (1.4)	23 °C, 45 h	92:8	47%
4	Et_2AlCl (1.4)	23 °C, 66 h	88:12	27%

Table 3-10

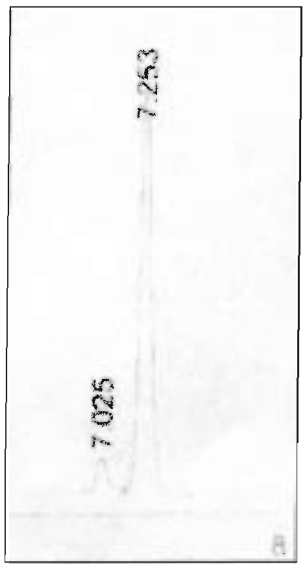


Figure 3-9

The cyclisation was also performed with (*R*)-4-isopropyl-2-oxazolidinone auxiliary as depicted in Scheme 3-4. The IMDA reaction of **129c** afforded a mixture of two diastereoisomers **130c** and **131c** as a 78:22 ratio in yield ranging between 35% to 45%. Both Lewis acids (Me_3Al and Me_2AlCl) gave the same ratio which was lower than the one observed for **130b/131b**.

[g] Ratio determined by analytical RP-HPLC.

entry	*Lewis acid (equiv)*	*conditions*	*ratio (130c/131c)*[h]	*yield of 130c/131c*
1	Me_3Al (1.4)	23° C, 68 h	78:22	35%
2	Me_2AlCl (1.4)	23 °C, 68 h	78:22	45%

Table 3-11

The stereochemistry obtained for the cycloadducts **130b-c** and **131b-c** was confirmed by comparing the H-5 signals with the H-5 signals obtained for **130a** and **131a** by ^1H NMR. The data are summarised in Table 3-12 . The signals for H-5 always appears as a td with a coupling constant ranging between 9.0 to 10.5 Hz corresponding to an axial-axial coupling and a coupling constant ranging between 6.0 to 6.5 Hz corresponding an equatorial-axial coupling. All the cycloadducts prepared **130a-c** and **131a-c** have a *trans*-fused junction confirming an *endo* transition state.

entry	*cycloadduct*	*^1H NMR of H-5*	*NMR solvent*
1	**130a**	δ 4.20, td, J = 10.2, 6.0 Hz	C_6D_6
2	**130b**	δ 3.95, td, J = 10.5, 6.0 Hz	$CDCl_3$
3	**130c**	δ 4.30, td, J = 10.5, 6.0 Hz	C_6D_6
4	**131a**	δ 4.17, td, J = 9.5, 6.5 Hz	C_6D_6
5	**131b**	δ 3.93, td, J = 10.5, 6.0 Hz	$CDCl_3$
6	**131c**	δ 4.27, td, J = 9.0, 6.5 Hz	C_6D_6

Table 3-12

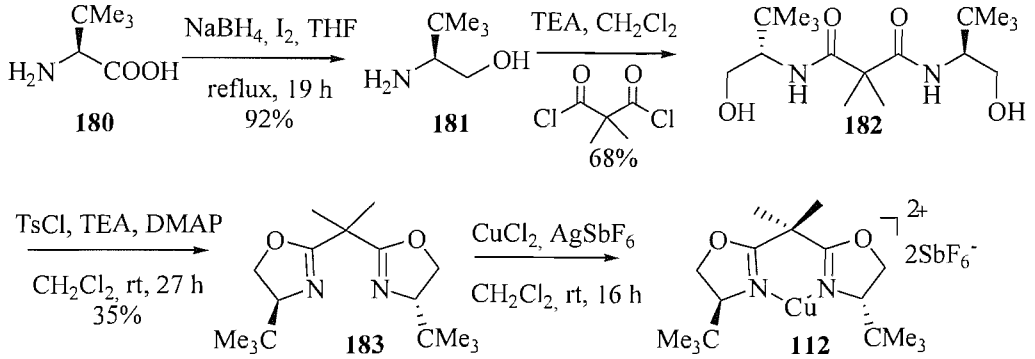
3.2.3 Chiral catalyst

3.2.3.1 Catalyst synthesis

The IMDA reaction was studied with a chiral catalyst. The Evans' catalyst **112** was chosen. The catalyst was prepared according to the procedure described in the literature (Scheme 3-5).[142,147] The carboxylic acid **180** was reduced with $NaBH_4$ to afford the corresponding amino alcohol **181** in 92% yield. The amino alcohol **181** was acylated with dimethylmalonyl dichloride to give the diol **182** in 68% yield. The cyclisation of the diol **182**, *via* formation of the

[h] Ratio determined by ^1H NMR in C_6D_6

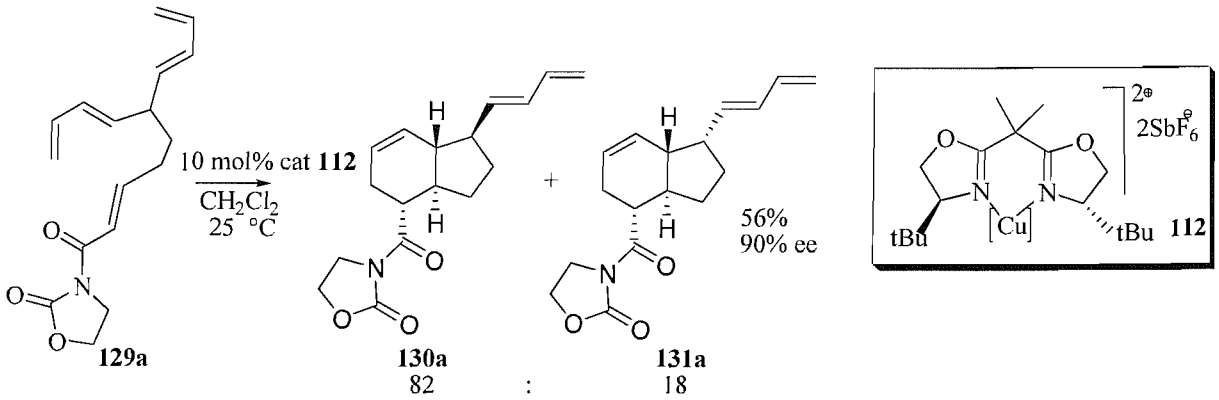
bis(tosylate), afforded the bis(oxazoline) **183** in 35% yield. The catalyst **112** was formed by reacting the bis(oxazoline) **183** with $CuCl_2$ and $AgSbF_6$ to give after filtration a stock solution which was used within the next day.



Scheme 3-5

3.2.3.2 IMDA reaction with chiral catalyst

The catalyst **112** was reacted with the IMDA precursor **129a** to afford a mixture of cycloadducts **130a/131a** in 56% yield as a ratio of 82:18 (Scheme 3-6). The C-9 selectivity obtained was comparable to the selectivity obtained with a chiral auxiliary and Lewis acid catalysis.

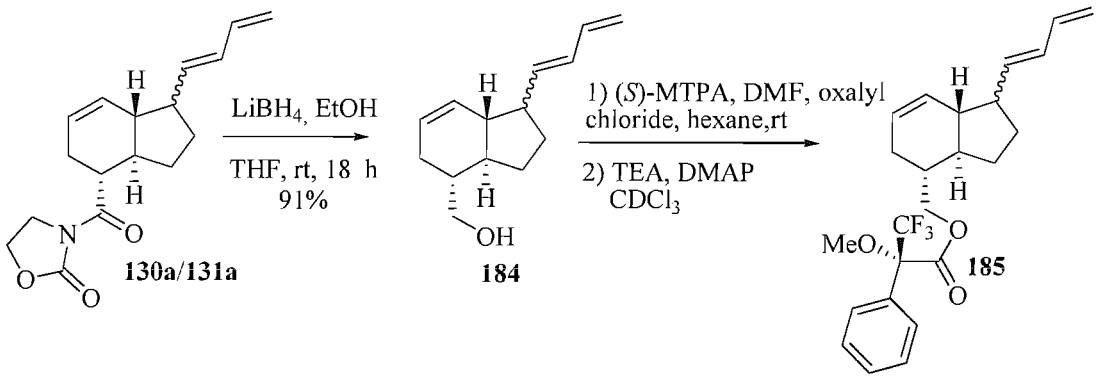


Scheme 3-6

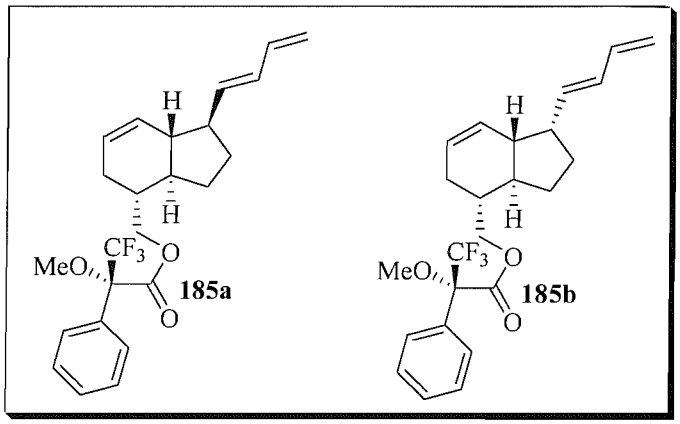
The enantiomeric excess was determined using the Mosher's ester method. The auxiliary in **130a/131a** was removed in good yield with $LiBH_4$ to afford the corresponding alcohol **184** in 91% yield (Scheme 3-7).[148,149] The Mosher's ester was prepared according to the literature procedure.[150] The Mosher's ester **185** was, first of all, prepared with the racemic cycloadduct **184**. The ^1H NMR spectra showed a complete overlap of the diastereoisomers. On the other hand, ^{19}F NMR spectra showed a separation between the four diastereoisomers (Figure 3-10). The

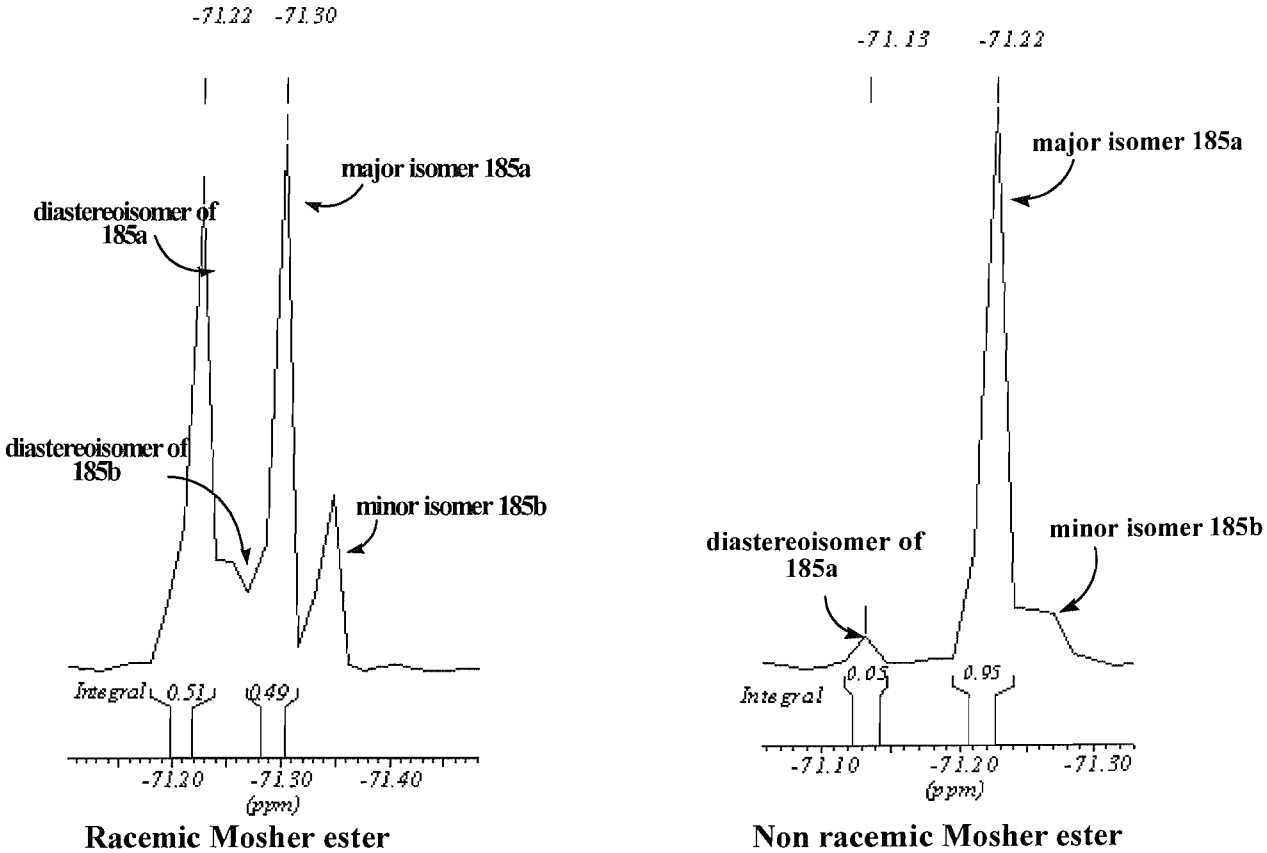
integration for the peaks of the two enantiomers was 51:49. The method was found to be accurate enough to determine the ee on the non racemic mixture.

The alcohol **184** (deriving from the cycloadduct **130a/131a** prepared with Evans' catalyst **112**) was reacted with (*S*)-Mosher's acid chloride in $CDCl_3$. The ^{19}F NMR of the crude reaction mixture proved that the enantiomeric excess is 95:5 as shown on Figure 3-10. Interestingly, the 90% ee is slightly better than the one reported by Evans for the synthesis of **111** (86% ee) without substituent at C-9.[142]



Scheme 3-7





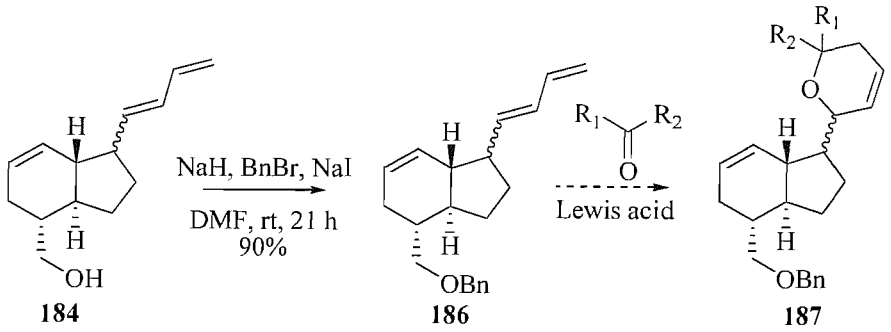
Racemic Mosher ester **Non racemic Mosher ester**

Figure 3-10

3.3 Final side chain elaboration

In order to further illustrate the use of this methodology for steroids synthesis, it was decided to elaborate the side chain of the model compound (Scheme 3-8). The reaction was carried out with **184** containing the two C-9 epimers.

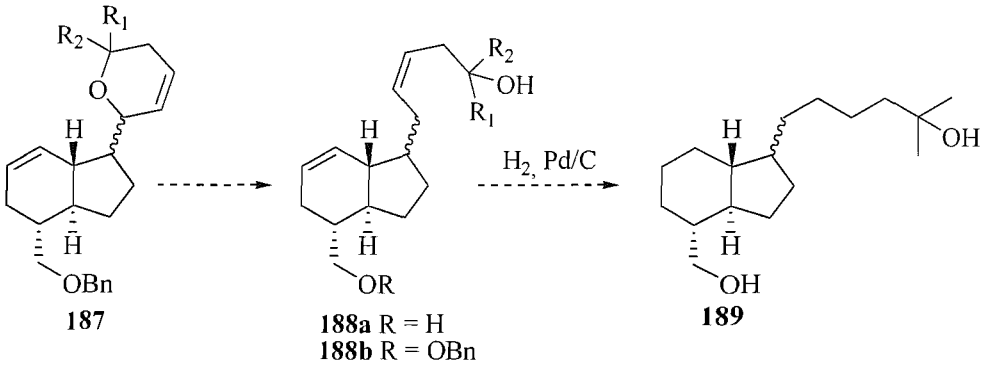
The alcohol **184** was protected with a benzyl group using standard conditions to give **186** in 90% yield.



Scheme 3-8

The HDA was then attempted with acetaldehyde (R_1 = H, R_2 = CH_3) and the diene **186** without avail. After a few days of reflux in a sealed tube, only the starting material was recovered. The reaction was then attempted with diethyl carbonate (R_1 = R_2 = OEt) and copper triflate to get a mixture of unidentified products. Unfortunately, the lack of time did not allow us to perform any other attempts.

The 3,6-dihydro-2*H*-pyran **187** would be reduced to get **188a** or **188b** by using lithium in ethylamine,[151] calcium in ethylenediamine[152] or sodium-liquid ammonia in ethanol.[152] In the last case, the double bond would isomerise to afford the rearrangement product but this should not be problematic since all the double bonds have to be reduced. Sodium-liquid ammonia should also deprotect the primary alcohol with a benzyl group to afford **188a**.[153] The reduction of the double bonds on **188** with H_2, Pd/C (and the deprotection of benzyl group) would afford the simplified CD-ring system **189**.



Scheme 3-9

3.4 Conclusions

The IMDA reaction was performed with achiral and chiral auxiliaries. A mixture of two diastereoisomers was isolated and the isomers were separated by RP-HPLC. The ratio of the major isomer was improved by using a chiral auxiliary or by using a chiral catalyst. The structure

of the major isomer was confirmed by X-ray analysis and proved to be the *trans*-fused hydrindene with the desired stereochemistry at C-9. A careful ^{1}H NMR analysis of the minor isomer strongly suggested that the minor isomer is the C-9 epimer of the major isomer with the *trans*-fused junction. Further functionalisation of the side chain has not been investigated fully due to the lack of time.

Chapter 4: Towards the synthesis of the CD-ring precursor

4.1 Introduction

The IMDA was successfully carried out with the simplified model compound **129a**. It was then decided to prepare the CD-ring precursor **128** in order to first of all study the IMDA selectivity and then prepare CD-ring systems of steroids.

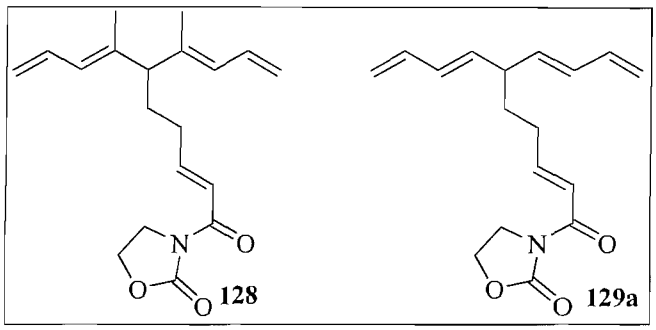
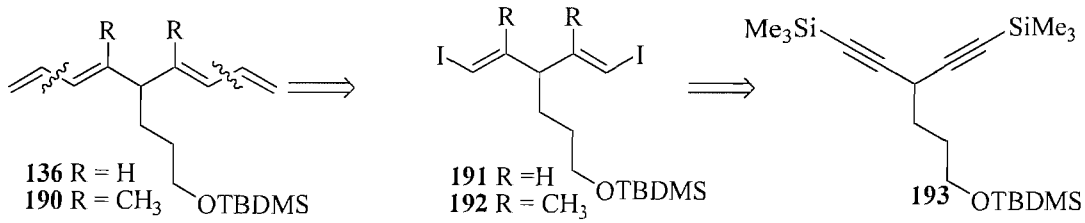


Figure 4-1

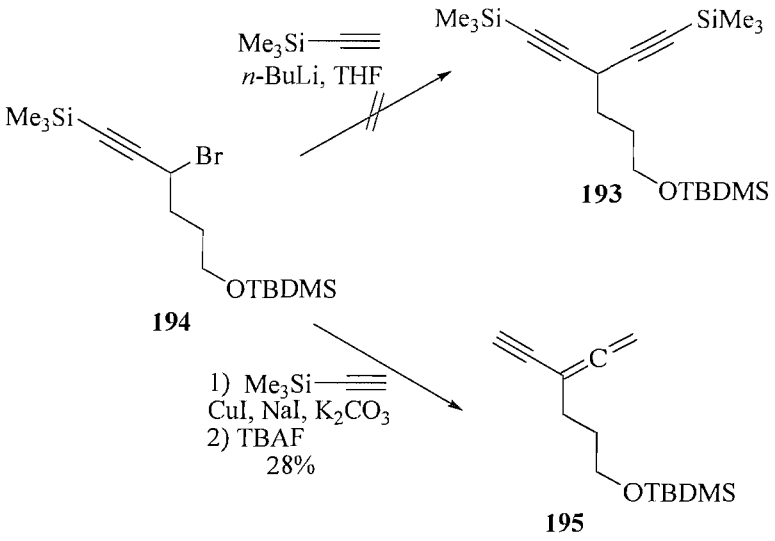
4.2 Retrosynthetic analysis

Different retrosyntheses for the CD-ring precursor were considered. First of all, a general method was envisioned to prepare both bis(diene) **136** and **190** from the bis(alkyne) **193**. Bis(diene) **136** and **190** could be prepared respectively from **191** and **192** *via* a Stille coupling. The bis(vinyl iodide) **191** and **192** would be accessible from the bis(diyne) **193** *via* a carbometallation.



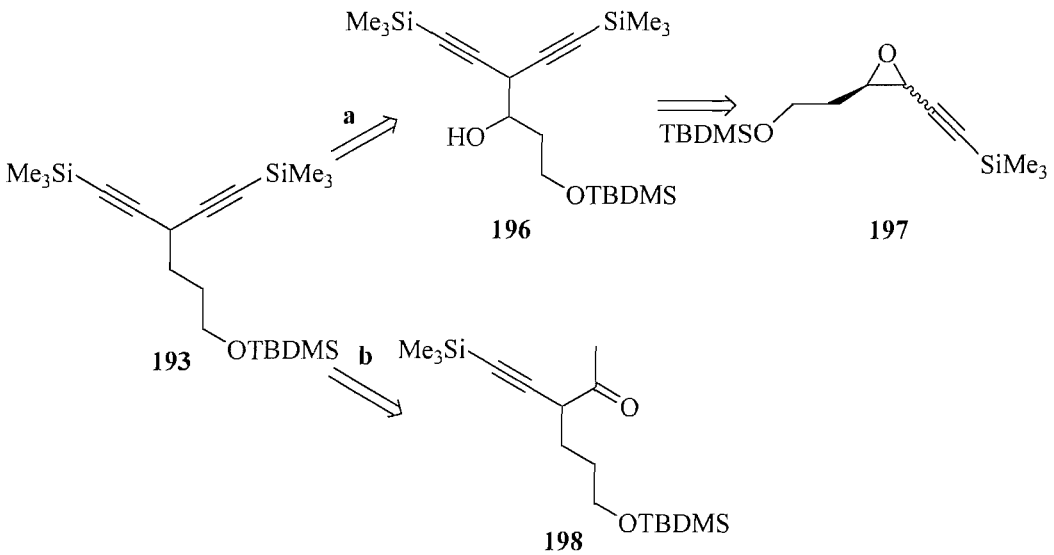
Scheme 4-1

Previous work done in our laboratory to prepare the bis(alkyne) **193** showed that substitution of bromide on **194** by an lithium alkynyl nucleophile met with failure. Eventually, the substitution of the bromide on **194** was successfully achieved using trimethylsilyl acetylene, CuI, NaI and K_2CO_3 to afford, after alcohol deprotection, the allene **195** in 28% yield. However, a careful IR analysis proved that the allene was present before the TBDMS removal (Scheme 4-2). The attempt to isomerise the allene back to the bis(diyne) system was unsucessful.[106]



Scheme 4-2

The bis(alkyne) **193** would be easily obtained through opening of propargylic epoxide **197**, followed by alcohol removal of **196** (Scheme 4-3, path a). The choice of epoxide as electrophilic system to introduce the second alkynyl moiety was based on previous work carried out in our laboratory. The second strategy (Scheme 4-3, path b) involves the formation of the methyl ketone **198**.

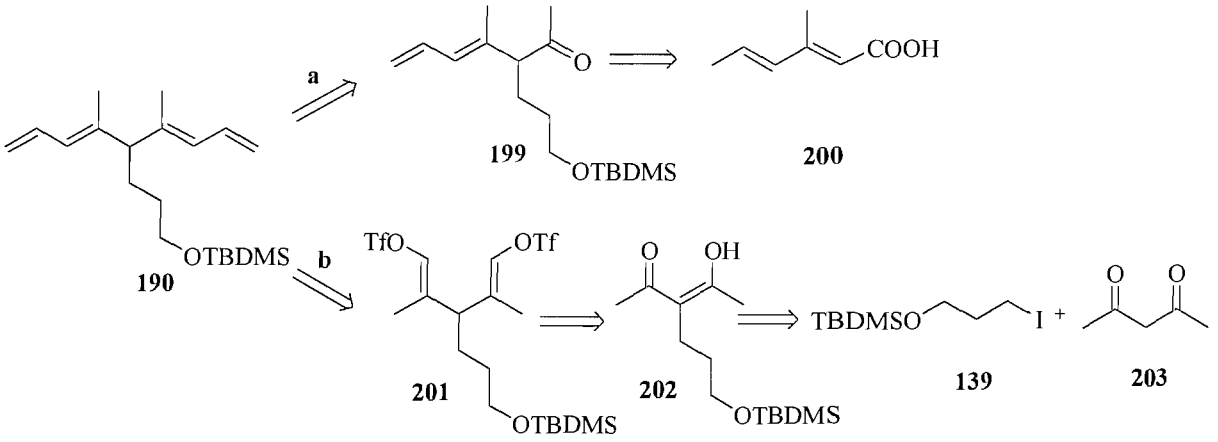


Scheme 4-3

On the other hand, syntheses leading specifically to the bis(diene) **190** were also considered (Scheme 4-4). A single disconnection involving one diene, through path a, leads to the ketone **199** which was hoped to be accessible from the 3-methyl-sorbic acid **200**.

A double disconnection involving both dienes through path b leads to the bis(vinyl triflate) **201**. This disconnection was based on previous work done in our laboratory to prepare

190 using a double Wittig strategy. The double Wittig between **202** and the ylide of allyltriphenyl phosphonium bromide was unsuccessful.[106] It was thought that bis(vinyl triflate) **201** can be prepared from the 1,3-diketone **202** *via* a one-carbon homologation, hydroboration, oxidation, enolisation, triflation type process. The 1,3–diketone **202** can be prepared by alkylation of pentane-2,4-dione **203** with **139**.

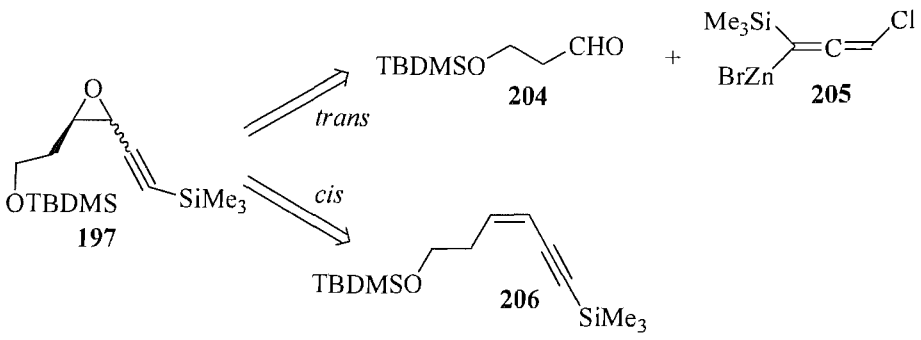


Scheme 4-4

4.3 Progress towards the synthesis of bis(yne)

4.3.1 Synthesis of propargylic epoxide

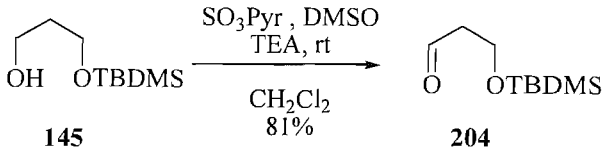
For reasons that will become clear later, both *cis* and *trans*-epoxide **197** were prepared, which required different strategies. The *trans*-epoxide was prepared following a procedure described in the literature[154] by reacting aldehyde **204** with the allenyl zinc **205**. The *cis*-epoxide was obtained from the enyne **206** *via* a direct epoxidation strategy (Scheme 4-5).



Scheme 4-5

4.3.1.1 Preparation of *trans*-propargylic epoxide

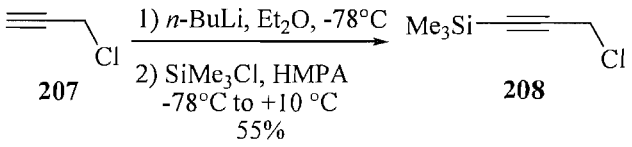
Both the starting materials, for the synthesis of the *trans*-propargylic epoxide, aldehyde **204** and trimethylsilyl propargylic chloride **208** were prepared using slightly modified literature procedure. The monoprotected alcohol **145**[109] was oxidised using Swern's conditions to afford the aldehyde **204** in 62% yield. The yield was improved to 81% when the oxidation was performed using the Parikh-Doering method (Scheme 4-6).



145 **204**

Scheme 4-6

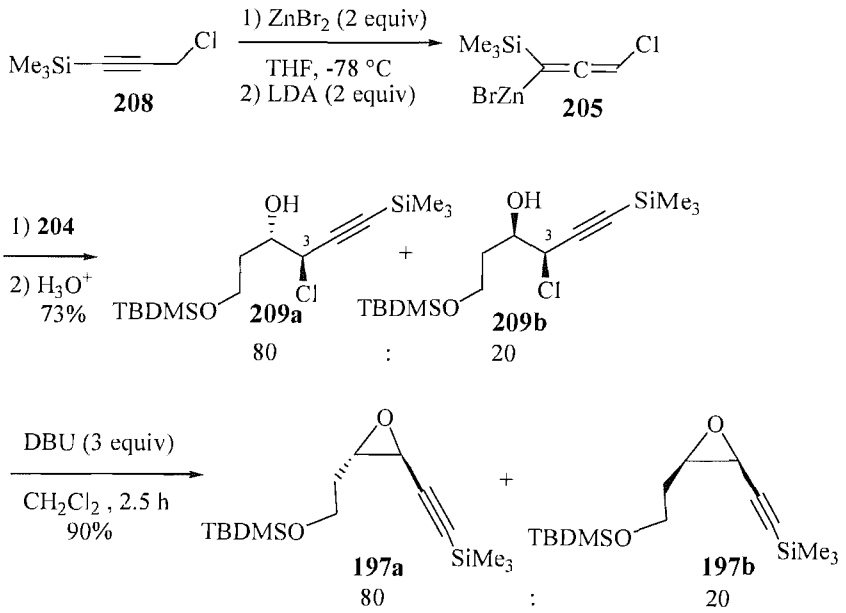
The trimethylsilyl propargylic chloride **208** was prepared in 55% yield by protection of propargyl chloride **207** with a trimethylsilyl group (Scheme 4-7).[155]



207 **208**

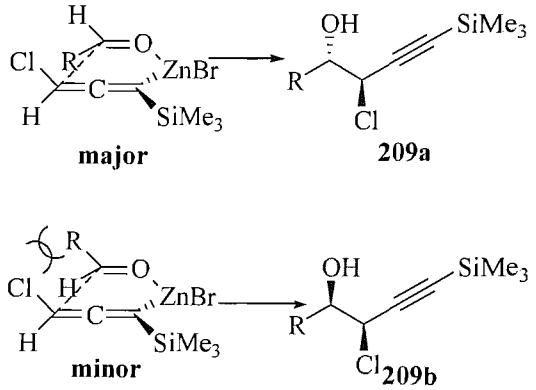
Scheme 4-7

The chlorohydrin **209** was formed by coupling 3-(*tert*-butyldimethylsiloxy)-propanal **204** and 3-chloro-1-trimethylsilylpropyne **208** according to the procedure established by Chemla *et al.*, (Scheme 4-8).[154] In the first step, 2 equivalents of $ZnBr_2$ were added to the trimethylsilyl propargylic chloride **208** at -78 °C followed by the addition of 2 equivalents of LDA to obtain the allene intermediate **205**. Then, 3-(*tert*-butyldimethylsiloxy)-propanal **204** was added to afford the chlorohydrin **209** in 73% yield (Scheme 4-8). A mixture of chlorohydrins **209a/209b** was isolated as a 80:20 ratio *anti/syn*, determined by ^{1}H NMR. The coupling constants for the *anti* **209a** and the *syn* **209b** were determined from the doublet for H-3. The coupling constant for **209a** (J_{anti} = 3.9 Hz) was found to be lower than for the **209b** (J_{syn} = 6.4 Hz) confirming the assigned stereochemistry.



Scheme 4-8

The selectivity observed is due to the more favourable approach of aldehyde **204** to the allene **205**. The C=O bond is coordinated to the zinc and the aldehyde adopts a position to minimize steric interactions with the chloride atom on the allene moiety (Scheme 4-9).



Scheme 4-9

The two diastereoisomers could not be separated by flash chromatography or by normal phase HPLC. The epoxide formation was carried out on the mixture **209a/209b**.

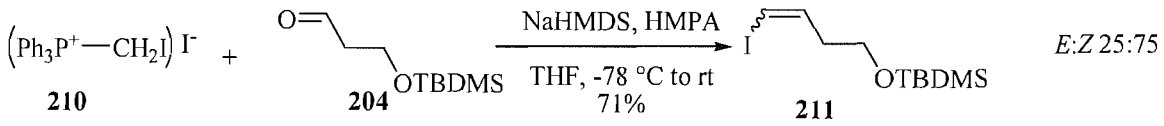
The subsequent ring closure to the epoxide was achieved by using the procedure established by Chemla.[154] The chlorohydrin **209** was reacted with 3 equivalents of DBU for 2.5 h at room temperature to afford the epoxide **197a/197b** in 90% yield, as an 80:20 ratio. Initially, when we used the recommended reaction time of 1 h, the mixture of epoxide **197a/197b** was only

isolated in 48% yield. However, by using a longer stirring time of 2.5 h, a yield of 90% was obtained on 5 g scale.

4.3.1.2 Preparation of the *cis*-propargylic epoxide

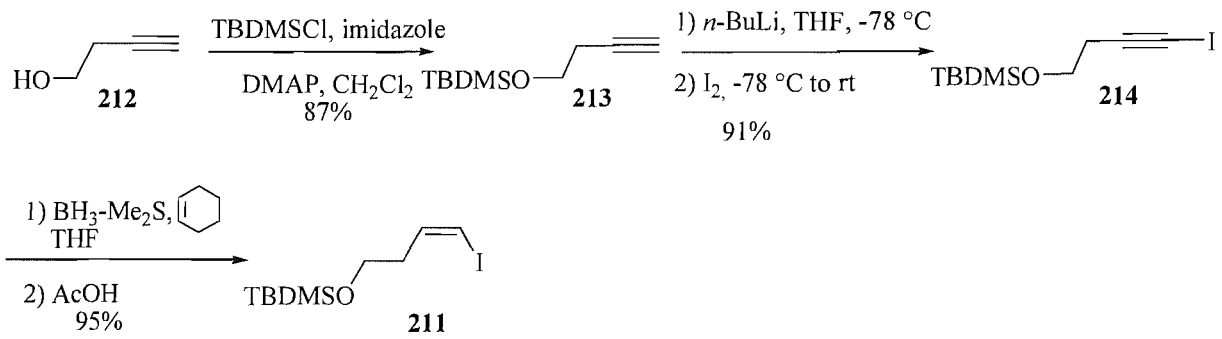
The *cis*-epoxide was prepared by epoxidation of the enyne using a slightly modified strategy literature procedure.[156]

First of all, a straightforward strategy was considered to prepare the intermediate **211** (Scheme 4-10). The 3-(*tert*-butyldimethylsiloxy)-propanal **204**[109] was coupled with iodomethyl triphenylphosphorane **210** to obtain the iodo-alkene **211**.[157] The iodomethyl triphenylphosphorane **210** was prepared according to literature procedure.[158] However, the iodo-alkene **211** was obtained as a 25:75 mixture of *E*:*Z* isomers in 71% yield. Unfortunately, this method did not afford pure (*Z*)-iodo-alkene **211**. It was decided to investigate a new strategy which would afford pure (*Z*)-iodo-alkene.



Scheme 4-10

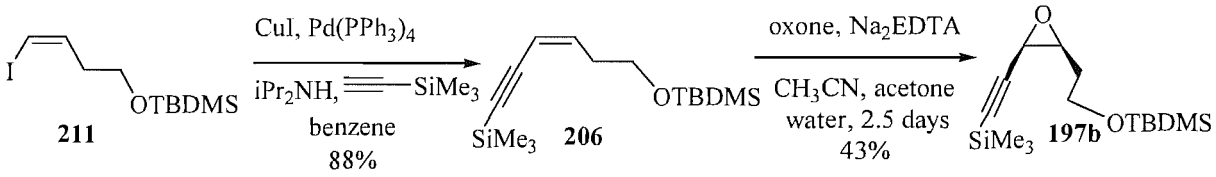
The pure (*Z*)-iodo-alkene **211** was prepared in three steps from 3-butyn-1-ol **212**. The 3-butyn-1-ol **212** was converted to the corresponding silyl ether[159] **213** in 87% yield by treatment with TBDMSCl and imidazole in CH_2Cl_2. The sequential treatment of the silyl ether **213** with *n*-BuLi and iodine in THF gave the iodo-alkyne **214** in 91% yield which upon reduction by hydroboration-protonolysis[160-162] sequence afforded the vinyl iodide **211** in 95% yield. The signals for the two protons on the double bond overlapped in the ^1H NMR spectrum. We were not able to fully confirm the *Z* stereochemistry of the double bond at this stage.



Scheme 4-11

Sonogashira coupling of **211** with trimethylsilyl acetylene (Scheme 4-12) affords the enyne **206** in 88% yield.[156,163,164] The presence of (*Z*)-alkene was confirmed at this stage with a coupling constant J_{cis} = 11 Hz for **206**.

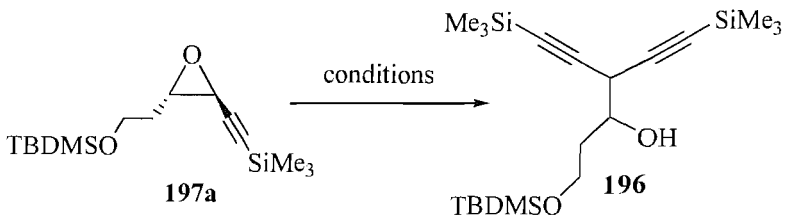
The enyne epoxidation appeared difficult to carry out. The epoxidation was attempted with *m*-CPBA[165,166] to get **197b** in 43% yield. The epoxidation of **206** was also performed with oxone[167] in CH_3CN and Na_2EDTA $4.5.10^{-4}$ N solution. However the reaction was very slow and needed at least 2.5 days of stirring at room temperature to obtain **197b** in 43% yield. The unreacted starting material was recovered after purification and could be submitted again to the epoxidation conditions.



Scheme 4-12

4.3.2 Opening of the propargylic epoxide

The epoxide opening was first studied with the *trans*-epoxide **197a** (Scheme 4-13). The epoxide opening was attempted with different Lewis acid (Et_2AlCl, $Ti(OiPr)_3Cl$, BF_3-Et_2O) used to activate the epoxide. The data are summarized in Table 4-1. The epoxide opening was first of all attempted with BF_3-Et_2O at low temperature, following the procedure established by Chemla.[167] Unfortunately, only the starting material was recovered. The reaction was then carried out at room temperature (entry 1) to get the alcohol **196** in 30% yield. The Lewis acid was changed to Et_2AlCl (entry 2) but the yield dropped to 9%. The reaction was then performed with $Ti(OiPr)_3Cl$ (entry 3) without avail, only the starting material was recovered.[168]



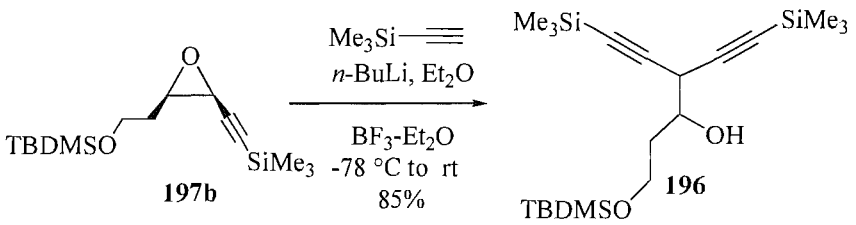
Scheme 4-13

entry	*conditions*	*yield of* **196**
1	BF_3-Et_2O (2 equiv), -78 °C to rt, 48 h	30%
2	Et_2AlCl (3 equiv), reflux, 1 h	9%
3	$TiCl(OiPr)_3$ (1 equiv), -50 °C to rt, 18 h	0%

Table 4-1

The epoxide opening was then tried on the *cis*-epoxide **197b**. Several parameters were taken in consideration for the epoxide opening. The BF_3-Et_2O Lewis acid appeared to be the most efficient Lewis acid to activate propargylic epoxide towards nucleophile. Et_2O was chosen as a solvent since no reaction was observed in THF at low temperature.[169] Et_2O is a weaker coordinating solvent than THF. THF interacts too strongly with the Lewis acid and prevents the epoxide activation.

The ring opening of **197b** by trimethylsilyl acetylene was carried out in Et_2O with BF_3-Et_2O as Lewis acid. No reaction was observed at -78 °C. The reaction mixture was stirred for 18 h at 0 °C to get **196** in 36% yield. The reaction was then performed at room temperature for 6.5 h to isolate **196** in 85% yield (Scheme 4-14). The reaction only occurs at the propargylic position. The *cis*-epoxide reacts under soft conditions and no by-product was observed by TLC analysis.

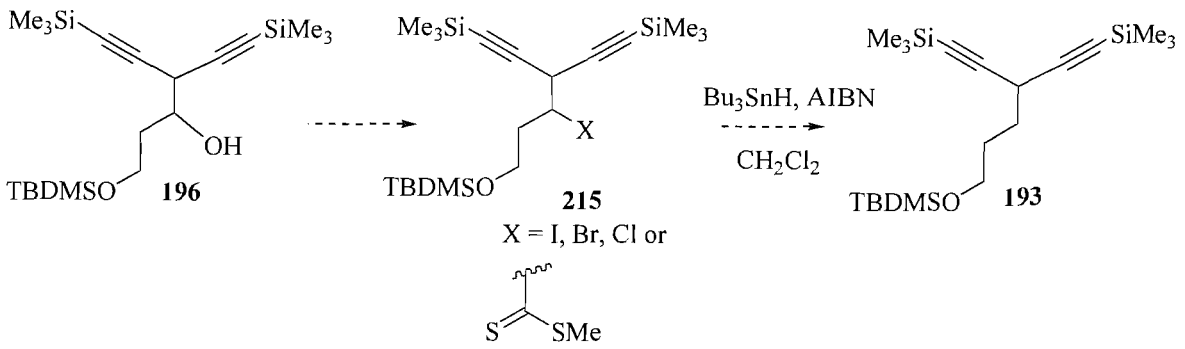


Scheme 4-14

The difference of reactivity between the *cis* and the *trans*-epoxide could be predicted. Chemla *et al.*,[167] showed that *trans*-propargylic epoxides are less reactive than *cis*-propargylic epoxides. The reaction needs to be achieved at higher temperature and usually gives lower yield. The survey showed when a *trans*:*cis*-propargylic epoxide mixture in 1:1 ratio was used, the *trans* epoxide was inert while the *cis*-epoxide was opened by organometallic reagents. The difference of reactivity might be due to steric effects. It was believed that the *cis*-epoxide was more strained than the *trans*-epoxide hence the *cis*-epoxide is more reactive than the *trans*.

4.3.3 Alcohol reduction

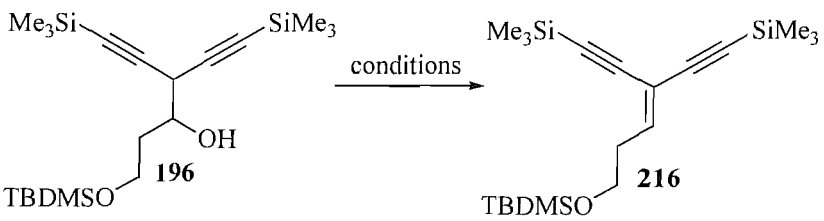
According to our retrosynthesis (Scheme 4-5), the next step was a deoxygenation of the alcohol **196**. The methods available for alcohol deoxygenation involved the alcohol transformation either to a xanthate, thiocarbonyl or halide, which can then be reduced by Bu_3SnH (Scheme 4-15).



Scheme 4-15

We attempted a range of alcohol derivatisation methods summarised in Table 4-2. The first attempt involved a xanthate formation using standard literature procedure.[170] However, the elimination product **216** was isolated in 48% yield (entry 1) (Scheme 4-16). The xanthate is actually the intermediate of Chugaev's pyrolysis which leads to the alkene formation at high temperature. We tried then to work in neutral and milder conditions using the 1,1'-thiocarbonyldiimidazole which allowed us to work at room temperature. However, once again, the elimination product **216** was isolated (entry2) with yield ranging between 40 to 90 %, depending on the reaction conditions.

The driving force of the elimination is the formation of the cross conjugated system **216**. The proton in α position of the diyne system is relatively acidic. It can be removed by bases such as sodium hydride, 2,4,6-collidine or 2,6-di-*tert*-butyl-4-methyl-pyridine (entry 3 and 4).



Scheme 4-16

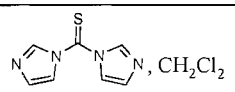
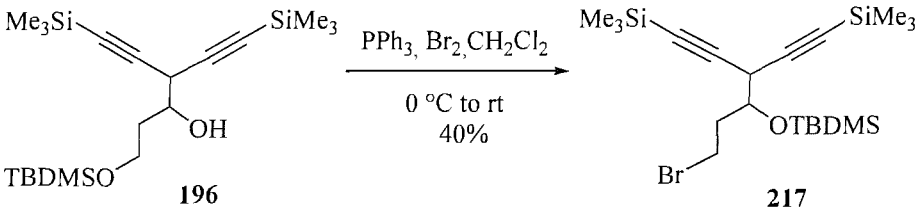
entry	*conditions*	*reaction time*	*temperature*	*yield of 216*
1	1) CS_2, imidazole, NaH, THF 2) MeI	2.5 h	reflux	48%
2		6.5 h	reflux	90%
		18 h	rt	40%
3	Br_2, PPh_3,  , CH_2Cl_2	18 h	rt	46%
4	CBr_4, PPh_3, collidine, CH_2Cl_2	2 h	- 30 °C	52%
5	CCl_4, PPh_3, CH_2Cl_2	2.5 h	rt	26%

Table 4-2

The derivatisation was attempted with PPh_3 and Br_2 but surprisingly the elimination product **216** was not obtained. A primary bromide was present and the TBDMS group was present on a secondary alcohol, consistent with the formation of **217** (Scheme 4-17). We are unsure about how **217** is formed from **196** under the reaction conditions. It seems that the alcohol was first deprotected then the bromination occurred on the more reactive primary alcohol followed by TBDMS protection of the secondary alcohol.



Scheme 4-17

The TBDMS deprotection of **196** was thought to occur because HBr was released in the reaction mixture. We then thought that CBr_4 would be the reactant of choice since the by-products are $HCBr_3$ and H_2CBr_2. However, in those conditions, both the transposition product **217** and the elimination product **216** were isolated. Bromination was also attempted using Br_2, PPh_3 and a bulky scavenger such as 2,6-di-*tert*-butyl-pyridine (entry 3) or CBr_4, PPh_3 and collidine (entry 4) but in those conditions **216** was also formed. Chlorination was attempted with CCl_4 and PPh_3 but as we expected the elimination product **216** was isolated along with some starting material (entry 5). On the other hand, iodination with I_2 and PPh_3 gave a mixture of unidentified products.

A lot of reactions were performed on the dialkyne **196** to remove the alcohol but all the attempts failed.

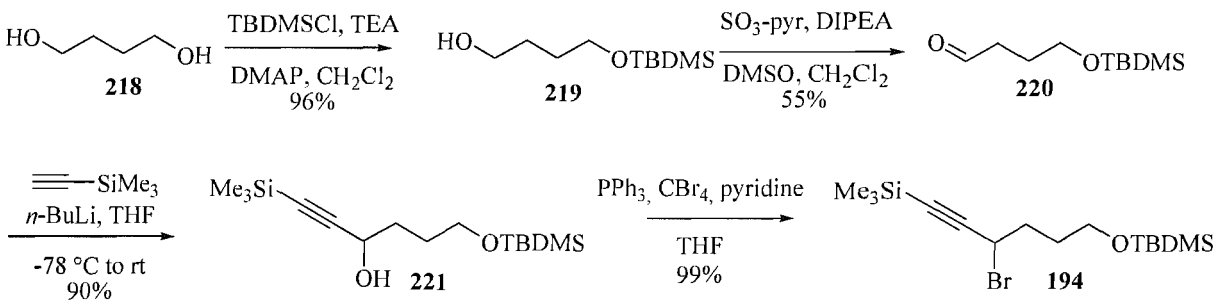
With the elimination product **216** in hand, we then tried to selectively reduce the double bond over the alkynes using tosyl hydrazine and sodium acetate. Unfortunately, none of the desired bis(diyne) **193** was isolated.

4.3.4 Substitution on propargyl bromide

Bis(alkyne) and bis(diene) moieties tend to polymerise very easily. Those moieties have to be introduced at the last stage of the synthesis. Furthermore, the bis(alkyne) moiety is very prone to allene formation.

It was envisaged to prepare the bis(alkyne) **193** from the propargylic bromide **194**. A one-carbon homologation would be achieved by substitution of a bromide by a cyanide. The cyanide could then be reacted with MeMgBr to give the corresponding methyl ketone. The cyanide could also be reduced to the corresponding aldehyde which could then be reacted with MeMgBr and oxidised to afford the desired methyl ketone. Both strategies will be studied.

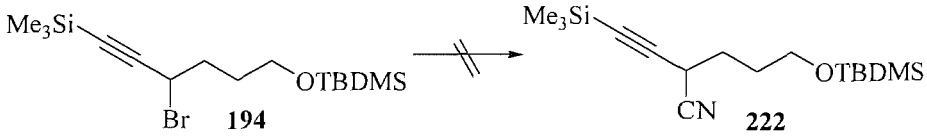
The bromide **194** was prepared using a slightly modified procedure established by Bush.[106] The 1,4-butanediol **218** was monoprotected in good yield with a TBDMS group to afford the alcohol **219**. The oxidation of the alcohol **219** using Parikh-Doering conditions[171] gave the aldehyde **220**[172] in 55% yield which was then reacted with trimethylsilyl acetylene to give the alcohol **221** in 90% yield.[173] The propargylic alcohol **221** was reacted with PPh_3, CBr_4, and pyridine in THF to afford the propargylic bromide **194** in quantitative yield.



Scheme 4-18

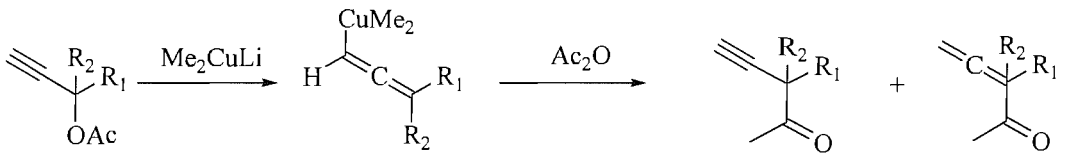
The nucleophilic substitution has been attempted on the bromide **194** with cyanide. Trost *et al.*,[174] reported the cyanation of secondary propargylic bromide using CuCN, LiBr in DMF at 80 °C. The cyanation of **194** was attempted using the same conditions but the desired cyanide **222** was not isolated. The reaction was also performed with CuCN, LiCl (or LiBr) in DMA for 30

min at 130 °C under microwave irradiation. Unfortunately, none of the desired cyanide was isolated. A product containing an allene moiety was detected by ^{13}C NMR.



Scheme 4-19

Crabbé *et al.*, reported the synthesis of propargylic methyl ketone in moderate yield from propargylic acetate using organocuprate and acetic anhydride.[175] The propargylic acetate **223** reacts with organocuprate to form an allene intermediate **224** which then reacts with acetic anhydride to form the methyl ketone **225**. The process is formally a "retro Baeyer-Villiger". The formation of α-allenic ketone **226** competes with the formation of β-acetylenic ketone **225**.

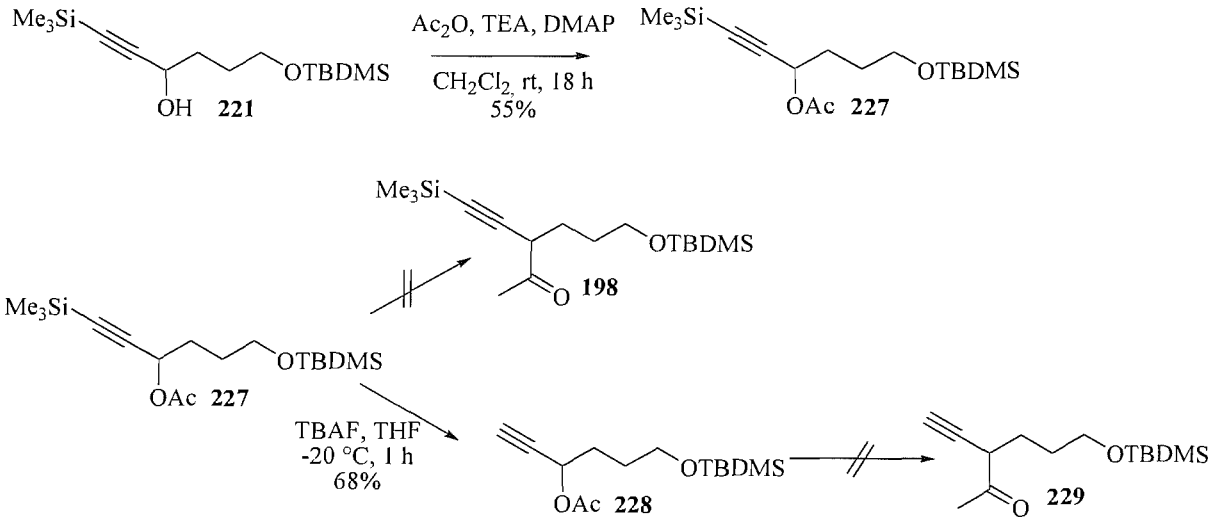


223 **224** **225** **226**

Scheme 4-20

The acetylation of the alcohol **221** was carried out with acetic anhydride, TEA and DMAP in CH_2Cl_2 to afford acetate **227** in moderate yield (Scheme 4-21). The acetate **227** was treated with Me_2CuLi and acetic anhydride in Et_2O. However, only the starting material was recovered.

The terminal alkyne was selectively deprotected by using a limited amount of TBAF (0.4 equivalent) at -20 °C to afford the deprotected acetylene **228** in 68 % yield.[176] The deprotected acetylene **228** was reacted with Me_2CuLi and acetic anhydride in Et_2O. However, once again, the starting material was recovered.



Scheme 4-21

4.4 3-Methyl sorbic acid approach

Based on our successful strategy the prepare the simplified bis(diene) **136** from sorbic acid, it was envisaged to use a similar strategy to prepare **190** starting from 3-methyl-sorbic acid (Figure 4-2).

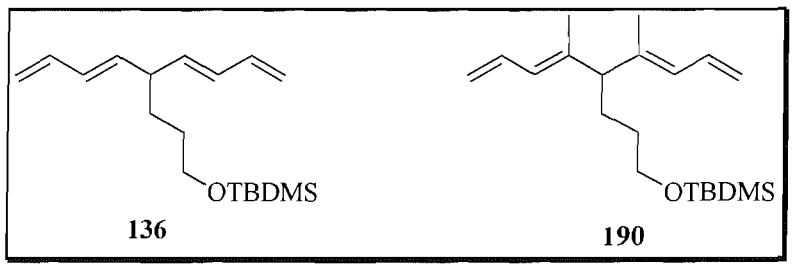
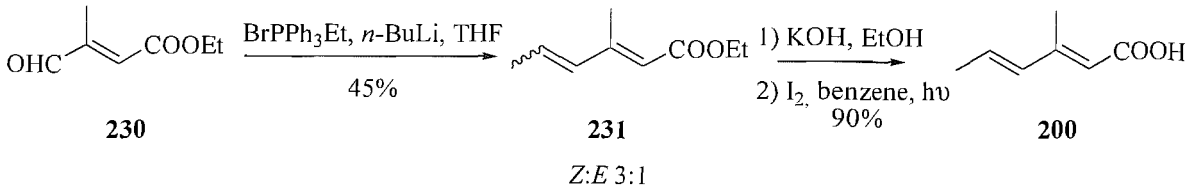


Figure 4-2

4.4.1 Preparation of 3-methyl sorbic acid

3-Methyl sorbic acid **200** (Scheme 4-22) was prepared from ethyl-3-methyl oxocrotonate **230** in three steps using a slightly modified literature procedure.[177] The Wittig reaction of aldehyde **230** with ethyltriphenylphosphonium bromide gave the conjugated ester **231** as a 3:1 *Z/E* mixture. The conjugated ester **231** was saponified to the corresponding carboxylic acid. The diene was then isomerised to the *E,E* configuration under photolytic conditions to afford the 3-methyl sorbic acid **200**.



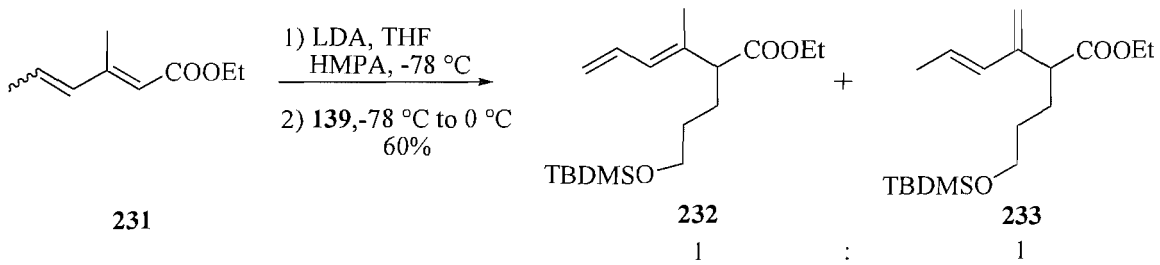
230 **231** **200**

Z:*E* 3:1

Scheme 4-22

4.4.2 Alkylation of 3-methyl sorbic acid derivatives

The alkylation was attempted on the ester **231** but only a 1:1 mixture of the desired ester **232** and the ester **233** with an isomerised diene were isolated in 60% (Scheme 4-23). The esters were not separable by HPLC. The isomerisation of **233** to **232** was attempted. Unfortunately, kinetic isomerisation of the mixture with LDA at -78 °C followed by quenching with acetic acid was unsuccessful.

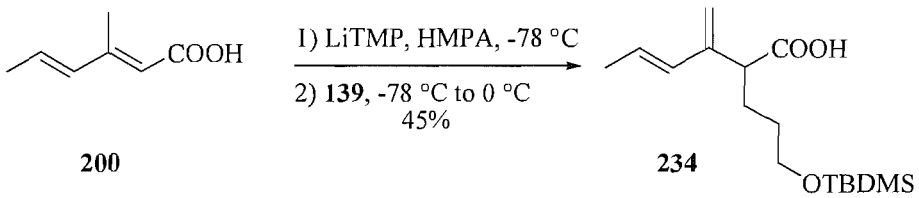


231 **232** : **233**

1 1

Scheme 4-23

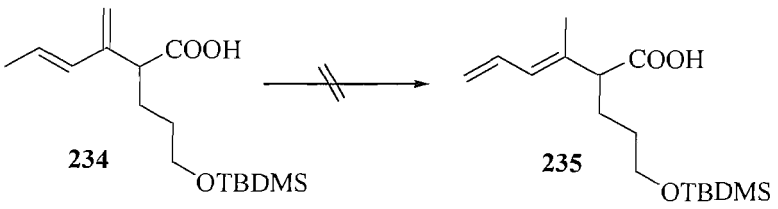
The alkylation of 3-methyl sorbic acid **200** was carried out using the same conditions as the sorbic acid alkylation.[116] Unfortunately, the carboxylic acid **234** was the only compound isolated. LDA was replaced by a more hindered base such as LiTMP but the same acid **234** was isolated in 45% yield (Scheme 4-24). The alkylation was performed at a different temperature in order to see if the desired compound could be formed using a kinetic control. At -78 °C, only a mixture of starting material **200** and carboxylic acid **234** were recovered along with a small amount of the desired compound **235**.



200 **234**

Scheme 4-24

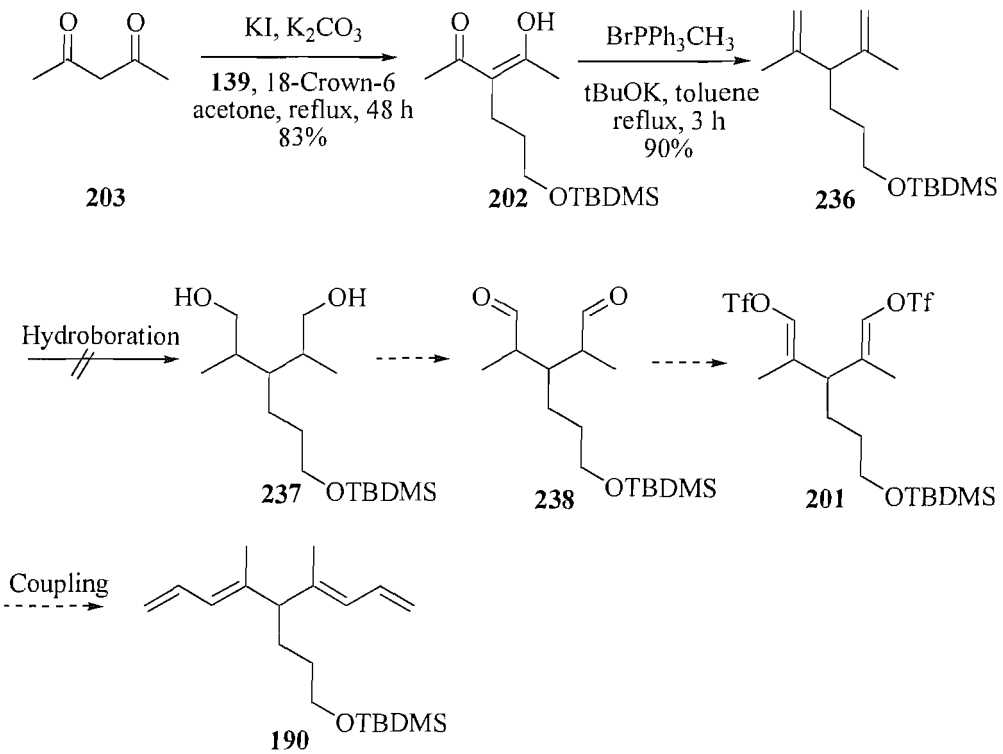
The isomerisation of **234** to **235** was attempted. The carboxylic acid **234** was deprotonated with 2.2 equivalents of LDA at -78 °C and the dianion was quenched with AcOH but only the starting material **234** was recovered (Scheme 4-25).



Scheme 4-25

4.5 Bis(vinyl triflate) approach

Tanaka *et al.*,[178] has reported that a double Wittig on 1,3-diketone could be achieved in good yield to form a 1,3-diene. The penta-2,4-dione **203** was alkylated using the iodide **139** and standard conditions to afford **202** in good yield. The double Wittig reaction was carried out on **202**[179] to afford the skipped diene **236** in good yield. Unfortunately, the double hydroboration on **236** was unsuccessful. The hydroboration has been attempted with different borane sources and under different reaction conditions.[180] However, none of the isolated product corresponded to the desired diol **236** (Scheme 4-26).



Scheme 4-26

4.5 Conclusion

Different strategies were considered to prepare the CD-ring precursor **190**. The formation of bis(acetylene) **196** was achieved in high yield but the alcohol removal was unsuccessful and often led to the formation of cross conjugated system **216**. The substitution of the bromide on **194** to form to the corresponding cyanide met with failure leading to formation of an allene. The bis(acetylene) moieties are sensitive and tend to isomerise to the corresponding allene. It was anticipated that deprotection of the TMS groups on the bis(acetylene) would favoure the allene formation.

The formation of the CD-ring precursor was also attempted from methyl sorbic acid. Unfortunately, the diene isomerised during the alkylation process to form the undesired product. Attempts to isomerise the diene met with failure. The formation of the diol **237**, precursor to the bis(vinyl triflate) **201**, also met with failure.

Chapter 5: General conclusions

In summary, the synthesis of a simplified bis(diene) **136** was achieved in 10 steps. The IMDA was then studied with the simplified model compound to give two diastereoisomers **130** and **131**. The two isomers were separated by RP-HPLC. The structure of the major isomer **130** was confirmed by X-ray and proved to be the *trans*-hydrindene with the desired stereochemistry at C-9. An extensive NMR study of the mixture of two diastereoisomers strongly suggested that the minor isomer **131** was the C-9 epimer of the major isomer **130**. The selectivity obtained for the C-9 epimers was ranging between 60:40 to 92:8, depending on the reaction conditions. None of the *exo* adduct was observed by NMR or by RP-HPLC. The reaction was also carried out with a chiral catalyst and the cycloadduct **130a** was isolated with 90% ee.

It was then attempted to apply the use of this methodology to steroid synthesis. Efforts to functionalise the side chain on C-9 of the hydrindene moiety met with failure mainly due to the lack of time.

The synthesis of the CD-ring system precursor **190** was undertaken. A number of strategies were attempted without avail. The synthesis of bis(alkyne) moiety **193** was unsuccessful and led to the formation of cross conjugated system **216**. It was also observed that bis(alkyne) easily isomerised to give the corresponding allene. It was disappointing to find out that the 3-methyl sorbic acid strategy did not give the compound with the diene in the correct position.

Chapter 6: Experimental

6.1 General experimental and instrumentation

All moisture and air sensitive reactions were carried out in flame dried glassware using magnetic stirring and a positive pressure of nitrogen. For reactions performed at low temperature, dry ice was used as a cryogenic substance. Acetone and dry ice were used for -78 °C bath while CH_3CN and dry ice were used for -30 °C bath. Solvents were purchased from Fisher Chemicals. THF, Et_2O and dioxane were distilled from sodium benzophenone ketyl prior to use. CH_2Cl_2, iPr_2NH and TEA were distilled over CaH_2 prior to use. Toluene was distilled from sodium. Pyridine, HMPA and DMSO were distilled over CaH_2 and stored under anhydrous conditions. Ethyl sorbate was distilled prior to use. DMP was purchased from Lancaster.

Purifications were performed on Fisher Chemicals silica gel 60A (35-70 micron). Analytical thin layer chromatography was performed on pre-coated silica gel plates (Macheney-Nagel SIL G-25 UV_{254}). Visualization was accomplished by UV (254 nm) and with $KMnO_4$ in water or anisaldehyde in ethanol. Reverse phase HPLC was performed on X-Terra Prep RP_{18} column 5μm 100 × 19 mm eluted with 0.1% NH_3/H_2O to 0.1% NH_3/CH_3CN. Reverse phase analytical HPLC were carried out on phenomex GE10CM5U with a Agilent 1100 series system (eluent A: water +0.1% formic acid, eluent B: methanol + 0.1% formic acid. Gradient: 95% to 5% A over 10 min then 5% to 95% A over 3 min) coupled to a Polymer Lab 100 ES ELS Detector.

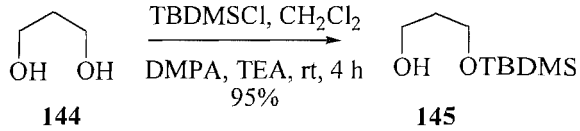
^1H NMR, ^{13}C NMR spectra were recorded on Brüker AV 300 and Brüker DPX 400 spectrometers. Chemical shifts (δ) are reported in ppm. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^1H NMR) served as the internal standard: $CDCl_3$ (7.27 ppm and 77.0 ppm), C_6D_6 (7.15 ppm and 128.6) and CD_2Cl_2 (5.31 ppm and 53.7 ppm). ^{31}P NMR and ^{19}F NMR spectra were recorded on Brüker AV 300. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). The lists of coupling constants (*J*) correspond to order of the multiplicity assignement and are reported in Hertz (Hz). IR spectra were recorded on a BIORAD Golden Gate FTS 135. All samples were run neat as solids or liquids. The low resolution mass spectra chemical ionisation (CI) or electron ionisation (EI) were recorded on thermoquest 2000 mass spectrometer using a gas chromatograph injection. The low resolution electrospray (ES) were recorded on Waters ZMD. The HRMS CI or EI were recorded on VG Analytical 70-250-SE. The HRMS ES were recorded on Brüker Apex III FT-ICR-MS with 4.7 T magnet. All melting points were uncorrected

and were recorded in open capillary tubes using Gallekamp electrothermal melting point apparatus. Optical rotations were recorded on Optical Activity Polaar 2001.

Microwave irradiation was performed on an Emrys Optimizer instrument.

6.2 Synthesis of a simplified model compound

3-*tert*-butyldimethylsilyloxy-propan-1-ol (145)



144 **145**

To a solution of 1,3-propanediol **144** (69.5 mL, 962.8 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (50.0 g, 332.0 mmol) in CH_2Cl_2 (100 mL) and DMAP (4.0 g, 33.2 mmol). After 5 minutes of stirring at this temperature, TEA (69.3 mL, 498.0 mmol) was added and the reaction was stirred for 4 h at room temperature. The organic phase was washed with water (3 × 150 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressure. The oily residue was placed in a high *vacuum* rotary evaporator to remove the excess of diol **144** and afford **145** as a yellow oil (59.8 g, 95%) which was used without further purification in the next step.

Mw 190 ($C_9H_{22}O_2Si$).

R_f 0.28 (hexane/AcOEt 80:20).

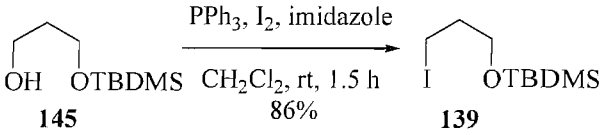
IR (film): 3484 (w), 2950 (s), 2855 (m), 1252 (s), 1100 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (2H, t, J = 5.6 Hz, **C$\underline{H_2}$**-OH); 3.78 (2H, t, J = 5.5 Hz, **C$\underline{H_2}$**-OTBDMS); 1.76 (2H, quint, J = 5.7 Hz, **C$\underline{H_2}$**-CH_2-OTBDMS); 0.89 (9H, s, **C$\underline{H_3}$**-C); 0.06 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 62.8 (**CH_2**-OH); 62.3 (**CH_2**-OTBDMS); 34.1 (**CH_2**-CH_2-OTBDMS); 25.8 (**CH_3**, tBu); 18.1 (**C**, tBu); -5.6 (**CH_3**-Si).

The analytical data corresponded to the reported data.[181]

1-iodo-3-*tert*-butyldimethylsilyloxy-propane (139)



145 139

To a solution of imidazole (23.8 g, 345.0 mmol) and PPh_3 (90.4 g, 345.0 mmol) in CH_2Cl_2 (600 mL) at 0 °C was added I_2 (87.6 g, 345.0 mmol). After 10 min, a solution of alcohol **145** (59.6 g, 313.7 mmol) in CH_2Cl_2 (40 mL) was added. The solution was warmed up to room temperature and stirred for 18 h at this temperature. The reaction was diluted with saturated aqueous $Na_2S_2O_3$ (50 mL). After the phase separation, the organic phase was washed with water (3 × 50 mL). The combined aqueous phases were extracted with CH_2Cl_2 (2 × 50 mL) and were dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 98:2) to give **139** as pale yellow oil (81.1 g, 86%).

Mw 300 ($C_9H_{21}IOSi$).

R_f 0.60 (hexane/AcOEt 90:10).

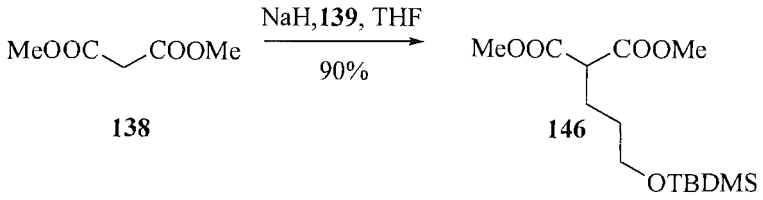
IR (film): 2945 (s), 2926 (s), 1474 (s), 1252 (s), 1096 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (2H, t, J = 5.7 Hz, **C$\underline{H_2}$**-OTBDMS); 3.28 (2H, t, J = 6.7 Hz, **C$\underline{H_2}$**-I); 1.99 (2H, quint, J = 6.2 Hz, **C$\underline{H_2}$**- CH_2-OTBDMS); 0.90 (9H, s, **C$\underline{H_3}$**-C); 0.07 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 62.3 (**CH_2**-OTBDMS); 36.1 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.3 (CH_3-**C**); 3.7 (**CH_2**-I); -5.3 (**CH_3**-Si).

The analytical data corresponded to the reported data.[110]

2-(3-*tert*-butyldimethylsilyloxy-propyl)-malonic acid dimethyl ester (146)



To a suspension of NaH (60% dispersion in mineral oil, 1.7 g, 43.6 mmol) in THF (80 mL) at 0 °C was added dimethyl malonate **138** (4.6 mL, 39.9 mmol), and the mixture was stirred at this temperature for 30 min. To the mixture was added a solution of **139** (10.9 g, 36.3 mmol) in THF (40 mL), and the reaction was refluxed for 5 h. The mixture was diluted with Et_2O (100 mL) and was quenched at 0 °C with water (5 mL). The organic phase was washed with saturated aqueous NH_4Cl (1 × 100 mL), saturated aqueous $NaHCO_3$ (3 × 100 mL), brine (2 × 100 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/Et_2O 70:10) to give **146** as a yellow oil (9.9 g, 90%).

Mw 304 ($C_{14}H_{28}O_5Si$).

R_f 0.18 (hexane/Et_2O 70:10).

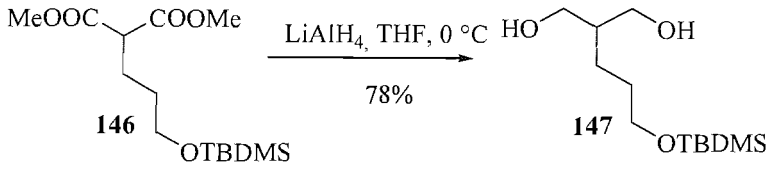
IR (film): 2955 (s), 2926 (s), 1753 (s), 1734 (s), 1474 (m), 1436 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (6H, s, O**C**$\underline{\mathbf{H}}_3$); 3.61 (2H, t, J = 6.2 Hz, **C**$\underline{\mathbf{H}}_2$-OTBDMS); 3.40 (1H, t, J = 7.6 Hz, **C**$\underline{\mathbf{H}}$-COOMe); 1.99-1.91 (2H, m, **C**$\underline{\mathbf{H}}_2$-CH); 1.57-1.50 (2H, m, **C**$\underline{\mathbf{H}}_2$-CH_2-OTBDMS); 0.87 (9H, s, **C**$\underline{\mathbf{H}}_3$-C); 0.03 (6H, s, **C**$\underline{\mathbf{H}}_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 169.9 (**C**=O); 62.4 (**CH_2**-OTBDMS); 52.4 (O-**CH_3**); 51.3 (**CH**-$COOCH_3$); 30.3 (CH-**CH_2**); 25.9 (**CH_3**, tBu); 25.5 (**CH_2**-CH_2-OTBDMS); 18.3 (**C**, tBu); -5.4 (**CH_3**-Si).

The analytical data corresponded to the reported data.[112]

2-(3-*tert*-butyldimethylsilyloxy-propyl)-propane-1,3-diol (147)



To a solution of $LiAlH_4$ (96 mL of 1 M solution in THF, 96.0 mmol) in THF (80 mL) at 0 °C was added a solution of **146** (11.7 g, 38.4 mmol) in THF (40 mL). The reaction was stirred for 30 min at 0 °C. To the solution was carefully added water (3.6 mL), 15% aqueous NaOH (10.9 mL) and water (10.9 mL) and the mixture was stirred for 30 min at room temperature. The solution was filtered through a pad of Celite eluted with THF, and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatography (hexane/acetone 1:2) to afford the diol **147** as a pale yellow oil (7.5 g, 78%).

Mw 248 ($C_{12}H_{28}O_3Si$)

R_f 0.56 (hexane/acetone 10:20)

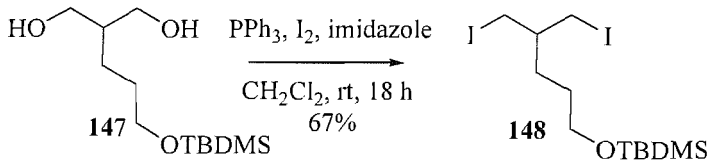
IR (film): 3376 (s), 2960 (s), 2855 (m), 1474 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (2H, dd, J = 10.7, 4.1 Hz, **C$\underline{H}_\alpha$H$_\beta$**-OH); 3.57-3.64 (4H, m, **CH$_\alpha\underline{H}_\beta$**-OH and **C$\underline{H}_2$**-OTBDMS); 1.72 (1H, m, **C$\underline{H}$**-CH_2-OH); 1.59-1.49 (2H, m, **C$\underline{H}_2$**-CH_2-OTBDMS); 1.41-1.23 (2H, m, CH-**C$\underline{H}_2$**-CH_2); 0.87 (9H, s, **C$\underline{H}_3$**-C); 0.03 (6H, s, **C$\underline{H}_3$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 65.8 (**CH_2**-OH); 63.2 (**CH_2**-OTBDMS); 41.7 (**CH**-CH_2-OH); 30.1 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 23.8 (**CH_2**-CH_2-CH_2-OTBDMS); 18.3 (**C**, tBu); -5.4 (**CH_3**-Si).

The analytical data corresponded to the reported data.[112]

1-*tert*-butyldimethylsilyloxy-5-iodo-4-iodomethyl-pentyl (148)



To a solution of PPh_3 (8.1 g, 31.0 mmol) and imidazole (2.1 g, 31.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added I_2 (7.9 g, 31.0 mmol). After 10 min, a solution of diol **147** (3.5 g, 14.1 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 18 h at room temperature. The reaction was washed with saturated aqueous $Na_2S_2O_3$ (2 × 40 mL), water (2 × 40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 98:2) to afford **148** as a yellow oil (4.5 g, 67%).

Mw 468 ($C_{12}H_{26}OSiI_2$).

R_f 0.58 (hexane/AcOEt 95:5).

IR (film): 2959 (s), 2931 (s), 2855 (s), 2732 (w), 1096 (s) cm^{-1}.

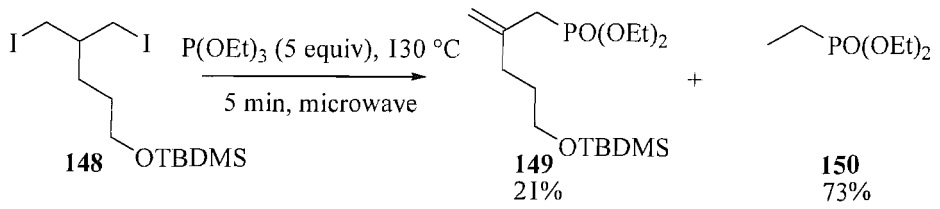
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (2H, t, J = 5.9 Hz, **C$\underline{H_2}$**-OTBDMS); 3.42 (2H, dd, J = 9.9, 4.0 Hz, **C$\underline{H_\alpha}$H$_\beta$**-I); 3.23 (2H, dd, J = 9.9, 4.0 Hz, **CH$_\alpha$$\underline{H_\beta}$**-I); 1.56-1.32 (5H, m, **C$\underline{H}$-C$\underline{H_2}$-C$\underline{H_2}$**); 0.91 (9H, s, **C$\underline{H_3}$**-C); 0.07 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 62.7 (**CH_2**-OTBDMS); 40.3 (**CH**-CH_2); 30.9 (CH-**CH_2**-CH_2); 30.0 (CH-CH_2-**CH_2**); 25.9 (**CH_3**, tBu); 18.3 (**C**, tBu); 14.2 (**CH_2**-I); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 469 ($(M+H)^+$, 12), 453 (2), 411 (24), 337 (10), 157 (100), 127 (36).

HRMS (EI) for $C_8H_{17}OSiI_2$ $(M\text{-}tBu)^+$ calcd 410.9138 found 410.9134.

diethyl-[2-(3-*tert*-butyldimethylsilyloxy-propyl)-allyl]-phosphonate (149) and diethyl ethylphosphonate (150)



The diodide **148** (300 mg, 0.64 mmol) was dissolved in triethyl phosphite (554 µL, 3.23 mmol). The reaction mixture was heated in the microwave for 5 min at 130 °C. The crude was purified by column chromatography (Et_2O/acetone 10:1) to afford **149** (47 mg, 21 %) and **150** (392 mg, 73 %) as colourless oils.

Data for 149:

Mw 350 ($C_{16}H_{35}O_4PSi$).

R_f 0.50 (Et_2O/acetone 10:1).

IR (film): 3418 (m), 3073 (w), 2955 (s), 2926 (s), 1644 (m), 1096 (s), 1054 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (2H, s br, **C$\underline{H_2}$**=C); 4.10 (4H, quint, J = 7.2 Hz, O-**C$\underline{H_2}$**-CH_3); 3.61 (2H, t, J = 6.4 Hz, **C$\underline{H_2}$**-OTBDMS); 2.63 (2H, d, J = 22.2 Hz, **C$\underline{H_2}$**-$PO(OEt)_2$); 2.18-2.23 (2H, m, C-**C$\underline{H_2}$**-CH_2); 1.67 (2H, quint, J = 6.6 Hz, **C$\underline{H_2}$**-CH_2-OTBDMS); 1.31 (6H, t, J = 7.1 Hz, O-CH_2-**C$\underline{H_3}$**); 0.89 (9H, s, **C$\underline{H_3}$**-C); 0.04 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 139.7 (CH_2=**C**); 114.4 (**CH_2**=C); 62.6 (**CH_2**-OTBDMS); 61.9 (d, $J_{C\text{-}P}$ = 6.7 Hz, O-**CH_2**-CH_3); 33.7 (d, $J_{C\text{-}P}$ = 127.5 Hz, **CH_2**-P); 32.9 (C-**CH_2**-CH_2); 30.6 (CH-CH_2-**CH_2**); 25.9 (**CH_3**, tBu); 18.3 (**C**, tBu); 16.4 (d, $J_{C\text{-}P}$ = 6.2 Hz, O-CH_2-**CH_3**); -5.3 (**CH_3**-Si).

^{31}P NMR (121 MHz, $CDCl_3$): δ 28.0 (**P**=O).

CIMS: *m/z* (%) 351 ($(M+H)^+$, 78), 335 (18), 293 (100), 237 (50), 219 (82), 177 (8).

HRMS (EI) for $C_{15}H_{32}O_4PSi$ $(M\text{-}Me)^+$ calcd 335.1808 found 335.1815.

Data for 150:

Mw 166 ($C_6H_{15}O_4P$).

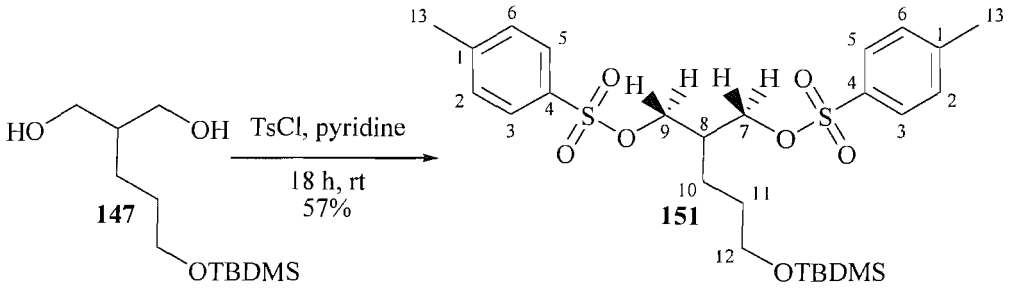
R_f 0.53 (Et_2O/acetone 10:1).

IR (film): 2981 (w), 2938 (w), 1224 (m), 1021 (s), 1007 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06-3.93 (4H, m, CH_3-**C$\underline{H_2}$**-O); 1.64 (2H, dq, J = 18.0, 7.5, CH_3-**C$\underline{H_2}$**-P); 1.23 (6H, t, J = 7.7 Hz, **C$\underline{H_3}$**-CH_2-O); 1.06 (3H, dt, J = 19.9, 7.7, **C$\underline{H_3}$**-CH_2-P).
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 61.2 (**CH_2**-O, $J_{C\text{-}P}$ = 7.5 Hz); 18.7 (d, $J_{C\text{-}P}$ = 142.5 Hz, **CH_2**-P); 16.3 (d, $J_{C\text{-}P}$ = 6.2 Hz, **CH_3**-CH_2-O); 6.3 (d, $J_{C\text{-}P}$ = 6.7 Hz, **CH_3**-CH_2-P).
^{31}P NMR (121 MHz, $CDCl_3$): δ 34.0 (**P**=O).

The analytical data corresponded to the reported data.[114]

1-*tert*-butyldimethylsilyloxy-5-tosyl-4-tosylmethyl-pentyl (151)



To a solution of p-toluenesulfonyl chloride (2.5 g, 13.2 mmol) in dry pyridine (4.5 mL) at 0 °C was added a solution of diol **147** (1.5 g, 6 mmol) in dry pyridine (1.5 mL). The mixture was stirred for 2 h at 0 °C followed by 18 h at room temperature. The solution was cooled at 0 °C and poured in saturated aqueous $NaHCO_3$ (10 mL) and stirred at room temperature for 30 min. The solution was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (3 × 40 mL), brine (1 × 20 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to give **151** as a pale yellow oil (1.9 g, 57%).

Mw 556 ($C_{26}H_{40}O_7S_2Si$).

R_f 0.24 (hexane/AcOEt 80:20).

IR (film): 3045 (w), 2950 (m), 2846 (m), 1593 (m), 1460 (m), 1176 (s), 1100 (s) cm^{-1}.

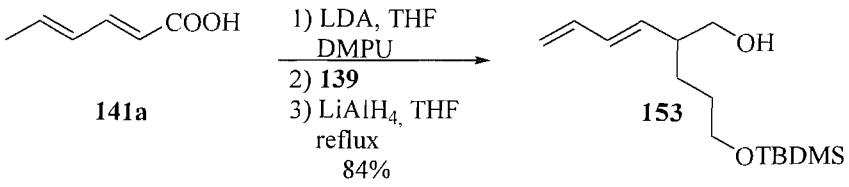
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (4H, d, J = 8.3 Hz, H_2 and H_6); 7.34 (4H, d, J = 8.1 Hz, H_3 and H_5); 3.97 (2H, dd, J = 9.7, 4.6 Hz, H_7 and H_9); 3.90 (2H, dd, J = 9.8, 6.1 Hz, H_9 and H_7); 3.49 (2H, t, J = 5.7 Hz, H_{12}); 2.45 (6H, s, H_{13}); 1.98 (1H, m, H_8); 1.42-1.29 (4H, m, H_{10} and H_{11}); 0.85 (9H, s, **C$\underline{H_3}$**-C); 0.00 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 145.0 (**C**, C_1); 132.4 (**C**, C_4); 130.0 (**CH**, C_2 and C_6); 127.8 (**CH**, C_3 and C_5); 68.7 (**CH_2**, C_7 and C_9); 62.4 (**CH_2**, C_{12}); 37.6 (**CH**, C_8); 29.3 (**CH_2**, C_{10}); 25.8 (**CH_3**-C); 23.4 (**CH_2**, C_{11}); 21.6 (**CH_3**, C_{13}); 18.2 (CH_3-**C**); -5.5 (**CH_3**-Si).

ESMS: *m/z* (%) 557 ($(M+H)^+$, 65), 574 (100), 579 (40).

HRMS (ES) for $C_{26}H_{40}O_7S_2SiNa$ $(M+Na)^+$ calcd 579.1877 found 579.1883.

(3*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-hex-3,5-dien-1-ol (153)



141a **153**

To a solution of diisopropylamine (18.9 mL, 136.5 mmol) in THF (140 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 54.6 mL, 136.5 mmol). The solution was stirred at the same temperature for 30 min. To the mixture at -78 °C was added a solution of sorbic acid **141a** (6.9 g, 62 mmol) in THF (70 mL) and the solution was stirred at 0 °C for 30 min. To the mixture was added DMPU (16.4 mL, 136.5 mmol) at -78 °C, and the solution was stirred at the same temperature for 15 min. To the mixture was added a solution of iodide **139** (27.3 g, 91 mmol) in THF (40 mL) at -78 °C, and the mixture was slowly warmed up to 0 °C over a period of about 3 h. The mixture was then stirred at 0 °C for 1.5 h, and 10% aqueous HCl solution was added to the solution until pH 4, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ (2 × 200 mL), brine (1 × 200 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the crude acid as a yellow oil which was used in the next step without further purification.

To a suspension of $LiAlH_4$ (2.0 g, 51.6 mmol) in THF (50 mL) at 0 °C was added a solution of crude acid in THF (50 mL). The reaction mixture was refluxed for 2.5 h. To the mixture cooled down at 0 °C was successively added water (2.0 mL), 15% aqueous NaOH (6.0 mL) and water (6.0 mL), and stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite eluted with THF and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **153** as a yellow oil (14.1 g, 84% from **141a**).

Mw 270 ($C_{15}H_{30}O_2Si$).

R_f 0.87 (hexane/acetone 10:20).

IR (film): 3357 (m), 2950 (s), 1801 (w), 1701 (m), 1649 (w), 1597 (w), 1252 (s) cm^{-1}.

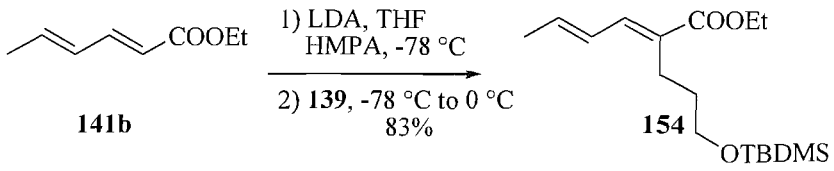
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.31 (1H, dt, *J* = 16.7, 10.3 Hz, CH_2=C**H**); 6.14 (1H, dd, *J* = 15.2, 10.5 Hz, CH_2=CH-C**H**); 5.47 (1H, dd, *J* = 15.1, 8.8 Hz, CH_2=CH-CH=C**H**); 5.14 (1H, dd, *J* = 16.9, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.02 (1H, dd, *J* = 9.8, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 3.62-3.54 (2H, m, C**H**$_2$-OTBDMS); 3.44 (2H, dd, *J* = 10.7, 7.7 Hz, C**H**$_2$-OH); 2.24 (1H, m, C**H**-CH_2-OH); 1.59-

1.21 (5H, m, **C<u>H</u>$_2$-C<u>H</u>$_2$**-CH_2-OTBDMS and CH_2-**O<u>H</u>**); 0.88 (9H, s, **C<u>H</u>$_3$**-C); 0.04 (6H, s, **C<u>H</u>$_3$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 136.7 (CH_2=**CH**); 135.6 (CH_2=CH-CH=**CH**); 133.4 (CH_2=CH-**CH**); 116.1 (**CH_2**=CH); 65.9 (**CH_2**-OH); 63.1 (**CH_2**-OTBDMS); 45.5 (**CH**-CH_2-OH); 30.2 (**CH_2**-CH_2-OTBDMS); 27.1 (**CH_2**-CH_2-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 18.3 (**C**, tBu); -5.4 (**CH_3**-Si).

The analytical data corresponded to the reported data.[112]

(2*Z*,4*E*)-ethyl-2-(4-*tert*-butyldimethylsilyloxy-propyl)-hex-2,4-dienoate (154)



141b **154**

To a solution of diisopropylamine (19.6 mL, 140.0 mmol) in THF (280 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 56 mL, 140.0 mmol), and the mixture was stirred at the same temperature for 30 min. To the mixture at -78 °C was added freshly distilled ethyl sorbate **141b** (17.3 mL, 116.9 mmol), and the solution was stirred at the same temperature for 1 h. To the mixture at -78 °C was added HMPA (22.2 mL, 140.0 mmol), and the solution was stirred at the same temperature for 15 min. To the mixture was added a solution of 1-*tert*-butyldimethylsilyloxy-3-iodopropane **139** (42.1 g, 140 mmol) in THF (140 mL), and the reaction was slowly warmed to 0 °C over a period of about 2.5 h. The mixture was stirred at 0 °C for 1.5 h, and 10% aqueous HCl solution was added to the mixture until pH 4. The aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ (2 × 200 mL), brine (1 × 200 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **154** as a yellow oil (30.4 g, 83%).

Mw 312 ($C_{17}H_{32}O_3Si$).

R_f 0.49 (hexane/AcOEt 80:20).

IR (film): 2954 (m), 2857 (m), 1704 (m), 1643 (m), 1607 (w), 1233 (m), 1095 (s) cm^{-1}.

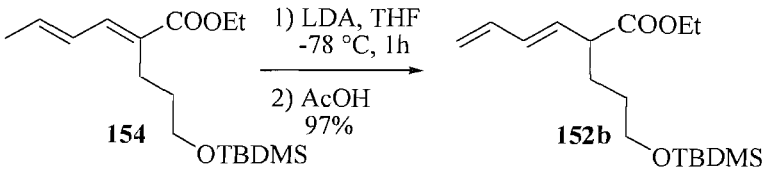
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (1H, d, *J* = 11.4 Hz, C**H**=C); 6.41 (1H, tq, *J* = 13.1, 1.7 Hz, CH_3-CH=C**H**); 6.09 (1H, dq, *J* = 13.6, 6.8 Hz, CH_3-C**H**=CH); 4.20 (2H, q, *J* = 7.0 Hz, C**H_2**-CH_3); 3.61 (2H, t, *J* = 6.2 Hz, C**H_2**-OTBDMS); 2.46 (2H, t, *J* = 7.4 Hz, C**H_2**-C); 1.86 (3H, dd, *J* = 6.8, 1.5 Hz, C**H_3**-CH=CH); 1.68-1.59 (2H, m, C**H_2**-CH_2-OTBDMS); 1.30 (3H, t, *J* = 7.2 Hz, C**H_3**-CH_2); 0.92 (9H, s, C**H_3**-C); 0.06 (6H, s, C**H_3**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 168.4 (**C**=O); 139.0 (**CH**=C); 137.9 (**CH**=CH-CH_3); 129.2 (CH=**C**); 127.3 (**CH**-CH_3); 62.4 (**CH_2**-OTBDMS); 60.3 (O-**CH_2**-CH_3); 32.6 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 23.2 (CH=C-**CH_2**); 18.9 (**CH_3**-CH=CH); 18.3 (**C**, tBu); 14.3 (CH_2-**CH_3**); -5.4 (**CH_3**-Si).

CIMS: *m/z* (%) 313 ($(M+H)^+$, 2), 57 (100).

HRMS (EI) for $C_{17}H_{32}O_3Si$ $(M)^+$ calcd 312.2121 found 312.2115.

(3*E*)-ethyl-2-(4-*tert*-butyldimethylsilyloxy-propyl)-hex-3,5-dienoate (152b)



To a solution of diisopropylamine (13.5 mL, 97.2 mmol) in THF (97 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 38.9 mL, 97.2 mmol) and the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of ester **154** (30.4 g, 97.2 mmol) in THF (20 mL), and the mixture was stirred at the same temperature for 1 h. The dark red solution was quenched by addition of AcOH/H_2O (1:2 v/v) (15 mL). After the phase separation, the organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), brine (1 × 200 mL) and dried over anhydrous $MgSO_4$ to afford **152b** as a yellow oil (29.5 g, 97%) which was used in the next step without further purification.

Mw 312 ($C_{17}H_{32}O_3Si$).

R_f 0.38 (hexane/AcOEt 90:10).

IR (film): 2954 (w), 2857 (w), 1734 (m), 1665 (w), 1618 (w), 1252 (m), 1097 (s) cm^{-1}.

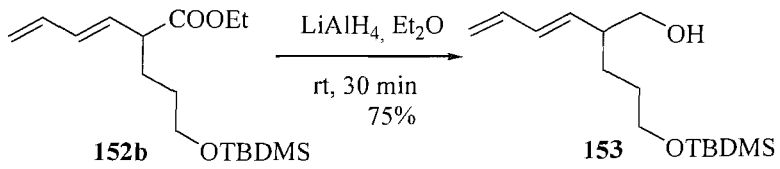
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (1H, dt, *J* = 16.9, 10.3 Hz, CH_2=C**H**); 6.12 (1H, dd, *J* = 15.1, 10.5 Hz, CH_2=CH-C**H**); 5.68 (1H, dd, *J* = 15.2, 9.0 Hz, CH_2=CH-CH=C**H**); 5.17 (1H, dd, *J* = 16.9, 1.5 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.06 (1H, dd, *J* = 10.0, 1.5 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 4.14 (2H, q, *J* = 7.1 Hz, C**H**$_2$-CH_3); 3.60 (2H, t, *J* = 6.2 Hz, C**H**$_2$-OTBS); 3.03 (1H, q, *J* = 7.8 Hz, C**H**-COOEt); 1.87-1.40 (4H, m, C**H**$_2$-C**H**$_2$-OTBS); 1.25 (3H, t, *J* = 7.1 Hz, C**H**$_3$-CH_2); 0.89 (9H, s, C**H**$_3$-C); 0.04 (6H, s, C**H**$_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.0 (**C**=O); 136.4 (**CH**=CH_2); 133.0 (**CH**-CH-COOEt); 131.7 (CH_2=CH-**CH**); 116.9 (**CH_2**=CH); 62.6 (**CH_2**-OTBS); 60.5 (O-**CH_2**-CH_3); 48.9 (**CH**-COOEt); 30.2 (CH-**CH_2**); 28.9 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 18.3 (**C**, tBu); 14.2 (CH_2-**CH_3**); -5.4 (**CH_3**-Si).

CIMS: *m/z* (%) 313 ($(M+H)^+$, 96), 297 (10), 267 (44), 255 (92), 181 (100).

HRMS (EI) for $C_{17}H_{32}O_3Si$ $(M)^+$ calcd 312.2121 found 312.2126.

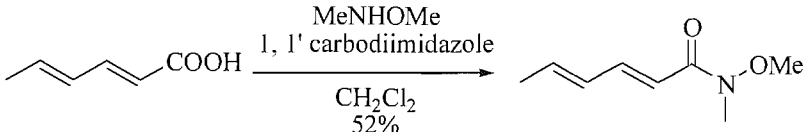
(3*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-hex-3,5-dien-1-ol (153)



To a suspension of $LiAlH_4$ (4.0 g, 108.1 mmol) in Et_2O (100 mL) at 0 °C was added **152b** dissolved in Et_2O (100 mL). The reaction mixture was stirred for 30 min at room temperature. To the mixture cooled down at 0 °C was successively added water (4.0 mL), 15% aqueous NaOH (12.0 mL) and water (12.0 mL). The mixture was stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite eluted with Et_2O and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 75:25) to afford **153** as a yellow oil (19.2 g, 75%).

The analytical data corresponded to the reported data.[112]

(2*E*,4*E*)-*N*-methoxy-*N*-methyl-hexa-2,4-dienamide (141c)



141a **141c**

To a solution of sorbic acid **141a** (2.0 g, 22.3 mmol) in CH_2Cl_2 was added portionwise 1,1'-carbonyldiimidazole (4.2 g, 25.8 mmol). The solution was stirred for 1 h at room temperature and *N,O*-dimethylhydroxylamine (2.8 g, 28.5 mmol) was added in one portion. The reaction mixture was stirred for 40 h at room temperature. The mixture was poured in saturated aqueous NH_4Cl (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (Et_2O/hexane 2:1) to afford **141c** as a yellow oil (1.8 g, 52%).

Mw 155 ($C_8H_{13}NO_2$).

R_f 0.26 (Et_2O/hexane 2:1).

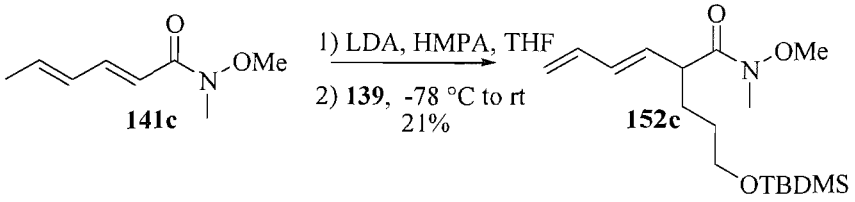
IR (film): 2964 (w), 2936 (w), 2913 (w), 1657 (m), 1630 (m), 1606 (m), 1370 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (1H, dd, *J* = 15.1, 10.7 Hz, **C<u>H</u>**=CH-C=O); 6.32 (1H, d, *J* = 15.3 Hz, CH=**C<u>H</u>**-C=O); 6.19 (1H, dd, *J* = 15.9, 11.2 Hz, CH_3-CH=**C<u>H</u>**); 6.06 (1H, dq, *J* = 12.7, 6.2 Hz, CH_3-**C<u>H</u>**=CH); 3.65 (3H, s, O-**C<u>H$_3$</u>**); 3.19 (3H, s, N-**C<u>H$_3$</u>**); 1.79 (3H, d, *J* = 6.3 Hz, **C<u>H$_3$</u>**-CH=CH).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 167.3 (**C**=O); 143.5 (CH_3-**CH**=CH); 138.3 (**CH**=CH-C=O); 130.1 (**CH**-C=O); 116.5 (CH_3-CH=**CH**); 61.5 (O-**CH_3**); 32.2 (N-**CH_3**); 18.5 (**CH_3**-CH=CH).

The analytical data corresponded to the reported data.[121]

(3*E*,5*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-*N*-methoxy-*N*-methyl-hexa-3,5-dienamide (152c)



To a solution of diisopropylamine (325 µL, 2.3 mmol) in THF (2 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 930 µL, 2.3 mmol) and the mixture was stirred at the same temperature for 30 min. To the mixture was added HMPA (370 µL, 2.3 mmol) and the solution was stirred for 15 min at -78 °C. Then, a solution of **141c** (300 mg, 1.9 mmol) in THF (2 mL) was added, and the bright yellow solution was stirred at -78 °C for 1 h. To the mixture was added a solution of 1-*tert*-butyldimethylsilyloxy-3-iodopropane **139** (696 mg, 2.3 mmol) in THF (2 mL) at -78 °C, and the mixture was slowly warmed up to room temperature over a period of about 2 h. The orange solution was stirred at the same temperature for 2.5 h, and 10% aqueous HCl solution was added to the mixture until pH 4. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (2 × 20 mL), brine (1 × 20 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **152c** as a yellow oil (132 mg, 21%).

Mw 327 ($C_{17}H_{33}NO_3Si$).

R_f 0.22 (hexane/AcOEt 80:20).

IR (film): 2954 (w), 2929 (w), 2857 (w), 1665 (m), 1647 (m), 1602 (w), 1383 (m), 1254 (m), 1096 (s) cm^{-1}.

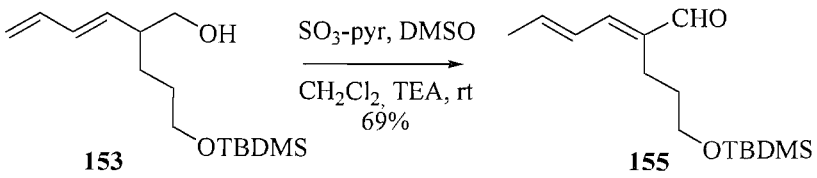
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.29 (1H, dt, *J* = 16.9, 10.3 Hz, CH_2=C**H**); 6.10 (1H, dd, *J* = 15.4, 10.3 Hz, CH_2=CH-C**H**); 5.71 (1H, dd, *J* = 15.5, 8.8 Hz, C**H**-CH-C=O); 5.13 (1H, d, *J* = 16.9 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.02 (1H, d, *J* = 9.5 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 3.67 (3H, s, C**H**$_3$-O); 3.59 (2H, t, *J* = 6.6 Hz, C**H**$_2$-OTBDMS); 3.17 (3H, s, C**H**$_3$-N); 1.78 (1H, m, C**H**-C=O); 1.66-1.43 (4H, m, C**H**$_2$-C**H**$_2$-CH_2-OTBDMS); 0.87 (9H, s, C**H**$_3$-C); 0.03 (6H, s, C**H**$_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.6 (**C**=O); 136.6 (CH_2=**CH**); 132.9 (**CH**-CH-C=O); 132.7 (CH_2=CH-**CH**); 116.5 (**CH_2**=CH); 62.8 (**CH_2**-OTBDMS); 61.5 (**CH_3**-O); 44.5 (**CH**-C=O); 32.1 (**CH_3**-N); 30.4 (**CH_2**-CH-C=O); 28.7 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 18.3 (**C**, tBu); -5.4 (**CH_3**-Si).

CIMS: *m/z* (%) 328 ($(M+H)^+$, 54), 298 (47), 270 (88), 240 (100), 196 (62).

HRMS (ES) for $C_{17}H_{34}NO_3Si$ $(M+H)^+$ calcd 328.2303 found 328.2306.

(2*Z*,4*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-hex-2,4-dien-1-al (155)



To a suspension of SO_3-pyridine (230 mg, 1.5 mmol) in CH_2Cl_2 (1 mL) was added freshly distilled DMSO (1 mL) and TEA (444 µL, 3.2 mmol). This solution was immediately added dropwise by cannula to a stirred solution of alcohol **153** (137 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) and DMSO (0.5 mL) at room temperature. The reaction was stirred at room temperature for 45 min. The solution was poured in saturated aqueous NH_4Cl (5 mL). After the phase separation, the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **155** as a yellow oil (94 mg, 69%).

Mw 268 ($C_{15}H_{28}O_2Si$).

R_f 0.38 (hexane/AcOEt 90:10).

IR (film): 3026 (w), 2960 (s), 2926 (s), 2855 (s), 2709 (w), 1678 (s), 1649 (s), 1593 (w), 1091 (s) cm^{-1}.

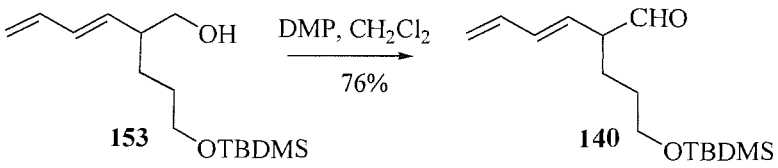
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.32 (1H, s, **C<u>H</u>**=O); 6.80 (1H, d, *J* = 11.2 Hz, **C<u>H</u>**=C); 6.60 (1H, tq, *J* = 13.0, 1.5 Hz, **C<u>H</u>**=CH-CH_3); 6.24 (1H, dq, *J* = 13.8, 6.8 Hz, CH=**C<u>H</u>**-CH_3); 3.58 (2H, t, *J* = 6.2 Hz, **C<u>H$_2$</u>**-OTBDMS); 2.39 (2H, t, *J* = 7.5 Hz, **C<u>H$_2$</u>**-C=CH); 1.91 (3H, dd, *J* = 6.8, 1.5 Hz, **C<u>H$_3$</u>**-CH=CH); 1.58 (2H, m, CH_2-**C<u>H$_2$</u>**-CH_2); 0.91 (9H, s, **C<u>H$_3$</u>**-C); 0.05 (6H, s, **C<u>H$_3$</u>**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 194.9 (**CH**=O); 149.8 (**CH**-CH_3); 140.7 (**CH**=C); 139.9 (CH=**C**); 127.3 (**CH**=CH-CH_3); 62.2 (**CH_2**-OTBDMS); 31.9 (**CH_2**-C=CH); 25.9 (**CH_3**, tBu); 20.4 (**CH_2**-CH_2-OTBDMS); 19.1 (**CH_3**-CH=CH); 18.3 (**C**, tBu); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 269 ($(M+H)^+$, 70), 253 (14), 211 (100), 137 (86).

HRMS (EI) for $C_{14}H_{25}O_2Si$ $(M-Me)^+$ calcd 253.1624 found 253.1628.

(3*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-hex-3,5-dien-1-al (140)



To a solution of alcohol **153** (2.9 g, 10.1 mmol) in CH_2Cl_2 (240 mL) at 0 °C was added DMP (5.0 g, 11.8 mmol) in one portion. The solution was stirred in the dark for 18 h at room temperature. Et_2O (240 mL), saturated aqueous $NaHCO_3$ (120 mL) and saturated aqueous $Na_2S_2O_3$ (120 mL) were added. The solution was allowed to vigorously stirr for 15 min. The organic layer was separated and was washed a second time with a 1:1 mixture of saturated aqueous $NaHCO_3/Na_2S_2O_3$ (240 mL), water (1 × 240 mL), brine (1 × 240 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **140** as a yellow oil (2.1 g, 76%). The aldehyde **139** was immediately used in the next step within the same day.

Mw 268 ($C_{15}H_{28}O_2Si$).

R_f 0.32 (hexane/AcOEt 90:10).

IR (film): 3026 (w), 2950 (s), 2851 (s), 2704 (w), 1810 (w), 1721 (s), 1678 (m), 1635 (w), 1593 (w), 1086 (s), 1001 (s) cm^{-1}.

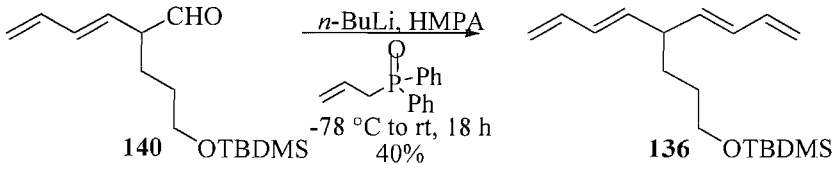
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (1H, d, J = 2.4 Hz, C**H**=O); 6.34 (1H, dt, J = 10.2, 16.7 Hz, CH_2=C**H**); 6.18 (1H, dd, J = 15.5, 10.5 Hz, CH_2=CH-C**H**); 5.56 (1H, dd, J = 15.3, 8.5 Hz, C**H**-CH-CHO); 5.20 (1H, dd, J = 16.9, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.10 (1H, dd, J = 10.1, 1.5 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 3.64-3.60 (2H, m, C**H**$_2$-OTBDMS); 3.03 (1H, m, C**H**-CHO); 1.94-1.80 (2H, m, CH-C**H**$_2$); 1.69-1.44 (2H, m, CH_2-C**H**$_2$-CH_2); 0.89 (9H, s, C**H**$_3$-C); 0.04 (6H, s, C**H**$_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 201.0 (**C**H=O); 136.2 (CH_2=**C**H); 135.3 (**C**H-CH-CHO); 128.5 (CH_2=CH-**C**H); 117.6 (**C**H$_2$=CH); 62.6 (**C**H$_2$-OTBDMS); 55.6 (**C**H-CHO); 29.9 (**C**H$_2$-CH_2-OTBDMS); 25.9 (**C**H$_3$, tBu); 25.2 (**C**H$_2$-CH-CHO); 18.3 (**C**, tBu); -5.4 (**C**H$_3$-Si).

ESMS: *m/z* (%) 291 ($(M+Na)^+$, 100), 561 (8).

HRMS (ES) for $C_{15}H_{28}O_2Si$ $(M)^+$ calcd 269.1931 found 269.1935.

(3*E*,6*E*)-5-(3-*tert*-butyldimethylsilyloxy-propyl)-nona-1,3,6,8-tetraene (136)



To a solution of allyl diphenylphosphine oxide (4.2 g, 17.2 mmol) and HMPA (5.4 mL, 34.3 mmol) in THF (270 mL) at -78 °C was added dropwise *n*-BuLi (2.5 M solution in hexane, 6.2 mL, 15.6 mmol). The resulting red solution was stirred for 5 min at this temperature and a solution of aldehyde **140** (4.2 g, 15.6 mmol) in THF (15 mL) was added dropwise. The resulting solution was slowly warmed up to room temperature overnight to get a brown solution. After quenching with water, the solution was diluted with Et_2O (270 mL). The phases were separated and the organic phase was washed with water (2 × 200 mL), brine (1 × 200 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **136** as a yellow oil (1.8 g, 40%).

Mw 292 ($C_{18}H_{32}OSi$).

R_f 0.67 (hexane/AcOEt 90:10).

IR (film): 3082 (w), 3035 (w), 2950 (s), 2922 (s), 2851 (s), 2737 (w), 1800 (w), 1640 (m), 1096 (s) cm^{-1}.

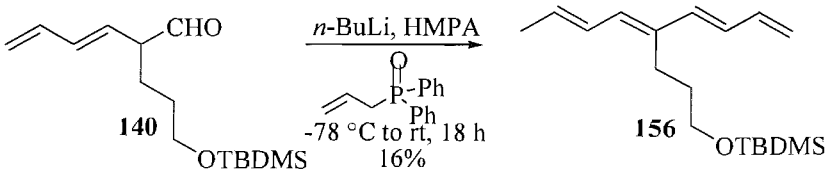
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.31 (2H, dt, J = 16.9, 10.3 Hz, **C<u>H</u>**=CH_2); 6.04 (2H, dd, J = 15.2, 10.3 Hz, **C<u>H</u>**-CH=CH_2); 5.60 (2H, dd, J = 15.2, 7.7 Hz, **C<u>H</u>**=CH-CH=CH_2); 5.12 (2H, dd, J = 16.9, 1.7 Hz, CH=**CH_{cis}<u>H_{trans}</u>**); 5.00 (2H, dd, J = 10.3, 1.9 Hz, CH=**<u>CH_{cis}</u>H_{trans}**); 3.63 (2H, m, **C<u>H</u>$_2$**-OTBDMS); 2.79 (1H, m, **C<u>H</u>**-CH_2); 1.59-1.36 (4H, m, **C<u>H</u>$_2$-C<u>H</u>$_2$**-CH_2-OTBDMS); 0.90 (9H, s, **C<u>H</u>$_3$**-C); 0.05 (6H, s, **C<u>H</u>$_3$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 137.2 (**CH**=CH_2); 137.0 (**CH**=CH-CH=CH_2); 130.7 (**CH**-CH=CH_2); 115.6 (CH=**CH_2**); 63.1 (**CH_2**-OTBDMS); 45.3 (**CH**-CH_2); 31.9 (**CH_2**-CH_2-OTBDMS); 30.4 (**CH_2**-CH_2-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 18.3 (**C**, tBu); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 293 ($(M+H)^+$, 18), 235 (30), 161 (88), 133 (20), 121 (56), 75 (100).

HRMS (EI) for $C_{18}H_{32}OSi$ $(M)^+$ calcd 292.2222 found 292.2222.

(3*E*,5*E*,7*E*)-5-(3-*tert*-butyldimethylsilyloxy-propyl)-nona-1,3,5,7-tetraene (156)



To a stirred solution of allyl diphenylphosphine oxide (5.7 g, 23.4 mmol) and HMPA (7.4 mL, 46.8 mmol) in THF (60 mL) at -78 °C was added dropwise *n*-BuLi (2.5 M solution in hexane, 7.8 mL, 19.5 mmol). The resulting red solution was stirred for 5 min at this temperature and a solution of aldehyde **140** (2.1 g, 7.8 mmol) in THF (30 mL) was added dropwise. The resulting solution was slowly warmed up to room temperature overnight to get a brown solution. After quenching with water, the solution was diluted with Et_2O (80 mL). The phases were separated and the organic phase was washed with water (2 × 50 mL), brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **156** as a yellow oil (364 mg, 16%).

Mw 292 ($C_{18}H_{32}OSi$).

R_f 0.77 (hexane/AcOEt 90:10).

IR (film): 3088 (w), 3024 (w), 2953 (m), 2928 (m), 2857 (m), 1786 (w), 1614 (w), 1097 (s) cm^{-1}.

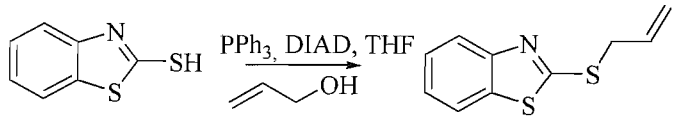
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47-6.26 (3H, m, C**H**-C**H**=CH_2, CH_3-CH=C**H**); 6.19 (1H, d, *J* = 15.0 Hz, C-C**H**); 6.06 (1H, d, *J* = 11.2 Hz, C=C**H**); 5.78 (1H, dq, *J* = 14.5, 6.7 Hz, CH_3-C**H**=CH); 5.20 (1H, dd, *J* = 16.7, 2 Hz, CH=C**H**$_{trans}$**H**$_{cis}$); 5.05 (1H, dd, *J* = 10.1, 2 Hz, CH=C**H**$_{trans}$**H**$_{cis}$); 3.65 (2H, t, *J* = 6.0 Hz, C**H**$_2$-OTBDMS); 2.43 (2H, m, C-C**H**$_2$); 1.83 (3H, dd, *J* = 7.0, 1.7 Hz, C**H**$_3$-CH=CH); 1.70-1.60 (2H, m, C**H**$_2$-CH_2-OTBDMS); 0.95 (9H, s, C**H**$_3$-C); 0.09 (6H, s, C**H**$_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 137.8 (CH_2=**CH**); 137.2 (**C**=CH); 137.1 (C-**CH**=CH); 132.2 (C=**CH**); 130.9 (**CH**-CH=CH_2); 128.2 (CH_3-**CH**); 127.8 (CH_3-CH=**CH**); 115.9 (**CH_2**=CH); 62.6 (**CH_2**-OTBDMS); 32.4 (**CH_2**-CH_2-OTBDMS); 26.0 (**CH_3**, tBu); 23.1 (**CH_2**-C); 18.6 (**CH_3**-CH=CH); 18.3 (**C**, tBu); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 292 ($(M)^+$, 10), 235 (48), 161 (88), 75 (100).

HRMS (EI) for $C_{18}H_{32}OSi$ $(M)^+$ calcd 292.2222 found 292.2221.

2-allylthio-benzothiazole (158)



157 **158**

To a solution of allyl alcohol (4 mL, 58.8 mmol) in THF (60 mL) at 0 °C were added 2-mercaptobenzothiazole **157** (14.7 g, 88.2 mmol) and PPh_3 (24.7 g, 94.1 mmol). After 5 min at this temperature, DIAD (17.4 mL, 88.2 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h at room temperature. The solution was concentrated *in vacuo*. The crude was purified by column chromatography (hexane/AcOEt 97:3) to afford **158** as a pale yellow oil (10.5 g, 86%).

Mw 207 ($C_{10}H_8NS_2$).

R_f 0.50 (hexane/AcOEt 80:20).

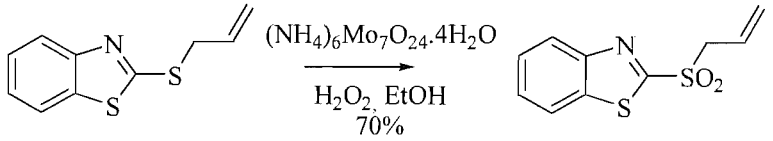
IR (film): 3058 (w), 1634 (w), 1558 (w), 1454 (m), 1422 (s), 1307 (m), 1235 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (1H, d, J = 8.0 Hz, N-C-**CH**=CH); 7.81 (1H, d, J = 7.5 Hz, CH=**CH**-C-S); 7.46 (1H, t, J = 7.8 Hz, **CH**=CH-C-S); 7.34 (1H, t, J = 7.8 Hz, N-C-CH=**CH**); 6.11 (1H, ddt, J = 17.1, 10.0, 7.0 Hz, **CH**=CH_2); 5.46 (1H, d, J = 16.6 Hz, CH=**$CH_{cis}H_{trans}$**); 5.25 (1H, d, J = 10.0 Hz, CH=**$CH_{cis}H_{trans}$**); 4.05 (1H, d, J = 7.0 Hz, **CH_2**-S).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.1 (S-**C**=N); 153.1 (N-**C**=C); 135.3 (N-C=**C**); 132.3 (CH_2=**CH**); 126.0 (**CH**=CH-C-S); 124.2 (N-C-CH=**CH**); 121.5 (N-C-**CH**=CH); 120.9 (CH=**CH**-C-S); 119.1 (**CH_2**=CH); 36.2 (S-**CH_2**).

The analytical data corresponded to the reported data.[182]

2-(prop-2-enylsulfonyl)-benzothiazole (159)



158 **159**

To a solution of sulphide **158** (3.5 g, 12.4 mmol) in EtOH (630 mL) was added a solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (3.1 g, 2.5 mmol) in 30% aqueous H_2O_2 (16 mL). The solution was stirred for 2.5 h at room temperature. The reaction was diluted with 20% aqueous $Na_2S_2O_5$ (100 mL) and Et_2O (500 mL). After the phase separation, the aqueous phase was extracted with Et_2O (3 × 500 mL). The combined organic phases were washed with brine (2 × 500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 70:30) to afford the sulfone **159** as a white solid (2.7 g, 70%).

Mw 315 ($C_{10}H_8NO_2S_2$).

R_f 0.20 (hexane/AcOEt 80:20).

Mp 61 °C, lit.[131] 67 °C.

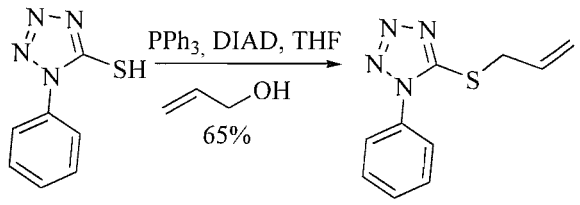
IR (film): 3063 (w), 2968 (w), 2896 (w), 1548 (w), 1467 (m), 1420 (m), 1323 (s), 1314 (s), 1140 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (1H, d, J = 8.0 Hz, N-C-**C<u>H</u>**=CH); 8.01 (1H, d, J = 8.0 Hz, CH=**C<u>H</u>**-C-S); 7.64 (1H, td, J = 7.5, 1.5 Hz, **C<u>H</u>**=CH-C-S); 7.60 (1H, td, J = 7.5, 1.5 Hz, N-C-CH=**C<u>H</u>**); 5.89 (1H, ddt, J = 17.5, 10.5, 7.5 Hz, **C<u>H</u>**=CH_2); 5.41 (1H, d, J = 10.0 Hz, CH=**C<u>H</u>$_{cis}$H$_{trans}$**); 5.35 (1H, d, J = 17.0 Hz, CH=**CH$_{cis}$<u>H</u>$_{trans}$**); 4.25 (1H, d, J = 7.5 Hz, **C<u>H</u>$_2$**-SO_2).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.1 (S-**C**=N); 152.6 (N-**C**=C); 136.8 (N-C=**C**); 128.0 (**CH**=CH-C-S); 127.6 (N-C-CH=**CH**); 126.2 (**CH_2**=CH); 125.4 (CH=**CH**-C-S); 123.1 (CH_2=**CH**); 122.3 (N-C-**CH**=CH); 59.0 (SO_2-**CH_2**).

The analytical data corresponded to the reported data.[131]

5-(allylthio)-1-phenyl-1*H*-tetrazole (161)



160 **161**

To a solution of allyl alcohol (4 mL, 58.8 mmol) in THF (60 mL) at 0 °C were added 1-phenyl-1*H*-tetrazole-5-thio **160** (15.7 g, 88.2 mmol) and PPh_3 (24.7 g, 94.1 mmol). After 5 min at this temperature, DIAD (17.4 mL, 88.2 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h at room temperature. The solution was concentrated *in vacuo*. The crude was purified by column chromatography (hexane/AcOEt 90:10) to afford **161** as a pale yellow oil (8.3 g, 65%).

Mw 218 ($C_{10}H_{10}N_4S$).

R_f 0.23 (hexane/AcOEt 80:20).

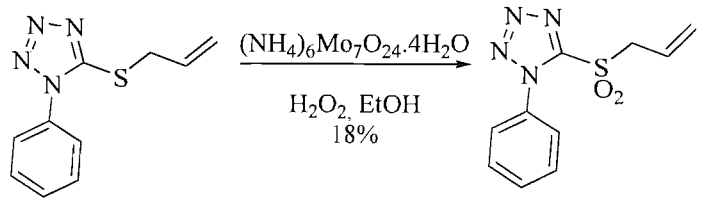
IR (film): 3063 (w), 2980 (w), 2929 (w), 2355 (w), 1635 (w), 1595 (m), 1497 (s), 1383 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.52 (5H, m, Ph); 5.98 (1H, ddt, *J* = 17.2, 10.3, 7.3 Hz, **C<u>H</u>**=CH_2); 5.37 (1H, dd, *J* = 17.2, 1.5 Hz, CH=**$CH_{\underline{cis}}H_{\underline{trans}}$**); 5.19 (1H, dd, *J* = 10.2, 0.7 Hz, CH=**$C\underline{H}_{\underline{cis}}H_{\underline{trans}}$**); 4.01 (2H, d, *J* = 7.0 Hz, **$C\underline{H}_2$**-S).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 153.6 (**C**=N); 133.5 (**C**-N); 131.4 (**CH**); 130.1 (**CH**); 129.7 (**CH**); 123.8 (CH=**CH**-C-S); 120.0 (**CH_2**=CH); 35.8 (S-**CH_2**).

The analytical data corresponded to the reported data.[183]

5-(allylsulfonyl)-1-phenyl-1*H*-tetrazole (162)



161 **162**

To a solution of sulphide **161** (7.2 g, 32.9 mmol) in EtOH (1300 mL) was added a solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (6.3 g, 2.5 mmol) in 30% aqueous H_2O_2 (32.6 mL). The solution was stirred for 6.5 h at room temperature. The reaction was diluted with 20% aqueous $Na_2S_2O_5$ (200 mL) and Et_2O (800 mL). After the phase separation, the aqueous phase was extracted with Et_2O (3 × 800 mL). The combined organic phases were washed with brine (2 × 800 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 90:10) to afford the sulfone **162** as a pale yellow oil (2.7 g, 18%).

Mw 250 ($C_{10}H_{10}N_4OS_2$).

R_f 0.18 (hexane/AcOEt 80:20).

IR (film): 3065 (w), 2984 (w), 2928 (w), 1733 (w), 1594 (m), 1496 (m), 1338 (s), 1147 (s) cm^{-1}.

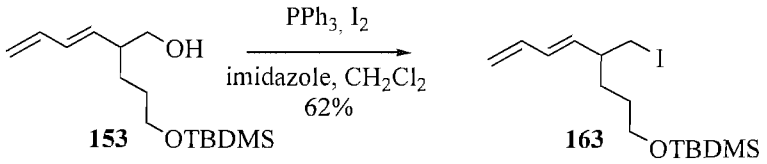
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.56 (5H, m, Ph); 5.89 (1H, ddt, J = 17.2, 9.9, 7.3 Hz, **C<u>H</u>**=CH_2); 5.56 (1H, d, J = 10.6 Hz, CH=**C<u>H</u>$_{cis}$H$_{trans}$**); 5.55 (1H, dd, J = 17.3, 0.7 Hz, CH=**CH$_{cis}$<u>H</u>$_{trans}$**); 4.43 (2H, d, J = 6.9 Hz, **C<u>H</u>$_2$**-S).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 153.0 (**C**=N); 132.9 (**C**-N); 131.4 (**CH**); 129.6 (**CH**); 127.7 (**CH_2**=CH); 125.1 (**CH**); 121.8 (CH_2=**CH**); 60.2 (S-**CH_2**).

ESMS: *m/z* (%) 251 ($(M+H)^+$, 100), 273 (88), 524 (52).

HRMS (ES) for $C_{10}H_{10}N_4SO_2Na$ $(M+Na)^+$ calcd 273.0417 found 273.0421.

(3*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-iodohex-3,5-diene (163)



To a solution of PPh_3 (1.5 g, 6.1 mmol) and imidazole (375 mg, 6.1 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added I_2 (1.5 g, 6.1 mmol). After 10 min at this temperature, a solution of alcohol **153** in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 18 h at room temperature. The reaction was diluted with saturated aqueous $Na_2S_2O_3$ (1 × 15 mL), water (2 × 15 mL) and the aqueous phases were extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 80:20) to afford the iodide **163** as a yellow oil (1.3 g, 62%).

Mw 380 ($C_{15}H_{29}OSiI$).

R_f 0.72 (hexane/AcOEt 80:20).

IR (film): 3087 (w), 2960 (s), 2922 (s), 1796 (w), 1640 (w), 1607 (w), 1470 (m), 1252 (m), 1100 (s) cm^{-1}.

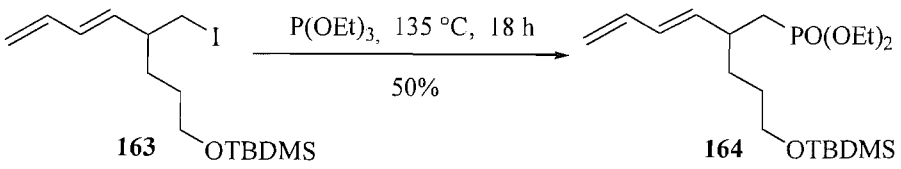
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (1H, dt, *J* = 16.9, 10.1 Hz, CH_2=C**H**); 6.09 (1H, dd, *J* = 15.1, 10.5 Hz, CH_2=CH-C**H**); 5.45 (1H, dd, *J* = 15.1, 8.5 Hz, C**H**=CH-CH=CH_2); 5.17 (1H, dd, *J* = 16.9, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.06 (1H, dd, *J* = 10.1, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 3.61 (2H, t, *J* = 6.3 Hz, C**H**$_2$-OTBDMS); 3.19 (2H, d, *J* = 6.1 Hz, C**H**$_2$-I); 2.20 (1H, m, C**H**-CH_2-I); 1.81-1.33 (4H, m, C**H**$_2$-C**H**$_2$-CH_2-OTBDMS); 0.90 (9H, s, C**H**$_3$-C); 0.05 (6H, s, C**H**$_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 136.6 (CH_2=**CH**); 136.3 (**CH**=CH-CH=CH_2); 132.6 (CH_2=CH-**CH**); 116.5 (**CH_2**=CH); 62.9 (**CH_2**-OTBDMS); 44.0 (**CH**-CH_2-I); 31.3 (**CH_2**-CH_2-OTBDMS); 30.2 (**CH_2**-CH_2-CH_2-OTBDMS); 26.0 (**CH_3**, tBu); 18.3 (**C**, tBu); 13.6 (**CH_2**-I); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 381 ($(M+H)^+$, 2), 323 (2), 253 (20), 75 (100).

HRMS (EI) for $C_{15}H_{29}OSiI$ $(M\text{-}tBu)^+$ calcd 323.0328 found 323.0316.

diethyl-(3*E*)-2-(3-*tert*-butyldimethylsilyloxy-propyl)-hex-3,5-diene-phosphonate 164)



A solution of iodide **163** (631 mg, 1.7 mmol) in neat triethyl phosphite (876 µl, 5 mmol) was heated at 135 °C for 18 h to afford an orange solution. The excess of triethyl phosphite was removed by Kugelrohr distillation and the oily residue was purified by column chromatography (Et_2O/acetone 10:1) to afford the phosphonate **164** as a yellow oil (186 mg, 50%).

Mw 390 ($C_{19}H_{39}O_4SiP$).

R_f 0.53 (Et_2O/acetone 10:1).

IR (film): 3087 (w), 2950 (s), 1791 (w), 1649 (w), 1607 (w), 1252 (s), 1058 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.25 (1H, dt, J = 16.9, 10.1 Hz, CH_2=C**H**); 6.09 (1H, dd, J = 15.1, 10.5 Hz, CH_2=CH-C**H**); 5.46 (1H, dd, J = 15.1, 9.0 Hz, C**H**=CH-CH-CH_2); 5.09 (1H, dd, J = 16.9, 0.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 4.96 (1H, dd, J = 10.1, 0.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 4.08-3.96 (4H, m, C**H**$_2$-CH_3); 3.55 (2H, t, J = 6.0 Hz, C**H**$_2$-OTBDMS); 2.47 (1H, m, C**H**-CH_2-P); 1.78 (2H, dt, J = 18.2, 5.0 Hz, C**H**$_2$-P); 1.61-1.31 (4H, m, C**H**$_2$-C**H**$_2$-CH_2-OTBDMS); 1.25 (6H, dt, J = 7.2, 3.7 Hz, CH_2-C**H**$_3$); 0.85 (9H, s, C**H**$_3$-C), 0.00 (6H, s, C**H**$_3$-Si).

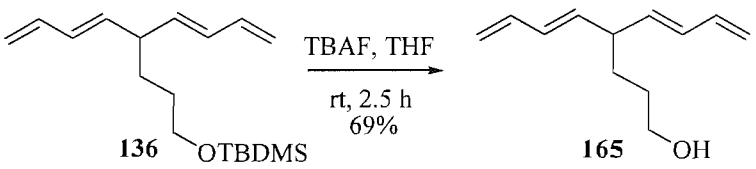
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 137.4 (CH_2=**CH**); 136.7 (**CH**=CH-CH=CH_2); 131.3 (CH_2=CH-**CH**); 115.8 (**CH_2**=CH); 62.9 (**CH_2**-OTBDMS); 61.3 (d, J_{C-P} = 6.7 Hz, **CH_2**-CH_3); 37.1 (**CH**-CH_2-P); 32.3 (**CH_2**-CH_2-CH_2-OTBDMS); 31.3 (d, J_{C-P} = 175.2 Hz, **CH_2**-P); 30.6 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**, tBu); 18.2 (**C**, tBu); 16.4 (d, J_{C-P} = 6.2 Hz CH_2-**CH_3**); -5.4 (**CH_3**-Si).

^{31}P NMR (121 MHz, $CDCl_3$): δ 31.14 (**P**=O).

CIMS: *m/z* (%) 391 ($(M+H)^+$, 10), 333 (30), 75 (100), 56 (58).

HRMS (EI) for $C_{19}H_{39}O_4SiP$ $(M)^+$ calcd 390.2355 found 390.2350.

(3*E*,6*E*)-5-(3-propanol)-nona-1,3,6,8-tetraene (165)



To a solution of bis(diene) **136** (50 mg, 0.17 mmol) in wet THF (1 mL) was added TBAF (95%, 1 M in THF, 179 µL, 0.17 mmol). The reaction mixture was stirred for 2.5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2.5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine (1 × 20 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **165** as a yellow oil (21 mg, 69%).

Mw 178 ($C_{12}H_{18}O$)

R_f 0.14 (hexane/AcOEt 80:20).

IR (film): 3329 (w), 3085 (w), 2936 (w), 1800 (w), 1646 (w), 1601 (w), 1000 (s) cm^{-1}.

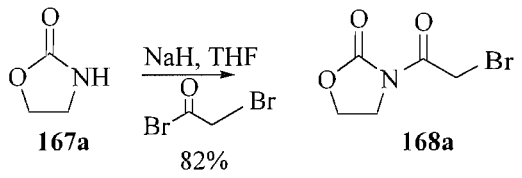
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.32 (2H, dt, *J* = 17.1, 10.3 Hz, CH_2=C**H**); 6.05 (2H, dd, *J* = 15.3, 10.5 Hz, CH_2=CH-C**H**); 5.59 (2H, dd, *J* = 15.3, 7.9 Hz, CH_2=CH-CH=C**H**); 5.13 (2H, ddd, *J* = 17.1, 1.7, 1.1 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.01 (2H, ddd, *J* = 10.3, 1.5, 0.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 3.64 (2H, t, *J* = 6.1 Hz, C**H$_2$**-OH); 2.80 (1H, quint, *J* = 7.2 Hz, C**H**-CH_2-CH_2); 1.62-1.48 (4H, m, CH- C**H$_2$**-C**H$_2$**).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 137.0 (CH_2=**CH**); 136.8 (CH_2=CH-**CH**); 130.9 (CH_2=CH-CH=**CH**); 115.7 (**CH_2**=CH); 62.8 (**CH_2**-OH); 45.3 (**CH**-CH_2-CH_2); 31.0 (CH-**CH_2**-CH_2); 30.4 (CH-CH_2-**CH_2**).

CIMS: *m/z* (%) 179 ($(M+H)^+$, 2), 119 (50), 91 (100).

HRMS (EI) for $C_{12}H_{18}O$ (M^+) calcd 178.1358 found 178.1359.

3-(2-bromoacetyl)-oxazolidin-2-one (168a)



To a suspension of NaH (60% dispersion in mineral oil, 3.4 g, 84 mmol) in THF (50 mL) was added 2-oxazolidinone **167a** (6.1 g, 70 mmol). The mixture was refluxed for 1 h, was then cooled to 0 °C and bromoacetyl bromide (6.1 mL, 70 mmol).The reaction was stirred at room temperature for 18 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with AcOEt (2 × 100 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (neat Et_2O) to afford pure bromide **168a** as a yellow oil (12.0 g, 82%).

Mw 208 ($C_5H_6BrNO_3$).

R_f 0.35 (neat Et_2O).

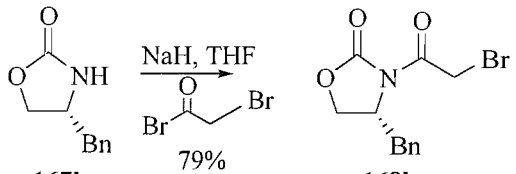
IR (film): 2969 (w), 2924 (w), 1768 (s), 1693 (s), 1387 (s), 1333 (s), 1204 (s), 1033 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.43 (2H, s, **C$\underline{H_2}$**-Br); 4.43 (2H, t, J = 8.0 Hz, **C$\underline{H_2}$**-O); 4.00 (2H, t, J = 8.0 Hz, **C$\underline{H_2}$**-N).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 165.6 (CH_2-**C**=O); 153.0 (O-**C**=O); 62.5 (**CH_2**-O); 42.4 (**CH_2**-N); 27.8 (**CH_2**-Br).

The analytical data corresponded to the reported data.[136]

(*R*)-4-benzyl-3-(2-bromoacetyl)-oxazolidin-2-one (168b)



167b **168b**

To a suspension of NaH (60% dispersion in mineral oil, 2.0 g, 50.4 mmol) in THF (100 mL) was added (*R*)-4-benzyl-2-oxazolidinone **167b** (5.0 g, 42 mmol). The mixture was refluxed for 1 h, was then cooled down to 0 °C and bromoacetyl bromide (3.6 mL, 42 mmol) was added. The reaction was stirred at room temperature for 18 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with AcOEt (2 × 100 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 50:50) to afford pure bromide **168b** as a yellow oil (9.9 g, 79%).

Mw 298 ($C_{12}H_{12}BrNO_3$).

R_f 0.39 (hexane/AcOEt 50:50).

$[\alpha]_D$: -71.2° (*c* 0.87, CH_2Cl_2, 24 °C), lit.[138,184] -75.4° (*c* 2.30, CH_2Cl_2, 21 °C).

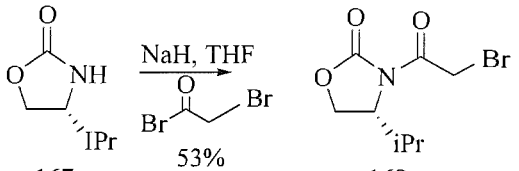
IR (film): 3029 (w), 2984 (w), 1776 (s), 1698 (s), 1389 (m), 1355 (s), 1200 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.22 (5H, m, Ar); 4.73 (1H, m, **C<u>H</u>**-N); 4.58 (1H, d, *J* = 12.8 Hz, **C<u>H</u>$_\alpha$H$_\beta$**-Br); 4.54 (1H, d, *J* = 12.8 Hz, **CH$_\alpha$<u>H</u>$_\beta$**-Br); 4.33-4.23 (2H, m, **C<u>H$_2$</u>**-O); 3.34 (1H, dd, *J* = 13.4, 3.3 Hz, **C<u>H</u>$_\alpha$H$_\beta$**-Ph); 2.83 (1H, dd, *J* = 13.5, 9.5 Hz, **CH$_\alpha$<u>H</u>$_\beta$**-Ph).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.0 (CH_2-**C**=O); 153.0 (O-**C**=O); 134.7 (**C**=CH); 129.4 (C=CH-**CH**); 129.0 (C=**CH**-CH); 127.5 (C=CH-CH=**CH**); 66.6 (**CH_2**-O); 55.4 (**CH**-N); 37.5 (**CH_2**-Ph); 28.1 (**CH_2**-Br).

The analytical data corresponded to the reported data.[138,184]

(*R*)-4-isopropyl-3-(2-bromoacetyl)-oxazolidin-2-one (168c)



167c **168c**

To a suspension of NaH (60% dispersion in mineral oil, 2.0 g, 51.1 mmol) in THF (80 mL) was added (*R*)-4-isopropyl-2-oxazolidinone **167c** (5.5 g, 42.6 mmol). The mixture was refluxed for 1 h, was then cooled down to 0 °C and bromoacetyl bromide (3.7 mL, 42.6 mmol) in THF (10 mL) was added. The reaction was stirred at room temperature for 18 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with AcOEt (3 × 100 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 3:1) to afford pure bromide **168c** as a yellow oil (5.5 g, 53%).

Mw 250 ($C_8H_{12}BrNO_3$).

R_f 0.28 (hexane/AcOEt 3:1).

$[\alpha]_D$: -81.0° (*c* 1.66, $CHCl_3$, 22 °C), lit.[185] -83.0° (*c* 1.00, CH_2Cl_2, 21 °C).

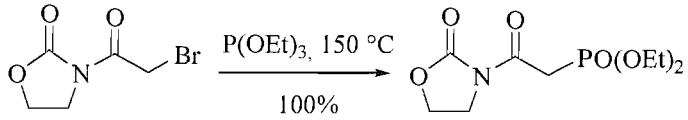
IR (film): 2965 (w), 2877 (w), 1774 (s), 1698 (s), 1387 (m), 1366 (s), 1323 (m), 1200 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (1H, d, *J* = 12.0 Hz, **C$\underline{H}_\alpha$H$_\beta$**-Br); 4.45 (1H, m, **C$\underline{H}$**-N); 4.40 (1H, d, *J* = 12.0 Hz, **CH$_\alpha$$\underline{H}_\beta$**-Br); 4.33 (1H, t, *J* = 8.8 Hz, **C$\underline{H}_\alpha$H$_\beta$**-O); 4.25 (1H, dd, *J* = 9.1, 3.5 Hz, **CH$_\alpha$$\underline{H}_\beta$**-O); 2.38 (1H, m, **C$\underline{H}$**-$CH_3$); 0.91 (3H, d, *J* = 7.0 Hz, CH-**C$\underline{H}_3$**); 0.88 (3H, d, *J* = 7.0 Hz, CH-**C$\underline{H}_3$**).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.9 (CH_2-**C**=O); 153.4 (O-**C**=O); 63.8 (**CH_2**-O); 58.6 (**CH**-N); 28.1 (**CH_2**-Br); 27.9 (**CH**-CH_3); 17.7 (CH-**CH_3**); 14.5 (CH-**CH_3**).

The analytical data corresponded to the reported data.[137,185]

3-(diethylphosphonoacetyl)-oxazolidin-2-one (134a)



168a **134a**

A solution of 3-(2-bromoacetyl)oxazolidin-2-one **168a** (7.3 g, 35.6 mmol) in triethyl phosphite (18 mL, 105.0 mmol) was heated at 150 °C for 18 h. The excess of triethyl phosphite was removed by Kugelrohr distillation under reduced pressure and the residue was purified by column chromatography (hexane/acetone 50:50 to neat acetone) to afford the phosphonate **134a** as a yellow oil (8.9 g, 100%).

Mw 265 ($C_9H_{16}NO_6P$).

R_f 0.18 (neat AcOEt).

IR (film): 2987 (w), 2914 (w), 1773 (m), 1693 (m), 1253 (m), 1014 (s) cm^{-1}.

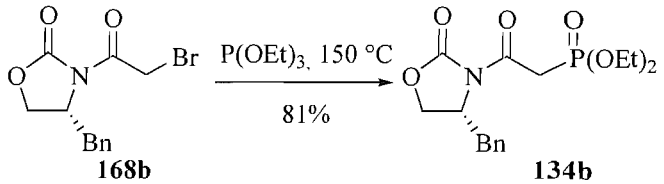
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.40 (2H, t, J = 8.0 Hz, N-CH_2-**C$\underline{H_2}$**); 4.16 (4H, quint, J = 7.5 Hz, **C$\underline{H_2}$**-CH_3); 4.03 (2H, t, J = 8.0 Hz, **C$\underline{H_2}$**-N); 3.74 (2H, dd, J = 22.1, 6.2 Hz, **C$\underline{H_2}$**-P); 1.31 (6H, t, J = 7.1 Hz, CH_2-**C$\underline{H_3}$**).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 165.0 (d, $J_{C\text{-}P}$ = 6.4 Hz, CH_2-**C**=O); 153.3 (O-**C**=O); 62.6 (d, $J_{C\text{-}P}$ = 6.4 Hz, **CH_2**-CH_3); 61.8 (**CH_2**-CH_2-N); 42.6 (CH_2-**CH_2**-N); 33.8 (d, $J_{C\text{-}P}$ = 131.9 Hz, **CH_2**-P); 16.2 (d, $J_{C\text{-}P}$ = 6.4 Hz, CH_2-**CH_3**).

^{31}P NMR (121 MHz, $CDCl_3$): δ 20.5 (**P**=O).

The analytical data corresponded to the reported data.[139]

(*R*)-4-benzyl-3-(diethylphosphonoacetyl)-oxazolidin-2-one (134b)



168b **134b**

A solution of (*R*)-4-benzyl-3-(2-bromoacetyl)-oxazolidin-2-one **168b** (9.9 g, 33 mmol) in triethyl phosphite (18.2 mL, 106 mmol) was heated at 150 °C for 18 h. The excess of triethyl phosphite was removed by Kugelrohr distillation under reduced pressure and the residue was purified by column chromatography (hexane/acetone 50:50 to neat acetone) to afford the phosphonate **134b** as a yellow oil (9.5 g, 81%).

Mw 355 ($C_{16}H_{22}NO_6P$).

R_f 0.36 (hexane/acetone 50:50).

$[\alpha]_D$: -53.2° (*c* 0.96, CH_2Cl_2, 24 °C), lit.[141] -55.2° (*c* 1.2, CH_2Cl_2, 20 °C).

IR (film): 2983 (w), 2929 (w), 1777 (m), 1695 (m), 1256 (m), 1017 (s) cm^{-1}.

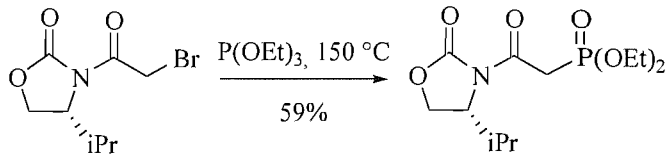
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (5H, m, Ph); 4.71 (1H, m, **CH**-N); 4.25-4.14 (6H, m, N-CH-**CH_2** and **CH_2**-CH_3); 3.82 (1H, dd, *J* = 22.1, 14.2 Hz, **$CH_\alpha H_\beta$**-P); 3.75 (1H, dd, *J* = 22.1, 14.2 Hz, **$CH_\alpha H_\beta$**-P); 3.35 (1H, dd, *J* = 13.5, 3.5 Hz, **$CH_\alpha H_\beta$**-Ph); 2.75 (1H, dd, *J* = 13.4, 9.7 Hz, **$CH_\alpha H_\beta$**-Ph); 1.35 (6H, dt, *J* = 7.0, 0.4 Hz, CH_2-**CH_3**).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 165.0 (d, *J* = 6.4 Hz, CH_2-**C**=O); 153.3 (O-**C**=O); 135.0 (**C**=CH); 129.3 (C=CH-**CH**); 128.9 (C=**CH**-CH); 127.3 (C=CH-CH=**CH**); 65.9 (**CH_2**-CH-N); 62.6 (d, $J_{C\text{-}P}$ = 6.4 Hz, **CH_2**-CH_3); 55.4 (CH_2-**CH**-N); 37.6 (**CH_2**-Ph); 34.3 (d, $J_{C\text{-}P}$ = 131.0 Hz, **CH_2**-P); 16.2 (d, $J_{C\text{-}P}$ = 6.4 Hz, CH_2-**CH_3**).

^{31}P NMR (121 MHz, $CDCl_3$): δ 19.4 (**P**=O).

The analytical data corresponded to the reported data.[141]

(*R*)-4-isopropyl-3-(diethylphosphonoacetyl)-oxazolidin-2-one (134c)



168c **134c**

A solution of (*R*)-4-isopropyl-3-(2-bromoacetyl)-oxazolidin-2-one **168c** (5.0 g, 20.0 mmol) in triethyl phosphite (10.6 mL, 61.9 mmol) was heated at 150 °C for 18 h. The excess of triethyl phosphite was removed by Kugelrohr distillation under reduced pressure and the residue was purified by column chromatography (hexane/acetone 40:60 to neat acetone) to afford the phosphonate **134c** as a yellow oil (3.6 g, 59%).

Mw 307 ($C_{12}H_{22}NO_6P$).

R_f 0.39 (hexane/acetone 40:60).

$[\alpha]_D$: -48.0° (*c* 1.53, CH_2Cl_2, 21 °C), lit.[140] -41.6° (*c* 5.2, CH_2Cl_2, 20 °C).

IR (film): 2978 (w), 2929 (w), 1777 (m), 1697 (m), 1256 (m), 1017 (s) cm^{-1}.

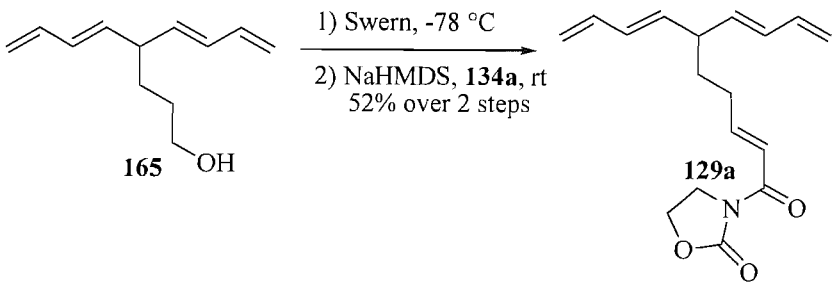
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (1H, m, C**H**-N); 4.28-4.05 (6H, m, N-CH-C**H_2** and C**H_2**-CH_3); 3.83 (1H, dd, *J* = 22.6, 14.0 Hz, C**$H_\alpha H_\beta$**-P); 3.69 (1H, dd, *J* = 22.1, 13.6 Hz, **$CH_\alpha H_\beta$**-P); 2.37 (1H, m, C**H**-CH_3); 1.35 (6H, dt, *J* = 7.0, 1.5 Hz, CH_2-C**H_3**); 0.90 (3H, d, *J* = 6.5 Hz, CH-C**H_3**); 0.88 (3H, d, *J* = 6.5 Hz, CH-C**H_3**).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 164.8 (d, $J_{C\text{-}P}$ = 6.5 Hz, CH_2-**C**=O); 153.8 (O-**C**=O); 63.2 (**CH_2**-CH-N); 62.6 (d, $J_{C\text{-}P}$ = 5.8 Hz, **CH_2**-CH_3); 62.5 (d, $J_{C\text{-}P}$ = 5.8 Hz, **CH_2**-CH_3); 58.7 (CH_2-**CH**-N); 34.2 (d, $J_{C\text{-}P}$ = 130.4 Hz, **CH_2**-P); 28.4 (**CH**-CH_3); 17.8 (CH-**CH_3**); 16.2 (d, $J_{C\text{-}P}$ = 5.8 Hz, CH_2-**CH_3**); 14.5 (CH-**CH_3**).

^{31}P NMR (121 MHz, $CDCl_3$): δ 20.1 (**P**=O).

The analytical data corresponded to the reported data.[140]

3-[(2*E*,7*E*)-6-((*E*)-buta-1,3-dienyl)-deca-2,7,9-trienoyl]-oxazolidin-2-one (129a)



To a solution of oxalyl chloride (754 µL, 6.8 mmol) in CH_2Cl_2 (3.4 mL) at -78 °C was added DMSO (963 µL, 13.6 mmol). After 20 min, a solution of alcohol **165** (417 mg, 2.3 mmol) in CH_2Cl_2 (1 mL) was added. After 2.5 h, TEA (1.9 mL, 13.6 mmol) was added. The reaction mixture was warmed up to 0 °C. After 30 min at this temperature, the reaction mixture was concentrated *in vacuo*. The resulting residue was suspended in THF and filtered through a glass frit followed by rinsing with THF. The filtrate was concentrated *in vacuo* to afford an orange oil which was used in the next step without further purification.

To a solution of phosphonate **134a** (1.4 g, 5.1 mmol) in THF (5 mL) at 0 °C was added NaHMDS (1 M in THF, 5.1 mL, 5.1 mmol). The bright yellow solution was stirred for 5 min at the same temperature and was warmed up to room temperature. A solution of crude aldehyde, as obtained above, in THF (1 mL) was added. The orange solution was stirred for 2 h. The reaction was quenched with phosphate buffer pH 7.2 (10 mL) and diluted with AcOEt (10 mL). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (1 × 10 mL), water (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), brine (1 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 2:1) to afford **129a** as a yellow oil (347 mg, 52% from **165**).

Mw 287 ($C_{17}H_{21}NO_3$).

R_f 0.14 (hexane/AcOEt 2:1).

IR (film): 2923 (w), 1773 (s), 1681 (m), 1633 (m), 1603 (w), 1360 (s), 1219 (s), 1004 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (1H, d, J = 15.5 Hz, CH=C**H**-C=O); 7.12 (1H, dt, J = 15.5, 6.4 Hz, **CH**=CH-C=O); 6.31 (2H, dt, J = 16.9, 10.2 Hz, CH_2=C**H**); 6.05 (2H, dd, J = 15.3, 10.3 Hz, CH_2=CH-C**H**); 5.57 (2H, dd, J = 15.3, 7.7 Hz, CH_2=CH-CH=C**H**); 5.14 (2H, dd, J = 17.0, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 5.01 (2H, dd, J = 10.2, 1.7 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 4.42 (2H, t, J = 8.0

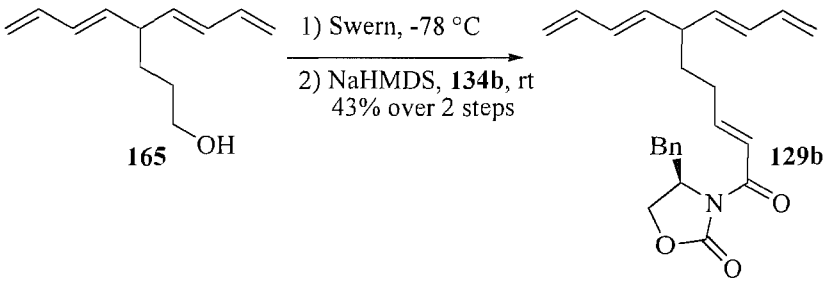
Hz, **C$\underline{H_2}$**-N); 4.06 (2H, t, J = 8.1 Hz, **C$\underline{H_2}$**-O); 2.81 (1H, quint, J = 7.4 Hz, **C$\underline{H}$**-CH_2-CH_2); 2.28 (2H, q, J = 7.3 Hz, **C$\underline{H_2}$**-CH=CH); 1.62 (2H, q, J = 7.5 Hz, CH-**C$\underline{H_2}$**-CH_2).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 165.2 (O-**C**=O); 153.4 (N-**C**=O); 150.9 (**CH**=CH-C=O); 136.8 (CH_2=**CH**); 136.1 (CH_2=CH-CH=**CH**); 131.3 (CH_2=CH-**CH**); 120.2 (CH=**CH**-C=O); 116.1 (**CH_2**=CH); 62.0 (**CH_2**-O); 45.0 (**CH**-CH_2-CH_2); 42.6 (**CH_2**-N); 32.9 (CH-CH_2-**CH_2**); 30.3 (CH-**CH_2**-CH_2).

CIMS: *m/z* (%) 288 ($(M+H)^+$, 26), 201 (30), 172 (18), 146 (92), 91 (100).

HRMS (ES) for $C_{17}H_{21}NO_3Na$ $(M+Na)^+$ calcd 310.1413 found 310.1417.

(*R*)-3-[(2*E*,7*E*)-6-((*E*)-buta-1,3-dienyl)deca-2,7,9-trienoyl]-4-benzyl-oxazolidin-2-one (129b)



To a solution of oxalyl chloride (666 µL, 7.6 mmol) in CH_2Cl_2 (3.5 mL) at -78 °C was added DMSO (1.1 mL, 15.2 mmol) dissolved in CH_2Cl_2 (3.5 mL). After 20 min, a solution of alcohol **165** (322 mg, 2.6 mmol) in CH_2Cl_2 (3.5 mL) was added. After 2.5 h, TEA (2.1 mL, 15.2 mmol) was added. The reaction mixture was warmed up to 0 °C. After 30 min at this temperature, the reaction mixture was concentrated *in vacuo*. The resulting residue was suspended in THF and filtered through a glass frit followed by rinsing with THF. The filtrate was concentrated *in vacuo* to afford a yellow oil which was used without further purification.

To a solution of phosphonate **134b** (2.0 g, 5.7 mmol) in THF (11 mL) at 0 °C was added NaHMDS (1 M in THF, 5.7 mL, 5.7 mmol). The bright yellow solution was stirred for 5 min at the same temperature and was warmed up to room temperature. A solution of crude aldehyde as obtained above dissolved in THF (2 mL) was added. The orange solution was stirred for 2 h. The reaction was quenched with phosphate buffer pH 7.2 (25 mL) and diluted with AcOEt (20 mL). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 20 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (1 × 20 mL), water (1 × 20 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), brine (1 × 20 mL) and dried over anhydrous

$MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 2:1) to afford **129b** as a yellow oil (426 mg, 43% from **165**).

Mw 377 ($C_{24}H_{27}NO_3$).

R_f 0.34 (hexane/AcOEt 2:1).

$[\alpha]_D$: -48.7° (*c* 0.54, CH_2Cl_2, 22 °C).

IR (film): 3026 (w), 2921 (w), 2852 (w), 1176 (m), 1680 (m), 1634 (m), 1354 (m) cm^{-1}.

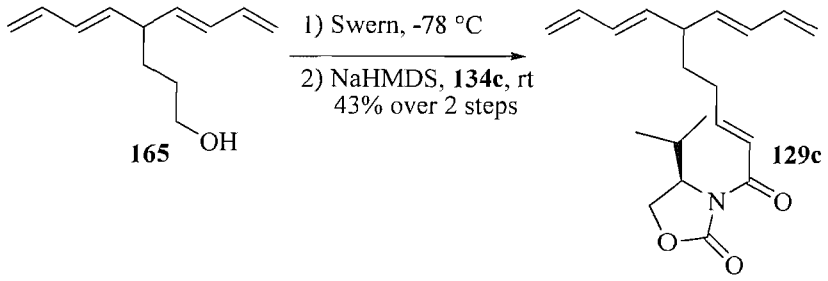
^{1}H NMR (400 MHz, C_6D_6): δ 7.30 (1H, dt, *J* = 15.6, 1.5 Hz, CH=C**H**-C=O); 7.31 (1H, dt, *J* = 15.6, 7.0 Hz, C**H**=CH-C=O); 7.07-6.96 (3H, m, Ph); 6.88 (2H, dd, *J* = 6.5, 1.5 Hz, Ph); 6.27 (2H, dt, *J* = 17.0, 9.6 Hz, CH_2=C**H**); 6.00 (2H, dd, *J* = 15.6, 10.5 Hz, CH_2=CH-C**H**); 5.33 (2H, dd, *J* = 15.0, 7.5 Hz, CH_2=CH-CH=C**H**); 5.10 (2H, dd, *J* = 17.1, 1.0 Hz, C**H**$_{trans}$**H**$_{cis}$=CH); 4.95 (2H, d, *J* = 10.0, 2.0 Hz, **CH**$_{trans}$**H**$_{cis}$=CH); 4.23 (1H, m, C**H**-N); 3.45 (1H, dd, *J* = 9.0, 3.0 Hz, C**H**$_\alpha$**H**$_\beta$-O); 3.15 (1H, t, *J* = 8.5 Hz, **CH**$_\alpha$**H**$_\beta$-O); 3.03 (1H, dd, *J* = 13.5, 3.0 Hz, C**H**$_\alpha$**H**$_\beta$-Ph); 2.60 (1H, quint, *J* = 7.5 Hz, C**H**-CH_2-CH_2); 2.33 (1H, dd, *J* = 13.0 ,9.5 **CH**$_\alpha$**H**$_\beta$-Ph); 1.99 (2H, q, *J* = 7.5 Hz, CH-CH_2-C**H**$_2$); 1.36 (2H, q, *J* = 7.5 Hz, CH-CH_2-C**H**$_2$).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.5 (O-**C**=O); 154.0 (N-**C**=O); 151.3 (**CH**=CH-C=O); 138.0 (**CH**=CH_2); 137.1 (CH_2=CH-CH=**CH**); 132.3 (CH_2=CH-**CH**); 130.2 (C-CH=**CH**); 129.5 (C-**CH**=CH); 128.6 (**C**-CH_2); 127.8 (C-CH=CH-**CH**); 122.1 (CH=**CH**-C=O); 116.6 (**CH_2**=CH); 66.2 (**CH_2**-O); 55.8 (**CH**-N); 45.9 (**CH**-CH_2-CH_2); 38.3 (**CH_2**-Ph); 33.8 (CH-**CH_2**-CH_2); 31.1 (CH-CH_2-**CH_2**).

ESMS: *m/z* (%) 777 ($(2M+Na)^+$, 17), 140 (100).

HRMS (ES) for $C_{24}H_{27}NO_3Na$ $(M+Na)^+$ calcd 400.1883 found 400.1890.

(*R*)-3-[(2*E*,7*E*)-6-((*E*)-buta-1,3-dienyl)deca-2,7,9-trienoyl]-4-isopropyl-oxazolidin-2-one (129c)



To a solution of oxalyl chloride (377 µL, 3.4 mmol) in CH_2Cl_2 (1.7 mL) at -78 °C was added DMSO (482 µL, 6.8 mmol) dissolved in CH_2Cl_2 (1.7 mL). After 20 min, a solution of alcohol **165** (206 mg, 1.2 mmol) in CH_2Cl_2 (1.2 mL) was added. After 2.5 h, TEA (948 µL, 6.8 mmol) was added. The reaction mixture was warmed up to 0 °C. After 30 min at this temperature, the reaction mixture was concentrated *in vacuo*. The resulting residue was suspended in THF and filtered through a glass frit followed by rinsing with THF. The filtrate was concentrated *in vacuo* to afford a yellow oil which was used without further purification.

To a solution of phosphonate **134c** (594 mg, 1.9 mmol) in THF (2.5 mL) at 0 °C was added NaHMDS (1 M in THF, 1.9 mL, 1.9 mmol). The bright yellow solution was stirred for 5 min at the same temperature and was warmed up to room temperature. A solution of crude aldehyde as obtained above dissolved in THF (2 mL) was added. The orange solution was stirred for 2 h. The reaction was quenched with phosphate buffer pH 7.2 (10 mL) and diluted with AcOEt (10 mL). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 20 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (1 × 20 mL), water (1 × 20 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), brine (1 × 20 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 2:1) to afford **129c** as a yellow oil (166 mg, 43% from **165**).

Mw 329 ($C_{20}H_{27}NO_3$).

R_f 0.55 (hexane/AcOEt 2:1).

$[\alpha]_D$: -61.1° (*c* 1.0, $CHCl_3$, 27 °C).

IR (film): 2967 (w), 2932 (w), 2875 (w), 1175 (s), 1681 (m), 1631 (m), 1365 (m), 1004 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ 7.68 (1H, d, *J* = 15.6 Hz, CH=C**H**-C=O); 7.28 (1H, dt, *J* = 15.6, 7.0 Hz, C**H**=CH-C=O); 6.26 (2H, dt, *J* = 17.0, 10.0 Hz, CH_2=C**H**); 6.00 (1H, dd, *J* = 10.5, 3.0

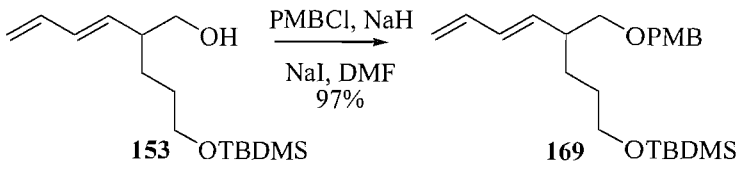
Hz, CH_2=CH-C**H**); 5.96 (1H, dd, *J* = 11.0, 3.0 Hz, CH_2=CH-C**H**); 5.31 (2H, dd, *J* = 15.6, 8.0 Hz, CH_2=CH-CH=C**H**); 5.07 (2H, ddd, *J* = 17.0, 5.0, 2.0 Hz, C**H**$_{trans}$**H**$_{cis}$=CH); 4.95 (2H, d, *J* = 10.0 Hz, **CH**$_{trans}$**H**$_{cis}$=CH); 4.01 (1H, m, C**H**-N); 3.38 (1H, dd, *J* = 9.0, 2.0 Hz, C**H**$_{\alpha}$**H**$_{\beta}$-O); 3.21 (1H, t, *J* = 8.8 Hz, **CH**$_{\alpha}$**H**$_{\beta}$-O); 2.57 (1H, quint, *J* = 7.5 Hz, C**H**-CH_2-CH_2); 2.22 (1H, m, C**H**-CH_3); 1.95 (2H, q, *J* = 7.4 Hz, CH-CH_2-C**H**$_2$); 1.32 (2H, q, *J* = 7.5 Hz, CH-C**H**$_2$-CH_2); 0.53 (3H, d, *J* = 7.0 Hz, CH-C**H**$_3$); 0.41 (3H, d, *J* = 7.0 Hz, CH-C**H**$_3$).

^{13}C NMR + DEPT (100 MHz, C_6D_6): δ 165.4 (O-**C**=O); 154.6 (N-**C**=O); 151.1 (**CH**=CH-C=O); 138.0 (**CH**=CH_2); 137.1 (CH_2=CH-CH=**CH**); 132.2 (CH_2=CH-**CH**); 122.0 (CH=**CH**-C=O); 116.5 (**CH_2**=CH); 63.4 (**CH_2**-O); 59.0 (**CH**-N); 45.9 (**CH**-CH_2-CH_2); 33.8 (CH-**CH_2**-CH_2); 31.0 (CH-CH_2-**CH_2**); 29.2 (CH_3-**CH**); 18.2 (**CH_3**-CH); 15.1 (**CH_3**-CH).

ESMS: *m/z* (%) 681 ($(2M+Na)^+$, 5), 352 (100).

HRMS (ES) for $C_{20}H_{27}NO_3Na$ $(M+Na)^+$ calcd 352.1883 found 352.1890.

(*E*)-1-*tert*-butyldimethylsilyloxy-4-[(4-methoxybenzyloxy)methyl]-octa-5,7-diene (169)



To a suspension of NaH (60% dispersion in mineral oil, 812 mg, 20.3 mmol) in DMF (20 mL) at 0 °C was added a solution of alcohol **153** (5.0 g, 18.4 mmol) in DMF (20 mL). After 30 min at this temperature, PMBCl (2.8 mL, 20.3 mmol) and NaI (3.0 g, 20.3 mmol) were added. The reaction was stirred for 42 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (40 mL). The aqueous layers were extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_4$ (1 × 80 mL), brine (1 × 80 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 70:30) to afford **169** as a yellow oil (4.2 g, 97%) along with some starting material **153** (2.0 g, 40%)

Mw 390 ($C_{23}H_{38}O_3Si$).

R_f 0.45 (hexane/AcOEt 90:10).

IR (film): 2950 (m), 2829 (w), 2855 (w), 1650(w), 1612 (w), 1512 (m), 1092 (s) cm^{-1}.

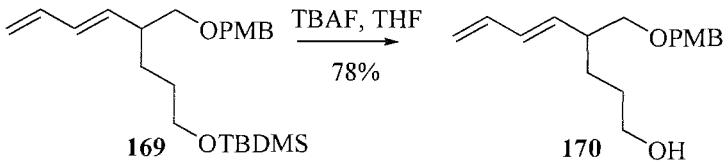
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (2H, d, *J* = 9.1 Hz, C**H**=CH-C-OCH_3); 6.83 (2H, d, *J* = 9.1 Hz, CH=C**H**-C-OCH_3); 6.27 (1H, dt, *J* = 17.1, 9.1 Hz, CH_2=C**H**); 6.05 (1H, dd, *J* = 15.1, 10.0 Hz, CH_2=CH-C**H**); 5.50 (1H, dd, *J* = 15.1, 9.1 Hz, CH_2=CH-CH=C**H**); 5.07 (1H, d, *J* = 16.5 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 4.94 (1H, d, *J* = 10.0 Hz, CH=C**H**$_{cis}$**H**$_{trans}$); 4.39 (2H, s, C**H**$_2$Ar); 3.76 (3H, s, C**H**$_3$O-Ar); 3.54 (2H, t, *J* = 6.3 Hz, C**H**$_2$-OTBDMS); 3.32 (2H, d, *J* = 6.0 Hz, C**H**$_2$-OCH_2); 2.37-2.28 (1H, m, C**H**-CH_2); 1.62-1.45 (2H, m, C**H**$_2$-CH_2-OTBDMS); 1.44-1.35 (2H, m, C**H**$_2$-CH_2-CH_2-OTBDMS); 0.85 (9H, s, C**H**$_3$-C) ; 0.00 (6H, s, C**H**$_3$-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 159.1 (**C**-OCH_3); 137.2 (CH_2=**CH**); 136.3 (CH_2=CH-CH=**CH**); 131.9 (CH_2=CH-**CH**); 130.6 (**C**-CH_2O); 129.1 (**CH**=CH-C-OCH_3); 115.3 (**CH_2**=CH); 113.7 (CH=**CH**-C-OCH_3); 73.5 (CH-**CH_2**O); 72.6 (C-**CH_2**O); 63.2 (**CH_2**-OTBDMS); 55.2 (C-O**CH_3**); 42.7 (**CH**-CH_2O); 30.3 (**CH_2**-CH_2-OTBDMS); 27.8 (**CH_2**-CH_2-CH_2-OTBDMS); 26.0 (**CH_3**, tBu); 18.3 (**C**, tBu); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 391 ($(M+H)^+$, 2), 241 (10), 137 (100), 121 (86).

HRMS (ES) for $C_{23}H_{38}O_3SiNa$ $(M+Na)^+$ calcd 413.2482 found 413.2487.

(*E*)-4-[(4-methoxybenzyloxy)-methyl]-octa-5,7-dien-1-ol (170)



To a solution of silyl ether **169** (4.2 g, 10.7 mmol) in THF (16 mL) was added TBAF (1 M in THF, 16.1 mL, 16.1 mmol). The reaction mixture was stirred for 3 h at room temperature and was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 50:50) to afford **170** as a yellow oil (2.3 g, 78%).

Mw 276 ($C_{17}H_{24}O_3$).

R_f 0.08 (hexane/AcOEt 75:25).

IR (film): 3378 (w), 2934 (w), 2858 (w), 1650(w), 1612 (w), 1512 (m), 1245 (s), 1004 (s) cm^{-1}.

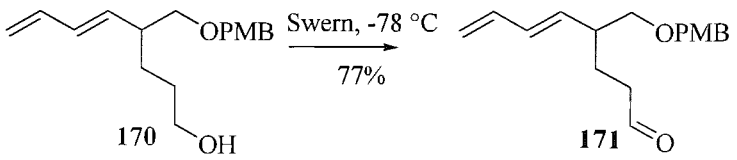
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (2H, d, J = 8.8 Hz, **C<u>H</u>**=CH-C-OCH_3); 6.80 (2H, d, J = 8.8 Hz, CH=**C<u>H</u>**-C-OCH_3); 6.27 (1H, dt, J = 17.6, 10.6 Hz, CH_2=**C<u>H</u>**); 6.01 (1H, ddd, J = 15.4, 10.2, 0.8 Hz, CH_2=CH-**C<u>H</u>**); 5.45 (1H, dd, J = 15.4, 8.8 Hz, CH_2=CH-CH=**C<u>H</u>**); 5.04 (1H, dd, J = 17.1, 1.8 Hz, CH=**$CH_{\underline{cis}}H_{\underline{trans}}$**); 4.92 (1H, dd, J = 10.2, 1.8 Hz, CH=**$CH_{\underline{cis}}H_{\underline{trans}}$**); 4.35 (2H, s, **$CH_2$**Ar); 3.72 (3H, s, **$CH_3$**O-Ar); 3.52 (2H, t, J = 6.2 Hz, **CH_2**-OH); 3.30 (1H, dd, J = 9.1, 6.2 Hz, **$CH_{\alpha}H_{\beta}$**-Ar); 3.27 (1H, dd, J = 9.1, 6.2 Hz, **$CH_{\alpha}H_{\beta}$**-Ar); 2.28 (1H, m, **C<u>H</u>**-CH_2); 1.72-1.36 (2H, m, **CH_2**-CH_2-OH); 1.32-1.17 (2H, m, **CH_2**-CH_2-CH_2-OH).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 159.1 (**C**-OCH_3); 137.0 (CH_2=**CH**); 135.8 (CH_2=CH-CH=**CH**); 132.1 (CH_2=CH-**CH**); 130.5 (**C**-CH_2O); 129.2 (**CH**=CH-C-OCH_3); 115.5 (**CH_2**=CH); 113.7 (CH=**CH**-C-OCH_3); 73.4 (CH-**CH_2**O); 72.7 (C-**CH_2**O); 62.9 (**CH_2**-OH); 55.2 (C-O**CH_3**); 42.7 (**CH**-CH_2O); 30.2 (**CH_2**-CH_2-OH); 27.7 (**CH_2**-CH_2-CH_2-OH).

ESMS: *m/z* (%) 299 ($(M+Na)^+$, 100), 575 (2).

HRMS (ES) for $C_{17}H_{24}O_3Na$ $(M+Na)^+$ calcd 299.1617 found 299.1610.

(*E*)-4-[(4-methoxybenzyloxy)-methyl]-octa-5,7-dien-1-al (171)



To a solution of oxalyl chloride (2.2 mL, 9 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added DMSO (2.3 mL, 32 mmol). After 10 min, a solution of alcohol **170** (2.5 g, 9.0 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was immediately warmed up to -40 °C. After 2 h at this temperature, TEA (4.5 mL, 32 mmol) was added. The reaction mixture was warmed up to 0 °C. After 30 min at this temperature, the reaction mixture was concentrated *in vacuo*. The resulting residue was suspended in THF and filtered through a glass frit followed by rinsing with THF. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **171** as a yellow oil (1.9 g, 77%).

Mw 274 ($C_{17}H_{22}O_3$).

R_f 0.08 (hexane/AcOEt 75:25).

IR (film): 2937 (w), 2853 (w), 2719 (w), 1721 (s), 1650(w), 1612 (m), 1512 (m), 1245 (s), 1004 (s) cm^{-1}.

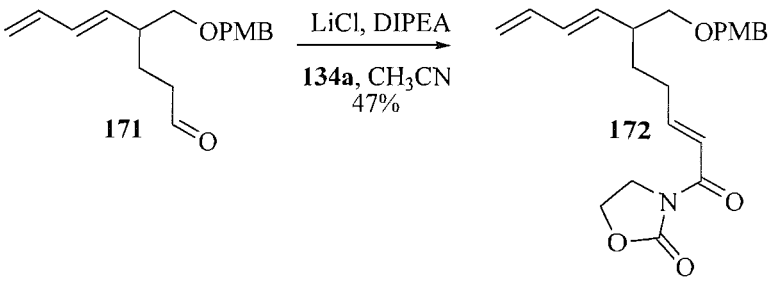
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (1H, m, **CH**O); 7.15 (2H, d, J = 8.5 Hz, **CH**=CH-C-OCH_3); 6.78 (2H, d, J = 8.5 Hz, CH=**CH**-C-OCH_3); 6.20 (1H, dt, J = 16.6, 10.0 Hz, CH_2=**CH**); 6.00 (1H, dd, J = 15.6, 10.5 Hz, CH_2=CH-**CH**); 5.4 (1H, dd, J = 15.1, 8.5 Hz, CH_2=CH-CH=**CH**); 5.05 (1H, d, J = 17.1 Hz, CH=**$CH_{cis}H_{trans}$**); 4.93 (1H, d, J = 10.0 Hz, CH=**$CH_{cis}H_{trans}$**); 4.34 (2H, s, **CH_2**Ar); 3.70 (3H, s, **CH_3**O-Ar); 3.31 (1H, dd, J = 9.0, 5.5 Hz, **$CH_\alpha H_\beta$**-Ar); 3.26 (1H, dd, J = 9.0, 6.5 Hz, **$CH_\alpha H_\beta$**-Ar); 2.39-2.25 (3H, m, **CH**-CH_2, **CH_2**-CHO); 1.85 (1H, m, **$CH_\alpha H_\beta$**-CH_2-CHO); 1.51 (1H, m, **$CH_\alpha H_\beta$**-CH_2-CHO).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 202.2 (**C**=O); 159.1 (**C**-OCH_3); 136.7 (CH_2=**CH**); 134.6 (CH_2=CH-CH=**CH**); 132.7 (CH_2=CH-**CH**); 130.3 (**C**-CH_2O); 129.1 (**CH**=CH-C-OCH_3); 116.1 (**CH_2**=CH); 113.7 (CH=**CH**-C-OCH_3); 73.0 (CH-**CH_2**O); 72.6 (C-**CH_2**O); 55.2 (C-O**CH_3**); 42.7 (**CH**-CH_2O); 41.5 (**CH_2**-CHO); 23.9 (**CH_2**-CH_2-CHO).

ESMS: *m/z* (%) 297 ($(M+Na)^+$, 100), 573 (5).

HRMS (ES) for $C_{17}H_{22}O_3Na$ $(M+Na)^+$ calcd 297.1461 found 297.1461.

3-{(2*E*,7*E*)-6-[(4-methoxybenzyloxy)methyl]deca-2,7,9-trienoyl}-oxazolidin-2-one (172)



To a solution of aldehyde **171** (200 mg, 0.72 mmol) in CH_3CN (2 mL) was added a solution of phosphonate **134a** (385 mg, 1.45 mmol) in CH_3CN (1 mL), followed by DIPEA (376 µl, 2.16 mmol). To the homogeneous solution was added LiCl (144 mg, 3.7 mmol). After 18 h, the mixture was poured in 5% aqueous $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (1 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 40:60) to afford **172** as a yellow oil (130 mg, 47%).

Mw 385 ($C_{22}H_{27}NO_5$).

R_f 0.29 (hexane/AcOEt 40:60).

IR (film): 3000 (w), 2949 (w), 2856 (w), 1774 (s), 1681(m), 1633 (m), 1612 (w), 1512 (m), 1245 (s), 1004 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (2H, d, *J* = 8.8 Hz, **C<u>H</u>**=CH-C-OCH_3); 7.15 (1H, d, *J* = 15.4 Hz, CH=**C<u>H</u>**-C=O); 7.05 (1H, dt, *J* = 15.4, 6.2 Hz, **C<u>H</u>**=CH-C=O); 6.80 (2H, d, *J* = 8.8 Hz, CH=**C<u>H</u>**-C-OCH_3); 6.23 (1H, dt, *J* = 16.8, 10.2 Hz, CH_2=**C<u>H</u>**); 6.03 (1H, dd, *J* = 15.4, 10.2 Hz, CH_2=CH-**C<u>H</u>**); 5.44 (1H, dd, *J* = 15.0, 8.8 Hz, CH_2=CH-CH=**C<u>H</u>**); 5.06 (1H, dd, *J* = 16.5, 1.8 Hz, CH=**CH_{cis}<u>H_{trans}</u>**); 4.93 (1H, dd, *J* = 9.9, 1.5 Hz, CH=**<u>CH_{cis}</u>H_{trans}**); 4.35 (2H, s, **C<u>H$_2$</u>**Ar); 4.33 (2H, t, *J* = 8.4 Hz, **C<u>H$_2$</u>**-N-C=O); 3.98 (2H, t, *J* = 8.1 Hz, **C<u>H$_2$</u>**-O-C=O); 3.73 (3H, s, **C<u>H$_3$</u>**O-Ar); 3.31 (1H, dd, *J* = 9.2, 5.9 Hz, **C<u>H$_α$</u>$H_β$**-Ar); 3.26 (1H, dd, *J* = 9.2, 6.6 Hz, **$CH_α$<u>$H_β$</u>**-Ar); 2.37-2.07 (3H, m, **C<u>H</u>**-CH_2, **C<u>H$_2$</u>**-CH=CH); 1.67 (1H, m, **$CH_α$<u>$H_β$</u>**-CH_2-CH=CH); 1.39 (1H, m, **C<u>H$_α$</u>$H_β$**-CH_2-CH=CH).

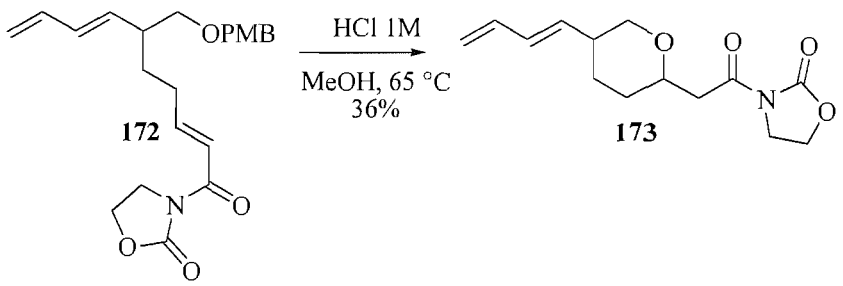
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 165.2 (CH=CH-**C**=O); 159.1 (**C**-OCH_3); 153.4 (N-**C**=O); 151.2 (**CH**=CH-C=O); 136.9 (CH_2=**CH**); 135.1 (CH_2=CH-CH=**CH**); 132.6 CH_2=CH-**CH**); 130.5 (**C**-CH_2O); 129.2 (**CH**=CH-C-OCH_3); 120.1 (CH=**CH**-C=O); 115.9 (**CH_2**=CH);

113.7 (CH=**CH**-C-OCH_3); 73.1 (CH-**CH_2**O); 72.7 (C-**CH_2**O); 62.0 (**CH_2**-O-C=O); 55.2 (C-**OCH_3**); 42.7 (**CH**-CH_2O); 42.6 (**CH_2**-N-C=O); 30.2 (CH-CH_2-**CH_2**); 29.9 (CH-**CH_2**-CH_2).

ESMS: *m/z* (%) 385($(M)^+$, 3), 407 (100), 408 (20), 793 (3).

HRMS (ES) for $C_{22}H_{27}NO_5Na$ $(M+Na)^+$ calcd 408.1781 found 408.1786.

3-(2-(5*E*-buta-1,3-dienyl)-tetrahydro-2*H*-pyran-2-yl)acetyl)-oxazolidin-2-one (173)



To a solution of **172** (180 mg, 0.47 mmol) in MeOH (3.3 mL) was added concentrated aqueous HCl (11µL) and the reaction was refluxed. After 18 h, the mixture was poured in saturated aqueous $NaHCO_3$ until basic pH. The solution was concentrated *in vacuo* and diluted with Et_2O. The organic phase layer was washed with water (2 × 5 mL), brine (1 × 5 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 40:60) to afford **173** as a white solid (40 mg, 36%).

Mw 265 ($C_{14}H_{19}NO_4$).

R_f 0.37 (hexane/AcOEt 40:60).

Mp 91 °C.

IR (film): 2925 (w), 2851 (w), 1770 (s), 1695 (s), 1649 (w), 1601 (w), 1384 (s), 1200 (s), 1079 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (1H, dt, *J* = 17.1, 10.6 Hz, CH_2=C**H**); 6.07(1H, dd, *J* = 15.0, 10.0 Hz, CH_2=CH-C**H**); 5.46 (1H, dd, *J* = 15.5, 7.5 Hz, CH_2=CH-CH=C**H**); 5.14 (1H, d, *J* = 16.6 Hz, CH=C$H_{cis}H_{trans}$); 5.01 (1H, d, *J* = 10.0 Hz, CH=C$H_{cis}H_{trans}$); 4.40 (2H, t, *J* = 8.0 Hz, **CH_2**-O-C=O); 4.09-4.01 (2H, m, **CH_2**-N-C=O); 3.89 (1H, m, **CH**-O-CH_2); 3.24 (1H, dd, *J* = 16.0, 8.5 Hz, **$CH_\alpha H_\beta$**-C=O); 3.18 (2H, d, *J* = 11.0 Hz, **CH_2**-O-CH); 2.97 (1H, dd, *J* = 16.6, 4.0 Hz, **$CH_\alpha H_\beta$**-C=O); 2.32 (1H, m, **CH**-CH_2-O); 1.91 (1H, m, CH-**$CH_\alpha H_\beta$**-CH_2); 1.78 (1H, m, CH-CH_2-**$CH_\alpha H_\beta$**); 1.50-1.36 (2H, m, CH- **$CH_\alpha H_\beta$**-**$CH_\alpha H_\beta$**).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 170.8 (CH-CH_2-**C**=O); 153.5 (N-**C**=O); 136.9 (CH_2=**CH**); 134.5 (CH_2=CH-CH=**CH**); 131.3 CH_2=CH-**CH**); 116.0 (**CH_2**=CH); 73.3 (**CH**-O-

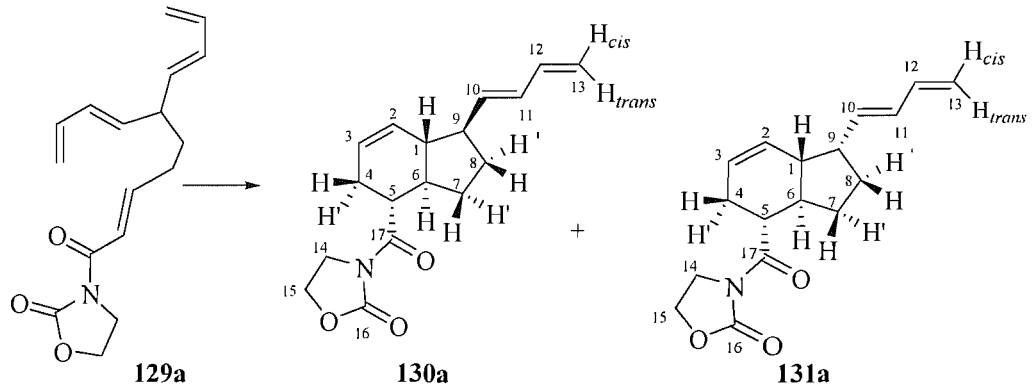
CH_2); 72.3 (**CH_2**-O-CH); 62.0 (**CH_2**-O-C=O); 42.5 (**CH_2**-N-C=O); 41.6 (**CH_2**-C=O); 39.0 (**CH**-CH_2-O); 31.0 (CH-CH_2-**CH_2**); 29.7 (CH-**CH_2**-CH_2).

ESMS: *m/z* (%) 265($(M)^+$, 3), 288 (100), 553 (3).

HRMS (ES) for $C_{14}H_{19}NO_4Na$ $(M+Na)^+$ calcd 288.1206 found 288.1204.

6.3 The IMDA reaction

[(1*S**,5*S**,6*S**,9*R**)-bicyclo[4.3.0]non-2'-ene-5'-carbonyl-9'-butadiene]-2-oxazolidinone (130a)



To a solution of **129a** (40 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (4.6 mL) at -78 °C was added Me_2AlCl (1 M in hexane, 200 μL, 0.20 mmol). The bright yellow solution was immediately warmed up to -30 °C. After 4 h at this temperature, the reaction was diluted with Et_2O (5 mL) and quenched with saturated aqueous solution of Rochelle's salt (5 mL). After the phase separation, the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (CH_2Cl_2/MeOH 99.5:0.5) to afford **130a/131a** as a white solid (24 mg, 59%) as a 69:31 **130a/131a** ratio. The diastereoisomers were separated by reverse phase HPLC (X-Terra Prep RP_{18} column 5μm 19×100 mm, mobile phase 50-55% 1% aqueous NH_3 in CH_3CN and the detection was performed at 230 nm).

Data for the major isomer 130a:

Mw 287 ($C_{17}H_{21}NO_3$).

R_f 0.47 (hexane/AcOEt 50:50).

Mp 94 °C.

IR (film): 2961 (w), 2911 (w), 2864 (w), 1784 (s), 1688 (s), 1650 (w), 1604 (w), 1385 (s), 1200 (s) cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ 6.33 (1H, dt, J = 17.1, 10.0 Hz, H_{12}); 6.02 (1H, dd, J = 15.0, 11.0 Hz, H_{11}); 5.84 (1H, d, J = 9.5, 2.0 Hz, H_2); 5.55 (1H, m, H_3); 5.41 (1H, dd, J = 15.0, 8.5 Hz, H_{10}); 5.07 (1H, dd, J = 17.0, 2.0 Hz, $H_{13trans}$); 4.95 (1H, dd, J = 10.0, 2.0 Hz, H_{13cis}); 4.20 (1H, td, J = 10.6, 6.0 Hz, H_5); 3.08-2.97 (4H, m, H_{14}, H_{15}); 2.62 (1H, m, H_4); 2.34 (1H, m, H_4); 2.09-1.97 (2H, m, H_9, H_6); 1.93 (1H, m, H_8); 1.82 (3H, m, H_1); 1.74 (1H, m, H_7); 1.39-1.24 (2H, m, H_7, H_8).

^{13}C NMR + DEPT (100 MHz, C_6D_6): δ 175.9 (**C**, C_{17}); 154.2 (**C**, C_{16}); 139.0 (**CH**, C_{10}); 138.2 (**CH**, C_{12}); 132.0 (**CH**, C_{11}); 128.9 (**CH**, C_2); 126.9 (**CH**, C_3); 115.7 (**CH_2**, C_{13}); 61.7 (**CH_2**, C_{15}); 49.7 (**CH**, C_6); 47.2 (**CH**, C_9); 46.4 (**CH**, C_1); 44.2 (**CH**, C_5); 42.9 (**CH_2**, C_{14}); 31.2 (**CH_2**, C_4); 30.9 (**CH_2**, C_7); 27.8 (**CH_2**, C_8).

CIMS: *m/z* (%) 288 ($(M+H)^+$, 82), 201 (22), 173 (8), 91 (100).

HRMS (EI) for $C_{17}H_{21}NO_3$ $(M)^+$ calcd 287.1521 found 287.1525.

Partial data for the minor isomer 131a:

Mw 287 ($C_{17}H_{21}NO_3$).

R_f 0.47 (hexane/AcOEt 50:50).

Mp 94 °C.

IR (film): 2961 (w), 2911 (w), 2864 (w), 1784 (s), 1688 (s), 1650 (w), 1604 (w), 1385 (s), 1200 (s) cm^{-1}.

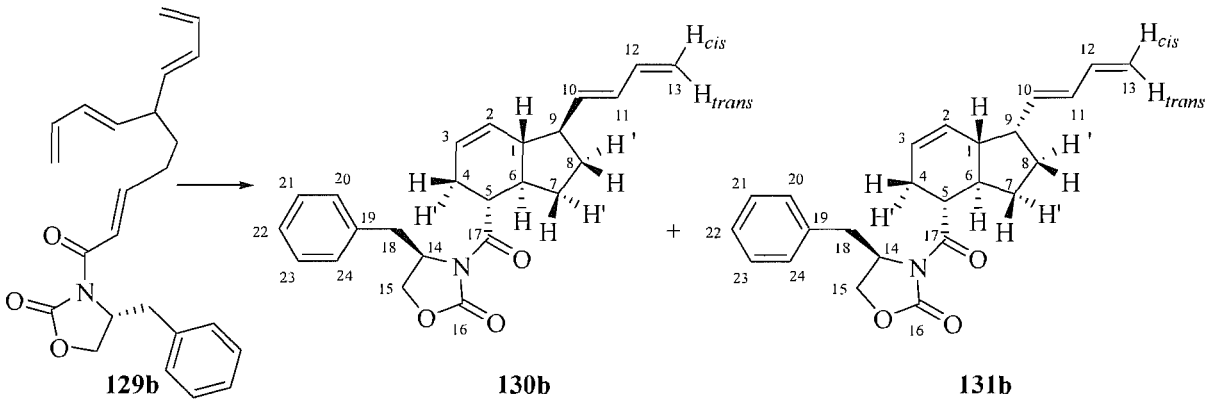
^{1}H NMR (400 MHz, C_6D_6): δ 6.36 (1H, dt, J = 17.1, 10.2 Hz, H_{12}); 6.08 (1H, dd, J = 15.0, 10.0 Hz, H_{11}); 5.87 (1H, d, J = 9.5 Hz, H_2); 5.17 (1H, d, J = 16.6 Hz, $H_{13trans}$); 5.01 (1H, d, J = 10.5, 1.5 Hz, H_{13cis}); 4.27 (1H, td, J = 9.5, 6.5 Hz, H_5).

^{13}C NMR + DEPT (100 MHz, C_6D_6): 175.9 (**C**, C_{17}); 154.2 (**C**, C_{16}); 138.8 (**CH**, C_{10}); 138.2 (**CH**, C_{12}); 129.3 (**CH**, C_{11}); 128.9 (**CH**, C_2); 126.9 (**CH**, C_3); 115.7 (**CH_2**, C_{13}); 61.7 (**CH_2**, C_{15}); 48.1 (**CH**, C_6); 44.4 (**CH**, C_9); 43.9 (**CH**, C_1); 43.2 (**CH**, C_5); 42.9 (**CH_2**, C_{14}); 31.3 (**CH_2**, C_7); 31.2 (**CH_2**, C_4); 28.6 (**CH_2**, C_8).

CIMS: *m/z* (%) 288 ($(M+H)^+$, 82), 201 (22), 173 (8), 91 (100).

HRMS (EI) for $C_{17}H_{21}NO_3$ $(M)^+$ calcd 287.1521 found 287.1525.

[(1*S*,5*S*,6*S*,9*R*)-bicyclo[4.3.0]non-2'-ene-5'-carbonyl-9'-butadiene]-4*R*-benzyl-2-oxazolidinone (130b)



To a solution of **129b** (80 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (7 mL) at -78 °C was added Me_3Al (2 M in toluene 150 μL, 0.30 mmol). The bright yellow solution was immediately warmed up to room temperature. After 45 h at this temperature, the crude was purified by column chromatography (neat CH_2Cl_2) to afford **130b/131b** as a white solid (37 mg, 47%) in a ratio **130b/131b** 92:8.

Data for the major isomer 130b:

Mw 377 ($C_{24}H_{27}NO_3$).

R_f 0.47 (neat CH_2Cl_2).

IR (film): 3024 (w), 2960 (w), 2868 (w), 1777 (s), 1695 (m), 1650 (w), 1603 (w), 1384 (m), 1351 (m), 1209 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.27 (5H, m, Ph); 6.40 (1H, dt, J = 17.1, 10.5 Hz, H_{12}); 6.16 (1H, dd, J = 15.6, 10.0 Hz, H_{11}); 5.87 (1H, d, J = 9.5 Hz, H_2); 5.74-5.65 (2H, m, H_{10}, H_3); 5.18 (1H, d, J = 17.1 Hz, $H_{13trans}$); 5.05 (1H, dd, J = 10.0, 1.5 Hz, H_{13cis}); 4.78 (1H, m, H_{14}); 4.30-4.23 (2H, m, H_{15}); 3.95 (1H, td, J = 10.5, 6.0 Hz, H_5); 3.33 (1H, dd, J = 13.5, 3.5 Hz, $H_{18\alpha}$); 2.84 (1H, dd, J = 13.1, 9.5 Hz, $H_{18\beta}$); 2.68 (1H, m, H_4); 2.34-2.19 (2H, m, H_4, H_1); 2.12-2.00 (1H, m, H_9); 1.93 (1H, m, H_6); 1.67-1.55 (2H, m, H_8); 1.47-1.21 (2H, m, H_7).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 175.6 (**C**, C_{17}); 153.1 (**C**, C_{16}); 138.1 (**CH**, C_{10}); 137.1 (**CH**, C_{12}); 135.2 (**C**, C_{19}); 130.9 (**CH**, C_{11}); 129.4 (**CH**, C_{21}, C_{23}); 128.9 (**CH**, C_{20}, C_{24}); 128.0 (**CH**, C_2); 127.3 (**CH**, C_{22}); 125.9 (**CH**, C_3); 115.1 (**CH_2**, C_{13}); 66.1 (**CH_2**, C_{15}); 55.3 (**CH**, C_{14}); 48.9 (**CH**, C_6); 46.2 (**CH**, C_1); 45.1 (**CH**, C_9); 43.6 (**CH**, C_5); 38.0 (**CH_2**, C_{18}); 30.3 (**CH_2**, C_4); 30.1 (**CH_2**, C_7); 26.9 (**CH_2**, C_8).

CIMS: *m/z* (%) 378 ($(M+H)^+$, 100), 91 (56).

HRMS (EI) for $C_{24}H_{27}NO_3$ $(M)^+$ calcd 377.1991 found 377.1986.

Partial data for the minor isomer 131b:

Mw 377 ($C_{24}H_{27}NO_3$).

R_f 0.47 (neat CH_2Cl_2).

IR (film): 3024 (w), 2960 (w), 2868 (w), 1777 (s), 1695 (m), 1650 (w), 1603 (w), 1384 (m), 1351 (m), 1209 (m) cm^{-1}.

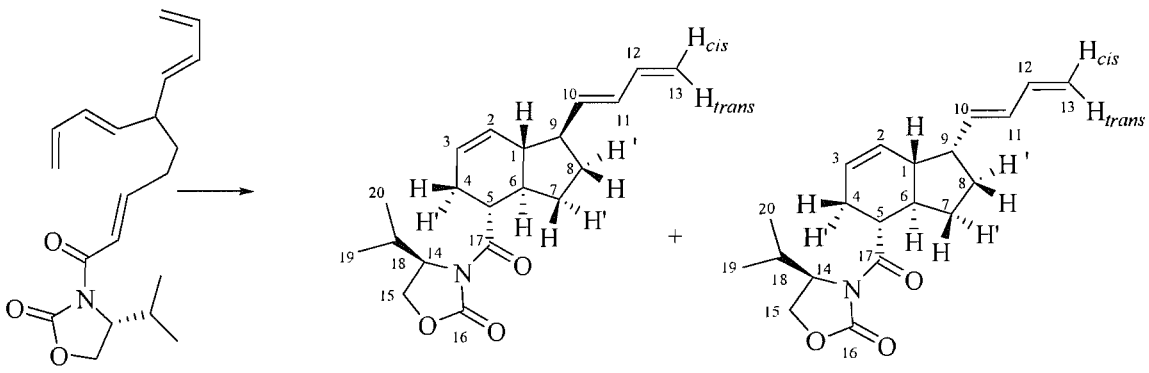
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (1H, dd, J = 15.0, 9.5 Hz, H_{11}); 5.83 (1H, d, J = 10.0 Hz, H_2); 5.17 (1H, d, J = 17.1 Hz, $H_{13trans}$); 5.03 (1H, d, J = 10.7 Hz, H_{13cis}); 3.93 (1H, td, J = 9.3, 6.0 Hz, H_5).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 175.6 (**C**, C_{17}); 153.1 (**C**, C_{16}); 137.8 (**CH**, C_{10}); 137.2 (**CH**, C_{12}); 135.2 (**C**, C_{19}); 130.6 (**CH**, C_{11}); 129.4 (**CH**, C_{21}, C_{23}); 128.9 (**CH**, C_{20}, C_{24}); 128.2 (**CH**, C_2); 127.3 (**CH**, C_{22}); 125.9 (**CH**, C_3); 115.0 (**CH_2**, C_{13}); 66.1 (**CH_2**, C_{15}); 55.2 (**CH**, C_{14}); 47.2 (**CH**, C_6); 43.8 (**CH**, C_1); 42.4 (**CH**, C_9); 42.1 (**CH**, C_5); 38.0 (**CH_2**, C_{18}); 30.3 (**CH_2**, C_4); 30.1 (**CH_2**, C_7); 27.8 (**CH_2**, C_8).

CIMS: *m/z* (%) 378 ($(M+H)^+$, 100), 91 (56).

HRMS (EI) for $C_{24}H_{27}NO_3$ $(M)^+$ calcd 377.1991 found 377.1986.

[(1*S*,5*S*,6*S*,9*R*)-bicyclo[4.3.0]non-2'-ene-5'-carbonyl-9'-butadiene]-4*R*-isopropyl-2-oxazolidinone (130c)



129c **130c** **131c**

To a solution of **129c** (66 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (6.7 mL) at -78 °C was added Me_3Al (2 M in toluene 140 µL, 0.28 mmol). The bright yellow solution was immediately warmed up to room temperature. After 68 h at this temperature, the crude was purified by column chromatography (neat CH_2Cl_2) to afford **130c/131c** as a colourless oil (37 mg, 47%) in a ratio **130c/131c** 78:22.

Data for the major isomer 130c:

Mw 329 ($C_{20}H_{27}NO_3$).

R_f 0.76 (neat CH_2Cl_2).

IR (film): 3017 (w), 2961 (w), 2872 (w), 1777 (s), 1697 (m), 1649 (w), 1602 (w), 1384 (m), 1351 (m), 1201 (m) cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ 6.34 (1H, dt, J = 17.0, 10.0 Hz, H_{12}); 6.03 (1H, dd, J = 15.0, 10.5 Hz, H_{11}); 5.94 (1H, dd, J = 10.0, 1.5 Hz, H_2); 5.52 (1H, m, H_3); 5.43 (1H, dd, J = 15.0, 8.5, H_{10}); 5.09 (1H, d, J = 17.6 Hz, $H_{13trans}$); 4.95 (1H, d, J = 9.5 Hz, H_{13cis}); 4.30 (1H, td, J = 10.5, 6.0 Hz, H_5); 3.98 (1H, m, H_{14}); 3.38 (1H, dd, J = 11.6, 2.5 Hz, H_{15}); 3.22 (1H, t, J = 17.6 Hz, H_{15}); 2.73 (1H, m, H_4); 2.33 (1H, m, H_4); 2.23-2.11 (3H, m, H_6, H_{18}, H_9); 1.94-1.76 (2H, m, H_7, H_8); 1.70 (1H, m, H_1); 1.37 (1H, m, H_8); 1.22 (1H, m, H_7); 0.52 (3H, d, J = 7.0 Hz, H_{19}); 0.41 (3H, d, J = 7.0 Hz, H_{20}).

^{13}C NMR + DEPT (100 MHz, C_6D_6): δ 175.8 (**C**, C_{17}); 154.3 (**C**, C_{16}); 139.1 (**CH**, C_{10}); 138.3 (**CH**, C_{12}); 132.0 (**CH**, C_{11}); 129.2 (**CH**, C_2); 126.9 (**CH**, C_3); 115.7 (**CH_2**, C_{13}); 63.4 (**CH_2**, C_{15}); 58.8 (**CH**, C_{14}); 49.6 (**CH**, C_1); 47.2 (**CH**, C_9); 45.8 (**CH**, C_6); 45.0 (**CH**, C_5); 31.8 (**CH_2**, C_4); 31.1 (**CH_2**, C_8); 29.2 (**CH_2**, C_7); 28.1 (**CH**, C_{18}); 18.1 (**CH_3**, C_{19}); 15.2 (**CH_3**, C_{20}).

CIMS: *m/z* (%) 330 ($(M+H)^+$, 100), 201 (20).

HRMS (ES) for $C_{20}H_{27}NO_3Na$ $(M+Na)^+$ calcd 352.1883 found 352.1890.

Partial data for the minor isomer 131c:

Mw 329 ($C_{20}H_{27}NO_3$).

R_f 0.76 (neat CH_2Cl_2).

IR (film): 3017 (w), 2961 (w), 2872 (w), 1777 (s), 1697 (m), 1649 (w), 1602 (w), 1384 (m), 1351 (m), 1201 (m) cm^{-1}.

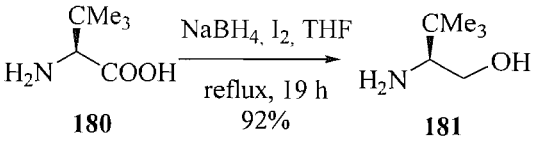
^1H NMR (400 MHz, C_6D_6): δ 6.36 (1H, dt, J = 17.1, 10.6 Hz, H_{12}); 6.09 (1H, dd, J = 15.0, 10.5 Hz, H_{11}); 5.87 (1H, d, J = 10.0 Hz, H_2); 5.08 (1H, d, J = 17.1 Hz, $H_{13trans}$); 4.91 (1H, d, J = 10.0 Hz, H_{13cis}); 4.27 (1H, td, J = 9.0, 6.5 Hz, H_5).

^{13}C NMR + DEPT (100 MHz, C_6D_6): δ 175.9 (**C**, C_{17}); 153.1 (**C**, C_{16}); 138.8 (**CH**, C_{10}); 138.3 (**CH**, C_{12}); 131.7 (**CH**, C_{11}); 128.9 (**CH**, C_2); 126.8 (**CH**, C_3); 115.7 (**CH_2**, C_{13}); 63.4 (**CH_2**, C_{15}); 58.9 (**CH**, C_{14}); 48.0 (**CH**, C_1); 45.2 (**CH**, C_9); 43.2 (**CH**, C_6); 43.2 (**CH**, C_5); 31.5 (**CH_2**, C_4); 31.3 (**CH_2**, C_8); 28.8 (**CH_2**, C_7); 28.1 (**CH**, C_{18}); 18.1 (**CH_3**, C_{19}); 15.2 (**CH_3**, C_{20}).

CIMS: *m/z* (%) 330 ($(M+H)^+$, 100), 201 (20).

HRMS (ES) for $C_{20}H_{27}NO_3Na$ $(M+Na)^+$ calcd 352.1883 found 352.1890.

(*S*)-*tert*-leucinol (181)



180 **181**

To a solution of $NaBH_4$ (1.7 g, 45.7 mmol) in THF (50 mL) was added (*S*)-*tert*-leucine **180** (2.5 g, 19.1 mmol) in one portion. The solution was cooled at 0 °C and a solution of I_2 (4.8 g, 19.1 mmol) in THF (6 mL) was added dropwise. The reaction mixture was stirred at room temperature until getting a white solution. The solution was then refluxed for 19 h. The cloudy white solution was cooled down to room temperature and the reaction was quenched with MeOH until all of the white solid had dissolved. The solution was concentrated and dissolved in 20% (w/w) aqueous KOH and stirred for 6 h at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to afford **181** as a colourless oil (2.1 g, 92%) which solidified upon cooling at room temperature.

Mw 117 ($C_6H_{15}NO$).

Bp 100-105 °C at 3 mbar, lit.[147] 70-73 °C at 2 mmHg.

$[\alpha]_D$: +36.6° (*c* 1.3, EtOH, 24 °C), lit.[147] +36.5° (*c* 1.2, EtOH, 25 °C).

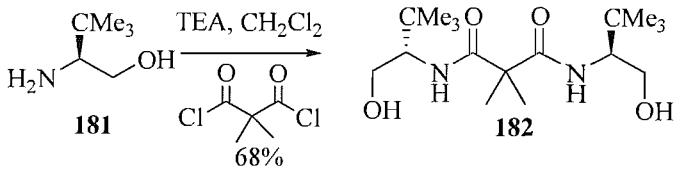
IR (film): 3285 (m, OH), 2954 (m), 2870 (m), 1590 (m), 1475 (m), 1364 (m), 1043 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (1H, dd, J = 13.8, 5.3 Hz, **C$\underline{H}_\alpha$H$_\beta$**-OH); 3.20 (1H, t, J = 13.6 Hz, **C$\underline{H}$**-CH_2-OH); 2.50 (1H, dd, J = 13.6, 5.3 Hz, **CH$_\alpha$$\underline{H}_\beta$**-OH); 1.79 (3H, br s, **N$\underline{H}_2$** and **O$\underline{H}$**); 0.90 (9H, s, C-**C$\underline{H}_3$**).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 62.3 (**CH_2**-OH); 61.8 (**CH**-NH_2); 33.2 (**C**-CH_3); 26.2 (C- **CH_3**).

The analytical data corresponded to the reported data.[147]

(*S*)-*N*,*N*-bis[1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-dimethyl-1,3-propanediamide (182)



To a solution of (*S*)-*tert*-leucinol **181** (2.0 g, 17.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added TEA (11.9 mL, 85.5 mmol) and a solution of dimethylmalonyl dichloride (1.4 g, 8.5 mmol) in CH_2Cl_2 (7 mL). The reaction was stirred for 35 min at room temperature and CH_2Cl_2 (50 mL) was added. The reaction was quenched with 1 N aqueous HCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (1 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (1 × 15 mL). The aqueous layer was back-extracted with CH_2Cl_2 (1 × 15 mL). The combined organic phases were washed with brine (1 × 15 mL). The aqueous layer was back-extracted with CH_2Cl_2 (1 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give a white solid which was recrystallized from ethyl acetate to afford **182** as a white solid (1.9 g, 68%).

Mw 330 ($C_{17}H_{34}N_2O_4$).

Mp 158 °C, lit.[147] 163 °C.

$[\alpha]_D$: +3.2° (*c* 0.9, MeOH, 23 °C), lit.[147] + 2.5° (*c* 2.5, MeOH, 25 °C).

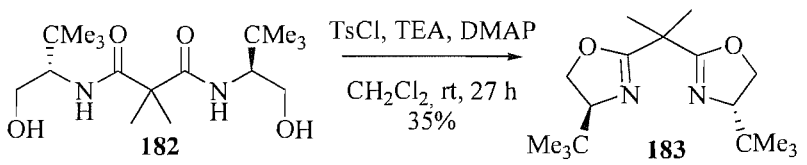
IR (film): 3347 (m), 2967 (m), 2910 (w), 1645 (s), 1537 (m), 1520 (m), 1050 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (2H, br d, J = 11.8 Hz, **NH**); 3.87 (4H, m, **CH$_2$**-OH); 3.46 (2H, m, **CH**-tBu); 2.45 (2H, br s, **OH**); 1.52 (6H, s, **CH$_3$**-C); 0.94 (18H, s, tBu).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 174.7 (**C**=O); 62.6 (**CH$_2$**-OH); 60.0 (**CH**-tBu); 33.4 (**C**-C=O); 26.8 (**CH$_3$** of tBu); 24.0 (**C**-tBu); 23.7 (**CH$_3$**).

The analytical data corresponded to the reported data.[147]

2,2-bis[2-[4-(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [(*S*,*S*)-*tert*-butyl bis(oxazoline)] (183)



To a solution of diol **182** (1 g, 3.0 mmol) and DMAP (36 mg, 0.3 mmol) in CH_2Cl_2 (12 mL) was added TEA (1.8 mL, 13.2 mmol). The flask was placed in a room temperature water bath and a solution of *p*-toluenesulfonyl chloride (1.1 g, 6.0 mmol) in CH_2Cl_2 (2 mL) was added. The bright yellow solution was stirred for 27 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous NH_4Cl (1 × 10 mL). Water (10 mL) was added, the layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and the aqueous layer was back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After removing the solvent *in vacuo*, the obtained white solid was triturated with hot pentane followed by hot gravity filtration. The colourless extracts were concentrated *in vacuo* to give **183** as white solid (306 mg, 35 %).

Mw 294 ($C_{17}H_{30}N_2O_2$).

Mp 82 °C, lit.[147] 89 °C.

$[\alpha]_D$: -112.8° (*c* 1.1, CH_2Cl_2, 24 °C), lit.[147] + 113.2° (*c* 1.2, CH_2Cl_2, 25 °C).

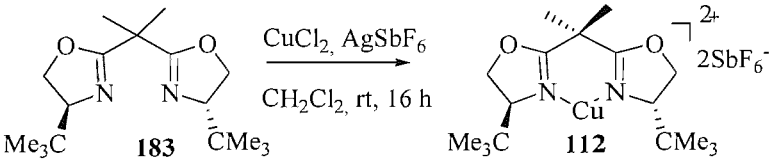
IR (film): 2951 (w), 2901 (w), 2869 (w), 1657 (m), 1145 (m), 1123 (m), 973 (m), 924 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14 (2H, dd, *J* = 10.1, 8.8 Hz, **CHH**); 4.07 (2H, dd, *J* = 8.6, 6.9 Hz, **CHH**); 3.83 (2H, dd, *J* = 10.1, 7.0 Hz, **CH**-tBu); 1.51 (6H, s, **CH_3**-C-C=O); 0.87 (18H, s, **CH_3**-C-CH).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 168.6 (**C**=N); 75.3 (**CH**-tBu); 68.9 (**CH_2**-O); 38.6 (**C**-C=N); 33.9 (**C**, tBu); 25.6 (**CH_3**, tBu); 24.4 (C-**CH_3**).

The analytical data corresponded to the reported data.[147]

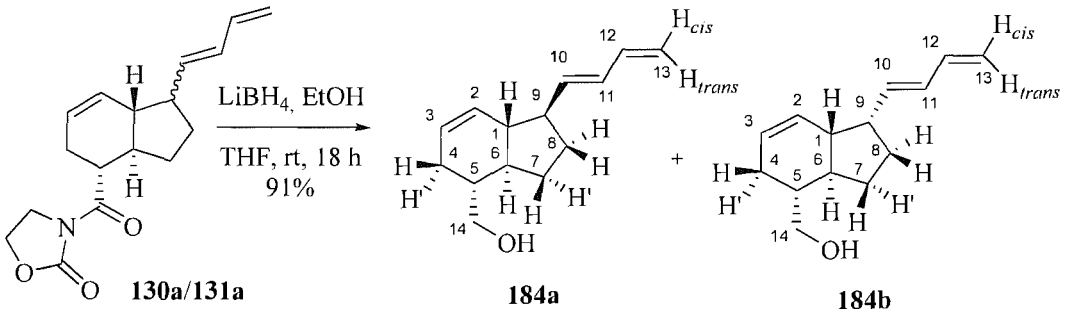
[Cu(*S*,*S*)-bis(*tert*-butyloxazoline)](SbF$_6$)$_2$ (112)



A flame dried flask was charged with [(*S*,*S*)-*tert*-butyl bis(oxazoline)] **183** (65 mg, 0.22 mmol), $AgSbF_6$ (137 mg, 0.40 mmol) and $CuCl_2$ (27 mg, 0.20 mmol) in an inert atmosphere (N_2) glove box. The flask was brought out of the glove box and CH_2Cl_2 (4 mL) was added. The reaction was stirred for 14 h in the dark to give a blue solution with a white solid. The mixture was filtered in air through oven dried Celite, washed through with CH_2Cl_2 (10 mL). The resulting blue solution was employed as a stock solution (0.014 M) for the Diels-Alder reactions.

The only analytical datum reported in the literature are the X-ray crystallography.[142,147]

[(1*S**,5*S**,6*S**,9*R**)-bicyclo[4.3.0]non-2'-ene-5'-methanol-9'-buta-1,3-diene] (184a)



To a solution of mixture of **130a/131a** (37 mg, 0.13 mmol) in THF (7.8 mL) was added absolute EtOH (7.8 µL, 0.13 mmol). The reaction mixture was cooled down to 0 °C and $LiBH_4$ (2 M in THF, 71 µL, 0.14 mmol) was added dropwise. The solution was stirred for 18 h at room temperature. The reaction was quenched with 1 M aqueous NaOH solution, stirred until both layers were clear and were poured into Et_2O (5 mL) and water (5 mL). The organic phase was washed with brine (3 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 50:50) to afford **184** as a white solid (24 mg, 91%).

Data for the major isomer 184a:

Mw 204 ($C_{14}H_{20}O$).

R_f 0.43 (hexane/AcOEt 50:50).

Mp 44 °C

IR (film): 3330 (m), 3013 (m), 2936 (m), 2903 (m), 2864 (m), 1648 (w) and 1602 (w), 1000 (s) cm^{-1}.

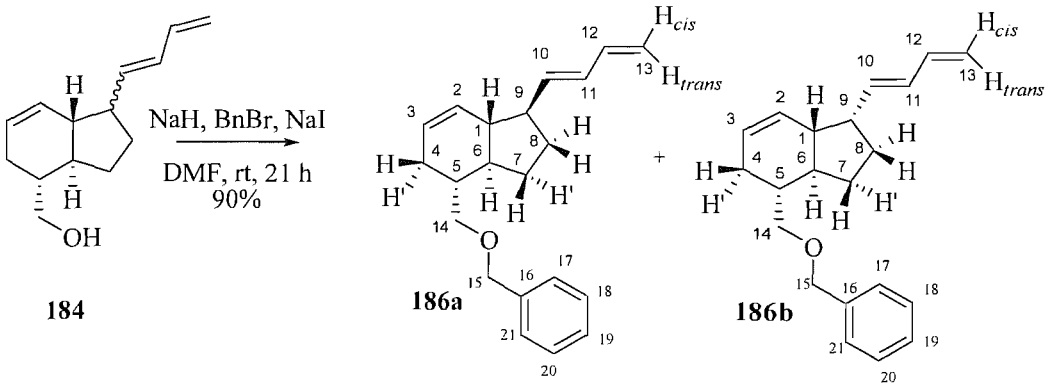
^{1}H NMR (400 MHz, C_6D_6): δ 6.34 (1H, dt, J = 17.1, 10.0 Hz, H_{12}); 6.08 (1H, dd, J = 15.0, 10.6 Hz, H_{11}); 5.84 (1H, d, J = 9.6 Hz, H_2); 5.60 (1H, m, H_3); 5.50 (1H, dd, J = 15.0, 8.5 Hz, H_{10}); 5.08 (1H, d, J = 17.0 Hz, $H_{13trans}$); 4.94 (1H, d, J = 10.0 Hz, H_{13cis}); 3.36 (1H, dd, J = 10.0, 4.0 Hz, H_{14}); 3.21 (1H, dd, J = 10.0, 6.0 Hz, H_{14}); 2.15 (1H, m, H_4); 1.99 (1H, m, H_9); 1.84-1.77 (2H, m, H_8, H_4); 1.65-1.59 (2H, m, H_1, H_7); 1.53 (1H, m, H_5); 1.39 (1H, m, H_8); 1.22 (1H, m, H_6); 1.11 (1H, m, H_7).

^{13}C NMR + DEPT (100 MHz, C_6D_6): δ 139.5 (**CH**, C_{10}); 138.2 (**CH**, C_{12}); 131.8 (**CH**, C_{11}); 128.8 (**CH**, C_2); 128.3 (**CH**, C_3); 115.6 (**CH_2**, C_{13}); 67.0 (**CH_2**, C_{14}); 51.3 (**CH**, C_1); 47.5 (**CH**, C_9); 46.7 (**CH**, C_6); 43.0 (**CH**, C_5); 31.4 (**CH_2**, C_4); 31.3 (**CH_2**, C_8); 28.0 (**CH_2**, C_7).

CIMS: *m/z* (%) 205 ($(M+H)^+$, 100), 187 (35), 171 (39).

HRMS (EI) for $C_{14}H_{20}O$ $(M)^+$ calcd 204.1514 found 204.1510.

[(1*S**,5*S**,6*S**,9*R**)-bicyclo[4.3.0]non-2'-ene-5'-benzyloxymethyl-9'-buta-1,3-diene] (186a)



To a suspension of NaH (60% dispersion in mineral oil, 15 mg, 0.38 mmol) in DMF (2 mL) at 0 °C was added a solution of alcohol **184** (65 mg, 0.32 mmol) in DMF (1.5 mL). After 30 min at this temperature, BnBr (45 μL, 0.38 mmol) and NaI (57 mg, 0.38 mmol) were added. The reaction was stirred for 21 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (4 mL). The aqueous layers were extracted with Et_2O (3 × 4 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_4$ (1 × 8 mL), brine (1 × 8 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford **186** as a pale yellow oil (79 g, 90%) along with some starting material **184** (3 mg, 5%).

Data for the major isomer 186a:

Mw 294 ($C_{21}H_{26}O$).

R_f 0.69 (hexane/AcOEt 80:20).

IR (film): 3082 (w), 3014 (w), 2940 (m), 2884 (m), 1648 (w), 1602 (w), 1095 (s), 1000 (s) cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ 7.24 (2H, d, J = 7.5 Hz, H_{17}, H_{21}); 7.16-7.10 (2H, m, H_{18}, H_{20}); 7.06 (1H, t, J = 6.8 Hz, H_{19}); 6.32 (1H, dt, J = 17.1, 10.0 Hz, H_{12}); 6.03 (1H, dd, J = 15.0, 10.5 Hz, H_{11}); 5.81 (1H, d, J = 9.5 Hz, H_2); 5.58 (1H, m, H_3); 5.45 (1H, dd, J = 15.1, 8.6 Hz, H_{10}); 5.06 (1H, d, J = 17.1 Hz, $H_{13trans}$); 4.90 (1H, d, J = 10.5 Hz, H_{13cis}); 4.30 (1H, d, J = 12.0 Hz, H_{15}); 4.25 (1H, d, J = 12.0 Hz, H_{15}); 3.26 (1H, dd, J = 9.0, 4.5 Hz, H_{14}); 3.21 (1H, dd, J = 9.0, 6.5 Hz, H_{14}); 2.24 (1H, m, H_4); 2.04-1.84 (2H, m, H_9, H_4); 1.81-1.71 (2H, m, H_8, H_5); 1.68-1.58 (2H, m, H_1, H_7); 1.45-1.24 (2H, m, H_8, H_6); 1.09 (1H, m, H_7).

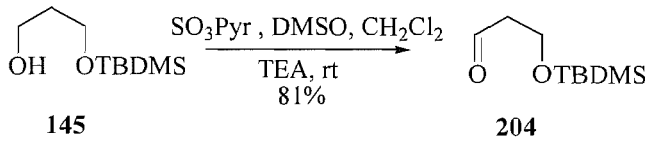
^{13}C NMR + DEPT (100 MHz, C_6D_6): δ 140.1 (**C**, C_{16}); 139.6 (**CH**, C_{10}); 138.3 (**CH**, C_{12}); 131.8 (**CH**, C_{11}); 129.1 (**CH**, C_{18}, C_{20}); 128.8 (**CH**, C_2); 128.4 (**CH**, C_3); 128.2 (**CH**, C_{17}, C_{21}); 128.2 (**CH**, C_{19}); ; 115.6 (**CH_2**, C_{13}); 75.0 (**CH_2**, C_{15}); 74.9 (**CH_2**, C_{14}); 51.4 (**CH**, C_1); 47.6 (**CH**, C_9); 47.2 (**CH**, C_6); 41.1 (**CH**, C_5); 31.9 (**CH_2**, C_4); 31.5 (**CH_2**, C_8); 28.2 (**CH_2**, C_7).

CIMS: *m/z* (%) 295 ($(M+H)^+$, 10), 312 (12), 187 (19), 106 (100), 91 (44).

HRMS (EI) for $C_{21}H_{26}O$ $(M)^+$ calcd 294.1984 found 294.1983.

6.4 *Toward the synthesis of CD-ring precursor*

3-*tert*-butyldimethylsiloxy-propanal (204)



145 **204**

To a suspension of SO_3-pyridine (50.2 g, 315.6 mmol) in CH_2Cl_2 (100 mL) and DMSO (100 mL) was added TEA (95.3 mL, 683.8 mmol). This solution was immediately added dropwise by cannula to a stirred solution of alcohol **145** (20.0 g, 105.2 mmol) in CH_2Cl_2 (100 mL) and DMSO (75 mL) at room temperature. After 18 h at room temperature, the solution was poured in saturated aqueous NH_4Cl (500 ml). After the phase separation, the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with water (2 × 100 mL), brine (1 × 100 mL) and dried over anhydrous $MgSO_4$. After removing the solvent under reduce pressure, the residue was purified by column chromatography (hexane/AcOEt 80:20) to afford the aldehyde **204** as a yellow oil (16.1 g, 81%).

Mw 188 ($C_9H_{20}O_2Si$).

R_f 0.38 (hexane/AcOEt 90:10).

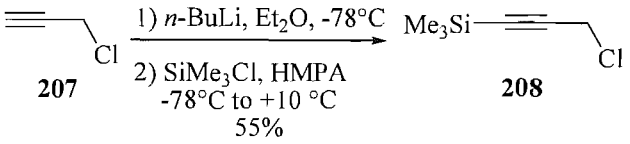
IR (film): 2945 (s), 2860 (s), 2723 (w), 1720 (m), 1247 (s), 1091 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (1H, t, J = 2.1 Hz, **CHO**); 3.98 (2H, t, J = 6.1 Hz, **CH_2**-OTBDMS); 2.59 (2H, dt, J = 6.1, 2.2 Hz, **CH_2**-CH_2-OTBDMS); 0.87 (9H, s, **CH_3**-C); 0.06 (6H, s, **CH_3**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 202.1 (**C**=O); 57.3 (**CH_2**-OTBDMS); 46.5 (**CH_2**-CH_2-OTBDMS); 25.8 (**CH_3**, tBu); 18.2 (**C**, tBu); -5.5 (**CH_3**-Si).

The analytical data corresponded to the reported data.[181]

3-chloro-1-trimethylsilyl-propyne (208)



207 **208**

To a solution of propargyl chloride **207** (1.5 mL, 20.7 mmol) in Et_2O (20 mL) at -78°C was added dropwise *n*-BuLi (8.3 mL of 2.5 M solution in hexane, 20.7 mmol). Then freshly distilled chlorotrimethylsilane (2.6 mL, 20.7 mmol) was added over few minutes. Subsequently, a solution of HMPA/THF (2 mL/1 mL) was added. The solution was warmed up to 10°C over 1 h. The orange solution was carefully quenched with cold water (20 mL). After the phase separation, the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic phase were washed with water (3 × 50 mL) and dried over anhydrous $MgSO_4$. After removing the solvent by distillation at atmospheric pressure, the crude oil was purified by Kugelrohr distillation (20 °C, 8 mbar) to afford **208** as a colourless oil (1.7 g, 55%).

Mw 146 ($C_6H_{11}ClSi$).

R_f not detectable by TLC.

Bp 20 °C at 20 mbar, lit.[186] 134 °C-136 °C.

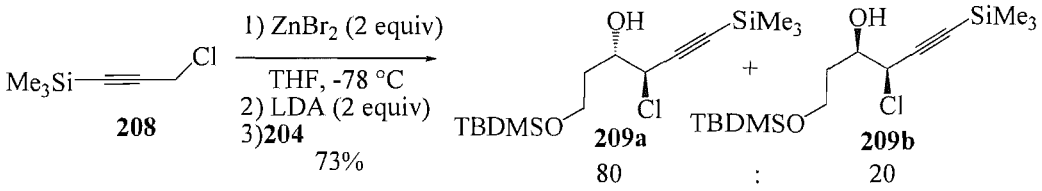
IR (film): 2950 (s), 2903 (s), 2184 (s), 1252 (s), 1030 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13 (2H, s, **C$\underline{H_2}$**-Cl); 0.18 (9H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 99.6 (**C**≡C-Si); 91.7 (C≡**C**-Si); 30.7 (**CH_2**-Cl); -0.4 (**CH_3**-Si).

The analytical data corresponded to the reported data.[186]

(3*S,4*S**)-3-chloro-6-*tert*-butyldimethylsilyloxy-1-trimethylsilyl-hex-1-yn-4-ol (209a)**



To a solution of $ZnBr_2$ (18.8 g, 83.4 mmol) in THF (90 mL) at -20 °C was added 3-chloro-1-trimethylsilyl-propyne **208** (6.2 g, 41.7 mmol). The reaction mixture was cooled down to -78 °C and LDA (55.5 mL of 1.5 M solution in THF, 83.4 mmol) was added dropwise. The yellow reaction mixture was stirred for 1 h at -78 °C, and the aldehyde **204** (7.8 g, 41.7 mmol) was added in one portion. The reaction mixture was stirred for 1 h at -78 °C and was then allowed to warm up to -20 °C over 1 h. The reaction was quenched with 22.5 mL of a mixture 2:1 of saturated aqueous NH_4Cl solution and 35% aqueous NH_3. After warming up to room temperature, the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL), brine (1 × 100 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness under reduce pressure. The residue was purified by column chromatography (hexane/AcOEt 90:10) to afford the chlorohydrin **209a/209b** as a yellow oil (10.3 g, 73%) as a 80:20 *trans/cis* ratio.

Data for the major isomer 209a:

Mw 334 ($C_{15}H_{31}ClO_2Si_2$).

R_f 0.29 (hexane/AcOEt 90:10).

IR (film): 3461 (m), 2950 (s), 2855 (s), 2179 (w), 1247 (s), 1096 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.64 (1H, d, J = 3.9 Hz, **CH**-Cl); 4.01 (1H, m, **CH**-OH); 3.93-3.80 (2H, m, **CH_2**-OTBDMS); 3.35 (1H, s br, CH-**OH**); 2.00-1.78 (2H, m, **CH_2**-CH_2-OTBDMS); 0.91 (9H, s, **CH_3**-C); 0.19 (9H, s, **CH_3**-Si of TMS); 0.09 (6H, s, **CH_3**-Si of TBDMS).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 100.0 (Si-C≡**C**); 93.3 (Si-**C**≡C); 73.5 (**CH**-OH); 61.1 (**CH_2**-OTBDMS); 53.9 (**CH**-Cl); 34.4 (**CH_2**-CH_2-OTBDMS); 25.8 (**CH_3**, tBu); 18.1 (**C**, tBu); -0.3 (**CH_3**-Si of TMS); -5.5 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 335 ($(M+H)^+$, 2), 299 (2), 283 (18), 225 (38), 73 (100).

HRMS (EI) for $C_{15}H_{31}O_2Si_2$ $(M-Cl)^+$ calcd 299.1863 found 299.1857.

Data for the minor isomer 209b:

Mw 334 ($C_{15}H_{31}ClO_2Si_2$).

R_f 0.29 (hexane/AcOEt 90:10).

IR (film): 3461 (m), 2950 (s), 2855 (s), 2179 (w), 1247 (s), 1096 (s) cm^{-1}.

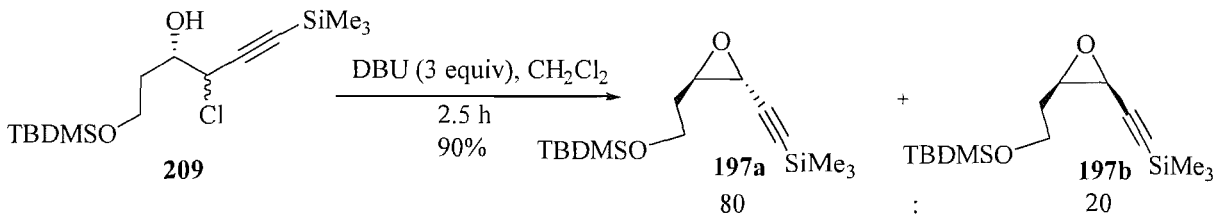
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51 (1H, d, J = 6.4 Hz, C**H**-Cl); 4.01 (1H, m, C**H**-OH); 3.93-3.80 (2H, m, C**H$_2$**-OTBDMS); 3.57 (1H, s br, CH-O**H**); 2.00-1.78 (2H, m, C**H$_2$**-CH_2-OTBDMS); 0.91 (9H, s, C**H$_3$**-C); 0.19 (9H, s, C**H$_3$**-Si of TMS); 0.09 (6H, s, C**H$_3$**-Si of TBDMS).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 100.0 (Si-C≡**C**); 93.3 (Si-**C**≡C); 74.1 (**CH**-OH); 73.5 61.1 (**CH$_2$**-OTBDMS); 53.7 (**CH**-Cl); 34.4 (**CH$_2$**-CH_2-OTBDMS); 25.8 (**CH$_3$**, tBu); 18.1 (**C**, tBu); -0.3 (**CH$_3$**-Si of TMS); -5.5 (**CH$_3$**-Si of TBDMS).

CIMS: *m/z* (%) 335 ($(M+H)^+$, 2), 299 (2), 283 (18), 225 (38), 73 (100).

HRMS (EI) for $C_{15}H_{31}O_2Si_2$ $(M-Cl)^+$ calcd 299.1863 found 299.1857.

(3*R,4*R**)-1-trimethylsilyl-3,4-epoxy-6-*tert*-butyldimethylsilyloxy-hex-1-yne (197a)**



To a solution of chlorohydrin **209** (5.0 g, 14.9 mmol) in CH_2Cl_2 (80 mL) was added DBU (6.7 mL, 44.7 mmol). The reaction mixture was stirred for 2.5 h at room temperature. Then, CH_2Cl_2 (100 mL) was added and the reaction was quenched with 1 M aqueous HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer were washed with brine (3 × 100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduce pressure until dryness and the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford the epoxide **197a/197b** as a yellow oil (3.8 g, 90%) as a 80:20 *trans/cis* ratio.

Data for the major isomer 197a:

Mw 298 ($C_{15}H_{30}O_2Si_2$).

R_f 0.37 (hexane/AcOEt 90:10).

IR (film): 2950 (s), 2855 (s), 2174 (m), 1247 (s), 1096 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (2H, t, *J* = 5.9 Hz, CH-C**H**$_2$); 3.19 (1H, td, *J* = 5.7, 2.2 Hz, C**H**-C≡C); 3.14 (1H, d, *J* = 2.2 Hz, C**H**-CH_2); 1.73 (2H, q, *J* = 5.9 Hz, C**H**$_2$-OTBDMS); 0.90 (9H, s, C**H**$_3$-C); 0.17 (9H, s, C**H**$_3$-Si of TMS); 0.07 (6H, s, C**H**$_3$-Si of TBDMS).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 101.9 (Si-C≡**C**); 89.2 (Si-**C**≡C); 59.4 (**CH_2**-OTBDMS); 58.6 (**CH**-CH_2); 45.6 (**CH**-C≡C); 35.0 (**CH_2**-CH); 25.8 (**CH_3**, tBu); 18.2 (**C**, tBu); -0.4 (**CH_3**-Si of TMS); -5.5 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 299 ($(M+H)^+$, 12), 283 (38), 242 (18), 225 (94), (26), 147 (84), 73 (100).

HRMS (EI) for $C_{14}H_{27}O_2Si_2$ $(M-Me)^+$ calcd 283.1550 found 283.1552.

Data for the major isomer 197b:

Mw 298 ($C_{15}H_{30}O_2Si_2$).

R_f 0.37 (hexane/AcOEt 90:10).

IR (film): 2950 (s), 2855 (s), 2174 (m), 1247 (s), 1096 (s) cm^{-1}.

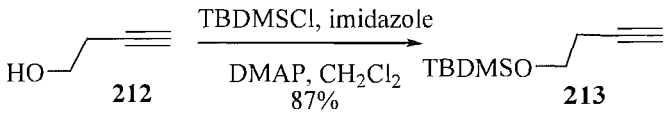
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (2H, dd, J = 6.6, 5.5 Hz, CH-**C**$\underline{\mathbf{H}}_2$); 3.43 (1H, d, J = 4.0 Hz, **C**$\underline{\mathbf{H}}$-CH_2); 1.88 (1H, m, **C**$\underline{\mathbf{H}}$-C≡C); 1.73 (2H, q, J = 5.9 Hz, $\underline{\mathbf{CH_2}}$-OTBDMS); 0.90 (9H, s, **C**$\underline{\mathbf{H}}_3$-C); 0.17 (9H, s, **C**$\underline{\mathbf{H}}_3$-Si of TMS); 0.07 (6H, s, **C**$\underline{\mathbf{H}}_3$-Si of TBDMS).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 100.3 (Si-C≡**C**); 91.2 (Si-**C**≡C); 59.9 (**CH_2**-OTBDMS); 55.9 (**CH**-CH_2); 45.2 (**CH**-C≡C); 32.6 (**CH_2**-CH); 25.8 (**CH_3**, tBu); 18.2 (**C**, tBu); -0.4 (**CH_3**-Si of TMS); -5.5 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 299 ($(M+H)^+$, 12), 283 (38), 242 (18), 225 (94), (26), 147 (84), 73 (100).

HRMS (EI) for $C_{14}H_{27}O_2Si_2$ $(M-Me)^+$ calcd 283.1550 found 283.1552.

4-*tert*-butyldimethylsilyloxy-but-1-yne (213)



To a solution of 3-butyn-1-ol **212** (10 g, 142.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added in one portion imidazole (10.7 g, 156.4 mmol). Then, *tert*-butyldimethylsilyl chloride (23.6 g, 156.6 mmol) in CH_2Cl_2 (50 mL) and DMAP (165 mg, 1.35 mmol) were added. The solution was stirred for 1 h at 0 °C and 18 h at room temperature. The reaction mixture was diluted with a 4:1 mixture of Et_2O/hexane (200 mL). The solution was filtered through a pad of Celite eluted with a 4:1 mixture Et_2O/hexane. The solvent was removed under reduce pressure until dryness and the residue was purified by Kugelrohr distillation (64 °C, 19 mbar) to afford **213** as a colourless oil (22.8 g, 87%).

Mw 184 ($C_{10}H_{20}OSi$).

R_f 0.37 (hexane/AcOEt 90:10).

Bp 64 °C at 19 mbar, lit.[187] 80-83 °C at 25 mmHg.

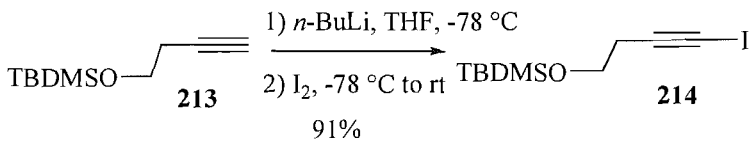
IR (film): 3315 (m), 2926 (s), 2855 (s), 2113 (w), 1474 (m), 1261 (s), 1100 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (2H, t, J = 7.2 Hz, **C**$\underline{\mathbf{H}}_2$-OTBDMS); 2.41 (2H, td, J = 7.2, 2.6 Hz, **C**$\underline{\mathbf{H}}_2$-C≡C); 1.91 (1H, t, J = 2.6 Hz, C≡**C**$\underline{\mathbf{H}}$); 0.90 (9H, s, **C**$\underline{\mathbf{H}}_3$-C); 0.08 (6H, s, **C**$\underline{\mathbf{H}}_3$-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 81.5 (**C**≡CH); 69.3 (C≡**CH**); 61.7 (**CH_2**-OTBDMS); 25.9 (**CH_3**-C); 22.8 (**CH_2**-CH_2-OTBDMS); 18.3 (CH_3-**C**); -5.3 (**CH_3**-Si).

The analytical data corresponded to the reported data.[188]

4-*tert*-butyldimethylsilyloxy-1-iodobut-1-yne (214)



91%

To a solution of **213** (18.0 g, 97.7 mmol) in THF (100 mL) at -78 °C was added *n*-BuLi (43 mL of 2.5 M solution in hexane, 107.4 mmol). The solution was stirred for 1 h at -78 °C. A solution of I_2 (27.3 g, 107.4 mmol) in THF (50 mL) was transferred by cannula to the reaction mixture over a period of 45 min to get a brown solution. The reaction mixture was stirred for 18 h at room temperature and was then diluted with Et_2O (100 mL). The reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 × 80 mL), saturated aqueous $Na_2S_2O_3$ (3 × 80 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the yellow residue was purified by Kugelrohr distillation (120 °C, 20 mbar) to obtain **214** as a yellow oil (27.5 g, 91%).

Mw 310 ($C_{10}H_{19}IOSi$).

R_f 0.83 (hexane/AcOEt 90:10).

Bp 120 °C at 20 mbar.

IR (film): 2940 (m), 2850 (m), 2368 (w), 1100 (s) cm^{-1}.

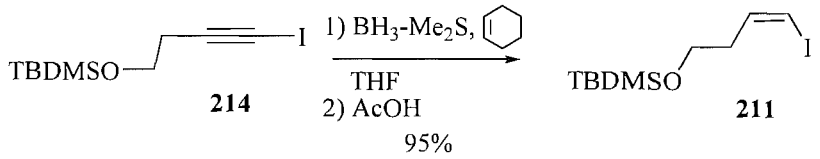
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (2H, t, J = 7.0 Hz, **C$\underline{H_2}$**-OTBDMS); 2.58 (2H, t, J = 7.0 Hz, **C$\underline{H_2}$**-C≡C); 0.90 (9H, s, **C$\underline{H_3}$**-C); 0.08 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 91.7 (**C**≡C-I); 61.7 (**CH_2**-OTBDMS); 25.9 (**CH_3**-C); 25.1 (**CH_2**-CH_2-OTBDMS); 18.3 (CH_3-**C**); -5.3 (**CH_3**-Si); -5.5 (C≡**C**-I).

CIMS: *m/z* (%): 311 ($(M+H)^+$, 82), 295 (4), 253 (26), 185 (34), 165 (24), 57 (100).

HRMS (EI) for $C_9H_{16}IOSi$ $(M-Me)^+$ calcd 295.0015 found 295.0011.

(1*Z*)-4-*tert*-butyldimethylsilyloxy-1-iodobut-1-ene (211)



To a solution of BH_3-Me_2S complex (17.7 mL of 2 M solution in THF, 35.4 mmol) in THF (50 mL) at 0 °C was added dropwise cyclohexene (7.8 mL, 77.3 mmol). The white suspension was stirred for 50 min at room temperature. The suspension was cooled at 0 °C and the iodo-alkyne **214** (10 g, 32.2 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C and an additional 1 h at room temperature. The yellow solution was cooled down to 0 °C and glacial AcOH (36.9 mL, 644.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h followed by addition of Et_2O (50 mL). The organic phase was washed with water (3 × 100 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the yellow residue was purified by column chromatography (hexane/CH_2Cl_2 10:1) to give **211** as pale yellow oil (9.6 g, 95%).

Mw 312 ($C_{10}H_{21}IOSi$).

R_f 0.50 (hexane/CH_2Cl_2 10:1).

Bp 164 °C at 11 mbar.

IR (film): 3073 (w), 2931 (s), 2850 (s), 1692 (m), 1602 (m), 1105 (s) cm^{-1}.

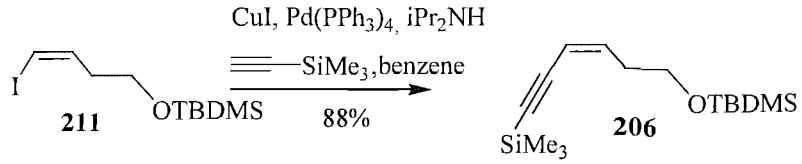
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32-6.24 (2H, m, **CH=CH**); 3.69 (2H, t, J = 6.5 Hz, **CH_2**-OTBDMS); 2.40-2.34 (2H, m, **CH_2**-C=C); 0.90 (9H, s, **CH_3**-C); 0.07 (6H, s, **CH_3**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 138.3 (CH=**CH**-I); 83.7 (**CH**=CH-I); 61.2 (**CH_2**-OTBDMS); 38.3 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.4 (CH_3-**C**); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 313 ($(M+H)^+$, 96), 272 (50), 181 (38), 75 (34), 57 (100).

HRMS (EI) for $C_9H_{18}IOSi$ $(M-Me)^+$ calcd 297.0172 found 297.0167.

(1*Z*)-6-*tert*-butyldimethylsilyloxy-1-trimethylsilyl-hex-3-en-1-yne (206)



To a solution of (*Z*)-iodo-alkene **211** (6.9 g, 22.1 mmol) in benzene (80 mL) was added trimethylsilylacetylene (3.1 mL, 22.1 mmol). Then, $Pd(PPh_3)_4$ (1.0 g, 0.9 mmol), CuI (664 mg, 3.5 mmol) and iPr_2NH (9.30 mL, 66.3 mmol) were successively added. The reaction mixture was stirred at room temperature for 1.5 h. The dark green solution was diluted with hexane (80 mL). The organic phase was washed with water (3 × 80 mL), brine (2 × 80 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the brown residue was purified by column chromatography (hexane/CH_2Cl_2 10:1) to give the enyne **206** as a bright yellow oil (5.5g, 88%).

Mw 282 ($C_{15}H_{30}OSi_2$).

R_f 0.65 (hexane/AcOEt 90:10).

IR (film): 2959 (s), 2850 (s), 2150 (m), 1578 (w), 1474 (m), 1252 (s), 1100 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01 (1H, dt, *J* = 11.0, 7.4 Hz, CH_2-**C<u>H</u>**=CH); 5.56 (1H, dt, *J* = 10.9, 1.3 Hz, CH_2-CH=**C<u>H</u>**); 3.69 (2H, t, *J* = 6.7 Hz, **C<u>H</u>$_2$**-OTBDMS); 2.55 (2H, dq, *J* = 6.8, 1.5 Hz, **C<u>H</u>$_2$**-C=C); 0.90 (9H, s, **C<u>H</u>$_3$**-C); 0.20 (9H, s, **C<u>H</u>$_3$**-Si); 0.07 (6H, s, **C<u>H</u>$_3$**-Si).

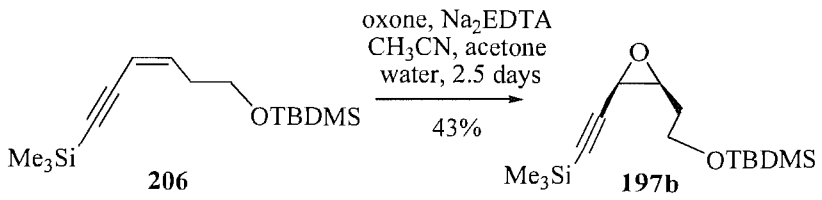
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 141.6 (CH_2-**CH**=CH); 110.6 (CH_2-CH=**CH**); 101.9 (**C**≡C-Si); 98.8 (C≡**C**-Si); 62.0 (**CH_2**-OTBDMS); 34.1 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.3 (CH_3-**C**); 0.0 (**CH_3**-Si of TMS); -5.3 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 283 ($(M+H)^+$, 100), 225 (82), 267 (10), 242 (8), 209 (12), 73 (94).

HRMS (EI) for $C_{14}H_{27}OSi_2$ $(M-Me)^+$ calcd 267.1601 found 267.1602.

(3*R**,4*S**)-1-trimethylsilyl-3,4-epoxy-6-*tert*-butyldimethylsilyloxy-hex-1-yne (197b)

Oxone procedure



To a solution of enyne **206** (500 mg, 1.8 mmol) in CH_3CN (25 mL), acetone (1.3 mL) and Na_2EDTA (15.3 mL of $4.5.10^{-4}$ N solution in water) were added simultaneously by small portions Oxone (5.4 g, 8.8 mmol) and $NaHCO_3$ (2.3 g, 27.6 mmol) in order to keep the pH solution at 7. The reaction mixture was stirred for 2.5 days at room temperature. Then Et_2O (30 mL) was added. After the phase separation, the organic phase was washed with water (1 × 30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (3 × 40 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/Et_2O 15:1) to give **197b** as a pale yellow oil (230 mg, 43%).

Mw 298 ($C_{15}H_{30}O_2Si_2$).

R_f 0.49 (hexane/Et_2O 15:1).

IR (film): 2955 (s), 2846 (m), 2170 (w), 1247(s), 1100 (s) cm^{-1}.

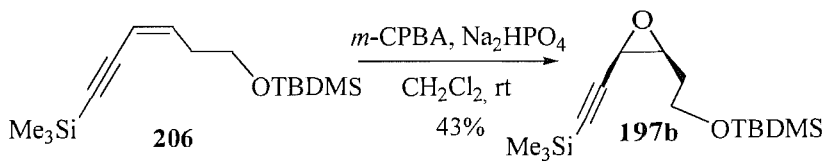
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (2H, dd, J = 6.8, 5.8 Hz, **C$\underline{H}_2$**-OTBDMS); 3.45 (1H, d, J = 4.0 Hz, **C$\underline{H}$**-C≡C); 3.22 (1H, ddd, J = 6.5, 5.1, 4.1 Hz, **C$\underline{H}$**-CH_2); 2.02-1.82 (2H, m, **C$\underline{H}_2$**-CH_2-OTBDMS); 0.90 (9H, s, **C$\underline{H}_3$**-C); 0.18 (9H, s, **C$\underline{H}_3$**-Si); 0.08 (6H, s, **C$\underline{H}_3$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 101.0 (**C**≡C-Si); 89.0 (C≡**C**-Si); 60.0 (**CH_2**-OTBDMS); 56.0 (**CH**-CH_2); 45.2 (**CH**-C≡C); 32.7 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.3 (CH_3-**C**); -0.3 (**CH_3**-Si of TMS); -5.4 (**CH_3**-Si of TBDMS).

CIMS *m/z* (%) 299 ($(M+H)^+$, 38), 283 (66), 242 (10), 225 (42), 90 (100), 73 (96).

HRMS (EI) for $C_{14}H_{27}O_2Si_2$ $(M-Me)^+$ calcd 283.1550 found 283.1558.

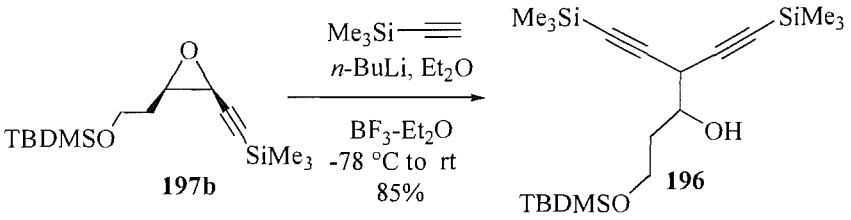
***m*-CPBA procedure**



To a solution of enyne **206** (3.3 g, 11.5 mmol) in CH_2Cl_2 (70 mL) was added Na_2HPO_4 (16.4 g, 115.4 mmol). The reaction mixture was cooled at 0 °C. Then *m*-CPBA (80% purity, 4.8 g, 27.7 mmol) was added by small portions. The solution was stirred for 20 min at 0 °C and 18 h at room temperature. The white suspension was filtrated and the filtrate was washed with 10% aqueous Na_2SO_3 (3 × 80 mL), water (4 × 80 mL), brine (1 × 80 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/Et_2O 15:1) to give **197b** as a pale yellow oil (1.5 g, 43%).

The ^1H and ^{13}C NMR spectra corresponded to the data previously reported.

1-*tert*-butyldimethylsilyloxy-6-trimethylsilyl-4-trimethylsilylethynyl-hex-5-yn-3-ol (196)



To a solution of trimethylsilyl acetylene (1.5 mL, 10.8 mmol) in Et_2O (10 mL) at -78 °C was added *n*-BuLi (4.5 mL of a 2.5 M solution in hexane, 10.8 mmol). The solution was stirred for 15 min at -78 °C. Then BF_3-Et_2O (910 µL, 7.2 mmol) was added. The solution was stirred for 15 min at -78 °C. A solution of epoxide **197b** (1.1 g, 3.6 mmol) in Et_2O (5 mL) was added. The solution was stirred for 45 min at -78 °C and 6.5 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. After the phase separation, the organic phase was washed with saturated aqueous NH_4Cl (3 × 20 mL), brine (3 × 20 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 95:5) to give **196** as a pale yellow oil (1.2 g, 85%).

Mw 396 ($C_{20}H_{40}O_2Si_3$).

R_f 0.16 (hexane/Et_2O 15:1).

IR (film): 3489 (m), 2955 (s), 2851 (s), 2179 (s), 1100 (s) cm^{-1}.

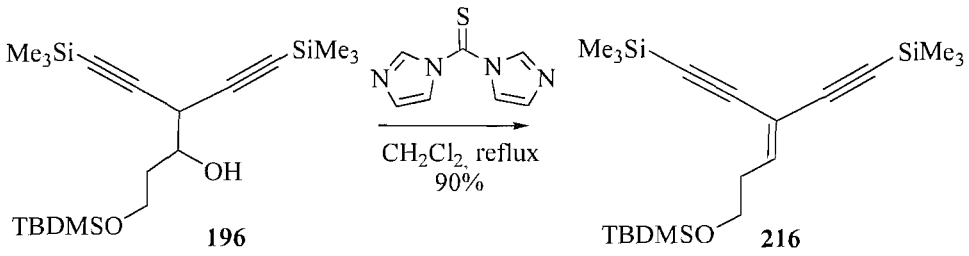
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93-3.72 (2H, m, **C<u>H</u>$_2$**-OTBDMS); 3.55 (1H, d, J = 5.7 Hz, **C<u>H</u>**-C≡C-TMS); 3.19 (1H, m, **C<u>H</u>**-OH); 2.03-1.72 (2H, m, **C<u>H</u>$_2$**-CH_2-OTBDMS); 0.89 (9H, s, **C<u>H</u>$_3$**-C); 0.16 (18H, s, **C<u>H</u>$_3$**-Si); 0.07 (6H, s, **C<u>H</u>$_3$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 101.0 (**C**≡C-Si); 87.5 (C≡**C**-Si); 72.4 (**CH**-OH); 61.4 (**CH_2**-OTBDMS); 35.5 (**CH_2**-CH_2-OTBDMS); 33.5 (**CH**-C≡C); 25.9 (**CH_3**-C); 18.2 (CH_3-**C**); -0.1 (**CH_3**-Si of TMS); -5.4 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 397 ($(M+H)^+$, 2), 379 (10), 209 (65), 131 (64), 73 (100).

HRMS (EI) for $C_{20}H_{41}O_2Si_3$ $(M+H)^+$ calcd 397.2414 found 397.2404.

6-*tert*-butyldimethylsilyloxy-1-trimethylsilyl-3-trimethylsilylethynyl-hex-3-en-1-yne (216)



To a solution of diyne **196** (400 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added 1,1'thiocarbonyldiimidazole (356 mg, 2 mmol). The orange solution was refluxed 6.5 h. The reaction mixture was washed with water (3 × 10 mL), 1 M aqueous HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), water (3 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 95:5) to afford **216** as an orange oil (344 mg, 90%).

Mw 378 ($C_{20}H_{38}OSi_3$).

R_f 0.64 (hexane/AcOEt 95:5).

IR (film): 2955 (m), 2860 (m), 2160 (m), 1611 (w), 1470 (m), 1247 (s), 1100 (m) cm^{-1}.

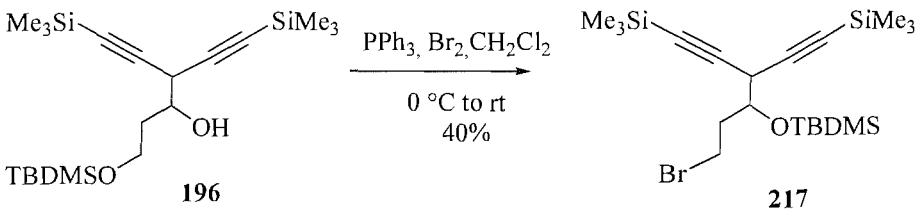
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (1H, t, J = 7.6 Hz, **C<u>H</u>**=C); 3.68 (2H, t, J = 6.7 Hz, **C<u>H$_2$</u>**-OTBDMS); 2.57 (2H, q, J = 7.0 Hz, **C<u>H$_2$</u>**-CH_2-OTBDMS); 0.90 (9H, s, **<u>tBu</u>**-Si); 0.22 (9H, s, **C<u>H$_3$</u>**-Si of TMS); 0.20 (9H, s, **C<u>H$_3$</u>**-Si of TMS); 0.07 (6H, s, **C<u>H$_3$</u>**-Si of TBDMS).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 147.8 (**CH**=C); 107.2 (**C**≡C-Si); 102.4 (**C**≡C-Si); 99.6 (C≡**C**-Si); 98.6 (C≡**C**-Si); 91.8 (CH=**C**); 61.6 (**CH_2**-OTBDMS); 34.7 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.3 (CH_3-**C**); -0.1 (**CH_3**-Si of TMS); -0.2 (**CH_3**-Si of TMS); -5.3 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 379 ($(M+H)^+$, 36), 321 (44), 247 (46), 132 (10), 73 (100), 57 (10).

HRMS (EI) for $C_{16}H_{29}OSi_3$ $(M\text{-}tBu)^+$ calcd 321.1526 found 321.1530.

6-bromo-4-*tert*-butyldimethylsilyloxy-1-trimethylsilyl-3-trimethylsilylethynyl-hex-1-yne (217)



To a solution of PPh_3 (218 mg, 0.83 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C were added Br_2 (43 µL, 0.83 mmol) and the alcohol **196** (300 mg, 0.76 mmol). The solution was stirred for 1 h at room temperature to afford a green solution. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 95:5) to give **217** as a yellow oil (139 mg, 40%).

Mw 459 ($C_{20}H_{39}BrOSi_3$).

R_f 0.59 (hexane/AcOEt 95:5).

IR (film): 2950 (m), 2855 (m), 2174 (w), 1100 (m) cm^{-1}.

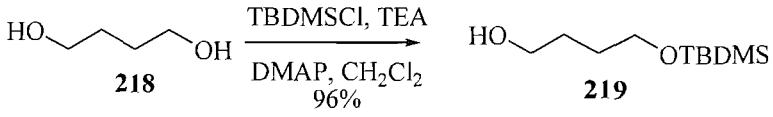
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (1H, dt, J = 6.5, 4.5 Hz, **CH**-OTBDMS); 3.53 (1H, d, J = 6.0 Hz, **CH**-C≡C); 3.48-3.40 (3H, m, **CH_2**-Br); 2.27-2.22 (2H, m, **CH_2**-CH_2-Br); 0.92 (9H, s, **CH_3**-C); 0.17 (24H, s, **CH_3**-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 101.1 (**C**≡C-Si); 87.7 (C≡**C**-Si); 87.5 (C≡**C**-Si); 72.0 (**CH**-OTBDMS); 37.0 (**CH_2**-Br); 33.2 (**CH**-C≡C); 30.4 (**CH_2**-CH_2-Br); 25.8 (**CH_3**-C); 18.1 (CH_3-**C**); -0.1 (**CH_3**-Si of TMS); -4.5 (**CH_3**-Si of TBDMS).

CIMS: *m/z* (%) 461 and 459 ($(M+H)^+$,7), 403 (10), 381 (20), 132 (48), 73 (100).

HRMS (EI) for $C_{19}H_{36}OSi_3{}^{79}Br$ $(M-Me)^+$ calcd 443.1257 found 443.1263.

3-*tert*-butyldimethylsilyloxy-butan-1-ol (219)



To a solution of 1,4-butanediol **218** (24.6 mL, 329.0 mmol) in CH_2Cl_2 (200 mL) at 0 °C were added a solution of *tert*-butyldimethylsilyl chloride (17.2 g, 114.0 mmol) in CH_2Cl_2 (20 mL) and DMAP (1.6 g, 12.5 mmol). After 5 minutes of stirring at this temperature, TEA (16.7 mL, 120 mmol) was added and the reaction was stirred for 4 h at room temperature. The organic phase was washed with water (3 × 150 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt 60:40) to afford **219** as a colourless oil (22.2 g, 96%).

Mw 204 ($C_{10}H_{24}O_2Si$)

R_f 0.44 (hexane/AcOEt 60:40)

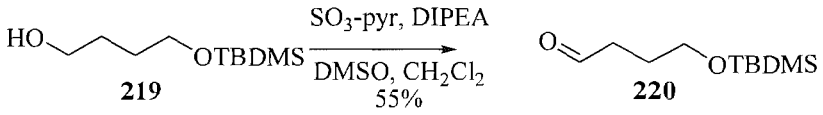
IR (film): 3336 (w), 2950 (m), 2855 (m), 1254 (m), 1100 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68-3.62 (4H, m, **C$\underline{H_2}$**-OH and **C$\underline{H_2}$**-OTBDMS); 2.58 (1H, br s, CH_2-**O$\underline{H}$**); 1.67-1.61 (4H, m, **C$\underline{H_2}$-C$\underline{H_2}$**-OTBDMS); 0.90 (9H, s, **C$\underline{H_3}$**-C); 0.07 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 63.3 (**CH_2**-OH); 62.7 (**CH_2**-OTBDMS); 30.1 (**CH_2**-CH_2-OH); 29.8 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.3 (CH_3-**C**); -5.4 (**CH_3**-Si).

The analytical data corresponded to the reported data.[172]

3-*tert*-butyldimethylsilyloxy-butan-1-al (220)



To solution of 3-*tert*-butyldimethylsilyloxy-butan-1-ol **219** (21.7 g, 106.3 mmol) in CH_2Cl_2 (110 mL) and DMSO (220 mL) at 0 °C was added diisopropylethyl amine (38.8 mL, 319.1 mmol). After 5 minutes of stirring at this temperature, pyridinium sulphur trioxide (50.8 g, 319.1 mmol) was added and the reaction was stirred for 1 h at room temperature. The solution was poured in saturated aqueous NH_4Cl. After the phase separation, the aqueous layer was extracted with Et_2O (5 × 100 mL). The combined organic layers were washed with brine (1 × 500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **220** as a yellow oil (11.9 g, 55%).

Mw 202 ($C_{10}H_{22}O_2Si$).

R_f 0.48 (hexane/AcOEt 80:20).

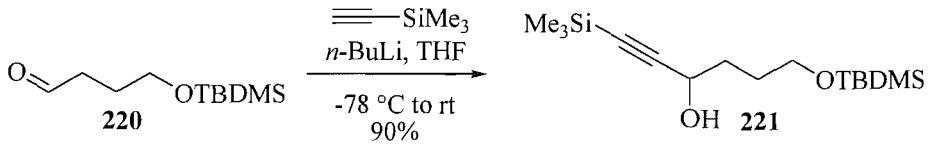
IR (film): 2954 (m), 2929 (m), 2860 (m), 2718 (w), 1726 (s), 1254 (s), 1095 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (1H, t, *J* = 2.3 Hz, **CHO**) 3.64 (2H, t, *J* = 8.0 Hz, **CH_2**-OTBDMS); 2.49 (2H, dt, *J* = 9.5, 2.5 Hz, **CH_2**-CHO); 1.85 (2H, tt, *J* = 9.5, 8 Hz, **CH_2**-CH_2-OTBDMS); 0.88 (9H, s, **CH_3**-C); 0.03 (6H, s, **CH_3**-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 202.4 (**C**=O); 62.0 (**CH_2**-OTBDMS); 40.7 (**CH_2**-CH_2-OTBDMS); 25.8 (**CH_3**-C); 25.5 (**CH_2**-CH_2-OTBDMS); 18.2 (CH_3-**C**); -5.5 (**CH_3**-Si).

The analytical data corresponded to the reported data.[172]

1-trimethylsilyl-6-*tert*-butyldimethylsilyloxy-1-hexyne-3-ol (221)



To a solution of trimethylsilyl acetylene (6.5 mL, 43.6 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M in hexane, 17.4 mL, 43.6 mmol). The solution was stirred at 0 °C for 30 min. To the mixture was added the aldehyde **220** (8.0 g, 39.6 mmol). The reaction was warmed up to room temperature over 1 h and the solution was stirred at the same temperature for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was washed with brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography with (hexane/AcOEt 90:10) to afford **221** as a yellow oil (11.0 g, 90%).

Mw 300 ($C_{15}H_{32}O_2Si_2$).

R_f 0.17 (hexane/AcOEt 95:15).

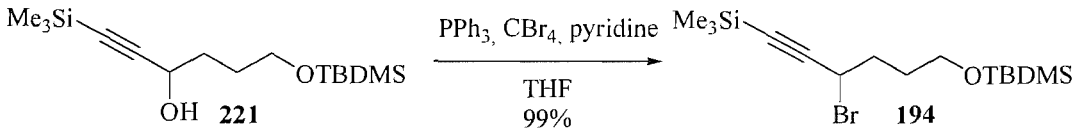
IR (film): 3367 (w), 2955 (w), 2929 (w), 2860 (w), 2173 (w), 1247 (m), 1098 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.42 (1H, q, J = 5.5 Hz, C**H**-OH); 3.74-3.63 (2H, m, C**H$_2$**-OTBDMS); 3.16 (1H, d, J = 6.0 Hz, CH-O**H**); 1.89-1.77 (2H, m, C**H$_2$**-CH-OH); 1.72-1.64 (2H, m, C**H$_2$**-CH_2-OTBDMS); 0.91 (9H, s, C**H$_3$**-C); 0.17 (9H, s, C**H$_3$**-Si); 0.08 (6H, s, C**H$_3$**-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 106.9 (**C**≡C-Si); 89.0 (C≡**C**-Si); 63.2 (**CH**-OH); 62.5 (**CH_2**-OTBDMS); 35.3 (CH-**CH_2**); 28.5 (**CH_2**-CH_2-OTBDMS); 25.9 (CH_3, **CH_3**-C); 18.3 (C, CH_3-**C**); -0.1 (**CH_3**-Si, TMS); -5.4 (**CH_3**-Si, TBDMS).

The analytical data corresponded to the reported data.[106]

1-trimethylsilyl-3-bromo-6-*tert*-butyldimethylsilyloxy-1-hexyne (194)



To a solution of alcohol **221** (2.0 g, 6.7 mmol) in THF (40 mL) at room temperature was successively added PPh_3 (1.92, 7.3 mmol) and pyridine (813 µL, 10.0 mmol). After 5 min at this temperature, CBr_4 (2.4 g, 7.3 mmol) was added. The reaction was stirred for 3 h at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in hexane (40 mL) and filtered. The filtrate was washed with 1 M aqueous HCl (1 × 20 mL), saturated aqueous Na_2SO_4 (2 × 20 mL), brine (1 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **194** as a yellow oil (2.3 g, 95%).

Mw 363 ($C_{15}H_{31}BrOSi_2$).

R_f 0.62 (hexane/AcOEt 90:10).

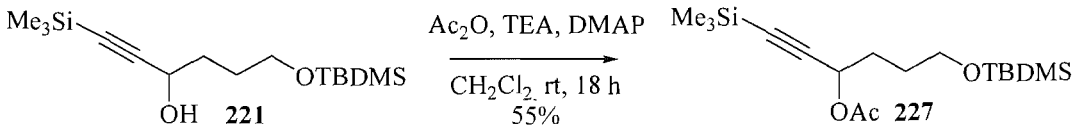
IR (film): 2953 (w), 2927 (w), 2855 (w), 2169 (w), 1249 (s), 1094 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.57 (1H, t, J = 6.8 Hz, **CH**-Br); 3.67 (2H, t, J = 6.0 Hz, **CH_2**-OTBDMS); 2.12-2.05 (2H, m, **CH_2**-CH-Br); 1.80-1.70 (2H, m, **CH_2**-CH_2-OTBDMS); 0.90 (9H, s, **CH_3**-C); 0.18 (9H, s, **CH_3**-Si); 0.06 (6H, s, **CH_3**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 103.9 (**C**≡C-Si); 92.0 (C≡**C**-Si); 62.1 (**CH_2**-OTBDMS); 37.2 (**CH**-Br); 36.5 (CH-**CH_2**); 30.5 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 18.3 (CH_3-**C**); -0.3 (**CH_3**-Si, TMS); -5.3 (**CH_3**-Si, TBDMS).

The analytical data corresponded to the reported data.[106]

1-trimethylsilyl-3-acetate-6-*tert*-butyldimethylsilyloxy-1-hexyne (227)



To a solution of alcohol **221** (1.0 g, 5.6 mmol) in CH_2Cl_2 (10 mL) were added TEA (780 µL, 5.6 mmol) and DMAP (27 mg, 0.2 mmol). The solution was cooled down to 0 °C and acetic anhydride (591 µL, 5.6 mmol) was added. The reaction was warmed up to room temperature and was stirred at this temperature for 18 h. The solution was poured in saturated aqueous $NaHCO_3$ (10 mL). After the phase separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **227** as a colourless oil (1.0 g, 55%).

Mw 342 ($C_{17}H_{34}O_3Si_2$).

R_f 0.55 (hexane/AcOEt 90:10).

IR (film): 2955 (w), 2929 (w), 2860 (w), 2179 (w), 1746 (m), 1228 (m), 1097 (m) cm^{-1}.

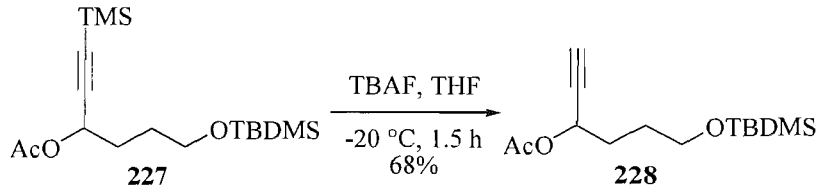
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.42 (1H, t, J = 6.5 Hz, **CH**-OAc); 3.64 (2H, t, J = 6.2 Hz, **CH_2**-OTBDMS); 2.07 (3H, s, **CH_3**-C=O); 1.85-1.77 (2H, m, CH-**CH_2**); 1.70-1.60 (2H, m, **CH_2**-CH_2-OTBDMS); 0.89 (9H, s, **CH_3**-C); 0.16 (9H, s, **CH_3**-Si); 0.05 (6H, s, **CH_3**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 169.8 (**C**=O); 102.6 (**C**≡C-Si); 90.3 (C≡**C**-Si); 64.2 (**CH**-OAc); 62.5 (**CH_2**-OTBDMS); 31.4 (CH-**CH_2**); 28.3 (**CH_2**-CH_2-OTBDMS); 25.9 (**CH_3**-C); 21.0 (**CH_3**-C=O); 18.3 (CH_3-**C**); -0.2 (**CH_3**-Si, TMS); -5.3 (**CH_3**-Si, TBDMS).

CIMS: *m/z* (%) 343 ($(M+H)^+$, 4), 283 (88), 73 (100).

HRMS (EI) for $C_{13}H_{25}O_3Si_2$ $(M\text{-}tBu)^+$ calcd 285.1342 found 285.1346.

3-acetate-6-*tert*-butyldimethylsilyloxy-1-hexyne (228)



To a solution of acetate **227** (481 mg, 1.4 mmol) in THF (2 mL) at -20 °C was added TBAF (1 M in THF, 700 µL, 1.4 mmol). The reaction was stirred at -20 °C for 1.5 h. The solution was poured in saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (1 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **228** as a colourless oil (280 mg, 74%).

Mw 270 ($C_{14}H_{26}O_3Si$).

R_f 0.40 (hexane/AcOEt 90:10).

IR (film): 3311 (w), 2954 (w), 2930 (w), 2857 (w), 2161 (w), 1743 (m), 1228 (s), 1097 (m), 1018 (m) cm^{-1}.

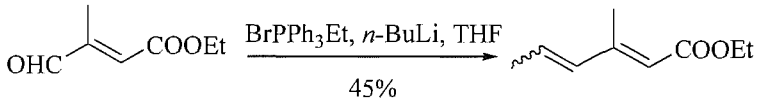
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (1H, td, J = 10.3, 3.0 Hz, C**H**-OAc); 3.63 (2H, t, J = 8.3 Hz, C**H$_2$**-OTBDMS); 2.44 (1H, d, J = 3.0 Hz, C≡C-**H**); 2.08 (3H, s, C**H$_3$**-C=O); 1.87-1.80 (2H, m, C**H$_2$**-CH_2-OTBDMS); 1.70-1.61 (2H, m, C**H$_2$**-CH-OH); 0.88 (9H, s, C**H$_3$**-C); 0.03 (6H, s, C**H$_3$**-Si).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 169.7 (**C**=O); 81.1 (**C**≡C-H); 73.5 (C≡**C**-H); 63.6 (**CH**-O); 62.3 (**CH_2**-OTBDMS); 31.2 (**CH_2**-CH_2-OTBDMS); 28.1 (**CH_2**-CH_2-OTBDMS); 25.9 (CH_3, **CH_3**-C); 20.9 (**CH_3**-C=O); 18.2 (C, CH_3-**C**); -5.4 (**CH_3**-Si).

CIMS: *m/z* (%) 271 ($(M+H)^+$, 66), 229 (20), 211 (100), 171 (12).

HRMS (CI) for $C_{14}H_{27}O_3Si$ $(M+H)^+$ calcd 271.1730 found 271.1739.

(2*E*)-ethyl-3-methyl-hex-2,4-dienoate (231)



230 **231**

Z:*E* 3:1

To a solution of ethyltriphenylphosphonium bromide (1 g, 2.7 mmol) in THF (4 mL) at room temperature was added *n*-BuLi (2.5 M in hexane, 1.1 mL, 2.7 mmol). The solution was stirred for 5 min and cooled down to -78 °C. The aldehyde **230** (283 µL, 2.1 mmol) was added and the reaction mixture was stirred for 1 h at -78 °C and 18 h at room temperature. The solution was filtered. The filtrate was washed with water (3 × 2 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was distilled under reduced pressure (48 °C, 12 mbar) to give **231** as yellow oil (145 mg, 45 %) as a 3:1 *Z*/*E* ratio.

Data for the major *Z* isomer:

Mw 154 ($C_9H_{14}O_2$).

R_f 0.51 (hexane/AcOEt 80:20).

Bp 48 °C at 12 mbar, lit.[177] 42 °C at 3 mmHg.

IR (film): 2980 (w), 2943 (w), 1710 (s), 1638 (m), 1612 (m), 1211 (m), 1141 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.10 (1H, m, CH_3-**C<u>H</u>**=CH); 5.88 (1H, m, **C<u>H</u>**-COOEt); 5.69 (1H, m, CH_3-CH=**C<u>H</u>**); 4.14 (2H, q, *J* = 7.1 Hz, **C<u>H$_2$</u>**-CH_3); 2.24 (3H, d, *J* = 1.1 Hz, C-**C<u>H$_3$</u>**); 1.83 (3H, dd, *J* = 7.3, 1.7 Hz, **C<u>H$_3$</u>**-CH=CH); 1.26 (3H, t, *J* = 7.1 Hz, CH_2-**C<u>H$_3$</u>**).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 167.2 (**C**=O); 153.0 (**C**-CH_3); 134.9 (**CH**=CH-CH_3); 131.9 (CH=**CH**-CH_3); 117.4 (**CH**-COOEt); 59.5 (O-**CH_2**); 18.5 (CH=CH-**CH_3**); 15.0 (O-CH_2-**CH_3**); 13.7 (C-**CH_3**).

The analytical data corresponded to the reported data.[177]

Data for the major *E* isomer:

Mw 154 ($C_9H_{14}O_2$).

R_f 0.51 (hexane/AcOEt 80:20).

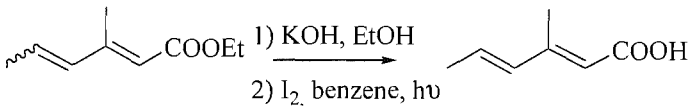
IR (film): 2980 (w), 2943 (w), 1710 (s), 1638 (m), 1612 (m), 1211 (m), 1141 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.10 (1H, m, CH_3-**C<u>H</u>**=CH); 5.88 (1H, m, **C<u>H</u>**-COOEt); 5.69 (1H, m, CH_3-CH=**C<u>H</u>**); 4.15 (2H, q, J = 7.1 Hz, **C<u>H$_2$</u>**-CH_3); 2.25 (3H, d, J = 1.3 Hz, C-**C<u>H$_3$</u>**); 1.83 (3H, dd, J = 7.3, 1.7 Hz, **C<u>H$_3$</u>**-CH=CH); 1.27 (3H, t, J = 7.1 Hz, CH_2-**C<u>H$_3$</u>**).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.9 (**C**=O); 152.4 (**C**-CH_3); 132.7 (**CH**=CH-CH_3); 129.3 (CH=**CH**-CH_3); 118.3 (**CH**-COOEt); 59.5 (O-**CH_2**); 19.0 (CH=CH-**CH_3**); 15.0 (O-CH_2-**CH_3**); 14.2 (C-**CH_3**).

The analytical data corresponded to the reported data.[177]

(2*E*,4*E*)-3-methylhexa-2,4-dienoic acid (200)



231 **200**

Z:*E* 3:1

To a solution of ester **231** (3 g, 19.5 mmol) in EtOH (20 mL) at 0 °C was added KOH (3.1 g, 54.5 mmol) in EtOH (67 mL). The reaction mixture was heated at 50-60 °C for 2 h and was stirred for 18 h at room temperature. After removing the solvent *in vacuo*, the residue was dissolved in water and acified until pH 4. The aqueous phase was extracted with AcOEt (4 × 70 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was dissolved in Et_2O (170 mL) and iodine (0.5% in benzene, 7 mL) was added. The dark orange solution was stirred at room temperature for 1 h while illuminated with a 100 W standard desk lamp at 32 cm. The organic phase was washed with saturated aqueous $Na_2S_2O_3$ (2 × 60 mL), brine (1 × 60 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was washed with hexane to give **200** as yellow solid (2.20 g, 90 %).

Mw 126 ($C_7H_{10}O_2$).

R_f 0.30 (hexane/AcOEt 90:10).

Mp 115 °C, lit.[177] 117 °C.

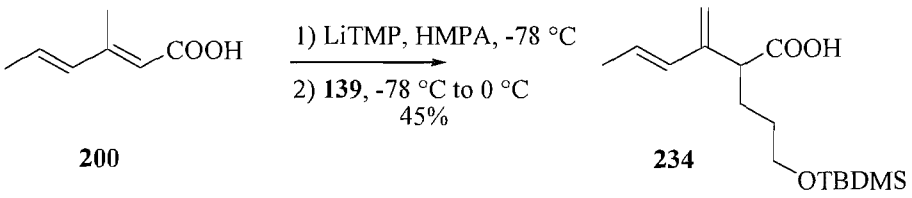
IR (film): 3029 (w), 1675 (m), 1636 (m), 1600 (s), 1256 (s), 1100 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.28-613 (2H, m, **C<u>H</u>**=**C<u>H</u>**-CH_3); 5.72 (1H, s, **C<u>H</u>**-COOH); 2.28 (3H, s, C-**C<u>H$_3$</u>**); 1.87 (3H, d, J = 5.3 Hz, CH=CH-**C<u>H$_3$</u>**).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.7 (**C**=O); 155.2 (**C**-CH_3); 134.9 (**CH**=CH-CH_3); 133.2 (CH=**CH**-CH_3); 116.7 (**CH**-COOH); 18.6 (CH=CH-**CH_3**); 14.0 (C-**CH_3**).

The analytical data corresponded to the reported data.[177]

2-[3-(*tert*-butyldimethylsilyloxy)-propyl]-3-methylene-hex-4-enoic acid (234)



200 **234**

To a solution of tetramethylpiperidine (270 µL, 1.6 mmol) in THF (2 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 640 µL, 1.6 mmol). The solution was stirred for 30 min at 0 °C and HMPA (255 µL, 1.6 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C and a solution of carboxylic acid **200** (92 mg, 0.7 mmol) in THF (1 mL) was added. After 30 min at this temperature, the mixture was cooled down to -78 °C and 1-*tert*-butyldimethylsilyloxy-3-iodopropane **139** (330 mg, 1.1 mmol) was added. The solution was warmed up to 0 °C over 3 h and stirred at this temperature for 1.5 h, followed by the addition of 10% aqueous HCl solution until pH 4. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with 10% aqueous $Na_2S_2O_3$ (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 90:10) to afford **234** as a yellow oil (99 mg, 45%).

Mw 298 ($C_{16}H_{30}O_3Si$).

R_f 0.09 (hexane/AcOEt 90:10).

IR (film): 2952 (m), 2929 (m), 2857 (m), 1704 (m), 1650 (w), 1605 (w), 1253 (m), 1097 (m) cm^{-1}.

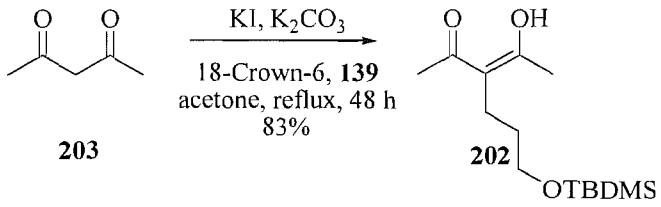
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09 (1H, dd, J = 15.7, 0.9 Hz, C**H**=CH-CH_3); 5.87 (1H, dq, J = 15.7, 6.6 Hz, CH=C**H**-CH_3); 5.12 (1H, s, C**H**H=CH); 5.06 (1H, s, CH**H**=CH); 3.67-3.57 (2H, m, C**H$_2$**-OTBDMS); 3.34 (2H, t, J = 7.5 Hz, C**H**-COOH); 1.98-1.84 (2H, m, C**H$_2$**-CH_2-CH_2-OTBDMS); 1.78 (3H, dd, J = 6.6, 1.5 Hz, C**H$_3$**-CH=CH); 1.60-1.47 (2H, m, **CH$_2$**-CH_2-OTBDMS); 0.90 (9H, s, C**H$_3$**-C); 0.06 (6H, s, C**H$_3$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 180.2 (**C**=O); 143.3 (**C**=CH_2); 132.0 (**CH**=CH-CH_3); 125.8 (CH=**CH**-CH_3); 114.6 (C=**CH$_2$**); 62.7 (**CH$_2$**-OTBDMS); 47.3 (**CH**-COOH); 30.6 (**CH$_2$**-CH_2-OTBDMS); 27.6 (**CH$_2$**-CH_2-CH_2-OTBDMS); 25.9 (**CH$_3$**, tBu); 18.3 (**CH$_3$**-CH=CH); 18.3 (**C**, tBu); -5.3 (**CH$_3$**-Si).

ESMS: *m/z* (%) 299 ($(M+H)^+$, 8), 321 (100), 619 (35).

HRMS (ES) for $C_{16}H_{31}O_3Si$ $(M+H)^+$ calcd 299.2037 found 299.2041.

6-*tert*-butyldimethylsilyloxy-3-acetyl-hexa-2-one (202)



To a solution of **139** (5.3 g, 17.6 mmol) in acetone (48 mL) were successively added penta-2,4-dione **203** (2 mL, 19.4 mmol), anhydrous K_2CO_3 (3.0 g, 19.4 mmol), KI (cat. amount) and 18-Crown-6 (0.5 g, 1.9 mmol). The reaction mixture was refluxed for 48 h. The mixture was filtered. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 75:25) to afford **202** as a yellow oil (4.4 g, 83%).

Mw 272 ($C_{14}H_{28}O_3Si$).

R_f 0.44 (hexane/AcOEt 80:20).

IR (film): 2950 (w), 2926 (w), 2855 (w), 1700 (w), 1639 (w), 1582 (m), 1252 (m), 1093 (s) cm^{-1}.

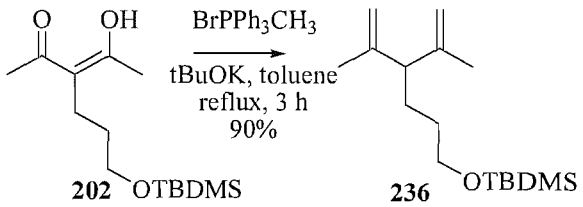
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (2H, t, J = 5.7 Hz, **C$\underline{H_2}$**-C=C); 2.31 (2H, t, J = 7.9 Hz, **CH_2**-OTBDMS); 2.14 (6H, s, **C$\underline{H_3}$**-C); 1.64-1.54 (2H, m, **CH_2**-CH_2-OTBDMS); 0.91 (9H, s, tBu); 0.06 (6H, s, **C$\underline{H_3}$**-Si).

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 209.7 (**C**=O); 191.1 (C=**C**-OH); 110.0 (**C**=C-OH); 62.0 (**CH_2**-OTBDMS); 33.6 (**CH_2**-C=C); 25.9 (**CH_3**, tBu); 23.8 (**CH_2**-CH_2-OTBDMS); 20.2 (**CH_3**-C); 18.2 (**C**, tBu); -5.4 (**CH_3**-Si).

ESMS: *m/z* (%) 295 ($(M+Na)^+$, 100).

HRMS (ES) for $C_{14}H_{28}O_3Si$ $(M)^+$ calcd 273.1880 found 273.1877.

6-*tert*-butyldimethylsilyloxy-3-isopropenyl-2-methyl-pent-1-ene (236)



To a solution of methyltriphenylphosphonium bromide (4.4 g, 12.3 mmol) in toluene (60 mL) was added tBuOK (1.4 g, 12.3 mmol). The reaction mixture was refluxed for 1 h. The solution was cooled down to room temperature and a solution of the diketone **202** (1.0 g, 4.1 mmol) in toluene (6 mL) was added. The reaction mixture was refluxed for 3 h. The solution was cooled down to room temperature and was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt 98:2) to give **236** as yellow oil (980 mg, 90 %).

Mw 268 ($C_{16}H_{32}OSi$).

R_f 0.65 (hexane/AcOEt 90:10).

IR (film): 2949 (w), 2930 (w), 2857 (w), 1791 (w), 1639 (w), 1253 (m), 1097 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.84 (2H, s, C**H**H=CH); 4.78 (2H, s, CH**H**=CH); 3.63 (2H, t, J = 6.2 Hz, C**H$_2$**-OTBDMS); 2.59 (1H, t, J = 7.2 Hz, C**H**-CH=CH_2); 1.61 (6H, s, C**H$_3$**-CH=CH_2); 1.59-1.41 (4H, m, C**H$_2$**-C**H$_2$**-CH); 0.91 (9H, s, tBu); 0.06 (6H, s, C**H$_3$**-Si).

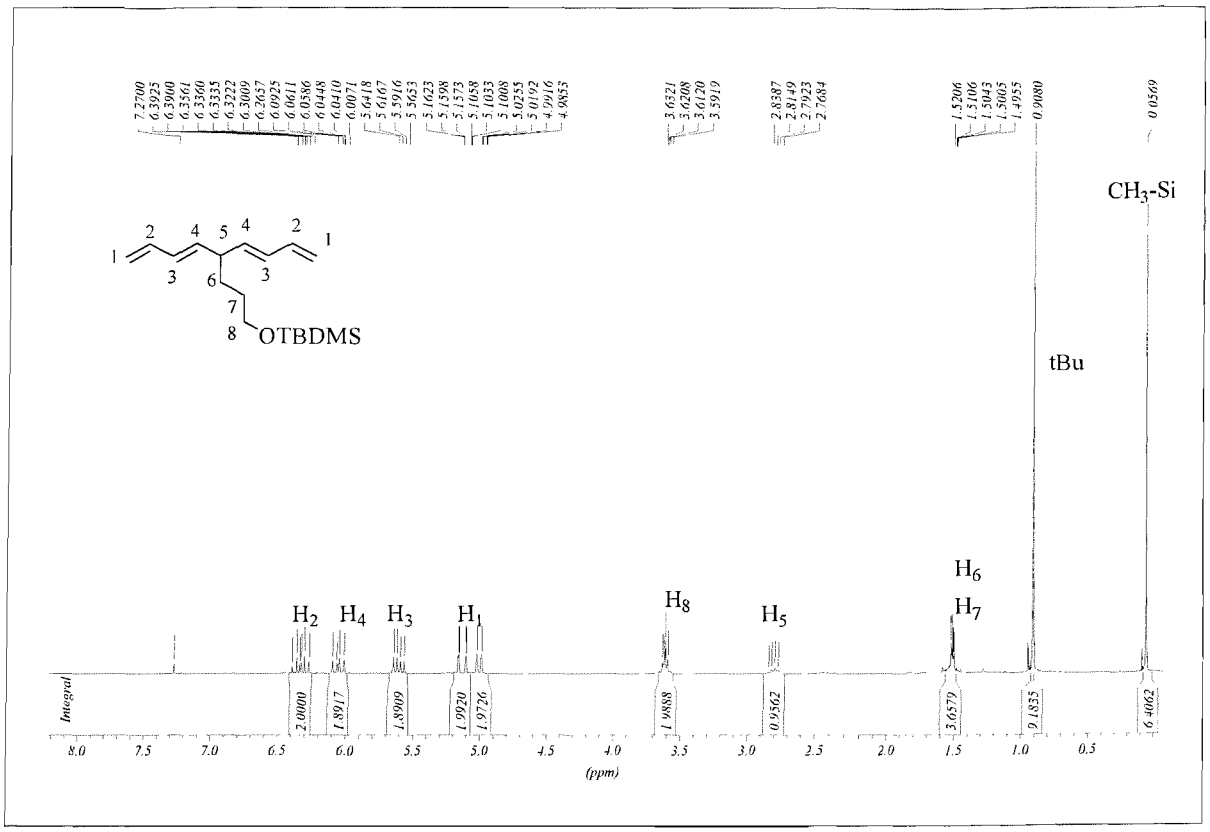
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 146.3 (**C**=CH_2); 111.1 (C=**CH_2**); 63.2 (**CH_2**-OTBDMS); 54.0 (**CH**-CH=CH_2); 31.0 (CH_2-**CH_2**-CH); 26.5 (**CH_2**-CH_2-CH); 26.0 (**CH_3**, tBu); 20.2 (**CH_3**-CH=CH_2); 18.4 (**C**, tBu); -5.3 (**CH_3**-Si).

CIMS: *m/z* (%) 269 ($(M+H)^+$, 30), 253 (8), 211 (86), 169 (100).

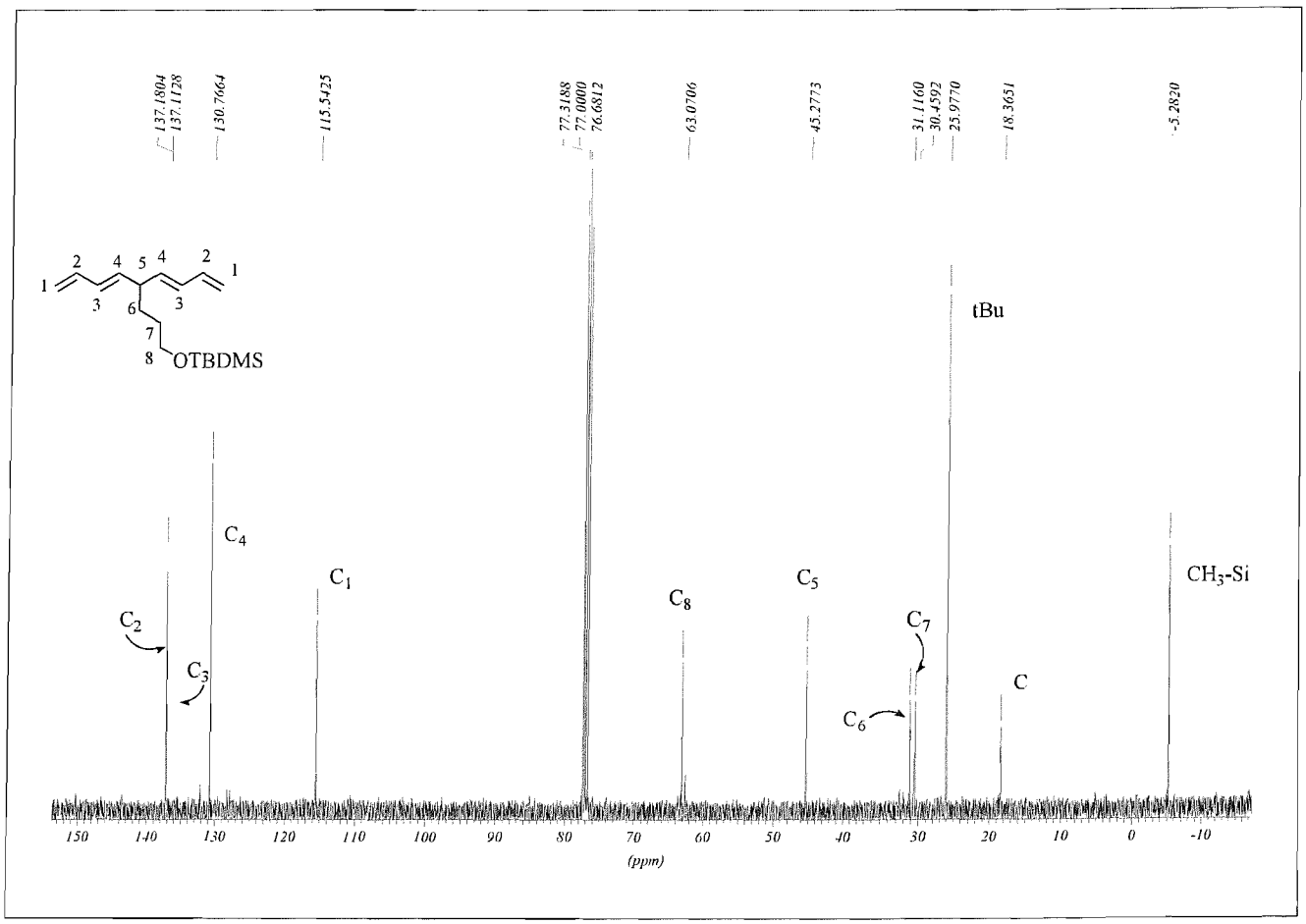
HRMS (EI) for $C_{16}H_{33}OSi$ $(M+H)^+$ calcd 269.2301 found 269.2291.

Appendix I:

^{1}H NMR spectrum ($CDCl_3$, 300 MHz) of **136**



^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **136**



Appendix II:

Table 1. Crystal data and structure refinement details.

Identification code	**04sot0856r (NA/4027/63)**
Empirical formula	$C_{17}H_{21}NO_3$
Formula weight	287.35
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*Pc*
Unit cell dimensions	$a = 5.0398(17)$ Å
	$b = 10.910(4)$ Å $\beta = 90.36(2)°$
	$c = 27.268(7)$ Å
Volume	1499.3(8) Å^3
Z	4 (2 molecules)
Density (calculated)	1.273 Mg / m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	616
Crystal	Rod; Colourless
Crystal size	0.15 × 0.03 × 0.02 mm^3
θ range for data collection	2.92 – 27.58°
Index ranges	$-6 \le h \le 6$, $-13 \le k \le 14$, $-35 \le l \le 35$
Reflections collected	18459
Independent reflections	3464 [$R_{int} = 0.0879$]
Completeness to $\theta = 25.00°$	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9983 and 0.9871
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3464 / 2 / 379
Goodness-of-fit on F^2	1.183
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0654, *wR2* = 0.1119
R indices (all data)	*R1* = 0.0924, *wR2* = 0.1197
Largest diff. peak and hole	0.326 and –0.272 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination**: DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection**: Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics**: Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and then refined using constraints. Relative chirality: C5 = S, C9 = R, C10 = S, C13 = S : C22 = R, C26 = S, C27 = R, C30 = R

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
N1	3697(6)	5074(3)	755(1)	24(1)	1
O1	1117(5)	4100(3)	153(1)	32(1)	1
O2	622(5)	6086(2)	329(1)	27(1)	1
O3	7101(6)	4434(3)	1215(1)	41(1)	1
C1	1756(7)	4981(4)	396(1)	23(1)	1
C2	1750(8)	6973(3)	667(2)	29(1)	1
C3	4219(7)	6354(3)	873(1)	23(1)	1
C4	5217(7)	4141(4)	964(1)	29(1)	1
C5	4399(8)	2822(3)	885(2)	29(1)	1
C6	6314(8)	2189(4)	531(2)	35(1)	1
C7	6151(8)	818(4)	550(2)	34(1)	1
C8	4796(8)	188(4)	882(2)	31(1)	1
C9	3244(7)	839(3)	1265(1)	25(1)	1
C10	3022(8)	289(4)	1777(2)	28(1)	1
C11	1952(9)	1394(4)	2081(2)	36(1)	1
C12	2602(9)	2570(4)	1783(2)	35(1)	1
C13	4323(8)	2117(3)	1363(1)	27(1)	1
C14	1330(8)	−824(4)	1799(1)	29(1)	1
C15	2029(8)	−1936(4)	1954(1)	26(1)	1
C16	358(8)	−3015(4)	1941(2)	29(1)	1
C17	1126(9)	−4134(4)	2047(2)	37(1)	1
N2	8624(6)	12974(3)	4288(1)	24(1)	1
O4	6124(6)	12009(3)	4892(1)	33(1)	1
O5	5587(5)	13987(2)	4713(1)	27(1)	1
O6	11992(6)	12327(3)	3828(1)	42(1)	1
C18	6721(7)	12886(4)	4650(1)	25(1)	1
C19	6658(8)	14865(4)	4374(2)	30(1)	1
C20	9121(7)	14264(3)	4170(1)	24(1)	1
C21	10123(8)	12042(4)	4081(2)	29(1)	1
C22	9320(8)	10725(3)	4164(2)	27(1)	1
C23	11296(8)	10090(4)	4513(2)	34(1)	1
C24	11103(8)	8713(4)	4493(2)	32(1)	1
C25	9706(7)	8102(4)	4166(2)	29(1)	1
C26	8108(7)	8742(3)	3782(1)	23(1)	1
C27	7796(8)	8201(4)	3273(1)	28(1)	1
C28	6705(8)	9303(4)	2973(2)	31(1)	1
C29	7395(8)	10481(4)	3268(2)	31(1)	1
C30	9183(7)	10018(3)	3686(2)	26(1)	1
C31	6092(8)	7084(4)	3251(2)	29(1)	1
C32	6816(8)	5985(4)	3097(1)	28(1)	1
C33	5166(9)	4898(4)	3098(2)	36(1)	1
C34	5917(10)	3788(4)	2959(2)	46(1)	1

Table 3. Bond lengths [Å] and angles [°].

N1–C1	1.383(5)	N2–C18	1.384(5)
N1–C4	1.394(5)	N2–C21	1.389(5)
N1–C3	1.457(4)	N2–C20	1.466(5)
O1–C1	1.211(4)	O4–C18	1.200(4)
O2–C1	1.346(4)	O5–C18	1.342(5)
O2–C2	1.451(5)	O5–C19	1.440(5)
O3–C4	1.210(4)	O6–C21	1.212(5)
C2–C3	1.520(5)	C19–C20	1.513(5)
C4–C5	1.512(5)	C21–C22	1.511(5)
C5–C13	1.515(5)	C22–C30	1.516(6)
C5–C6	1.534(6)	C22–C23	1.538(6)
C6–C7	1.499(6)	C23–C24	1.506(6)
C7–C8	1.330(6)	C24–C25	1.314(6)
C8–C9	1.488(6)	C25–C26	1.489(5)
C9–C13	1.519(5)	C26–C27	1.517(5)
C9–C10	1.527(6)	C26–C30	1.518(5)
C10–C14	1.485(6)	C27–C31	1.492(6)
C10–C11	1.561(6)	C27–C28	1.552(6)
C11–C12	1.555(6)	C28–C29	1.553(5)
C12–C13	1.523(6)	C29–C30	1.534(6)
C14–C15	1.331(5)	C31–C32	1.322(5)
C15–C16	1.448(5)	C32–C33	1.448(6)
C16–C17	1.312(5)	C33–C34	1.325(6)
C1–N1–C4	128.4(3)	C8–C9–C10	119.7(3)
C1–N1–C3	110.6(3)	C13–C9–C10	103.1(3)
C4–N1–C3	120.8(3)	C14–C10–C9	113.8(3)
C1–O2–C2	110.2(3)	C14–C10–C11	114.2(3)
O1–C1–O2	121.7(3)	C9–C10–C11	102.1(3)
O1–C1–N1	129.0(4)	C12–C11–C10	106.6(3)
O2–C1–N1	109.2(3)	C13–C12–C11	104.4(3)
O2–C2–C3	104.8(3)	C5–C13–C9	109.0(3)
N1–C3–C2	101.5(3)	C5–C13–C12	120.0(3)
O3–C4–N1	117.7(4)	C9–C13–C12	103.0(3)
O3–C4–C5	123.0(4)	C15–C14–C10	127.3(4)
N1–C4–C5	119.2(3)	C14–C15–C16	125.5(4)
C4–C5–C13	111.6(3)	C17–C16–C15	125.5(4)
C4–C5–C6	110.3(3)	C18–N2–C21	128.3(3)
C13–C5–C6	109.4(3)	C18–N2–C20	110.1(3)
C7–C6–C5	113.2(3)	C21–N2–C20	121.3(3)
C8–C7–C6	124.6(4)	C18–O5–C19	110.6(3)
C7–C8–C9	120.4(4)	O4–C18–O5	122.3(4)
C8–C9–C13	111.9(3)	O4–C18–N2	128.6(4)

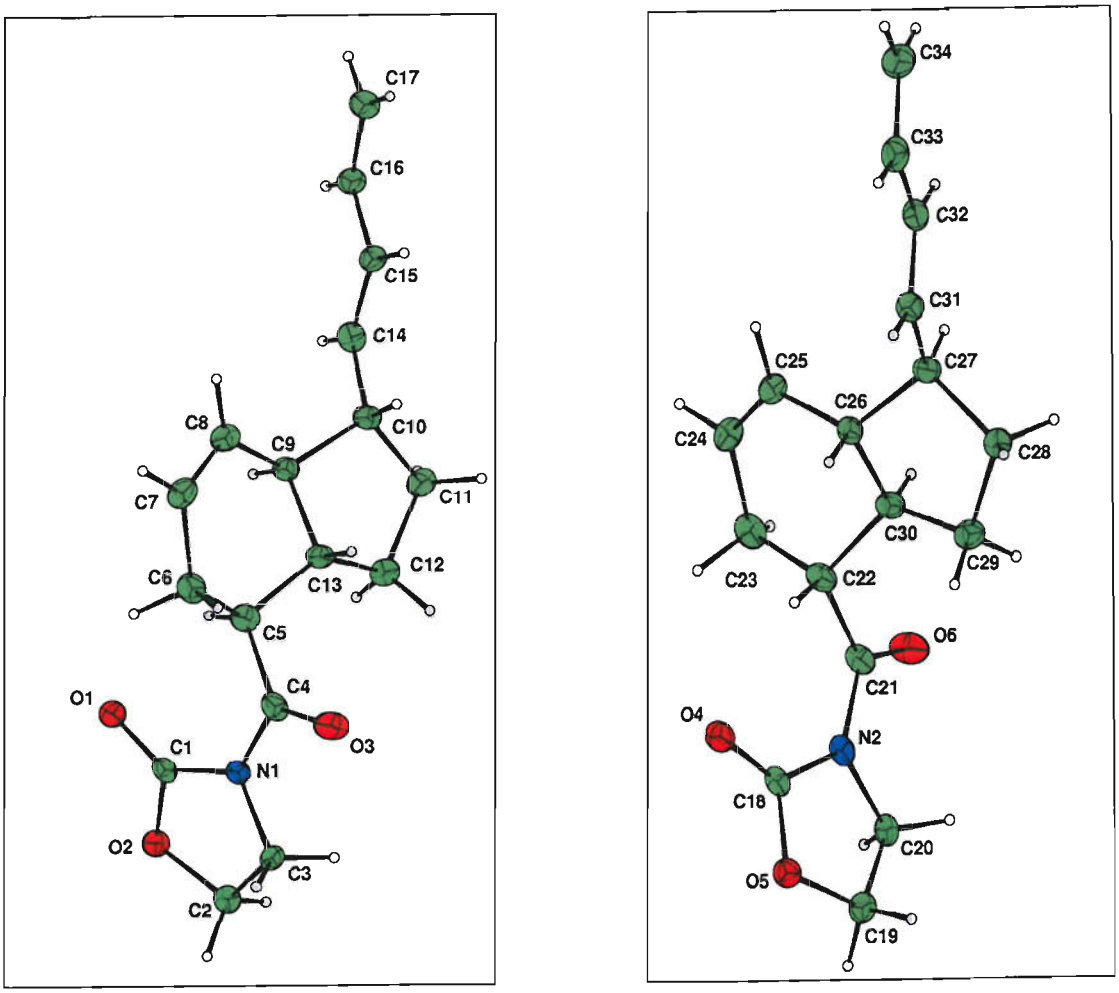
O5–C18–N2	109.1(3)
O5–C19–C20	105.0(3)
N2–C20–C19	101.1(3)
O6–C21–N2	118.1(4)
O6–C21–C22	122.6(4)
N2–C21–C22	119.3(3)
C21–C22–C30	111.5(3)
C21–C22–C23	110.3(3)
C30–C22–C23	109.2(3)
C24–C23–C22	112.6(3)
C25–C24–C23	124.4(4)
C24–C25–C26	121.6(4)
C25–C26–C27	120.9(3)
C25–C26–C30	111.1(3)
C27–C26–C30	103.5(3)
C31–C27–C26	114.2(3)
C31–C27–C28	114.2(3)
C26–C27–C28	102.4(3)
C27–C28–C29	106.9(3)
C30–C29–C28	103.9(3)
C22–C30–C26	109.4(3)
C22–C30–C29	119.7(3)
C26–C30–C29	102.8(3)
C32–C31–C27	126.4(4)
C31–C32–C33	125.6(4)
C34–C33–C32	125.7(5)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	24(2)	22(2)	24(2)	3(1)	−5(1)	−1(1)
O1	40(2)	27(2)	30(2)	3(1)	−11(1)	−8(1)
O2	25(1)	26(2)	29(2)	1(1)	−2(1)	0(1)
O3	38(2)	31(2)	55(2)	9(2)	−23(2)	−9(1)
C1	22(2)	27(2)	21(2)	6(2)	1(2)	−5(2)
C2	30(2)	29(2)	28(2)	1(2)	−2(2)	−1(2)
C3	26(2)	21(2)	22(2)	−2(2)	2(2)	−5(2)
C4	27(2)	32(2)	27(2)	7(2)	−6(2)	−5(2)
C5	23(2)	29(2)	36(2)	3(2)	−6(2)	−3(2)
C6	35(2)	37(2)	32(2)	6(2)	−2(2)	−11(2)
C7	33(2)	34(2)	34(2)	−8(2)	5(2)	−2(2)
C8	31(2)	26(2)	35(2)	−2(2)	−2(2)	−2(2)
C9	25(2)	21(2)	29(2)	2(2)	−3(2)	1(2)
C10	28(2)	23(2)	33(2)	3(2)	−2(2)	1(2)
C11	46(3)	30(2)	32(2)	−5(2)	3(2)	−4(2)
C12	44(3)	26(2)	35(2)	−2(2)	−3(2)	1(2)
C13	28(2)	21(2)	31(2)	2(2)	−7(2)	−1(2)
C14	24(2)	35(3)	28(2)	2(2)	0(2)	−3(2)
C15	30(2)	23(2)	27(2)	−3(2)	3(2)	2(2)
C16	36(2)	25(2)	28(2)	0(2)	6(2)	−2(2)
C17	49(3)	31(3)	32(2)	3(2)	6(2)	−2(2)
N2	22(2)	28(2)	22(2)	−2(1)	5(1)	−6(1)
O4	40(2)	28(2)	32(2)	−2(1)	12(1)	−6(1)
O5	26(2)	27(2)	28(2)	−1(1)	4(1)	1(1)
O6	37(2)	31(2)	58(2)	−5(2)	24(2)	−6(1)
C18	27(2)	28(2)	21(2)	−5(2)	2(2)	−5(2)
C19	32(2)	29(2)	29(2)	4(2)	5(2)	1(2)
C20	23(2)	29(2)	20(2)	0(2)	−2(2)	−6(2)
C21	29(2)	29(2)	27(2)	−6(2)	4(2)	−3(2)
C22	24(2)	28(2)	30(2)	−6(2)	8(2)	−2(2)
C23	30(2)	39(3)	33(2)	−6(2)	0(2)	−8(2)
C24	30(2)	32(2)	34(2)	6(2)	−5(2)	0(2)
C25	29(2)	25(2)	32(2)	3(2)	0(2)	−2(2)
C26	21(2)	25(2)	23(2)	−1(2)	4(2)	−1(2)
C27	30(2)	24(2)	29(2)	−3(2)	3(2)	1(2)
C28	38(2)	26(2)	28(2)	−1(2)	−3(2)	1(2)
C29	30(2)	25(2)	36(2)	1(2)	5(2)	−1(2)
C30	24(2)	24(2)	31(2)	−3(2)	6(2)	1(2)
C31	33(2)	27(2)	27(2)	−3(2)	−4(2)	1(2)
C32	32(2)	29(2)	24(2)	0(2)	1(2)	−4(2)
C33	47(3)	34(3)	28(2)	1(2)	−8(2)	−6(2)
C34	72(4)	26(3)	40(3)	−3(2)	−11(3)	−9(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2A	484	7166	932	35	1
H2B	2216	7741	494	35	1
H3A	5845	6654	710	28	1
H3B	4386	6482	1231	28	1
H5	2582	2812	735	35	1
H6A	5916	2465	192	42	1
H6B	8151	2444	611	42	1
H7	7081	367	307	40	1
H8	4820	−683	875	37	1
H9	1397	938	1134	30	1
H10	4840	76	1899	34	1
H11A	13	1318	2128	43	1
H11B	2825	1424	2407	43	1
H12A	959	2958	1656	42	1
H12B	3576	3171	1987	42	1
H13	6184	2033	1488	32	1
H14	−452	−733	1689	35	1
H15	3770	−2029	2085	32	1
H16	−1447	−2903	1849	35	1
H17A	2914	−4286	2141	45	1
H17B	−106	−4792	2028	45	1
H19A	7112	15640	4544	36	1
H19B	5366	15044	4108	36	1
H20A	9265	14393	3812	29	1
H20B	10749	14571	4334	29	1
H22	7525	10713	4318	33	1
H23A	13121	10341	4426	41	1
H23B	10954	10366	4853	41	1
H24	12056	8256	4732	39	1
H25	9715	7232	4174	34	1
H26	6281	8845	3917	28	1
H27	9596	7987	3146	33	1
H28A	4760	9230	2930	37	1
H28B	7536	9331	2645	37	1
H29A	8345	11080	3060	37	1
H29B	5771	10871	3398	37	1
H30	11027	9935	3557	32	1
H31	4313	7171	3358	35	1
H32	8570	5901	2976	34	1
H33	3392	4989	3208	44	1
H34A	7674	3656	2846	55	1
H34B	4698	3125	2971	55	1



The two molecules of opposite chirality in the asymmetric unit, thermal ellipsoids are drawn at the 35 % probability level.

Overlay of molecule 1 onto an inverted molecule 2.

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