SYNTHESIS OF INSECT LIPID USING ORGANOBISMUTH REMOTE STEREOCONTROL OF ACYCLIC 1,3,5-TRIMETHYL COMPOUNDS

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requirements for the award of the degree of
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Dedicated to

My Beloved Husband and Family

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ABSTRACT

The organometallic chemistry of the main group IV metals has been dominated by the widespread commercial exploitation of tin and lead. The high toxicity problems associated with organotin compounds has lead to the need to limit their use. Organobismuth chemistry is attracting interest. Bismuth metal is considered to be safe, as it is non-toxic and non-carcinogenic, in spite of its heavy metal status. Embodied in this thesis is a discussion concerning the use of organobismuth as a replacement for organotin compounds in remote stereoselective control by promoting coupling reactions of (2*R*,3*E*)-1-(benzyloxy)-5-bromo-2,4-dimethylpent-2-ene with aldehydes. (2*R*,3*E*)-1-(Benzyloxy)-5-bromo-2,4-dimethylpent-2-ene was synthesised from methyl (*2S*)-3-hydroxy-2-methylpropanoate in five steps with an overall yield of 41%. Addition of this bromide and an aldehyde to bismuth(III) iodide and zinc in THF at room temperature gave a ≥90:10 (1,5-*anti*:1,5-*syn*) ratio of homoallylic alcohols in *ca*. 70% yield. The generality of these bismuth(III) iodide promoted reactions is reported including the successful coupling of several aldehydes with consistently good yields and selectivities. Identification of the relative stereochemistry of the major isomer was achieved by means of ^{1}H NMR. When this was not possible, inversion of the newly formed chiral centre was employed to determine the selectivity of the reaction. The absolute configuration of the hydroxyl group in the major diastereoisomer was confirmed by comparison of the ^{1}H NMR spectra of its (*R*)- and (*S*)-*O*-acetylmandelates. The mechanism of these bismuth reactions has not been investigated, although it is suggested that it is similar to tin-Lewis acid reactions. Acyclic compounds with *syn*-and *anti*-disposed 1,3,5-trimethyl substituents were prepared from 1,5-stereocontrol homoallylic alcohol *via* stereoselective reduction of the trisubstituted alkenes. The application of this methodology to the synthesis of natural products was tested with the preliminary work on the synthesis of the cuticular hydrocarbon, 4,6,8,10,16-pentamethyldocosane isolated from the cane beetle *Antitrogus parvulus*.

ABSTRAK

Kimia organologam bagi logam utama kumpulan IV telah dikuasai penggunaanya dengan berleluasa secara komersil oleh logam timah dan plumbum. Masalah ketoksikan yang tinggi berkaitan dengan sebatian organotimah telah mendorong untuk menghadkan penggunaan sebatian daripada kelas tersebut. Kimia organobismut telah menarik banyak minat terhadapnya. Logam bismut dianggap selamat, kerana ianya tidak toksik dan tidak karsinogen walaupun mempunyai status sebagai logam berat. Rangkuman perbincangan di dalam tesis ini adalah berkaitan dengan penggunaan organobismut sebagai pengganti kepada sebatian organotimah dalam tindak balas penggandingan stereopilihan bagi (2*R*,3*E*)-1-(benziloksi)-5-bromo-2,4-dimetilpent-2-ena dan aldehid. (2*R*,3*E*)-1-(Benziloksi)-5-bromo-2,4-dimetilpent-2-ena telah disintesis daripada metil (2*S*)-3-hidroksi-2-metilpropanoat dalam lima langkah tindak balas dengan purata hasil sebanyak 41%. Penambahan bromida dan aldehid kepada bismut(III) iodida dan zink dalam THF pada suhu bilik memberikan nisbah ≥90:10 (1,5-*anti*:1,5-*syn*) bagi alkohol homoalilik dengan hasil sebanyak 70%. Tindak balas yang digalakkan oleh bismut(III) iodida secara umumnya dilaporkan berjaya melalui penggandingan bagi beberapa aldehid dengan menunjukkan hasil dan kepilihan yang tinggi secara konsisten. Pengenalpastian hubungan stereokimia bagi isomer utama telah dicapai berdasarkan kepada ^{1}H RMN. Kaedah lain yang digunakan adalah dengan melakukan penyongsangan pada pusat kiral yang baru untuk menentukan kepilihan bagi tindak balas tersebut. Konfigurasi mutlak kumpulan hidroksil bagi diastereoisomer utama telah ditentukan secara perbandingan spektrum ^{1}H RMN bagi sebatian (*R*)- dan (*S*)-*O*-acetilmandelat. Mekanisme tindak balas bagi sebatian bismut masih belum diselidik, namun begitu, mekanisme tindak balas ini dicadangkan mempunyai persamaan dengan tindak balas yang menggunakan timah sebagai asid Lewis. Sebatian rantai lurus dengan susunan *syn*- dan *anti*- bagi penukarganti 1,3,5-trimetil telah disediakan daripada alkohol homoalilik 1,5-stereokawalan secara penurunan stereopilihan bagi alkena dengan tiga kumpulan penukarganti. Penggunaan kaedah ini bagi sintesis sebatian semula jadi telah diuji ke atas sintesis awalan hidrokarbon rantai lurus, 4,6,8,10,16-pentametildokosana yang telah diasingkan daripada kulit luar kumbang tebu, *Antitrogus parvulus*.

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Ac	-	Acetyl
aq	-	Aqueous
Ar	-	Aryl
atm	-	Atmospheres
9-BBN	-	9-Borabicyclo[3.3.1]nonane
Bn	-	Benzyl
BOM	-	Benzyloxymethyl
bp	-	Boiling point
br	-	Broad
BTMG	-	2-Benzyl-1,1,3,3-tetramethyl guanidene
Bu	-	Butyl
c	-	Concentration
Cat.	-	Catalytic
CI	-	Chemical ionisation
conc.	-	Concentrated
COSY	-	^{1}H-^{1}H correlation spectrum
CSA	-	Camphor sulfonic acid
CuCN	-	Copper(I) cyanide
d	-	doublet
DCC	-	Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
dd	-	doublet of doublets
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	-	Distortionless enhancement of polarisation transfer
DHP	-	Dihydropyranyl
DIAD	-	Di-*iso*propylazodicarboxylate

DIBAL-H	-	Di-*iso*butylaluminium hydride
DMAP	-	4-(*N*,*N*-dimethylamino)pyridine
DME	-	1,2-dimethoxyethane
DMF	-	*N*,*N*-Dimethylformamide
DMP	-	Dess-Martin periodinane
DMSO	-	Dimethylsulfoxide
dr	-	Diastereomeric ratio
ds	-	Diastereoselection
EDC·HCl	-	1-(3-Dimethyllaminopropyl)-3-ethyl-carbodiimide hydrochloride
ee	-	Enantiomeric excess
EI	-	Electron impact ionisation
eq.	-	Equivalents
$ES^{+/-}$	-	Electrospray (positive *or* negative mode)
Et	-	Ethyl
Ether	-	Diethyl ether
FT	-	Fourier transform
g	-	Grams
GC	-	Gas chromatography
GCMS	-	Gas chromatography Mass Spectrometry
h	-	Hour (s)
HMBC	-	Heteronuclear multiple bond correlation
HMPA	-	Hexamethylphosphoramide
HMQC	-	^{1}H-^{13}C correlation spectrum
HOBT	-	1-Hydroxybenzotriazole hydrate
HPLC	-	High performance liquid chromatography
HSQC	-	Heteronuclear Single Quantum Coherence
HWE	-	Horner-Wadsworth-Emmons
Hz	-	Hertz
imid.	-	Imidazole
i-Pr	-	*iso*propyl
IR	-	Infrared
J	-	Coupling constant
KHMDS	-	Potassium bis(trimethylsilyl)amide

L	-	General ligand
LA	-	Lewis acid
LDA	-	Lithium di-*iso*-propylamide
LHMDS	-	Lithium bis(trimethylsilyl)amide
M	-	Molarity
m	-	Multiplet
m/z	-	Mass-to-charge ratio
M^+	-	Molecular ion
m-CPBA	-	*meta*-Chloroperbenzoic acid
Me	-	Methyl
MeLi	-	Methyllithium
mg	-	Milligrams
MHz	-	MegaHertz
Min	-	minute(s)
mmol	-	Millimoles
mol	-	Moles
mp	-	Melting point
MS	-	Mass spectrometry
Ms	-	Methanesulphonyl
MsCl	-	Mesyl chloride
MTPA	-	α-methoxy-α-(trifluoromethyl)phenylacetic acid
NaCN	-	Sodium cyanide
NaH	-	Sodium hydride
NaHMDS	-	Sodium bis(trimethylsilyl)amide
NaOAc	-	Sodium acetate
NaOMe	-	Sodium methoxide
n-BuLi	-	*normal*-Butyllithium
NMM	-	*N*-methylmorpholine
NMO	-	*N*-Methylmorpholine-*N*-oxide
NMR	-	Nuclear magnetic resonance
NOE	-	Nuclear Overhauser Effect
O/N	-	Overnight
o-DPPB	-	*ortho*-Diphenylphosphanylbenzoyl

OTf	-	Trifluoromethanesulfonate
OTs	-	*para*-Toluenesulfonate
P (P', P'' etc.)	-	General protecting group
PCC	-	Pyridinium chlorochromate
Petrol	-	Petroleum ether (40-60^{o}C)
Ph	-	Phenyl
PMB	-	*para*-Methoxybenzyl
PMP	-	*para*-Methoxyphenyl
p-NBA	-	*para*-Nitrobenzoic acid
ppm	-	Parts per million
PPTS	-	Pyridinium 4-toluenesulfonate
Pr	-	Propyl
p-TsOH	-	*para*-Toluenesulfonic acid
py	-	pyridine
q	-	quartet
qn	-	quintet
quant.	-	quantitative
R	-	General alkyl group
R_f	-	Retention factor
Rh-C	-	Rhodium-Carbon
rt	-	room temperature
s	-	singlet
SEM	-	2-(Trimethylsilyl)ethoxymethoxy
SET	-	Single electron transfer
sext	-	sextet
sm	-	starting material
t	-	triplet
TBAF	-	Tetra-*N*-butylammonium fluoride
TBAI	-	Tetra-*N*-butylammonium iodide
TBDMSCl	-	*tert*-Butylchlorodimethylsilyl chloride
TBDPS	-	*tert*-Butyldiphenylsilyl
TBS or TBDMS	-	*tert*-Butyldimethylsilyl
t-Bu	-	*tert*-Butyl
t-BuLi	-	*tert*-Butyllithium

tert	-	tertiary
THF	-	Tetrahydrofuran
THP	-	2-(Tetrahydropyranyl)
TIPS	-	Tri-*iso*-propylsilyl
TLC	-	Thin layer chromatography
TMS	-	Trimethylsilyl
TPAP	-	Tetra-*N*-propylammonium perruthenate
Ts	-	4-Toluenesulfonyl
tt	-	triplet of triplets
v	-	volume
wt	-	weight
X	-	General leaving group
ZACA	-	(-)-bis-(neomethylindenyl)zirconium dichloride
δ	-	chemical shift

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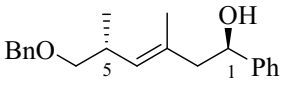
CHAPTER 1

INTRODUCTION

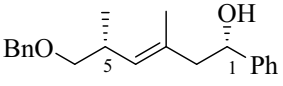
1.1 Preface

This thesis relates to the work performed by the author towards the stereoselective synthesis of a cuticular hydrocarbon, (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane of the cane beetle *Antitrogus parvulus*. The syntheses of this compound involved the assembly of the aliphatic chain from homochiral starting materials prepared using bismuth(III) iodide promoted reactions of an allylic bromide with aldehydes. Related insect lipids have attracted synthetic interest due to the tetradeoxypropionate unit which has four methyl-bearing stereocenters with different stereochemical orientations. Some of the reported syntheses are addressed in the introduction.

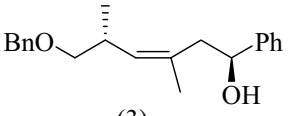
In this report the relationship between stereogenic centres in certain products is discussed. For ease of identification, the relationship between stereogenic centres will be referred to as either *syn* or *anti*. For example, homoallylic alcohol (1) has an *anti* relationship between the methyl group at C5 and the hydroxyl group at C1, whereas the other diastereoisomer (2) has a *syn* relationship between these substituents. Similarly alcohols (3) and (4) are described as *anti* and *syn* respectively.



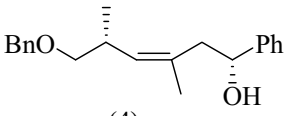
(1)
1,5-*anti*-(*E*)



(2)
1,5-*syn*-(*E*)

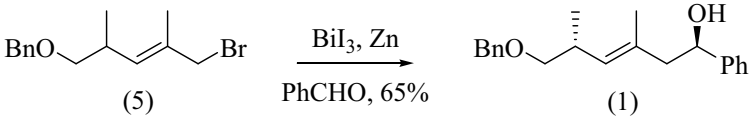


(3)
1,5-*anti*-(*Z*)



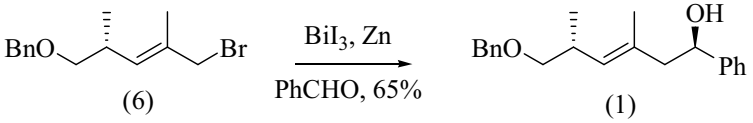
(4)
1,5-*syn*-(*Z*)

Also, most schemes in this report show only the major diastereoisomer formed in reactions. For example, alcohol (1) is the major product formed from compound (5), with the ratio of 96:4 referring to the 1,5-diastereotopic ratio and the yield representing the combined yield of both diastereoisomers.



(5) (1)
96:4

When racemic starting materials are used, one of the two possible major *anti*- or *syn*-diastereoisomers will be shown in the reaction scheme, as shown above. When enantiomerically enriched starting materials are used, example compound (6), the major product (1) of the coupling reaction will be presented as one diastereoisomer only (as shown below).



(6) (1)
96:4

1.2 Insect lipids

Larvae of melolonthine scarabs (collectively known as canegrubs) are the main pests affecting the production of sugar cane in Australia [1]. Canegrubs damage the roots of plants and the regenerative portion of underground stems. Currently, pest control is accomplished by the application of organophosphorus insecticides [2], but

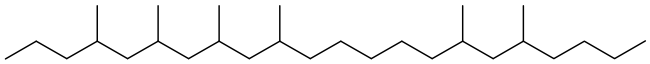
problems such as insecticidal breakdown and resistance emphasize the importance of the development of environmentally benign management strategies. Significant results have been achieved with formulations utilizing sex pheromones for monitoring and controlling herbivorous scarab beetles, and it has been proposed that pheromones may be useful for population control of the Australian canegrub complex.

Several species of Melolonthine scarabs have been investigated by Kitching and co-workers initially with a focus on volatile pheromonal components. This investigation led to a report of novel long chain hydrocarbons [1]. In the cuticular extract of one species, *Antitrogus parvulus*, two hydrocarbons were detected in a ratio of 45:38 by GCMS analysis. The same components were also present in extracts from adult male *A. parvulus* [3].

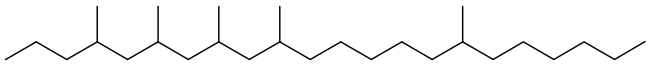
1.2.1 Lipid structures

The components of the female extract were separated by preparative gas chromatography and mass spectra exhibited molecular ions at *m*/*z* 380 and 394, respectively, indicating the formulas $C_{27}H_{56}$ and $C_{28}H_{58}$ and these were confirmed by accurate mass measurements. High-resolution ^{13}C NMR and DEPT spectra confirmed the presence of five and six methyl side-chains in the C27 and C28 hydrocarbons, respectively, with the requisite number of methine and methylene signals. The location of the methyl groups along the C22 carbon chain was based on mass spectral and NMR evidence and ^{13}C NMR shift calculations [4].

The C28 hydrocarbon was identified as 4,6,8,10,16,18-hexamethyldocosane (7) based on ^{13}C NMR shift calculations in best agreement with the experimental data and two-dimensional NMR experiments (COSY, HMBC, and HSQC) which provided the structure of (7). The constitution of the C27 hydrocarbon was similarly deduced to be 4,6,8,10,16-pentamethyldocosane (8), with the calculated ^{13}C NMR resonances being in very good agreement with those observed. Mass spectral fragmentation data are consistent with the structures of (7) and (8) [3] (Figure 1).



(7)



(8)

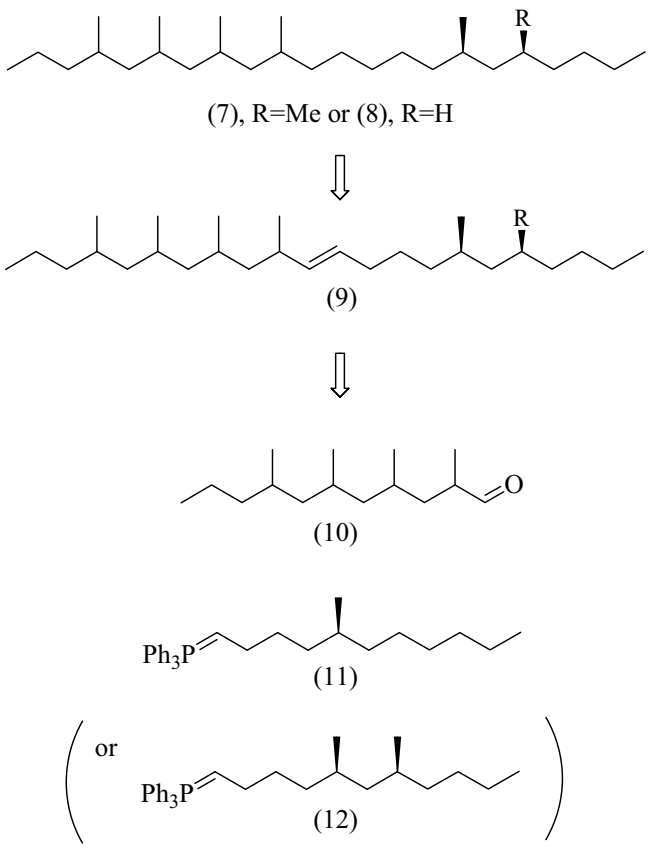
Figure 1 Structures of the insect lipids from *A. parvulus*.

Interest in the biological roles of the sex pheromones of cane beetles has led to a related interest in the synthesis of lipids (7) and (8). The small amount of material isolated from natural sources has not permitted a determination of their biological roles. The need for more material to assess biological trials is apparent and synthetic chemistry could address this concern. Moreover the synthesis of different diastereoisomers was essential to assign configuration of the methyl bearing stereogenic centres. Several papers have been published concerning the synthesis of lipids (7) and (8). There exist four total syntheses of lipid (7), each of this used different methodology for the construction of tetradeoxypropionate fragment.

1.3 Total syntheses of insect lipids

1.3.1 Kitching's total synthesis of different diastereoisomers of lipids (7) and (8)

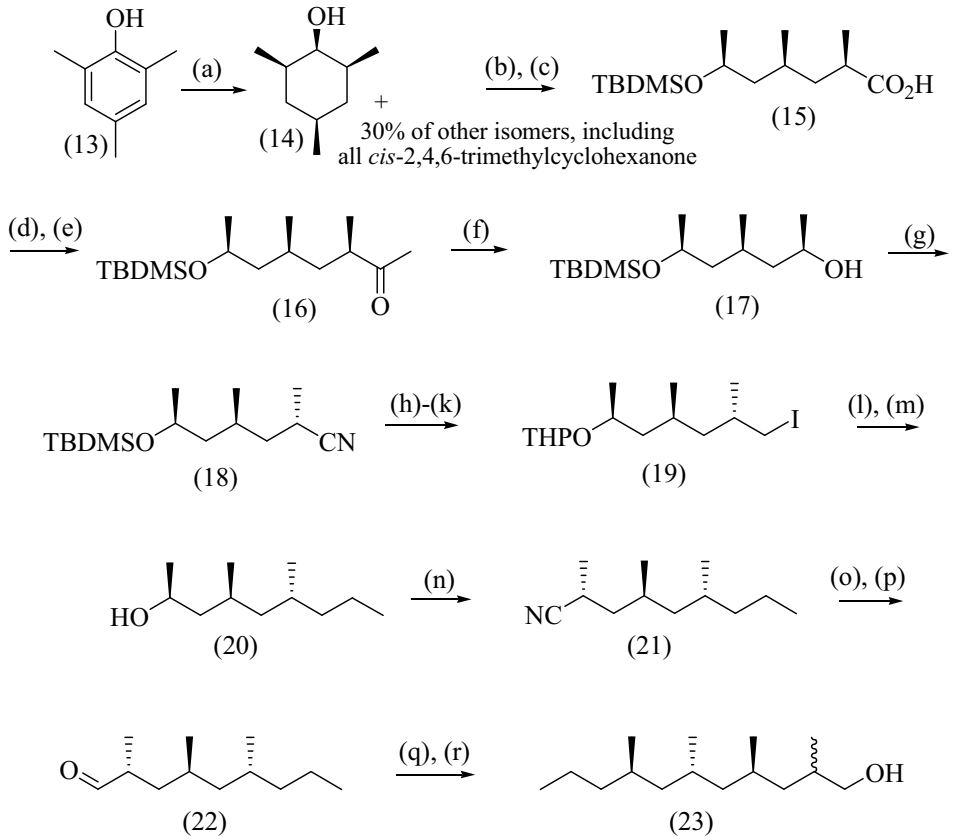
In 2003, Kitching and co-workers reported the first work on the synthesis of lipids (7) and (8) by making all possible diastereoisomers *via* route based on existing methodology [3,5]. A Wittig coupling approach was adopted for assembly for this system, based on the connection shown in Scheme 1. A tetramethyl fragment (10) was coupled with mono- (11) and dimethyl-substituted (12) fragments to furnish alkene (13), which was then undergo hydrogenation to afford stereoisomers of the target molecules (7) and (8).



Scheme 1 Retrosynthesis of lipids (7) and (8).

The synthesis of the tetramethyl substituted isomers began with reduction of 2,4,6-trimethylphenol (13) under forcing conditions (400-500 psi H_2) with a Rh-C catalyst for three days to give mainly the *all-cis*-cyclohexanol (14). Jones oxidation affected conversion of the product to the cyclohexanone with predominantly *all-cis* methyl groups had a Baeyer-Villiger oxidation, methanolysis, silyl protection and hydrolysis provided the silyl-protected hydroxyacid (15). This compound was converted to the methyl ketone (16) *via* the corresponding Weinweb amide. The ketone underwent a slow but efficient Baeyer-Villiger reaction to give the monoprotected diol (17). A one carbon chain extension by displacement of mesylate prepared from alcohol (17) by cyanide with inversion led to the desired protected hydroxyl-nitrile (18) which was then hydrolysed, protected and converted into the iodide (19). A two-carbon extension, followed by deprotection of *tert*-

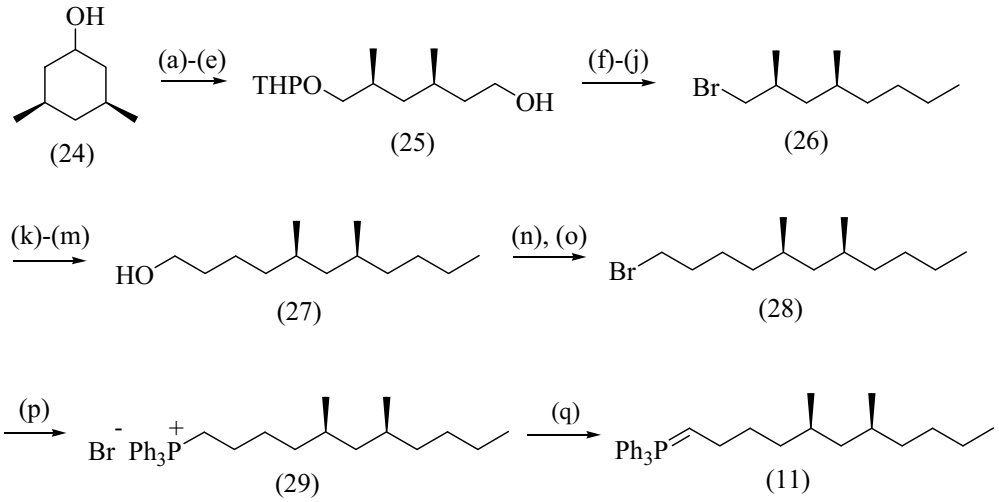
butyldimethylsilyl group afforded alcohol (20). A further one-carbon elongation, again with inversion gave the *anti-anti*-nitrile (21) and hence the aldehyde (22). Condensation with an ester phosphonate and reduction with magnesium-methanol and lithium aluminium hydride afforded *anti-anti-anti-* and *anti-anti-syn*-2,4,6,8-tetramethylundecan-1-ol (23) (Scheme 2).



Scheme 2 Synthesis of tetramethylundecan-1-ol (23).

Reagents and conditions: (a) Rh-C, H_2, 400-500psi, 3 days; (b) (i) Jones reagent, H_2O/ H_2SO_4, acetone, (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 48% (over 3 steps), (iii) NaOMe, MeOH, (iv) TBDMSCl, DMAP, NEt_3, toluene, 86% (over 2 steps); (c) LiOH, MeOH/ H_2O (4:1), 93%; (d) (i) EDC·HCl, NEt_3, CH_2Cl_2 then HOBT, (ii) $CH_3(CH_3O)NH{\cdot}HCl$, NEt_3, CH_2Cl_2, 71%; (e) MeMgI, THF, 88%; (f) (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, (ii) K_2CO_3, MeOH, 69% (over 2 steps); (g) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaCN, DMF, 66% (over 2 steps); (h) AcCl, MeOH, 70%; (i) DHP, TsOH, CH_2Cl_2, 85%; (j) $LiAlH_4$, Et_2O, 93%; (k) PPh_3, I_2, imidazole, THF, 97%; (l) EtMgBr, Li_2CuCl_4, THF, 70%; (m) *p*-TsOH, MeOH, 99%; (n) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaCN, DMF, 62% (over 2 steps); (o) AcCl, MeOH, 74%; (p) $LiAlH_4$, Et_2O (100%); (q) (i) $(COCl)_2$, DMSO, CH_2Cl_2, (ii) $Ph_3PC(CH_3)CO_2Et$, CH_2Cl_2, 64% (over 2 steps); (r) (i) Mg, MeOH, (ii) $LiAlH_4$, Et_2O, 61% (over 2 steps).

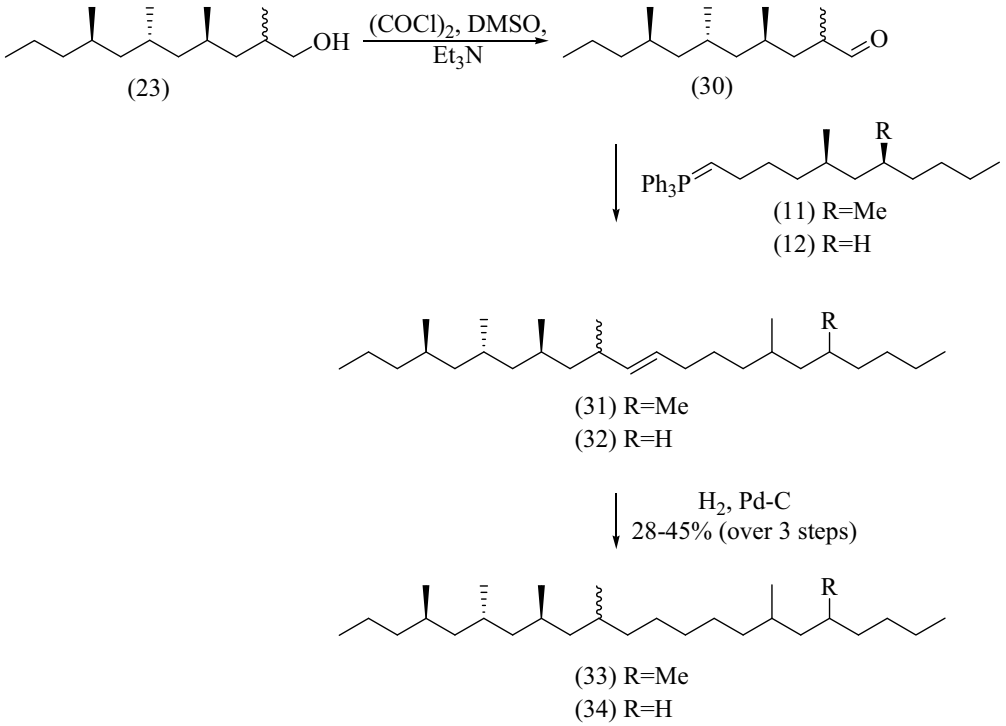
Using a similar strategy, but starting with *cis*-3,5-dimethylcyclohexanol (24) afforded the phosphonium salt (29), and deprotection with *n*-butylithium afforded the s*yn*-dimethyl phosphorane (11) as shown in Scheme 3.



Scheme 3 Preparation of dimethylalkyl ylide (11).

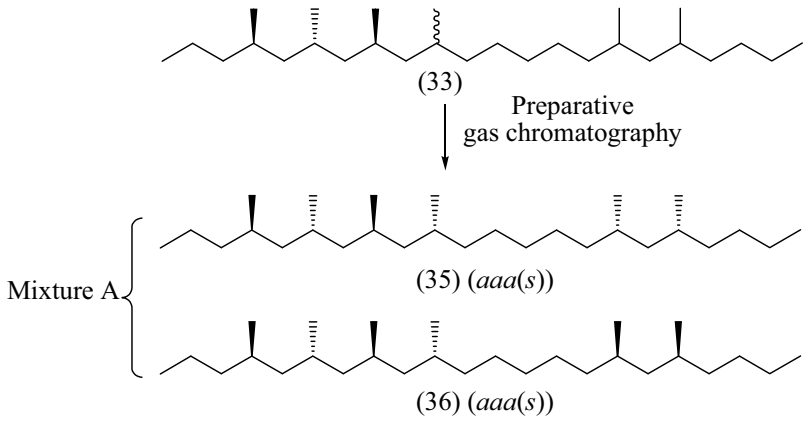
Reagents and conditions: (a) Jones reagent, H_2O/ H_2SO_4, 97%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 74%; (c) NaOMe, MeOH, 93%; (d) DHP, TsOH, CH_2Cl_2, 79%; (e) $LiAlH_4$, Et_2O, 85%; (f) TPAP, NMO, CH_2Cl_2, 85%; (g) EtMgBr, Et_2O, 78%; (h) Et_3N, MsCl, CH_2Cl_2; (i) $LiAlH_4$, Et_2O, 72% (over 2 steps); (j) Br_2, PPh_3, CH_2Cl_2, 81%; (k) AllylMgBr, Et_2O, 86%; (l) BH_3.DMS, EtOH; (m) NaOH, H_2O_2, 58% (over 2 steps); (n) Et_3N, MsCl, CH_2Cl_2; (o) LiBr, THF, heat, 79% (over 2 steps); (p) PPh_3, heat, MeCN, 95%; (q) *n*-BuLi.

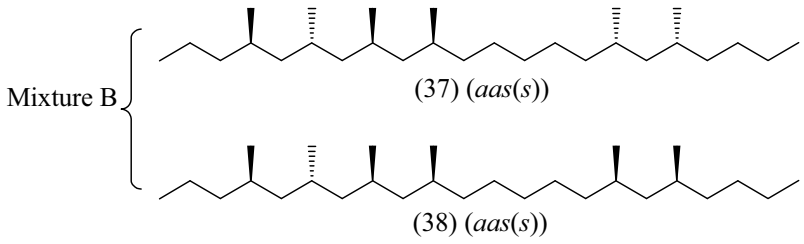
Swern oxidation of the mixture of *anti-anti-anti*- and *anti-anti-syn*-2,4,6,8-tetramethylundecan-1-ols (23) afforded the aldehydes (30) and coupling with the ylide (11) and (12) gave the alkenes (31) and (32), respectively. These were hydrogenated under mild conditions (Pd-C, H_2, 1 atm) to the hydrocarbons (33) and (34) as mixtures of diastereoisomers, see Scheme 4.



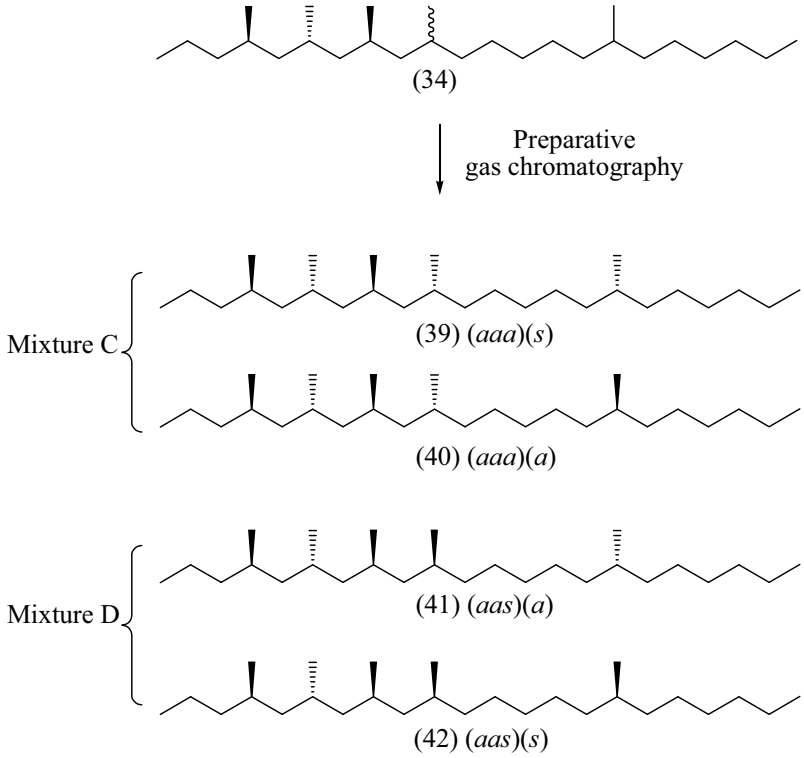
Scheme 4 Synthesis of hexamethyldocosanes and pentamethyldocosanes.

Preparative gas chromatography of hydrocarbons (33) and (34) permitted significant separation of the isomers, leading to mixtures A (compounds (35) and (36)), B (compounds (37 and 38)), C (compounds (39) and (40)) and D (compounds (41) and (42)) as indicated in Schemes 5 and 6.





Scheme 5 Formation of a mixture of four major diastereoisomers of hexamethyldocosanes.



Scheme 6 Formation of a mixture of four major diastereoisomers of pentamethyldocosanes.

The mass spectra of all of the C28 diastereoisomers synthesized were very similar and closely ressembled that of the natural hexamethyldocosane. Co-injection and capillary gas chromatographic comparisons of the synthetic hexamethyldocosane

isomers with the natural component established that the natural compound was a diastereoisomer of the *aaa*(*s*) system, (35) or enantiomer (43), or (36) or enantiomer (44). Similarly the pentamethyldocosane was either shown to be (39) or enantiomer (45), or (40) or enantiomer (46) as shown in Figures 2 and 3 [3,5].

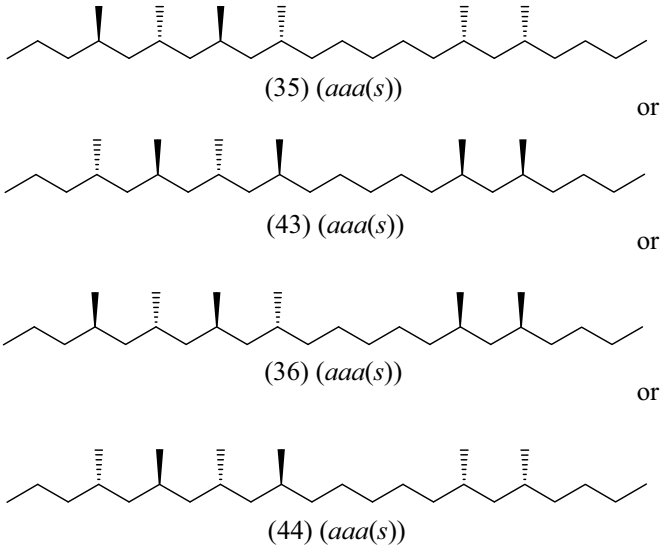


Figure 2 Possible structures of the natural lipid (7).

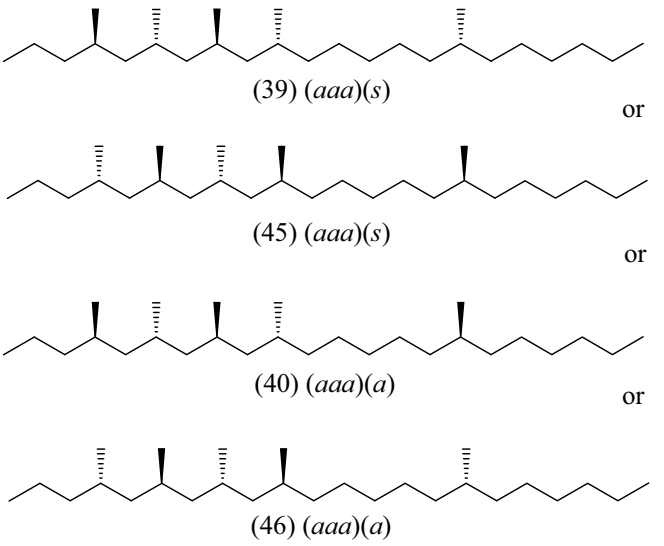
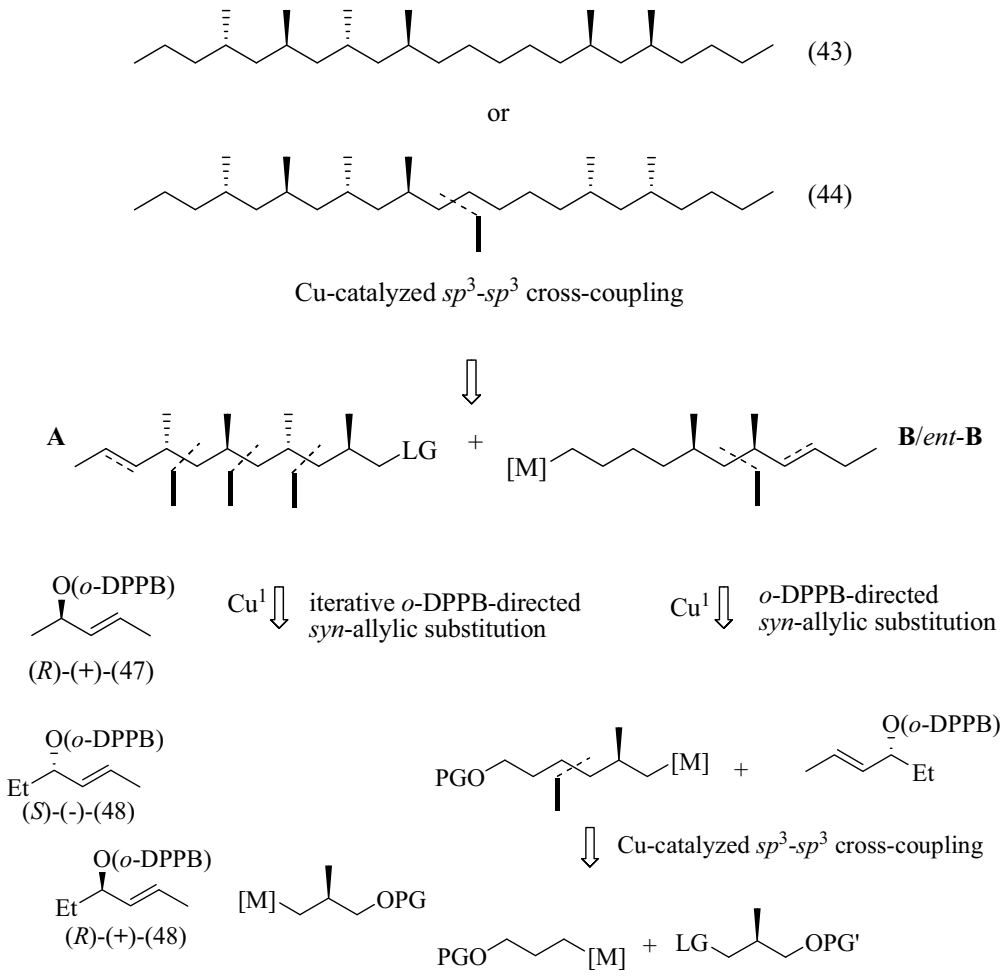


Figure 3 Possible structures of the natural lipid (8).

At this stage, a combined spectroscopic and another techniques have elucidated the relative *anti*-*anti*-*anti*-configuration of the four methyl bearing stereocentres in the tetrad unit of these natural products and the *syn* configuration within the methyl diad region. However the configurations of the all-*anti* tetrad relative to the *syn* diad, as well as the absolute configuration of these natural products were not established. This would require an enantiocontrolled synthesis utilizing the coupling of enantiopure tetramethyl- and dimethyl-substituted fragments [5].

1.3.2 Breit's total synthesis of diastereoisomers of lipids (43) and (44)

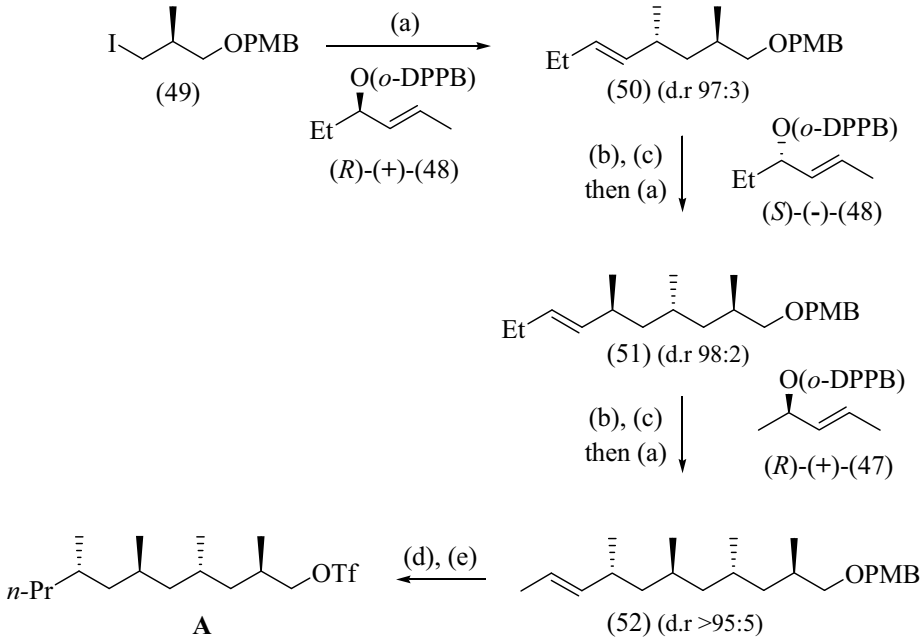
Breit and co-workers have published on the total synthesis of both diastereoisomers of (43) and (44) in enantiomerically pure form, enabling the determination of the relative and absolute configurations of the natural product [6,7]. The synthesis relied on recently developed copper-mediated and *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB)-directed *syn*-allylic substitution with Grignard reagents for iterative deoxypropionate synthesis [8,9]. The power of copper-catalyzed sp^3-sp^3 cross coupling was demonstrated for building block construction and as the fragment-coupling step in a convergent total synthesis as shown in Scheme 7.



Scheme 7 Retrosynthesis for lipids (43) and (44).
PG= protecting group, LG= leaving group, M= metal,
o-DPPB= *ortho*-diphenylphosphanylbenzoyl

The synthesis began with construction of the tetrad building block **A** (Scheme 8). Iodide (49), which was available in three steps from the Roche ester, was converted into a Grignard reagent and subjected to *o*-DPPB-directed *syn*-allylic substitution with allylic *o*-DPPB-ester (*R*)-(+)-(48) in the presence of 0.5 equivalent of copper bromide dimethylsulfide to give the dideoxypropionate (50) with a complete 1,3-chirality transfer. Two separate iterations consisting of three steps, alkene ozonolysis with a reductive workup with $NaBH_4$, transformation to the iodide and directed *syn*-allylic substitution with (*S*)-(-)-(48) and (*R*)-(+)-(47), respectively, furnished the tetradeoxypropionate (52) with all the carbon atoms and stereocenters

in place. Alkene hydrogenation and reductive cleavage of the *p*-methoxybenzyl ether occurred upon heterogenous catalytic hydrogenation to give building block A which was activated as the corresponding triflate prior to fragment coupling.

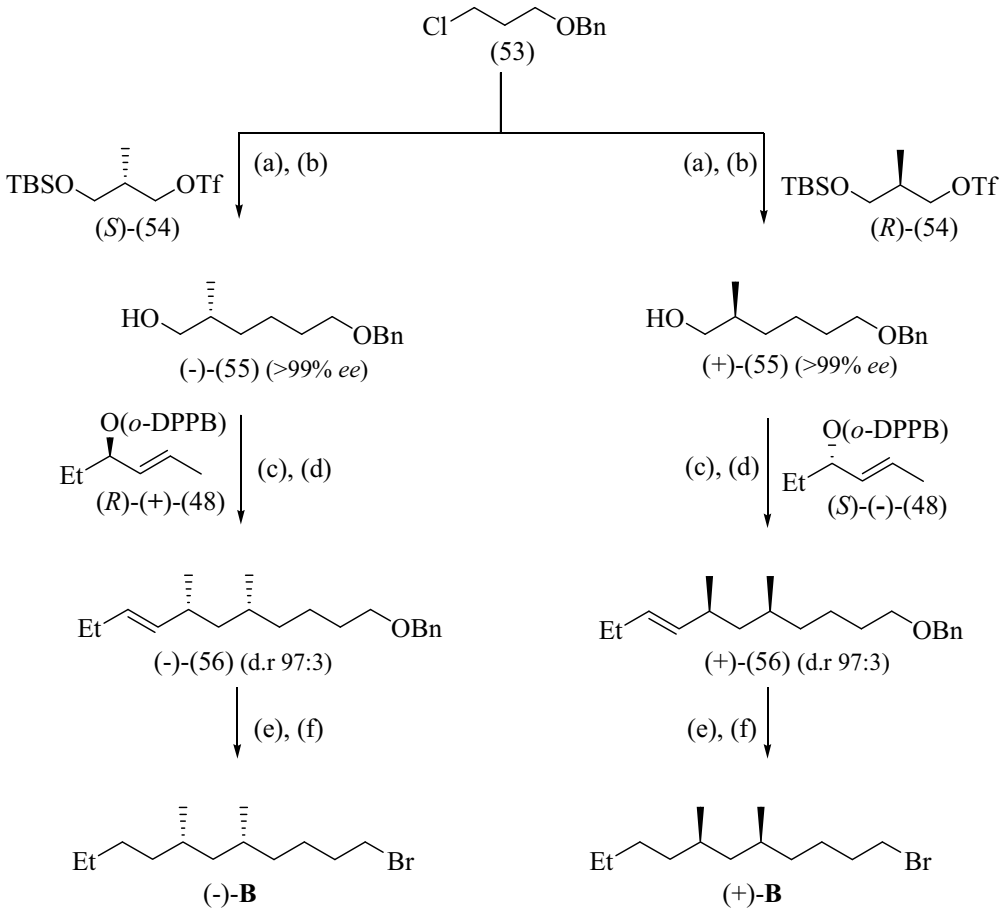


Scheme 8 Synthesis of tetradeoxypropionate building block **A**.

Reagents and conditions: (a) 2 *t*-BuLi, $MgBr_2.OEt_2$, then (*R*)-(48), (*S*)-(48) or (*R*)-(47), $CuBr.SMe_2$, Et_2O, 83%-85%; (b) O_3, $NaBH_4$, 95%; (c) Imidazole, PPh_3I_2, 92%; (d) PtO_2, H_2 (5 bar) then $Pd(OH)_2$, 98%; (e) Tf_2O, NEt_3, CH_2Cl_2, -78ºC, 97%.

Synthesis of the enantiomeric dideoxypropionate building blocks **B** commenced with the chloride (53) (Scheme 9). Triflates (*S*)-(54) and (*R*)-(54) underwent a copper catalyzed cross coupling at -20°C in the presence of 4 mol% of $[Li_2CuCl_4]$ with the Grignard reagent derived from the chloride (53) followed by desilylation of the crude coupling products with methanolic hydrogen chloride to give alcohols (-)-(55) and (+)-(55) respectively in 82% isolated yield over the two steps. A Mukaiyama redox condensation furnished the corresponding iodides, which were subjected for the directed *syn*-allylic substitution with (*R*)-(+)-(48) and (*S*)-(-)-(48), respectively, to furnish the dideoxypropionates (-)-(56) and (+)-(56) in

excellent yields with complete diastereoselectivities. A standard functional group manipulation thus led to the building blocks (-)-**B** and (+)-**B**.

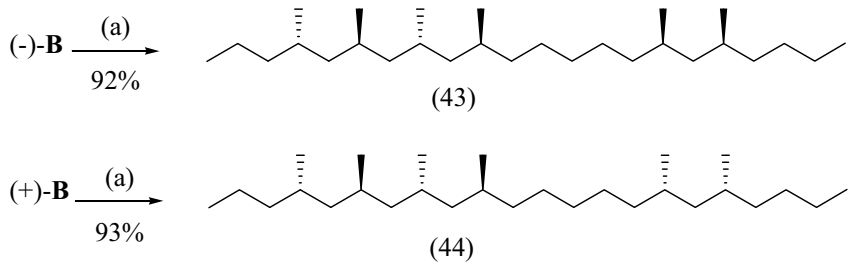


Scheme 9 Synthesis of the enantiomeric dideoxypropionate building blocks (-)-**B** /(+)-**B**.

Reagents and conditions: (a) Mg, THF, [Li_2CuCl_4] (4 mol%), then (*S*)-(54) or (*R*)-(54); (b) 5% HCl in MeOH, 82% over 2 steps; (c) PPh_3I_2, Imidazole, CH_2Cl_2, 93%; (d) 2 *t*-BuLi, $MgBr_2.OEt_2$ then (*R*)-(48) or (*S*)-(48), CuBr.SMe_2, Et_2O, 85%; (e) H_2, PtO_2, EtOAc, 12 h then H_2, Pd-C (10%) 24 h, 96%; (f) PPh_3, NBS, 97%.

The final coupling step (Scheme 10) employing a copper-catalyzed sp^3-sp^3 cross coupling of the Grignard reagent derived from (-)-**B** or (+)-**B** with triflate **A**. Addition of an ethereal solution of the triflate together with 4 mol% of the catalyst [Li_2CuCl_4] to an ethereal solution of the Grignard reagent derived form of **B** afforded

both distereoisomers (43) and (44) in an excellent yields. Comparison of ^{13}C NMR spectrum of synthetic and natural material showed a perfect match for diasteroisomer (43) [6,7]. Comparison of the optical rotation values of the natural and synthetic material determined the absolute configuration of the natural products of (43) and (44) as shown in Scheme 10.

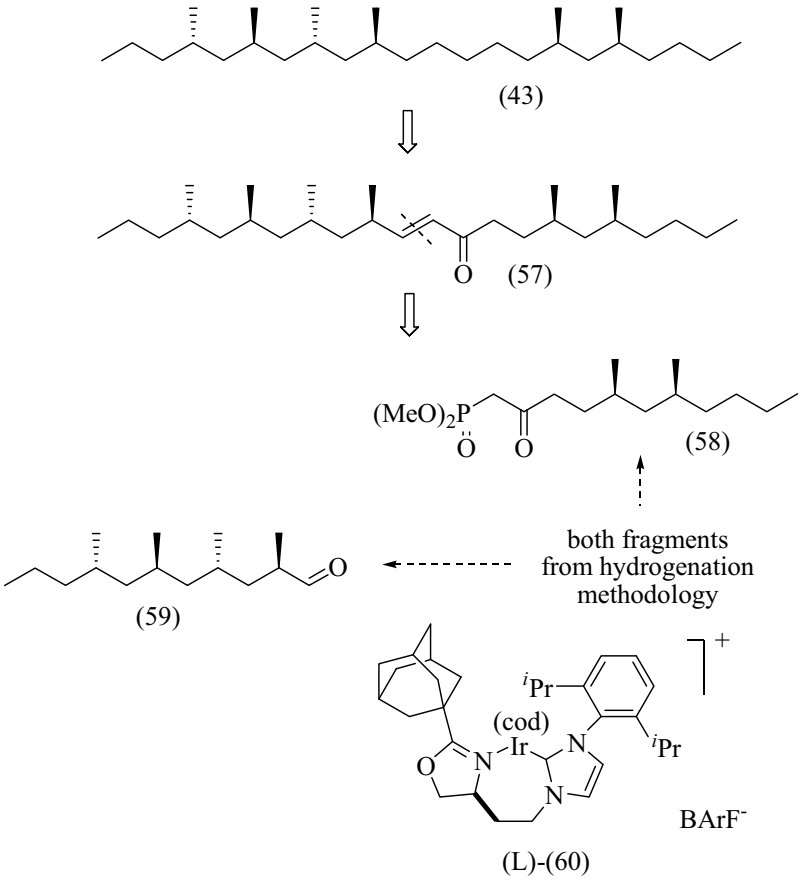


Scheme 10 Fragment coupling through Cu-catalyzed sp^3-sp^3 cross coupling.

Reagents and conditions: (a) Mg, Et_2O, $BrCH_2CH_2Br$ (0.4 equiv), $[Li_2CuCl_4]$ (4 mol%), then **A**.

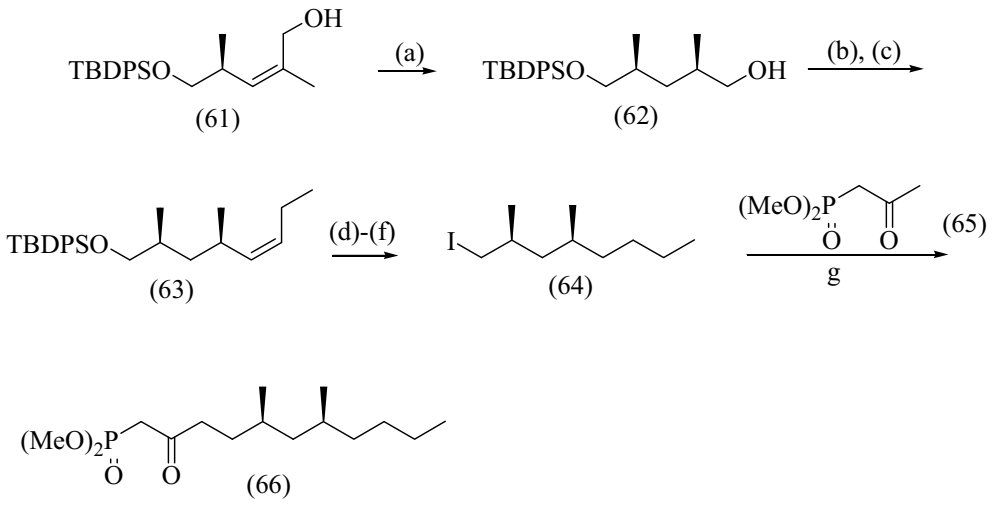
1.3.3 Burgess's total synthesis of lipid (43)

Burgess and co-workers [10] have developed a catalyst-controlled diastereoselective hydrogenation methodology for the syntheses of deoxypolyketide chirons. They have carried out considerable work on the used of carbene oxazoline complexes e.g. (L)-(60) on a broad range of substrates for which most other chiral catalysts are not effective [11]. A chiral analogue of Crabtree's catalyst, (L)-(60) was used in asymmetric hydrogenation of allylic alcohols and unsaturated esters with excellent diastereoselectivity [12]. Scheme 11 outlines the retrosynthetic approach towards a synthesis of lipid (43).



Scheme 11 Retrosynthetic analysis of lipid (43) according to Burgess.

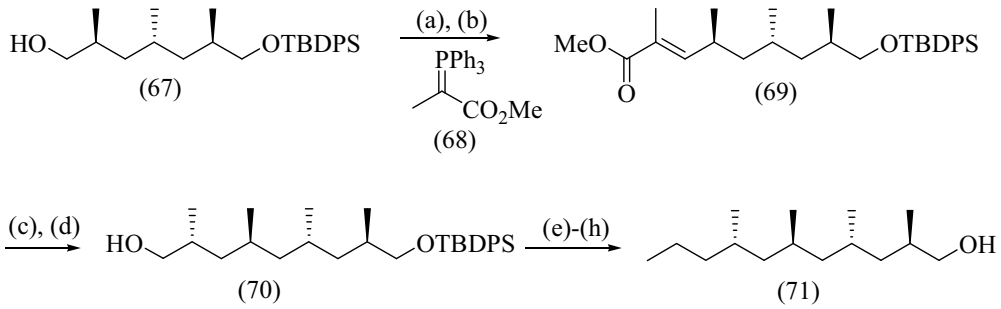
The allylic alcohol (61) was prepared in 87% yield over three steps from the commercially available Roche ester. Asymmetric hydrogenation of this *Z*-allylic alcohol with catalyst L-(60) favored the *syn*-product (62) [11]. The crude material formed in this step had a 34:1 *syn*- to *anti*-diastereomeric ratio as shown by GC analysis and 93% yield of 120:1 *syn*- to *anti*-product after chromatographic purification. Conversion of the alcohol (62) to the alkene (63) under Swern and Wittig conditions and subsequent reduction by heterogeneous hydrogenation produced the corresponding alkane which was desilylated and converted to the iodide (64). Alkylation of the dianion of keto-phosphonate (65) afforded keto-phosphonate (66) with the *syn* relative stereochemistry in 79% yield (Scheme 12).



Scheme 12 Synthesis of the eastern part of lipid (43).

Reagents and conditions: (a) 50 atm H_2, 0.2 mol% L-(60), CH_2Cl_2, 25ºC, 93%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78ºC, 10 min; (c) KHMDS, *n*-$PrPPh_3Br$, THF,-78ºC, 2h, 83%; (d) H_2, Pd-C, MeOH/ THF, 25ºC, 7 h, 99%; (e) TBAF, THF, 25ºC, 2 h; (f) PPh_3, I_2, imidazole, CH_2Cl_2, 25ºC, 30 min 86%; (g) (65), NaH then *n*-BuLi, 0ºC, 1 h, 79%.

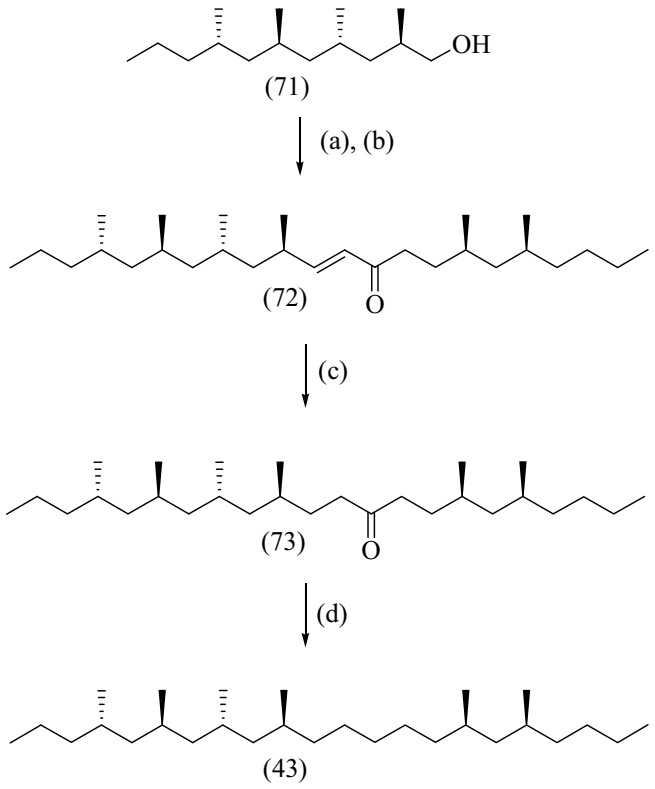
The western part of lipid (43) derived from aldehyde (59) contains a stereochemical tetrad. Alcohol (67) was prepared from the commercially available Roche ester. The *anti*-*anti*-stereochemical triad in the structure was obtained from the asymmetric hydrogenation using chiral analogue of Crabtree's catalyst [11,12]. Alcohol (67) was converted to the ester (69) in 80% yield, which was reduced using catalyst L-(60) with high stereoselectivity. The crude material was further reduced to alcohol (70) using di*iso*butylaluminium hydride. Oxidation of this alcohol followed by a Wittig reaction of the resultant aldehyde and heterogeneous hydrogenation followed by treatment with tetrabutylammonium fluoride resulted in desilylation to form the *anti*-*anti*-*anti*-tetramethyl intermediate (71) in 84% yield (Scheme 13).



Scheme 13 Synthesis of the western part of lipid (43).

Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, 25ºC, 30 min, 65%; (b) (68), PhMe, 80ºC, 12 h; (c) 50 atm H_2, 1 mol% L-(60); CH_2Cl_2, 25ºC, 4 h; (d) DIBAL-H, THF, 0ºC, 30 min, 80%; (e) TPAP, NMO, CH_2Cl_2, 25ºC, 30 min; (f) KHMDS, $EtPPh_3Br$, THF, -78ºC, 1 h; (g) H_2, Pd-C, MeOH/ THF, 25ºC, 7 h, 76%; (h) TBAF, THF, 25ºC, 1.5 h, 84%.

The synthesis of the target molecule (43) from the alcohol (71) using the aldehyde (59) and the phosphonate (66) was accomplished as shown in Scheme 14. The Horner-Wadsworth-Emmons coupling followed by heterogeneous hydrogenation of alkene (72) gave ketone (73). Reduction of the ketone tosylhydrazone using sodium cyanoborohydride gave lipid (43) in a good yield. The proton and ^{13}C NMR spectra of the synthetic product (43) were essentially identical to those reported in the literature by Kitching [3,5] and Breit [6,7].



Scheme 14 Completion of the synthesis of lipid (43).

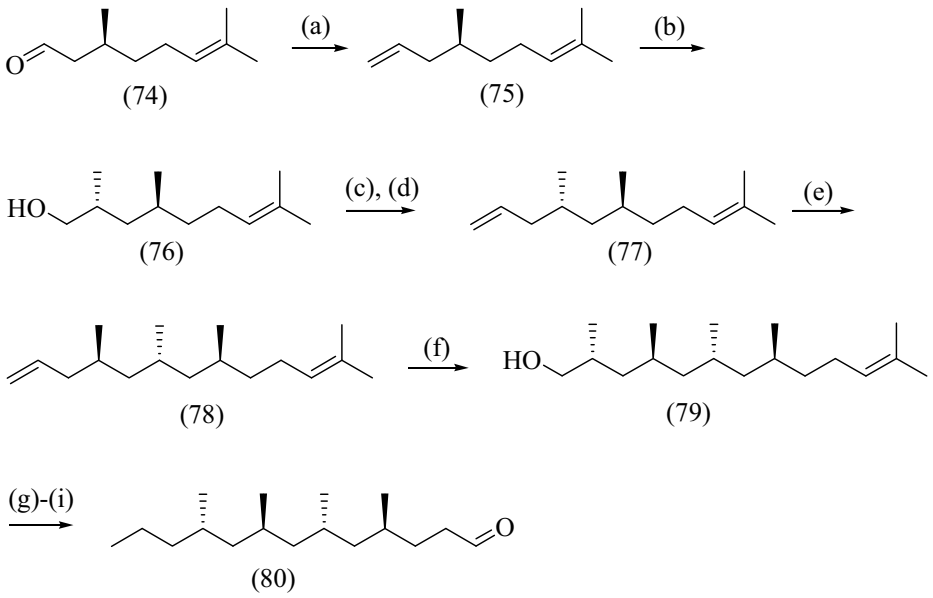
Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, 25ºC, 30 min; (b) $Ba(OH)_2$, then (66), wet THF, 25°C, 15 min, 86%; (c) H_2, Pd-C, MeOH/ THF, 25ºC, 4 h, 99%; (d) $TsNHNH_2$, $NaBH_3CN$, TsOH, DMF/ sulfolane, 110ºC, 2 h, 94%.

1.3.4 Negishi's total synthesis of lipid (43)

Negishi and co-workers have developed an efficient and enantio-face selective Zr-catalyzed asymmetric carboalumination (ZACA) reaction [13,14,15] which provides access to enantioselective carbon-carbon bond formation using terminal alkenes.

The terminal alkene (75) prepared from (*S*)-β-citronellal (74) using a simple Wittig reaction, reacted with Me_3Al in the presence of (-)-bis-(neomenthylindenyl)zirconium dichloride, (-)-$(NMI)_2ZrCl_2$ in dichloromethane at

23°C with oxidation of the carboalumination product with O_2 gave the alcohol (76) in a 60% yield. The purification of (76) was achieved by Amano PS lipase-catalyzed acetylation leading to higher recovery than that observed by chromatographic purification [13]. Installation of terminal olefin in (76) was achieved *via* a Pd-catalyzed vinylation of the primary iodide. Iteration of the Zr-catalyzed carboalumination of diene (77) followed by a Pd-catalyzed vinylation gave the terminal olefin (78) and subsequent iteration followed by quenching with O_2 gave end-differentiated deoxypropionate (79). The alcohol (79) was then subjected to standard reactions to give aldehyde (80) as shown in Scheme 15.

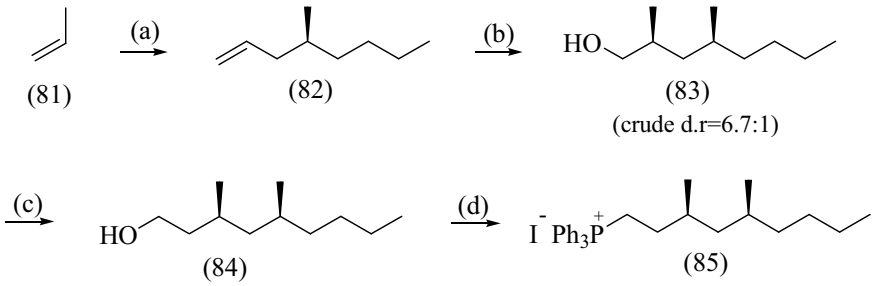


Scheme 15 Synthesis of the C1-C13 fragment.

Reagents and conditions: (a) CH_2=PPh_3, 95%; (b) (i) Me_3Al (2 equiv), (-)-$(NMI)_2ZrCl_2$ (4 mol%), CH_2Cl_2, 23°C, (ii) O_2, (iii) Amano PS lipase (30 mg/ mmol), vinyl acetate (5 equiv), CH_2Cl_2, 60%; (c) I_2, PPh_3; (d) (i) *t*-BuLi, Et_2O, -78°C, (ii) dry $ZnBr_2$, THF, (iii) CH_2=CHBr (3 equiv), $Pd(PPh_3)_4$ (2 mol%), 79% (over 2 steps); (e) (i) Me_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (3 mol%), CH_2Cl_2, (ii) evaporation of CH_2Cl_2 and Me_3Al, (iii) Dry $Zn(OTf)_2$ (1 equiv), DMF, 2 h, 70°C, (iv) Pd (DPEphos)Cl_2 (3 mol%), DIBAL-H (6 mol%), CH_2=CHBr (3 equiv), DMF, 70%; (f) (i) Me_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (4 mol%), CH_2Cl_2, 23°C, (ii) O_2, 45%; (g) TsCl, Et_3N; (h) EtMgBr, Li_2CuCl_4 (5%); (i) NMO (3 equiv), OsO_4 (1 %) then $NaIO_4$, 89% (over 3 steps).

The preparation of the *syn*-dimethylalkyl derivatives (83), (84) and (85) used a fully catalytic and reagent-controlled enantio-face selective ZACA route from

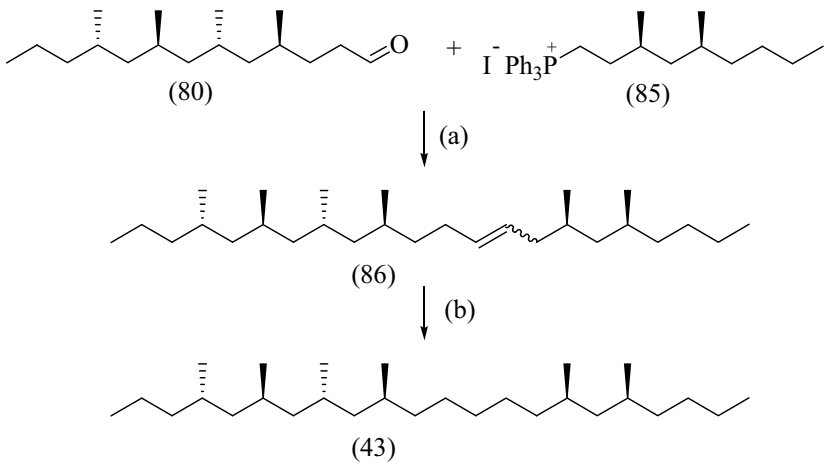
propene (81), as shown in Scheme 16. Transformation of (81) into the terminal olefin (82) set up a second stage asymmetric carboalumination in the presence of the same chiral Zr catalyst to give alcohol (83), which was highly enriched in the *syn* isomers, after isolation by chromatography. After hydroxyl group manipulations and a one carbon chain extension, the phosphonium salt (85) was prepared.



Scheme 16 Synthesis of the C14-C22 fragment.

Reagents and conditions: (a) (i) *n*-Bu_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (3 mol%), CH_2Cl_2, (ii) evaporation of CH_2Cl_2 and Me_3Al, (iii) dry $Zn(OTf)_2$ (1 equiv), DMF, 2 h, 70°C, (iv) Pd (DPEphos)Cl_2 (3 mol%), DIBAL-H (6 mol%), CH_2=CHBr (3 equiv), DMF, 67%; (b) (i) Me_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (4 mol%), CH_2Cl_2, 23°C, (ii) O_2, 48%; (c) (i) I_2, PPh_3, (ii) *t*-BuLi then HCHO, 83% (over 2 steps); (d) (i) I_2, PPh_3, (ii) PPh_3, toluene, 85% over 2 steps.

With the two key intermediates (80) and (85) as isomerically pure compounds, the final assembly of the target compound (43) was achieved in 85% yield by two steps *via* Wittig olefination and catalytic hydrogenation with H_2 over Pd-C (Scheme 17). The desired product (43) obtained exhibited ^1H and ^{13}C NMR spectra as well as an optical rotation which were in a good agreement with those reported previously [5,7,10].



Scheme 17 Final assembly of (43).

Reagents and conditions: (a) *n*-BuLi, THF; (b) H_2, Pd-C, 85% (over 2 steps).

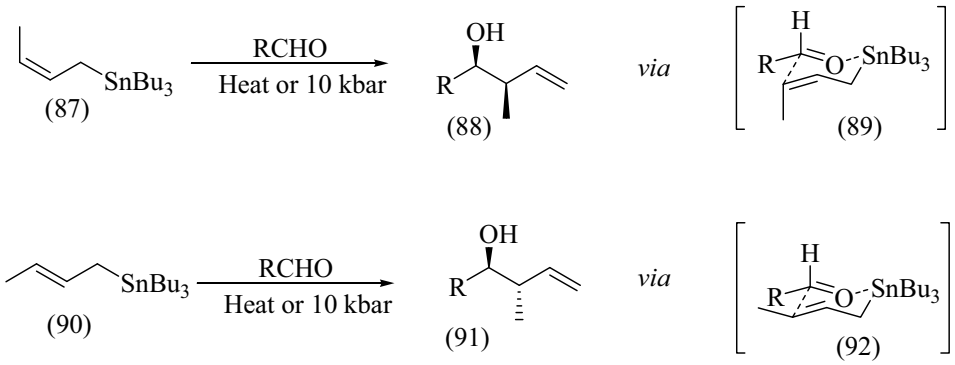
1.4 Remote Asymmetric Induction

Reactions leading to the control of the relative stereochemisty of two stereogenic centres are of great importance. Numerous reactions have been developed for effective 1,2- and 1,3-stereoinduction. As the separation of the two stereogenic centres extends further, stereoinduction becomes more difficult. This is especially the case for acyclic systems as they are intrinsically less ordered than their cyclic counterparts. In the area of acyclic stereocontrol there are now many excellent methods that give high 1,4-, 1,5-, 1,6- and 1,7-stereocontrol. This chapter is intended to review the highlights in this area for reactions that produce remote stereocontrol using the addition of an allyl-metal reagent to a carbonyl functionality to form a homoallylic alcohol with high enantio- and diastereocontrol [16]. A few representative examples of application of this chemistry in natural product synthesis are presented in the following chapter to show the diversity of this reaction.

1.5 Reactions of allylstannanes

1.5.1 Thermal reactions of alkylallylstannanes with aldehydes

The configurationally stable crotylstannanes have been shown to undergo highly diastereoselective reactions with aldehydes on heating to high temperatures [17]. The stereochemistry in thermal reactions of allylic tin derivatives generally depends upon the geometry of the but-2-enyl unit, as observed in ordinary allylic organometallic reactions. For example, as in Scheme 18, the (*Z*)-crotylstannane (87) produced the *syn*-homoallylic alcohol (88), while the (*E*)-isomer (90) afforded the *anti*-homoallylic alcohol (91) on heating with aldehydes [18]. The reaction of allylic trialkyltins with aldehydes also takes place at room temperature under neutral conditions by using the high-pressure technique (10 kbar in CH_2Cl_2 or Et_2O). The stereochemical outcome is the same as that in thermal reactions [19].

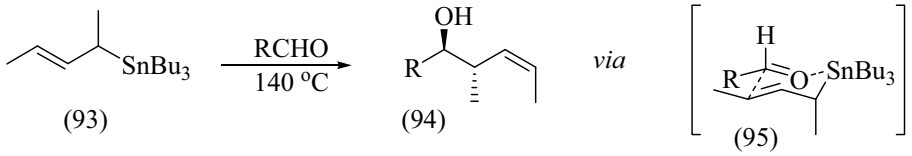


Scheme 18 Reaction of crotylstannanes with aldehyde on heating.

The stereoselectivities of these reactions are consistent with six-membered chair-like transition states (89) and (92). In these transition states, the metal is coordinated to the carbonyl oxygen and the larger R group of the aldehyde adopts an equatorial orientation. The attack at the carbonyl carbon is from the γ-position of the stannane double bond, with a concomitant allylic shift and migration of the tin to the

aldehyde oxygen. The trialkyltin group is then removed by hydrolysis on work-up [20].

The α-alkyl substituted crotylstannane (93) (*E*:*Z*-isomers, 90:10) produced the *anti*-homoallylic alcohol (94) containing a (*Z*)-double bond when heated with aldehyde [21]. The stereoselective origin of the reaction was interpreted in terms of the chair-like transition state (95) in which the methyl substituent α to tin, adopts an axial position (Scheme 19). No products arising from the (*Z*)-crotylstannane was isolated perhaps because of an unfavourable 1,3-diaxial interaction between an axial α-methyl group and the *cis*-disposed vinylic methyl group in the transition state analogous to (95).



(93) (94) (95)

Scheme 19 Reactions of α-alkyl crotylstannanes with aldehydes on heating.

A limitation to these thermal reactions of allylstannanes is the high temperatures required. This can lead to a competing self condensation reaction when primary alkyl aldehydes are used. Alternative procedures have been developed to overcome this problem. These include high pressure [19,22] photolysis [23] and more commonly, the use of a Lewis acid to activate the aldehyde, but this gave rise to different diastereoisomers.

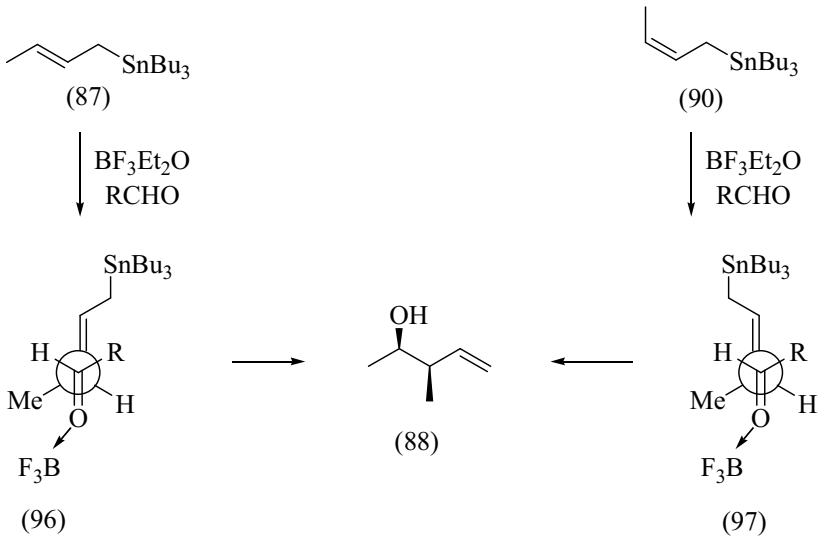
1.5.2 Lewis acid promoted reactions of alkylallylstannanes with aldehydes

Lewis acid activated reactions of alkylallylstannanes with aldehydes occur readily at low temperatures, typically at -78ºC. The structures of the products can be controlled by the choice of Lewis acid since there are two distinctly different reaction pathways available [24]. On the one hand, the transmetallation can take place between the Lewis acid and the allylstannane to form a more reactive allylmetal

species. Alternatively, the Lewis acid may coordinate to the carbonyl oxygen of the aldehyde, activating the carbonyl carbon to nucleophilic attack. Which process is preferred depends on the metal and/ or the Lewis acid used. Changing the Lewis acid can radically alter the regio- and stereochemistry of the products.

(*E*)- And (*Z*)-crotylstannanes (87) and (90) undergo stereoconvergent reactions with aldehydes in the presence of boron trifluoride diethyl etherate to give almost exclusively *syn*-homoallylic alcohol (88) [25]. This result is irrespective of the double-bond geometry of the crotylstannane (Scheme 20).

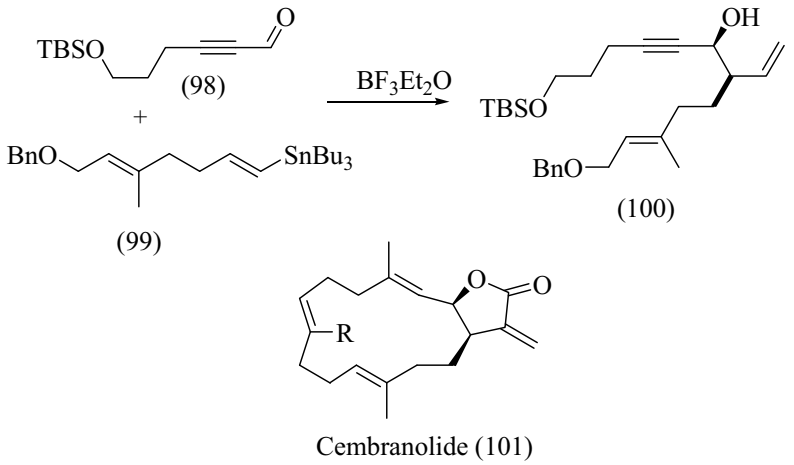
The *syn*-stereochemistry of these reactions cannot be explained by a conventional cyclic chair-like transition state. Instead, these reactions are believed to proceed *via* the open-chain, acyclic, transition states (96) and (97), in which the carbonyl oxygen is coordinated to the Lewis acid, thus preventing coordination by stannane [26]. Attack of the carbonyl group takes place from the γ–position of the stannane.



Scheme 20 Boron promoted reactions of crotylstannanes.

In connection with a synthesis of the cembranolide (101) [27], the boron trifluoride diethyl etherate mediated intermolecular reaction of the aldehyde (98)

with the allylstannane (99) was employed to form cembranolide precursor (100) as shown in Scheme 21.

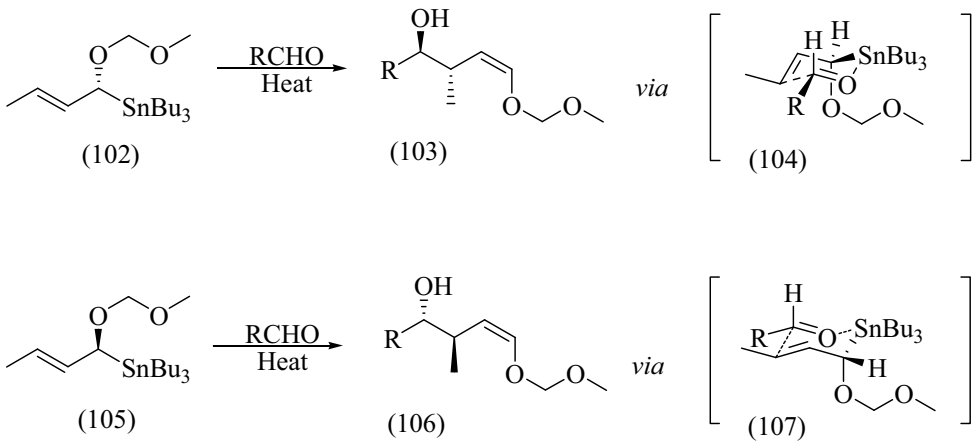


Scheme 21 An application of boron trifluoride diethyl etherate mediated reactions of allylstannanes.

1.5.3 α-Alkoxyallystannanes

The introduction of heteroelements into allylstannanes would be expected to enhance their applicability in synthesis. Reactions of alkoxyallylstannanes with aldehydes give rise to polyoxygenated products, and the oxygen in the substituent may influence the stereochemical outcome of reactions with aldehydes.

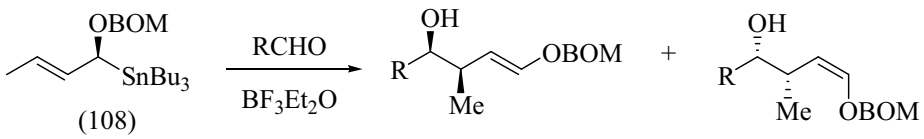
Thermal reactions of enantiomeric α-alkoxyallylstannanes (102) and (105) with aldehydes have been shown to give the *anti*-(*Z*)-enol ethers (103) and (106), respectively, [28] as shown in Scheme 22.



Scheme 22 Thermal reactions of α-alkoxy-(*E*)-allystannanes with aldehydes.

These products are believed to arise from the cyclic six-membered chair-like transition states, (104) and (107), in which the chiral α-alkoxyallylstannanes react with one face of the prochiral aldehyde with the alkoxy substituent α to tin adopting the axial orientation. This is consistent with the observation that α-alkoxy-(*Z*)-allylstannanes are much less reactive than the corresponding (*E*)-isomer [29]. The axial preference of the substituent α to tin would lead to severe 1,3-diaxial interactions in the transition state leading to products.

The addition of boron trifluoride diethyl etherate to the reactions of a chiral α-alkoxyallylstannane with an aldehyde reduces the reaction temperature required and change the stereochemical outcome (Scheme 23). For example, the reactions between the α-alkoxyallylstannane (108) and aliphatic aldehydes in the presence of boron trifluoride diethyl etherate gave rise predominantly to the *syn*-(*E*)-product (109) possibly *via* an open-chain antiperiplanar transition state [30]. When aromatic aldehydes were used, the *syn*-(*Z*)-product (110) was formed as the major product *via* a synclinal transition state. This may be due to differences in the structure of the aldehyde/ boron triflouride complexes [31].

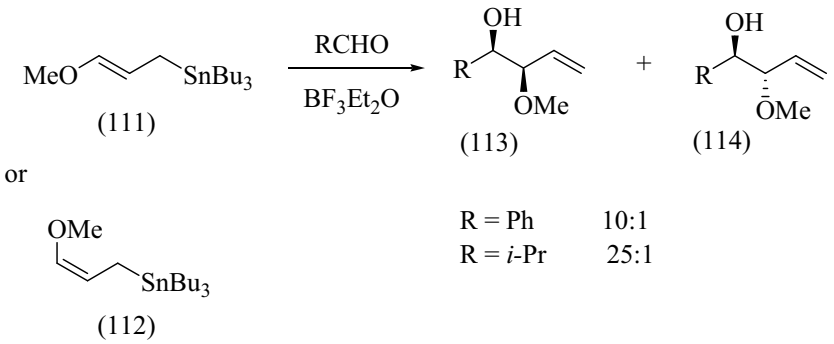


	syn-(*E*)	*syn*-(*Z*)
R = Alkyl	<1	>95
R = Aryl	80	20

Scheme 23 Boron trifluoride diethyl etherate promoted reactions of chiral α-alkoxyallylstannanes with aldehydes.

1.5.4 γ-Alkoxyallystannanes

The boron trifluoride diethyl etherate activated reactions of γ-alkoxyallystannanes of compounds (111) or (112) with aldehydes gave rise to mono-protected 1,2-diols (113) and (114) as shown in Scheme 24. The reactions afford predominantly *syn*-mono-protected diols (113), suggesting that an open chain antiperiplanar transition state is involved [32].

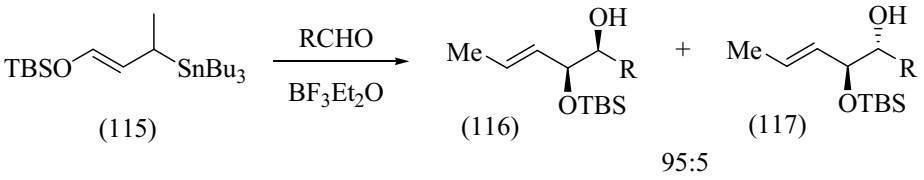


R = Ph 10:1
R = *i*-Pr 25:1

Scheme 24 Boron trifluoride diethyl etherate promoted reactions of γ-alkoxyallylstannanes with aldehydes.

γ-Alkoxyallystannanes with α-alkyl substituents have also been shown to undergo diastereoselective reactions with aldehydes in the presence of boron

trifluoride diethyl etherate. For example, as shown in Scheme 25, α-methyl-γ-alkoxyallylstannane (115) reacts with aldehydes possibly *via* an open-chain transition state to afford the *syn*-(*E*)-product (116) together with inseparable *anti*-(*E*)-isomer (117) [33].



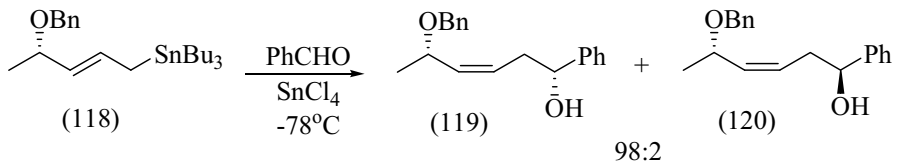
(115) (116) (117)

95:5

Scheme 25 Boron trifluoride diethyl etherate promoted reactions of α-methyl-γ-alkoxyallylstannanes with aldehydes.

1.5.5 δ-Alkoxyallystannanes

The δ-alkoxyallystannane (118) a 70:30 mixture of (*E*):(*Z*)-isomers has been prepared to investigate the influence of an oxygen substituted remote stereogenic centre on the diastereofacial selective reactions of allylstannanes with aldehydes [34,35]. Reaction of this compound with benzaldehyde in the presence of boron trifluoride diethyl etherate or at high temperature led to the formation of branched products. When tin(IV) chloride was reacted with (118) at -78°C followed after timing by the addition of benzaldehyde at this temperature, the linear homoallylic alcohol (119), containing a (*Z*)-double bond was formed with a *syn* (119) to *anti* (120) ratio of 98:2 (Scheme 26). This selectivity was observed to be general for a broad range of aldehydes [36,37].

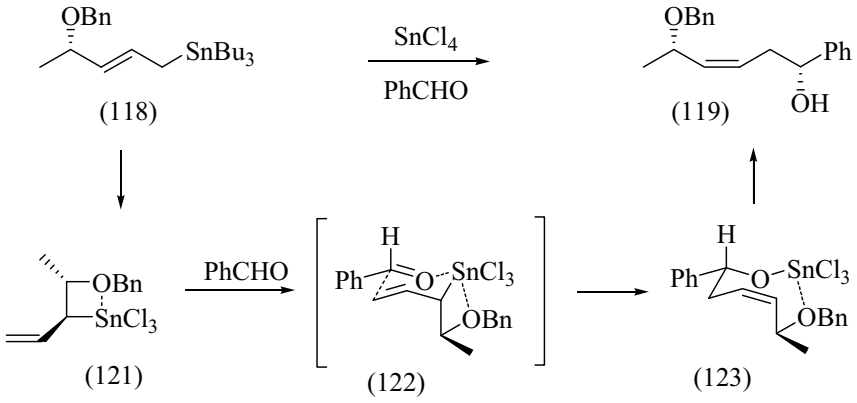


(118) (119) (120)

98:2

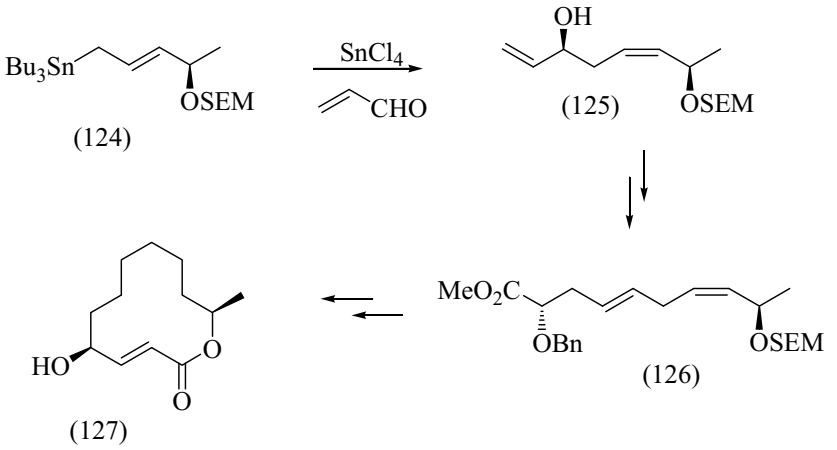
Scheme 26 Reaction of δ-alkoxyallylstannane (118) with $SnCl_4$ and aldehyde.

The formation of the 1,5-*syn*-(*Z*)-product from these reactions is consistent with the allyl(trialkyl)stannane (118) undergoing a stereoselective transmetallation with the tin(IV) chloride to form the allyl(trichloro)stannane (121), in which the methyl and vinyl group are *trans*-disposed [38,39]. This four-membered ring intermediate (121) is highly reactive towards aldehydes and is effectively configurationally stable due to the tin-oxygen interaction which prevents 1,3-isomerisation [40]. Recent work has shown that the proposed stereochemistry of (121) is correct, as treatment of (118) with tin(IV) chloride and an excess of phenylithium resulted in the trapping of this intermediate [41]. The reactions between the intermediate (121) and aldehydes proceed *via* a six-membered chair-like transition state (122) in which the bulky substituent α to tin is in the axial position [42] thus leading to the (*Z*)-double-bond (123). The configuration of the new chiral centre is controlled by the R group of the aldehyde which adopts an equatorial position, so determining which face of the prochiral aldehyde reacts as shown in Scheme 27.

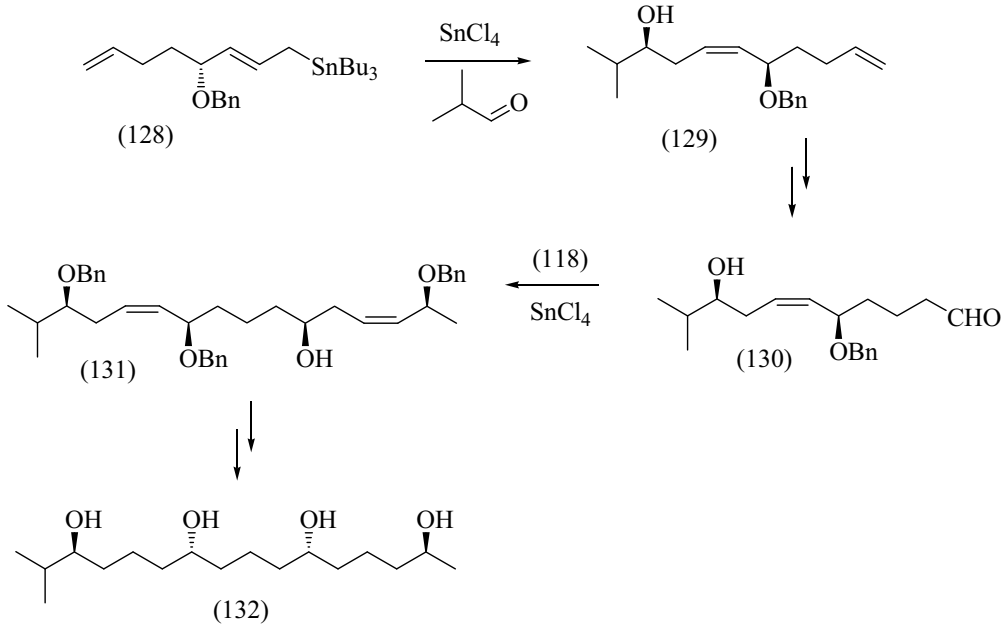


Scheme 27 The mechanism for formation of the *syn*-homoallylic alcohols (119).

Other δ-alkoxypent-2-enylstannanes have been prepared to investigate the applicability of this methodology. For example, the allylstannane (124) was used in a stereoselective total synthesis of patulolide C (127) *via* homoallylic alcohol (125) and ester (126) [36] (Scheme 28). Meanwhile, allylstannane (128) was used to synthesize stereoregular polyols such as compound (132) *via* homoallylic alcohols (129), (130) and (131) [37] (Scheme 29).



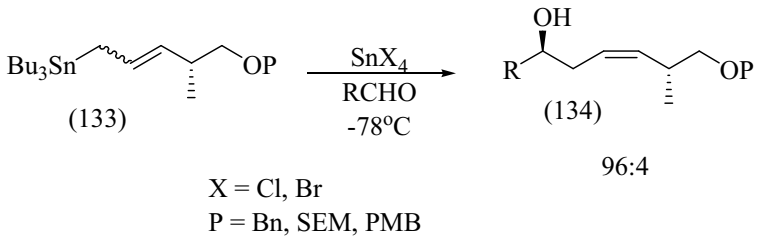
Scheme 28 Total synthesis of patulolide C (127) [36].



Scheme 29 Total synthesis of the stereoregular polyol (132) [37].

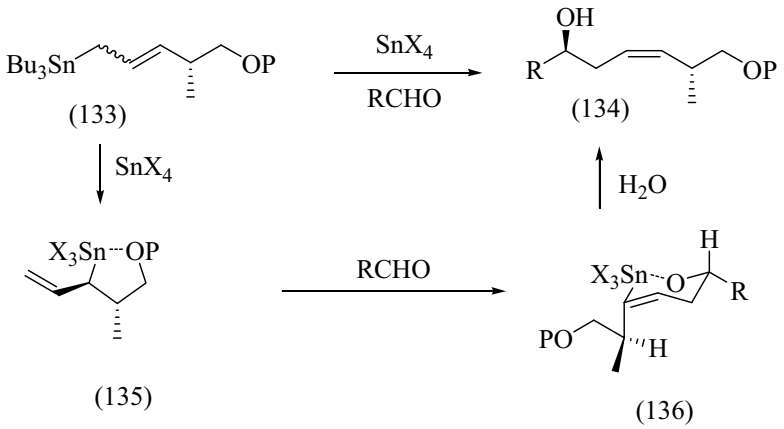
1.5.6 ε-Alkoxyallystannanes [43,44]

Reaction of the 5-substituted pent-2-enylstannanes (133) [35,45,46] with aldehydes at -78°C exhibited excellent 1,5-asymmetric induction after treatment with tin(IV) chloride or bromide (Scheme 30). The 1,5-*anti*- (*Z*)-homoallylic alcohol (134) was obtained as the major product of the reaction with 1,5-*anti*:1,5-*syn* of 96:4.



Scheme 30 Reaction of ε-alkoxyallystannanes (133) with SnX_4 and an aldehyde.

A transmetallation rapidly occurred on addition of the tin(IV) halide. During this process the Lewis acid is thought to be delivered to the double bond of the allylstannane stereoselectively following chelation to the oxygenated substituent. This gives rise to the five-membered oxastannane ring intermediate (135) where the vinyl and methyl groups are *trans*-disposed about the five-membered ring. The oxastannane then reacts with an aldehyde *via* a six-membered (136), chair-like transition state in which the substituent α to tin is in the axial position (Scheme 31).



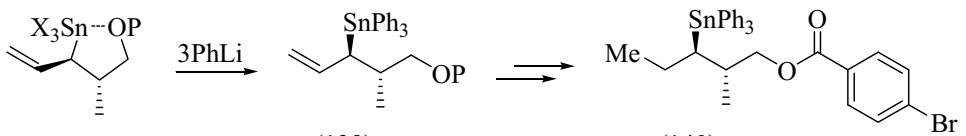
Scheme 31 Possible mechanism for formation of the *anti*-homoallylic alcohol (134).

In this reaction, there is a very high preference for the formation of *cis*-alkene irrespective of whether 1,5-, 1,6- or 1,7-induction is involved depending on the allylstannanes with heteroatom substituents at the 4-, 5- or 6-positions. If the oxygen substituent remains chelated to the tin during the reaction with aldehyde, an octahedral tin (137) is involved. However, if the aldehyde displace the oxygen substituent, the tin can remain as a trigonal bipyramid (138) during the reaction with the aldehyde (Scheme 32). From the thermal reaction of the α-substituted stannanes with aldehydes (see Scheme 22), there is a very strong preference to the group next to tin to adopt an axial position. This may well be the case here.

(137) (138)

Scheme 32 Possible transition structure for the reaction of allyltin trichloride (135) with aldehydes.

The intermediate allytin trichloride (135) (X=Cl) has been trapped by phenylithium to afford the 2,3-*anti*-triphenylalkyltin (139). The structure of major trapping product was established as 2,3-*anti*:2,3-*syn* in a ratio of 95:5 by X-ray diffraction of the *p*-bromobenzoate (140) [41,47] (Scheme 33).

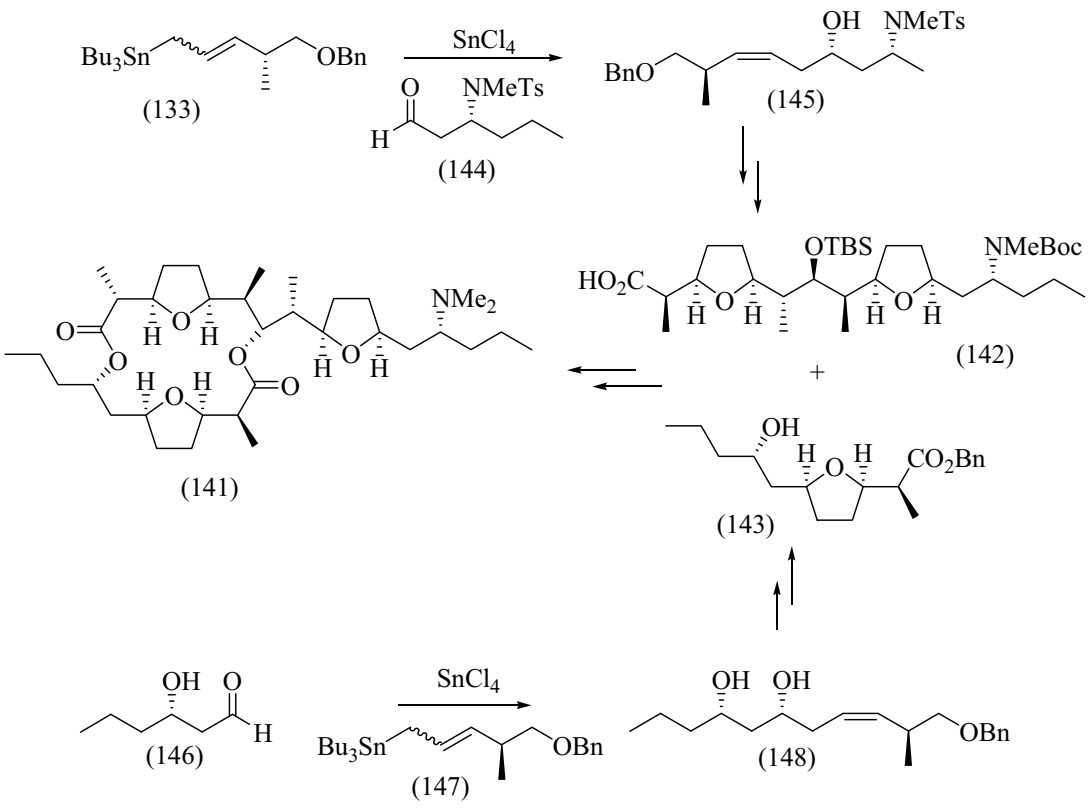


(135) (139) (140)

Scheme 33 Trapping the intermediate allyltin trichloride (135) with phenyllithium.

The usefulness of 1,5-asymmetric induction as a practical synthesis tool was further shown by the use of alkoxyallylstannane (133) in the total synthesis of

pamamaycin-607 (141) [48], which was synthesized by coupling of fragments (142) and (143). Fragment (142) was prepared by treating alkoxyallylstannane (133) with aldehyde (144) to afford the (*Z*)-1,5-*anti*-homoallylic alcohol (145). Alkoxyallylstannane (146) and aldehyde (147) were used to synthesize compound (143) *via* homoallylic alcohol (148) as shown in Scheme 34.



Scheme 34 Total synthesis of pamamycin-607 (148) [48].

1.6 Aspects of the chemistry of organobismuth compounds

1.6.1 Properties of bismuth metal [49] and organobismuth chemistry

Bismuth is the 83rd element in the periodic table and is the most metallic, the least abundant and the heaviest stable element in the nitrogen family. It is by far the

least toxic of the heavy metals and consequently an “ecofriendly” element. Natural bismuth consists of only one stable isotope, ^{209}Bi, with most of its compounds appearing colourless, unless they are attached to a chromophore. The bismuth atom usually utilizes its three *6p* electrons for use in bond formation and retains the two *6s* electrons as an inert pair, hence the oxidation state +3 is exhibited by bismuth in the majority of its compounds. Although it belongs to the group 15 family, the chemistry of bismuth differs greatly from the chemistry of the other lighter members such as phosphorus, arsenic and antimony. The decreasing availability of the diffuse *s* electrons makes the +5 oxidation state less stable when compared to the other elements. However, there are still a variety of organobismuth compounds that can contain the element in the +5 oxidation state.

Bismuth is uniquely characterised by its low toxicity and is non-carcinogenic. This is sharp contrast to closely located elements in the periodic table such as lead, antimony, arsenic and tin which are highly toxic with their use posing environmental hazards. Bismuth is used in a number of very different applications. Bismuth metal and several inorganic bismuth compounds are important as starting materials for industrial processes and they are commercially available at a low price. Currently, bismuth is used mainly in cosmetics, medicines and in medical applications. The majority of bismuth is consumed in a bismuth alloy, as the toxicity of lead has become more apparent in recent years. The alloy uses bismuth metal as a replacement for lead and has contributed to bismuth’s commercial importance. Bismuth forms stable complexes with polyhydrated carboxylic acids and phenols through bismuth-oxygen bonds and complex salts of this type are used as soothing agents for the treatment of digestive disorders, for outlining the alimentary tract during X-ray examinations, and treating skin injuries and infections.

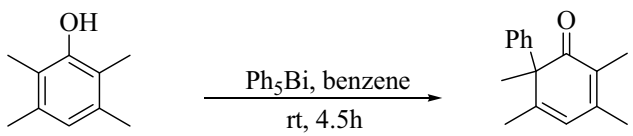
Accidental poisoning by bismuth compounds has been reported from the use of large doses during medical therapy rather than by exposure in the work place. The effects of acute intoxication of bismuth include gastro-intestinal disturbance, anorexia, headache and discolouration of the mucous membrane. Despite this, bismuth and its compounds do not appear to have been responsible for poisoning, either in the laboratory or in industry, and no strict limits have been set for bismuth in air, and drainage in industrialised countries.

1.6.2 Carbon-carbon bond formation with aryl compounds

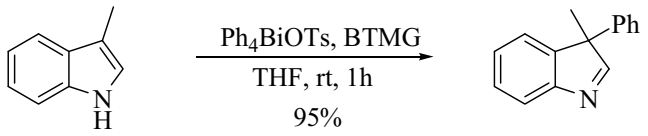
Since the beginning of the 1980s, the use of bismuth(III) derivatives as catalysts in organic synthesis has considerably increased. This new interest in bismuth compounds is justified by its friendly ecological behaviour. The usefulness of this element in organic synthesis was recognised when extensive work by the groups of Barton [50], Wada [51] and Suzuki [52] revealed the uniqueness and promising potential of bismuth as a reagent and catalyst for organic transformations. The present review focuses on some of the carbon-carbon bond forming reactions based on the use of metallic bismuth, inorganic bismuth salts and organobismuth compounds.

The arylation of organic materials remains a non-trivial issue for organic chemists. Using bismuth reagents, a wide range of functional groups can be arylated and in some cases, alkylated. The anionic chemistry associated with pentavalent bismuth has been extensively studied, showing that these derivatives are the reagent of choice for the arylation of compounds that containing a labile proton. Systematic studies have shown that *β*-dicarbonyl compounds, phenols, enolisable ketones and related compounds can be arylated with ease and often in good yields [53].

The *C*-arylation of phenolic compounds are usually conducted by a variety of tri- and tetra-aryl bismuth(V) derivatives under basic conditions in various solvents such as dichloromethane or tetrahydrofuran [54]. Similar *C*-arylation with pentaphenyl bismuth can be achieved under neutral conditions [55] (Scheme 35). For example, the reaction of alcohol (149) and indole (151) afforded dienone (150) and indole (152) in good yields. When compared with other arylbismuth(V) compounds, tetraarylbismuthonium salts require generally milder reaction conditions with shorter reaction times and are less likely to undergo oxidative side reactions [56].



(149) (150)

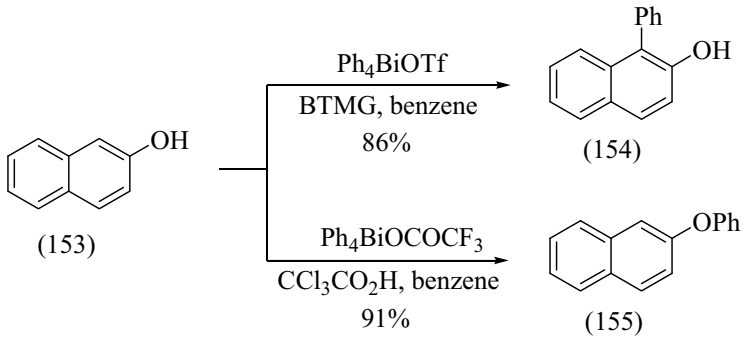


(151) (152)

Scheme 35 Representative arylation reaction using arylbismuth compounds. BTMG = 2-Benzyl-1,1,3,3-tetramethyl guanidene

The nature of the substituents on the aromatic rings in arylbismuth(V) reagents does not influence the yields of the arylated products, but it does appear to control the regioselectivity of the arylation, especially with phenols [57]. Phenols bearing an electron donating substituents are mostly *ortho C*-arylated, whereas phenols with electron withdrawing groups are predominantly or selectively *O*-arylated [58]. Other decomposition pathways are sometimes involved.

The *C*-arylation of 2-naphthol and 1,3-dicarbonyl compounds are readily performed with a variety of pentavalent organobismuth(V) reagents. The regioselectivity of phenylation, giving *O*- or *C*-phenylated products can be controlled by the choice of the organobismuth reagents under neutral, acidic or basic conditions [59]. For example, the reaction of 2-naphthol (153) with esters of tetraphenylbismuth under basic conditions favoured the *C*-phenylated product (154), while the *O*-phenylated product (155) becomes important under acidic conditions [60,61] (Scheme 36).

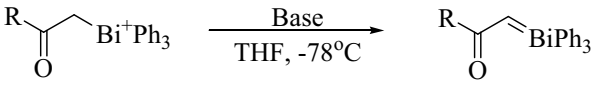


(153) (154) (155)

Scheme 36 Arylation of 2-naphthol under acidic and basic conditions. BTMG = 2-Benzyl-1,1,3,3-tetramethyl guanidene

1.6.3 Carbon-carbon bond forming reactions based on bismuthonium ylides

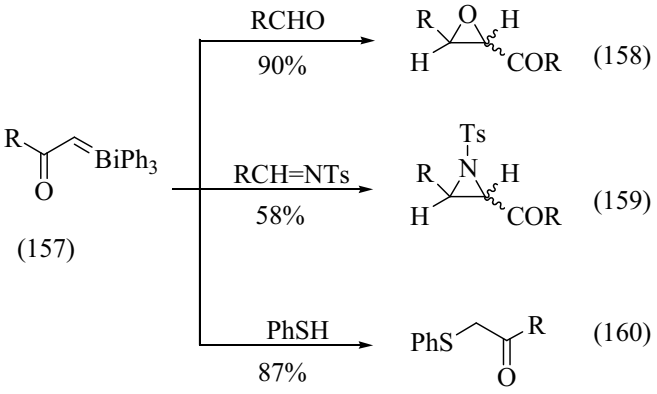
Ylide chemistry in carbon-carbon bond formation has been an active area of organic synthesis for a long time. Bismuthonium ylides have been known for many years, but their chemistry remains little explored. The first synthesis of stabilized bismuthonium ylides (157) was claimed by Lloyd *et al*. in 1967 [62]. Suzuki *et al*. isolated this ylide (R=*t*-Bu, Ph) in a crystalline form and its structure was characterised by X-ray analysis [63]. Treatment of an alkylbismuthonium salt (156) with potassium *t*-butoxide or lithium diisopropylamide at low temperatures gave expected ylide (157) as a yellow solution [64] (Scheme 37).



(156) (157)

Scheme 37 Synthesis of bismuthonium ylides (157).

These moderately stabilized bismuthonium 2-oxoalkylides (157) undergo reaction with a variety of aldehydes to give the corresponding α,β-epoxy ketones (158), but fail to react with ketones such as acetophenone and benzophenone [65]. On the other hand, these ylides readily react with activated imines and benzenethiol to give the corresponding α,β-aziridino (159) and α-phenylsulfanyl ketones (160) in good yields [65,66,67] (Scheme 38).

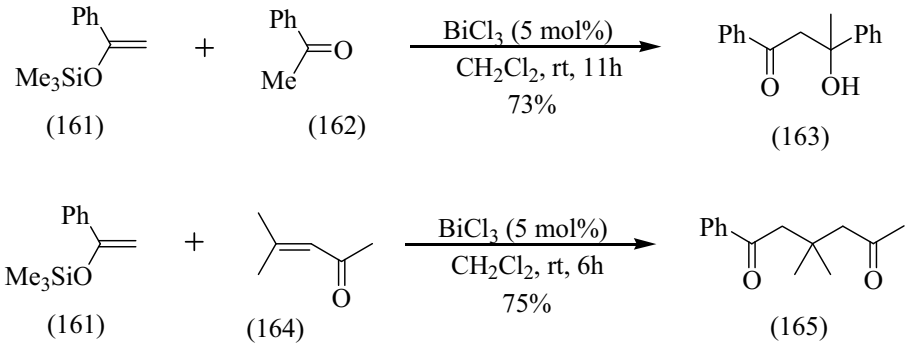


(157)

Scheme 38 Bismuthonium ylide reactions with aldehydes, imines and benzenethiol.

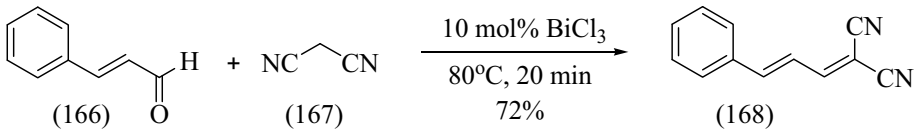
1.6.4 Bismuth(III) salt-catalysed carbon-carbon bond forming reactions

Bismuth(III) chloride is sometimes used as a soft Lewis acid catalyst for coupling and rearrangement reactions such as the Mukaiyama-aldol and the Michael reaction. In the presence of a catalytic amount of $BiCl_3$ (5 mol%), silyl enol ether (161) react smoothly with ketone (162) in dichloromethane at room temperature to give the corresponding aldol product (163) in good yield [68]. Similar reactions with silyl ketene acetals (161) give *β*-hydroxyketones (163) in moderate yield [69]. With *α*,*β*-unsaturated ketone (164), the Michael reaction takes place to afford the 1,5-dicarbonyl compound (165) [69] (Scheme 39). Cross aldolisation and Michael addition reaction are usually carried out using a stoichiometric amount of the bismuth promoter.



Scheme 39 $BiCl_3$ catalysed Mukaiyama-aldol and Michael type reactions.

The bismuth(III) chloride promoted Knoevenagel condensations of aldehydes with an active methylene compound produced olefinic products in good purity and high yields with no formation of Michael type addition products. This reaction can be carried out without complication under heterogeneous conditions using $BiCl_3$ as catalyst in the absence of solvent [70]. For example, the reaction of cinnamaldehyde (166) with malononitrile (167) afforded diene (168) in 72% yield (Scheme 40).



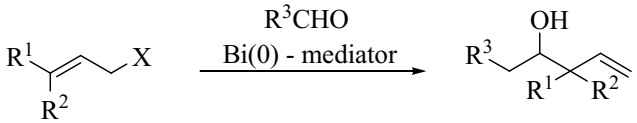
Scheme 40 A $BiCl_3$ catalysed Knoevenagel condensation.

1.6.5 Bi(0) promoted carbon-carbon bond forming reactions

The coupling reactions of organic halides and carbonyl compounds in the presence of a metal are fundamental procedures for making new carbon-carbon bonds [71]. Carbonyl allylation is an important synthetic transformation in organic and pharmaceutical chemistry because the homoallylic alcohols produced are valuable synthetic intermediates [72]. This type of functional group transformation has long been carried out using organometallic compounds such as Grignard reagents, organolithiums, organosilanes and organostannanes [73]. In recent years, however, an alternative approach involving a reductive allylation has become increasingly important. Here a combination of an allyl halide and a metal powder or a low valent metal halide is used for the *in situ* generation of the allylmetal species. This type of allylic carbonyl addition is called the Barbier-type allylation [71]. The Barbier reaction can be mediated by various metals including zinc [74], tin [75], indium [76] and manganese [77]. This methodology has attracted considerable attention since it can be carried out in aqueous media [72] or without solvent [78], sometimes with the assistance of dissolved salts, organic co-solvents or sonication to boost reactivity [72].

In 1985, Wada *et al*. reported that bismuth(0) can promote the Barbier-type allylation of aldehydes in dimethylformamide with high chemoselectivity over ketones [51]. Similar reactions were accomplished when bismuth(0) was generated *in situ* from a combination of bismuth(III) chloride and a variety of reducing agents such as zinc, iron, aluminium and magnesium [79], for example in allyl halide (169) system to afford homoallylic (170) (see Scheme 41 and Table 1). All allylations

proceed in high yields with high chemo-, regio- and stereo-selectivites from both aromatic and aliphatic aldehydes. Carboxylic acids, nitriles, esters, halides and alcohols were recovered unchanged under the allylation conditions [79]. The intermediate allylmetal species thus discriminated aldehydes from ketones and the carbonyl group from the carbonyl-conjugated double bonds. This reaction also proceeds smoothly in aqueous solvents and sometimes even catalytic amounts of $BiCl_3$ would achieve high yields [79].



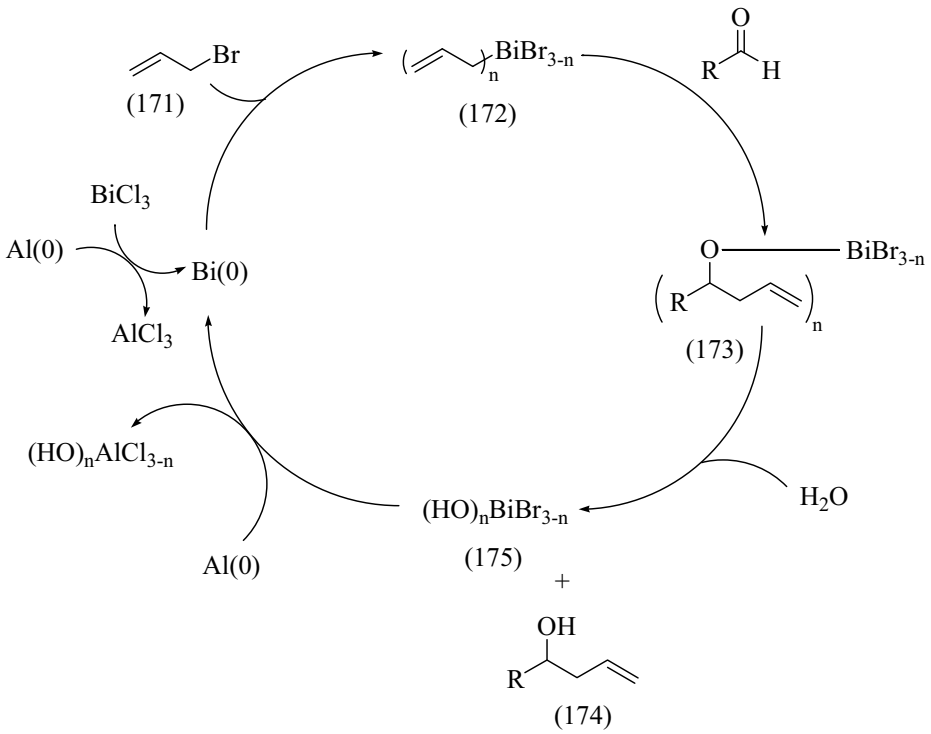
(169) (170)

Scheme 41 Reaction of allyl halide with aldehydes promoted by Bi(0)-mediator.

Table 1: Bismuth promoted allylation of aldehydes.

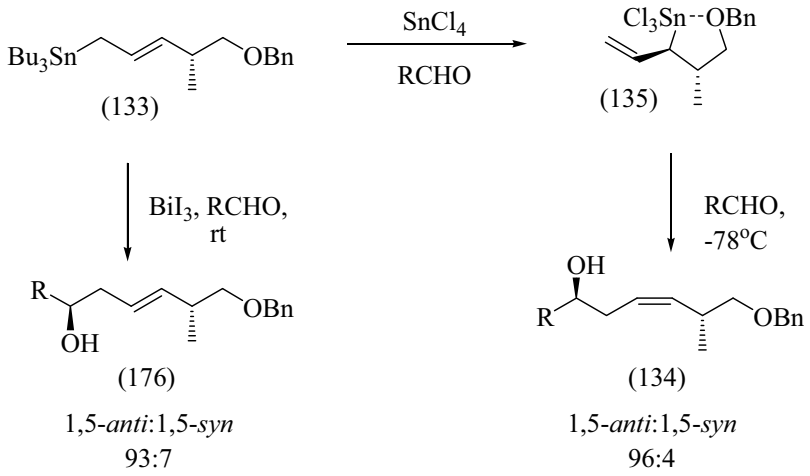
Bi-system	**Conditions**	**Yield, (%)**
$BiCl_3$-Al	THF/H_2O, rt, 10-22h	30 - 96
$BiCl_3$-Zn or Fe	THF, rt, 2-7h	45 - 99
$BiCl_3$-$NaBH_4$	THF, rt, 2-4h	74 - 96
$BiCl_3$-Mg	THF, rt, 2-7h	64 - 90
Bi(0)	DMF, rt, 2-12h	53 - 98

Although the reaction mechanism of the catalytic $BiCl_3$-aluminium mediated allylation was not properly investigated, the intermediate formation of allylbismuth species (172) through the oxidative addition of allylic halide (171) which react with aldehydes to give adduct (173) may be involved [79] (Scheme 42). The hydrolysis of these adduct (173) could then yield a homoallylic alcohol (174) and the bismuth(III) compound (175), which is reduced by Al(0), regenerating the Bi(0) catalyst [79].



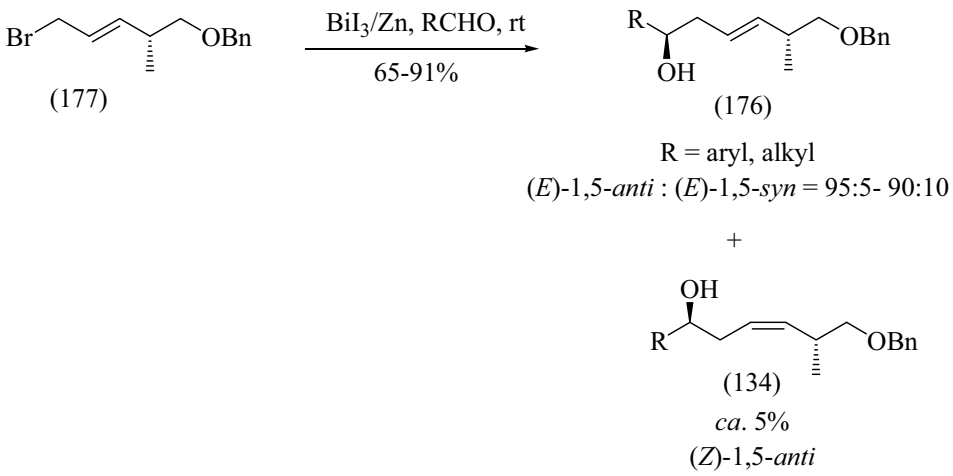
Scheme 42 Proposed mechanism of catalytic $BiCl_3$ mediated allylation of aldehydes.

Bismuth(III) iodide promoted reactions of the 5-subtituted pent-2-enylstannanes (133) with aldehydes in a mixed solvent of acetonitrile and dichloromethane gave the (3*E*)-1,5-*anti*-products (176) with useful stereoselectivity in a 93:7 ratio of the 1,5-*anti*:1,5-*syn* [80]. This product had the opposite configuration at the newly formed stereogenic centre from the major (3*Z*)-1,5-*anti* product (134) from the tin(IV) chloride promoted reactions of the pent-2-enylstannanes (133) [44] (see Scheme 43).



Scheme 43 Remote stereocontrol using organometal reagents.

The synthesis of 1,5-*anti*-substituted (*E*)-alkenols (176) using allylic organometallic reagents, but not involving allyl(trialkyl)stannanes, have been developed [80]. The reaction of the pent-2-enyl bromide (177) with "bismuth(0)," [78] prepared by reduction of bismuth(III) iodide using activated zinc powder, and aldehydes, gave (*E*)-alkenols in 65-91% yields and with *ca*. 95:5 stereoselectivity in favour of the 1,5-*anti*-(*E*)-isomers (176). The less polar, (3*Z*)-isomers (134) could be separated from the (3*E*)-isomers (176) by flash column chromatography [80]. These reactions of allylic bromide (177) mediated bismuth(III) iodide-zinc with aldehydes proceeded with stereochemistry which is complementary to that observed using 5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane (133) using bismuth(III) iodide, see Scheme 43, in that, the products were (*E*)-alkenes (176) with the same configuration at the newly formed stereogenic centres [80] (Scheme 44). The reaction of bromide (177) provides the tin-free 1,5-stereocontrol in good yield with a range of aldehydes.



Scheme 44 Remote stereocontrol using organobismuth reagents.

A synthesis of the synthetic intermediate (180) with *syn*-disposed 1,5-methyl bearing stereogenic centre has been reported [81]. The strategy relied on the application of organo-bismuth chemistry to affect a novel strategy based on remote stereocontrol. Analogous fragments are found in a range of natural products including terpenoids and lipids (178) found in *Archaea* bacteria and in vitamin E (179) [82] (Figure 4).

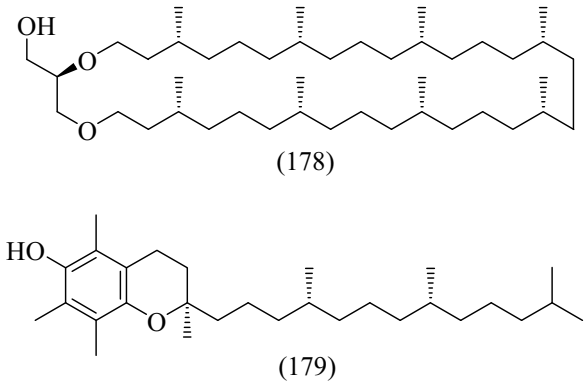
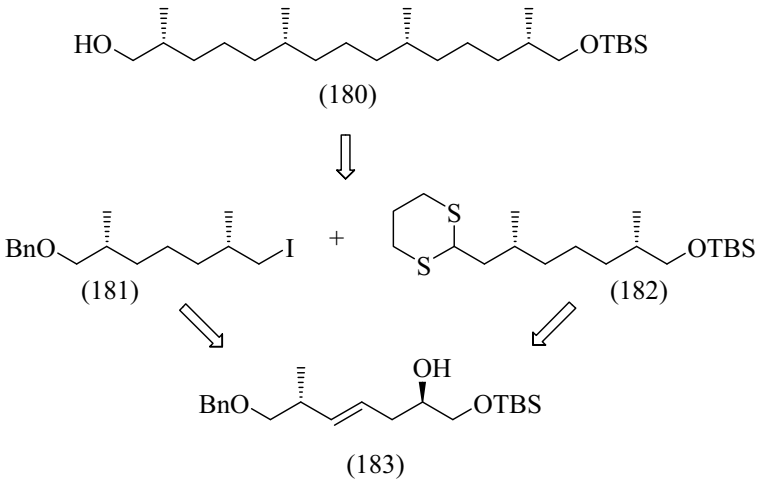


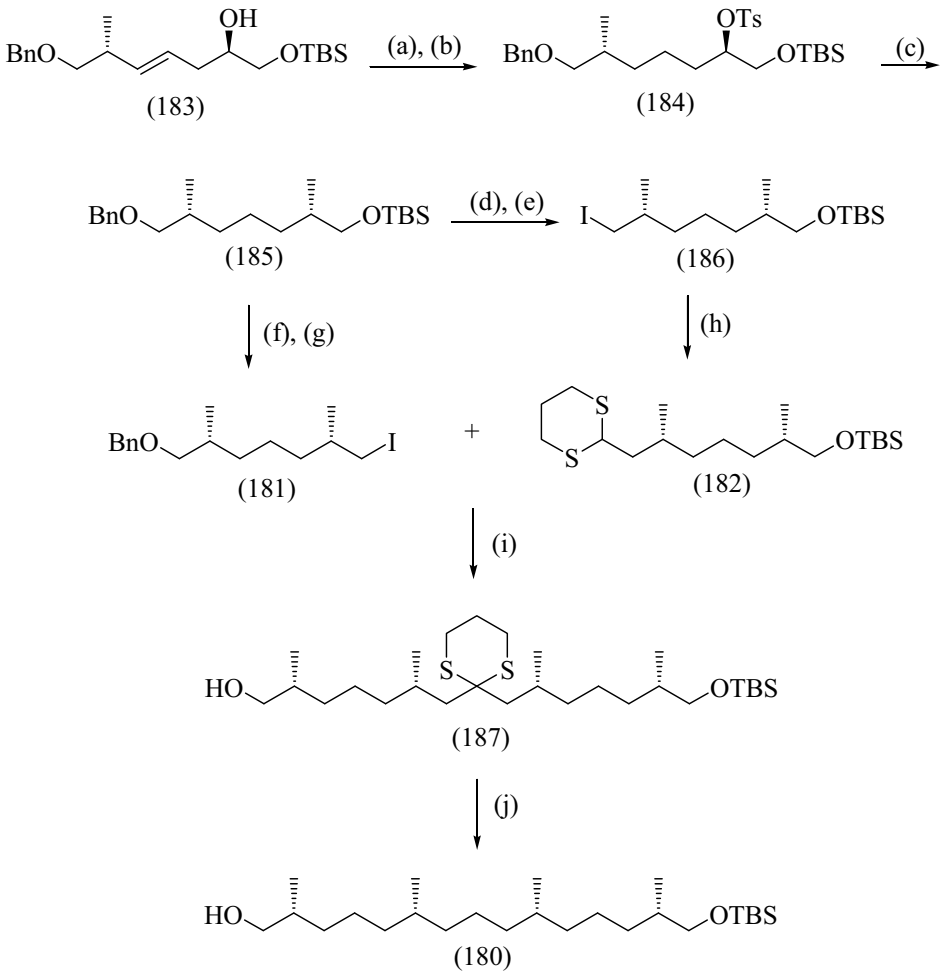
Figure 4 Representative terpenoids and lipids with *syn*-disposed 1,5-methyl substituents.

The synthesis of compound (180) was to involve a coupling of iodide (181) and dithiane (182) (Scheme 45), with the sulfur bonds and the benzyl protecting group being cleaved using Raney nickel in one step. Both iodide (181) and dithiane (182) were made from homoallylic alcohol (183), with reduction of the double-bond and displacement of the alcohol as its toluene *p*-sulfonate. Selective deprotection and functional group manipulation provided the iodide (181) and dithiane (182) [81].



Scheme 45 Retrosynthetic analysis of alcohol (180).

The synthesis of the alcohol (180) began with the bismuth(III) iodide/zinc-mediated reaction of bromide (177) and 2-(*t*-butyldimethylsilyloxy)ethanal which gave the 1,5-*anti*-adduct (183). This was reduced using diimide and esterified to give the toluene *p*-sulfonate (184). Reaction with a higher order cuprate reagent prepared from methyllithium and copper(I) cyanide in toluene as solvent gave the required *syn*-2,6-dimethyl-1-(*t*-butyldimethylsilyloxy)-7-benzyloxyheptane (185), which was taken through to the iodides (181) and (186) by selective deprotection and iodide formation. Sequential alkylation of dithiane (187) followed by reduction using Raney nickel then gave the monoprotected all *syn*-2,6,10,14-tetramethylpentadecane-1,15-diol derivative (180) [81] (Scheme 46).

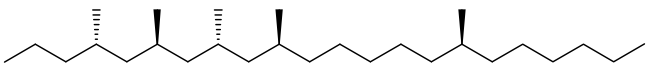


Scheme 46 Synthesis of open-chain compounds with 1,5-*syn*-oriented methyl groups.

Reagents and conditions. (a) $TsNHNH_2$, NaOAc, 92%; (b) TsCl, DMAP, CH_2Cl_2, rt, 90%; (c) MeLi (2 equiv), CuCN, toluene, 0°C, 5h then OsO_4 (cat), NMO, acetone, rt, 73%; (d) H_2/ Pd-C, EtOH, rt, 98%; (e) I_2, PPh_3, imidazole, THF, rt, 96%; (f) TBAF, THF, rt, 98%; (g) I_2, PPh_3, imidazole, THF, 94%; (h) *n*-BuLi, dithiane, 86%; (i) *n*-BuLi, HMPA, THF, -78°C, 78%; (j) Raney Ni, THF, rt, 94%.

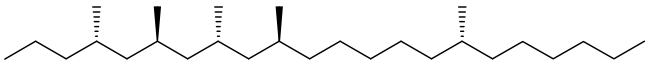
1.7 Aims of the project

It was proposed to extend the methodology for long range asymmetric induction using bismuth(III) iodide/zinc mediated reactions of allyl bromides with aldehydes. In the first place, the compatibility of this chemistry with a 2-methyl substituent in the allyl bromide has to be investigated. If successful the work has to be applied to complete stereoselective syntheses of open chain compound with 1,3,5-disposed methyl substituent and then extended to complete a synthesis of the insect lipid (45) notwithstanding that the full stereostructure of this natural product remains to be confirmed, *cf.* (45) (*aaa*)(*s*) or (46) (*aaa*)(*a*).



(45) (*aaa*)(*s*)

or



(46) (*aaa*)(*a*)

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Ac	-	Acetyl
aq	-	Aqueous
Ar	-	Aryl
atm	-	Atmospheres
9-BBN	-	9-Borabicyclo[3.3.1]nonane
Bn	-	Benzyl
BOM	-	Benzyloxymethyl
bp	-	Boiling point
br	-	Broad
BTMG	-	2-Benzyl-1,1,3,3-tetramethyl guanidene
Bu	-	Butyl
c	-	Concentration
Cat.	-	Catalytic
CI	-	Chemical ionisation
conc.	-	Concentrated
COSY	-	^{1}H-^{1}H correlation spectrum
CSA	-	Camphor sulfonic acid
CuCN	-	Copper(I) cyanide
d	-	doublet
DCC	-	Dicyclohexylcarbodiimide
DCM	-	Dichloromethane
dd	-	doublet of doublets
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	-	Distortionless enhancement of polarisation transfer
DHP	-	Dihydropyranyl
DIAD	-	Di-*iso*propylazodicarboxylate

DIBAL-H	-	Di-*iso*butylaluminium hydride
DMAP	-	4-(*N*,*N*-dimethylamino)pyridine
DME	-	1,2-dimethoxyethane
DMF	-	*N*,*N*-Dimethylformamide
DMP	-	Dess-Martin periodinane
DMSO	-	Dimethylsulfoxide
dr	-	Diastereomeric ratio
ds	-	Diastereoselection
EDC·HCl	-	1-(3-Dimethyllaminopropyl)-3-ethyl-carbodiimide hydrochloride
ee	-	Enantiomeric excess
EI	-	Electron impact ionisation
eq.	-	Equivalents
$ES^{+/-}$	-	Electrospray (positive *or* negative mode)
Et	-	Ethyl
Ether	-	Diethyl ether
FT	-	Fourier transform
g	-	Grams
GC	-	Gas chromatography
GCMS	-	Gas chromatography Mass Spectrometry
h	-	Hour (s)
HMBC	-	Heteronuclear multiple bond correlation
HMPA	-	Hexamethylphosphoramide
HMQC	-	^{1}H-^{13}C correlation spectrum
HOBT	-	1-Hydroxybenzotriazole hydrate
HPLC	-	High performance liquid chromatography
HSQC	-	Heteronuclear Single Quantum Coherence
HWE	-	Horner-Wadsworth-Emmons
Hz	-	Hertz
imid.	-	Imidazole
i-Pr	-	*iso*propyl
IR	-	Infrared
J	-	Coupling constant
KHMDS	-	Potassium bis(trimethylsilyl)amide

L	-	General ligand
LA	-	Lewis acid
LDA	-	Lithium di-*iso*-propylamide
LHMDS	-	Lithium bis(trimethylsilyl)amide
M	-	Molarity
m	-	Multiplet
m/z	-	Mass-to-charge ratio
M^+	-	Molecular ion
m-CPBA	-	*meta*-Chloroperbenzoic acid
Me	-	Methyl
MeLi	-	Methyllithium
mg	-	Milligrams
MHz	-	MegaHertz
Min	-	minute(s)
mmol	-	Millimoles
mol	-	Moles
mp	-	Melting point
MS	-	Mass spectrometry
Ms	-	Methanesulphonyl
MsCl	-	Mesyl chloride
MTPA	-	α-methoxy-α-(trifluoromethyl)phenylacetic acid
NaCN	-	Sodium cyanide
NaH	-	Sodium hydride
NaHMDS	-	Sodium bis(trimethylsilyl)amide
NaOAc	-	Sodium acetate
NaOMe	-	Sodium methoxide
n-BuLi	-	*normal*-Butyllithium
NMM	-	*N*-methylmorpholine
NMO	-	*N*-Methylmorpholine-*N*-oxide
NMR	-	Nuclear magnetic resonance
NOE	-	Nuclear Overhauser Effect
O/N	-	Overnight
o-DPPB	-	*ortho*-Diphenylphosphanylbenzoyl

OTf	-	Trifluoromethanesulfonate
OTs	-	*para*-Toluenesulfonate
P (P', P'' etc.)	-	General protecting group
PCC	-	Pyridinium chlorochromate
Petrol	-	Petroleum ether (40-60^{o}C)
Ph	-	Phenyl
PMB	-	*para*-Methoxybenzyl
PMP	-	*para*-Methoxyphenyl
p-NBA	-	*para*-Nitrobenzoic acid
ppm	-	Parts per million
PPTS	-	Pyridinium 4-toluenesulfonate
Pr	-	Propyl
p-TsOH	-	*para*-Toluenesulfonic acid
py	-	pyridine
q	-	quartet
qn	-	quintet
quant.	-	quantitative
R	-	General alkyl group
R_f	-	Retention factor
Rh-C	-	Rhodium-Carbon
rt	-	room temperature
s	-	singlet
SEM	-	2-(Trimethylsilyl)ethoxymethoxy
SET	-	Single electron transfer
sext	-	sextet
sm	-	starting material
t	-	triplet
TBAF	-	Tetra-*N*-butylammonium fluoride
TBAI	-	Tetra-*N*-butylammonium iodide
TBDMSCl	-	*tert*-Butylchlorodimethylsilyl chloride
TBDPS	-	*tert*-Butyldiphenylsilyl
TBS or TBDMS	-	*tert*-Butyldimethylsilyl
t-Bu	-	*tert*-Butyl
t-BuLi	-	*tert*-Butyllithium

tert	-	tertiary
THF	-	Tetrahydrofuran
THP	-	2-(Tetrahydropyranyl)
TIPS	-	Tri-*iso*-propylsilyl
TLC	-	Thin layer chromatography
TMS	-	Trimethylsilyl
TPAP	-	Tetra-*N*-propylammonium perruthenate
Ts	-	4-Toluenesulfonyl
tt	-	triplet of triplets
v	-	volume
wt	-	weight
X	-	General leaving group
ZACA	-	(-)-bis-(neomethylindenyl)zirconium dichloride
δ	-	chemical shift

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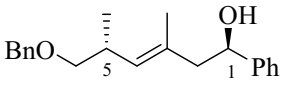
CHAPTER 1

INTRODUCTION

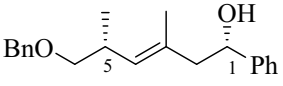
1.1 Preface

This thesis relates to the work performed by the author towards the stereoselective synthesis of a cuticular hydrocarbon, (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane of the cane beetle *Antitrogus parvulus*. The syntheses of this compound involved the assembly of the aliphatic chain from homochiral starting materials prepared using bismuth(III) iodide promoted reactions of an allylic bromide with aldehydes. Related insect lipids have attracted synthetic interest due to the tetradeoxypropionate unit which has four methyl-bearing stereocenters with different stereochemical orientations. Some of the reported syntheses are addressed in the introduction.

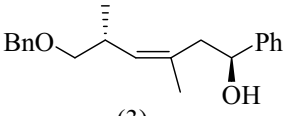
In this report the relationship between stereogenic centres in certain products is discussed. For ease of identification, the relationship between stereogenic centres will be referred to as either *syn* or *anti*. For example, homoallylic alcohol (1) has an *anti* relationship between the methyl group at C5 and the hydroxyl group at C1, whereas the other diastereoisomer (2) has a *syn* relationship between these substituents. Similarly alcohols (3) and (4) are described as *anti* and *syn* respectively.



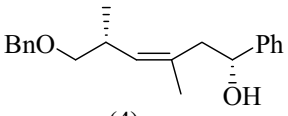
(1)
1,5-*anti*-(*E*)



(2)
1,5-*syn*-(*E*)

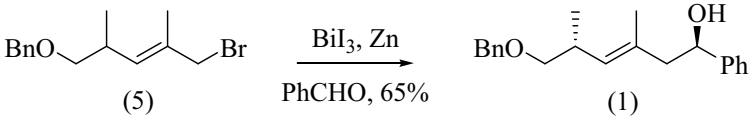


(3)
1,5-*anti*-(*Z*)



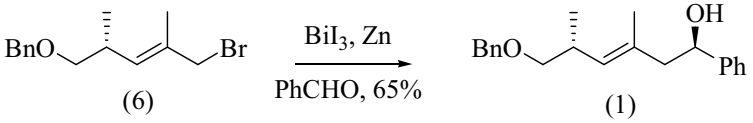
(4)
1,5-*syn*-(*Z*)

Also, most schemes in this report show only the major diastereoisomer formed in reactions. For example, alcohol (1) is the major product formed from compound (5), with the ratio of 96:4 referring to the 1,5-diastereotopic ratio and the yield representing the combined yield of both diastereoisomers.



(5) (1)
96:4

When racemic starting materials are used, one of the two possible major *anti*- or *syn*-diastereoisomers will be shown in the reaction scheme, as shown above. When enantiomerically enriched starting materials are used, example compound (6), the major product (1) of the coupling reaction will be presented as one diastereoisomer only (as shown below).



(6) (1)
96:4

1.2 Insect lipids

Larvae of melolonthine scarabs (collectively known as canegrubs) are the main pests affecting the production of sugar cane in Australia [1]. Canegrubs damage the roots of plants and the regenerative portion of underground stems. Currently, pest control is accomplished by the application of organophosphorus insecticides [2], but

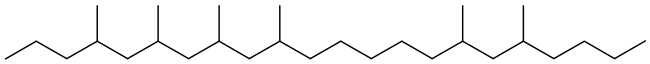
problems such as insecticidal breakdown and resistance emphasize the importance of the development of environmentally benign management strategies. Significant results have been achieved with formulations utilizing sex pheromones for monitoring and controlling herbivorous scarab beetles, and it has been proposed that pheromones may be useful for population control of the Australian canegrub complex.

Several species of Melolonthine scarabs have been investigated by Kitching and co-workers initially with a focus on volatile pheromonal components. This investigation led to a report of novel long chain hydrocarbons [1]. In the cuticular extract of one species, *Antitrogus parvulus*, two hydrocarbons were detected in a ratio of 45:38 by GCMS analysis. The same components were also present in extracts from adult male *A. parvulus* [3].

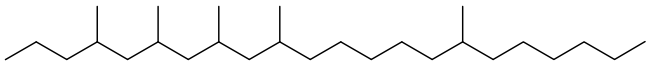
1.2.1 Lipid structures

The components of the female extract were separated by preparative gas chromatography and mass spectra exhibited molecular ions at *m*/*z* 380 and 394, respectively, indicating the formulas $C_{27}H_{56}$ and $C_{28}H_{58}$ and these were confirmed by accurate mass measurements. High-resolution ^{13}C NMR and DEPT spectra confirmed the presence of five and six methyl side-chains in the C27 and C28 hydrocarbons, respectively, with the requisite number of methine and methylene signals. The location of the methyl groups along the C22 carbon chain was based on mass spectral and NMR evidence and ^{13}C NMR shift calculations [4].

The C28 hydrocarbon was identified as 4,6,8,10,16,18-hexamethyldocosane (7) based on ^{13}C NMR shift calculations in best agreement with the experimental data and two-dimensional NMR experiments (COSY, HMBC, and HSQC) which provided the structure of (7). The constitution of the C27 hydrocarbon was similarly deduced to be 4,6,8,10,16-pentamethyldocosane (8), with the calculated ^{13}C NMR resonances being in very good agreement with those observed. Mass spectral fragmentation data are consistent with the structures of (7) and (8) [3] (Figure 1).



(7)



(8)

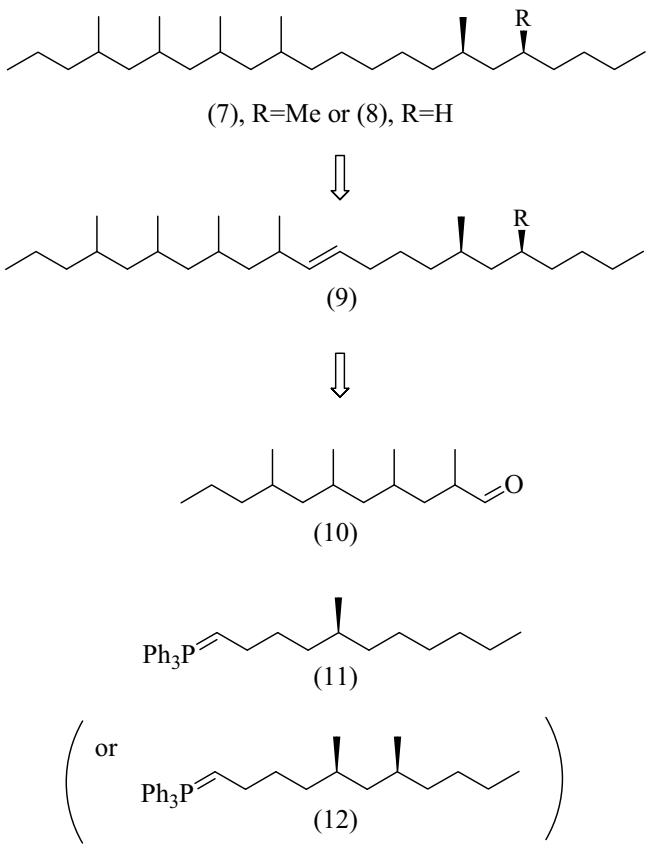
Figure 1 Structures of the insect lipids from *A. parvulus*.

Interest in the biological roles of the sex pheromones of cane beetles has led to a related interest in the synthesis of lipids (7) and (8). The small amount of material isolated from natural sources has not permitted a determination of their biological roles. The need for more material to assess biological trials is apparent and synthetic chemistry could address this concern. Moreover the synthesis of different diastereoisomers was essential to assign configuration of the methyl bearing stereogenic centres. Several papers have been published concerning the synthesis of lipids (7) and (8). There exist four total syntheses of lipid (7), each of this used different methodology for the construction of tetradeoxypropionate fragment.

1.3 Total syntheses of insect lipids

1.3.1 Kitching's total synthesis of different diastereoisomers of lipids (7) and (8)

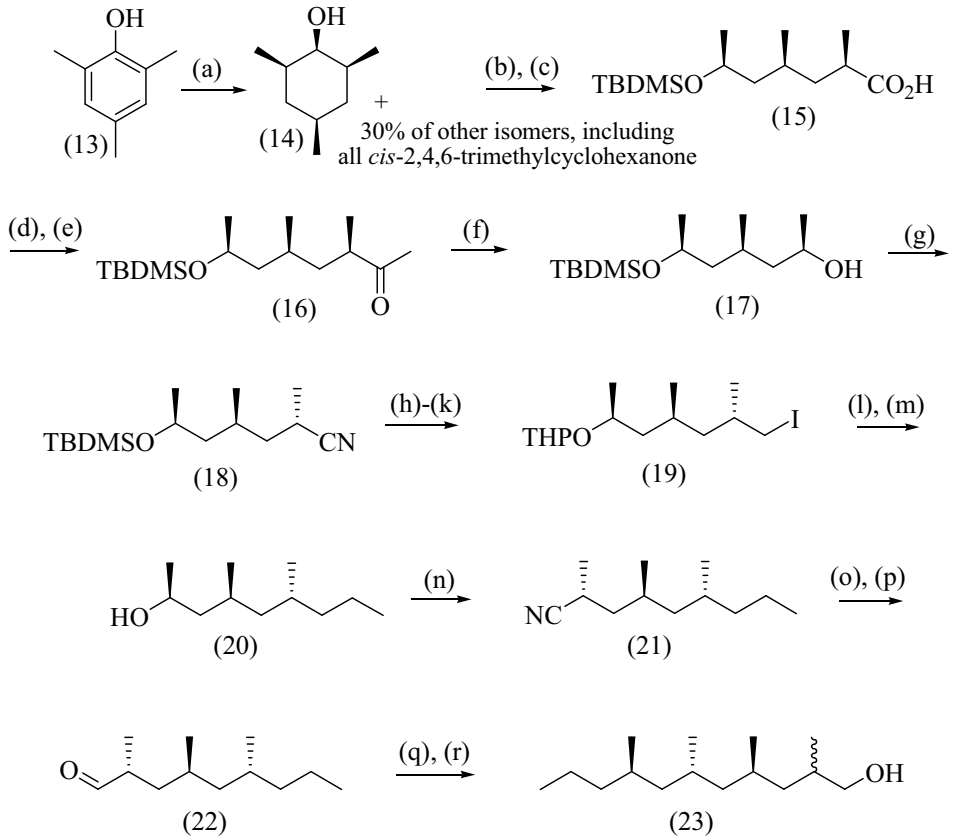
In 2003, Kitching and co-workers reported the first work on the synthesis of lipids (7) and (8) by making all possible diastereoisomers *via* route based on existing methodology [3,5]. A Wittig coupling approach was adopted for assembly for this system, based on the connection shown in Scheme 1. A tetramethyl fragment (10) was coupled with mono- (11) and dimethyl-substituted (12) fragments to furnish alkene (13), which was then undergo hydrogenation to afford stereoisomers of the target molecules (7) and (8).



Scheme 1 Retrosynthesis of lipids (7) and (8).

The synthesis of the tetramethyl substituted isomers began with reduction of 2,4,6-trimethylphenol (13) under forcing conditions (400-500 psi H_2) with a Rh-C catalyst for three days to give mainly the *all-cis*-cyclohexanol (14). Jones oxidation affected conversion of the product to the cyclohexanone with predominantly *all-cis* methyl groups had a Baeyer-Villiger oxidation, methanolysis, silyl protection and hydrolysis provided the silyl-protected hydroxyacid (15). This compound was converted to the methyl ketone (16) *via* the corresponding Weinweb amide. The ketone underwent a slow but efficient Baeyer-Villiger reaction to give the monoprotected diol (17). A one carbon chain extension by displacement of mesylate prepared from alcohol (17) by cyanide with inversion led to the desired protected hydroxyl-nitrile (18) which was then hydrolysed, protected and converted into the iodide (19). A two-carbon extension, followed by deprotection of *tert*-

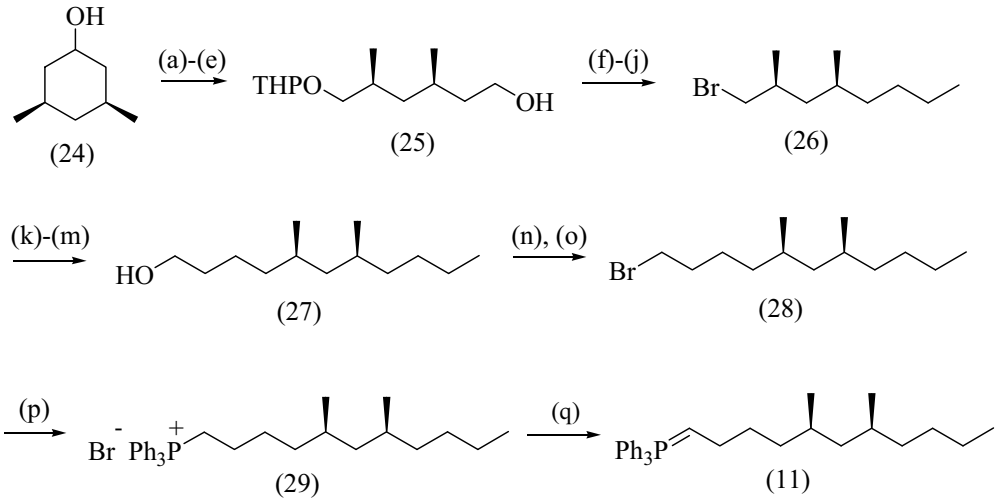
butyldimethylsilyl group afforded alcohol (20). A further one-carbon elongation, again with inversion gave the *anti-anti*-nitrile (21) and hence the aldehyde (22). Condensation with an ester phosphonate and reduction with magnesium-methanol and lithium aluminium hydride afforded *anti-anti-anti-* and *anti-anti-syn*-2,4,6,8-tetramethylundecan-1-ol (23) (Scheme 2).



Scheme 2 Synthesis of tetramethylundecan-1-ol (23).

Reagents and conditions: (a) Rh-C, H_2, 400-500psi, 3 days; (b) (i) Jones reagent, H_2O/ H_2SO_4, acetone, (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 48% (over 3 steps), (iii) NaOMe, MeOH, (iv) TBDMSCl, DMAP, NEt_3, toluene, 86% (over 2 steps); (c) LiOH, MeOH/ H_2O (4:1), 93%; (d) (i) EDC·HCl, NEt_3, CH_2Cl_2 then HOBT, (ii) $CH_3(CH_3O)NH{\cdot}HCl$, NEt_3, CH_2Cl_2, 71%; (e) MeMgI, THF, 88%; (f) (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, (ii) K_2CO_3, MeOH, 69% (over 2 steps); (g) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaCN, DMF, 66% (over 2 steps); (h) AcCl, MeOH, 70%; (i) DHP, TsOH, CH_2Cl_2, 85%; (j) $LiAlH_4$, Et_2O, 93%; (k) PPh_3, I_2, imidazole, THF, 97%; (l) EtMgBr, Li_2CuCl_4, THF, 70%; (m) *p*-TsOH, MeOH, 99%; (n) (i) MsCl, Et_3N, CH_2Cl_2, (ii) NaCN, DMF, 62% (over 2 steps); (o) AcCl, MeOH, 74%; (p) $LiAlH_4$, Et_2O (100%); (q) (i) $(COCl)_2$, DMSO, CH_2Cl_2, (ii) $Ph_3PC(CH_3)CO_2Et$, CH_2Cl_2, 64% (over 2 steps); (r) (i) Mg, MeOH, (ii) $LiAlH_4$, Et_2O, 61% (over 2 steps).

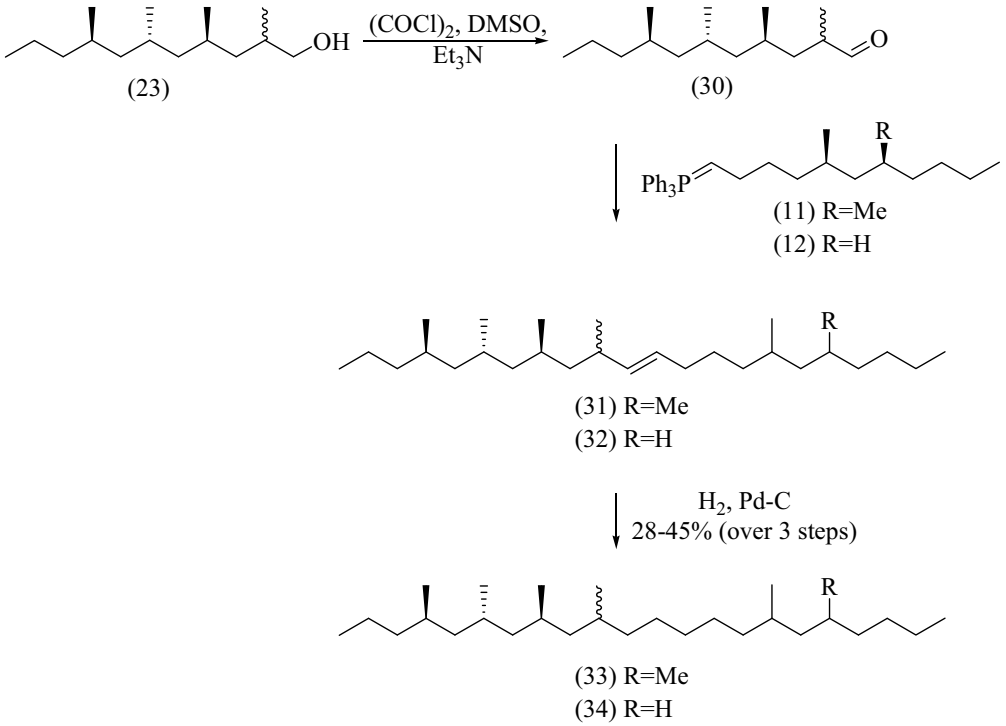
Using a similar strategy, but starting with *cis*-3,5-dimethylcyclohexanol (24) afforded the phosphonium salt (29), and deprotection with *n*-butylithium afforded the s*yn*-dimethyl phosphorane (11) as shown in Scheme 3.



Scheme 3 Preparation of dimethylalkyl ylide (11).

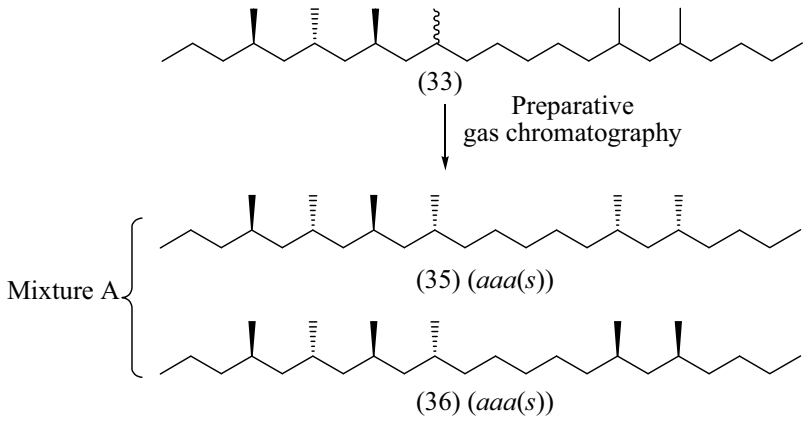
Reagents and conditions: (a) Jones reagent, H_2O/ H_2SO_4, 97%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 74%; (c) NaOMe, MeOH, 93%; (d) DHP, TsOH, CH_2Cl_2, 79%; (e) $LiAlH_4$, Et_2O, 85%; (f) TPAP, NMO, CH_2Cl_2, 85%; (g) EtMgBr, Et_2O, 78%; (h) Et_3N, MsCl, CH_2Cl_2; (i) $LiAlH_4$, Et_2O, 72% (over 2 steps); (j) Br_2, PPh_3, CH_2Cl_2, 81%; (k) AllylMgBr, Et_2O, 86%; (l) BH_3.DMS, EtOH; (m) NaOH, H_2O_2, 58% (over 2 steps); (n) Et_3N, MsCl, CH_2Cl_2; (o) LiBr, THF, heat, 79% (over 2 steps); (p) PPh_3, heat, MeCN, 95%; (q) *n*-BuLi.

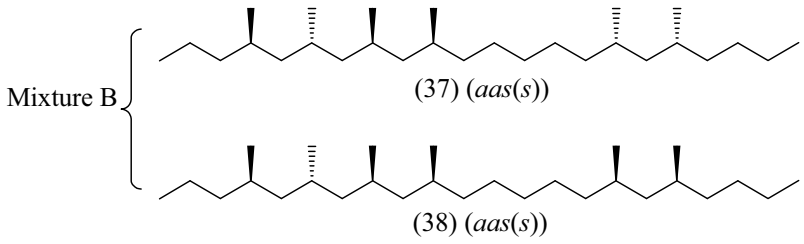
Swern oxidation of the mixture of *anti-anti-anti*- and *anti-anti-syn*-2,4,6,8-tetramethylundecan-1-ols (23) afforded the aldehydes (30) and coupling with the ylide (11) and (12) gave the alkenes (31) and (32), respectively. These were hydrogenated under mild conditions (Pd-C, H_2, 1 atm) to the hydrocarbons (33) and (34) as mixtures of diastereoisomers, see Scheme 4.



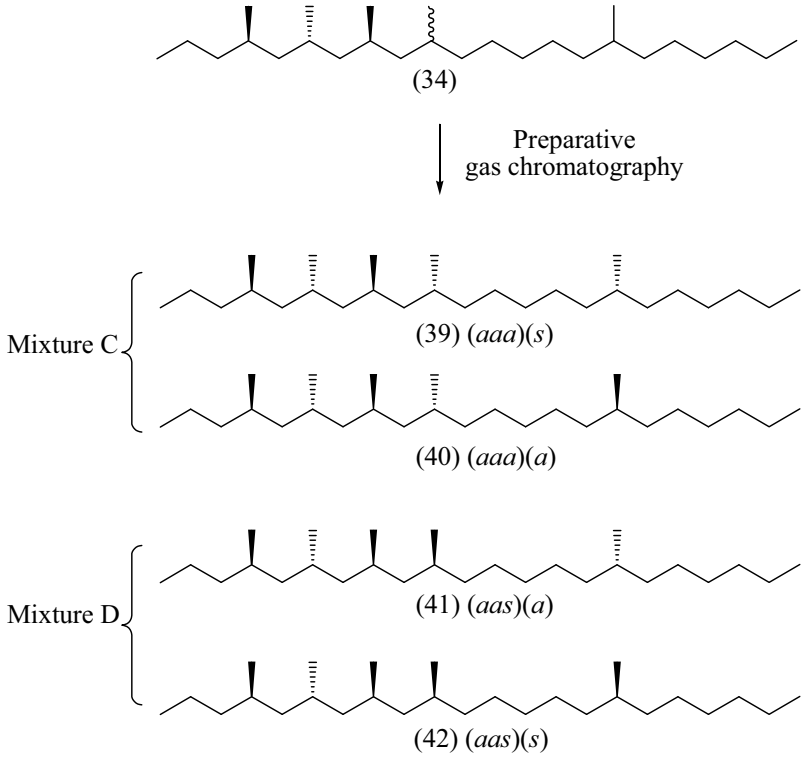
Scheme 4 Synthesis of hexamethyldocosanes and pentamethyldocosanes.

Preparative gas chromatography of hydrocarbons (33) and (34) permitted significant separation of the isomers, leading to mixtures A (compounds (35) and (36)), B (compounds (37 and 38)), C (compounds (39) and (40)) and D (compounds (41) and (42)) as indicated in Schemes 5 and 6.





Scheme 5 Formation of a mixture of four major diastereoisomers of hexamethyldocosanes.



Scheme 6 Formation of a mixture of four major diastereoisomers of pentamethyldocosanes.

The mass spectra of all of the C28 diastereoisomers synthesized were very similar and closely ressembled that of the natural hexamethyldocosane. Co-injection and capillary gas chromatographic comparisons of the synthetic hexamethyldocosane

isomers with the natural component established that the natural compound was a diastereoisomer of the *aaa*(*s*) system, (35) or enantiomer (43), or (36) or enantiomer (44). Similarly the pentamethyldocosane was either shown to be (39) or enantiomer (45), or (40) or enantiomer (46) as shown in Figures 2 and 3 [3,5].

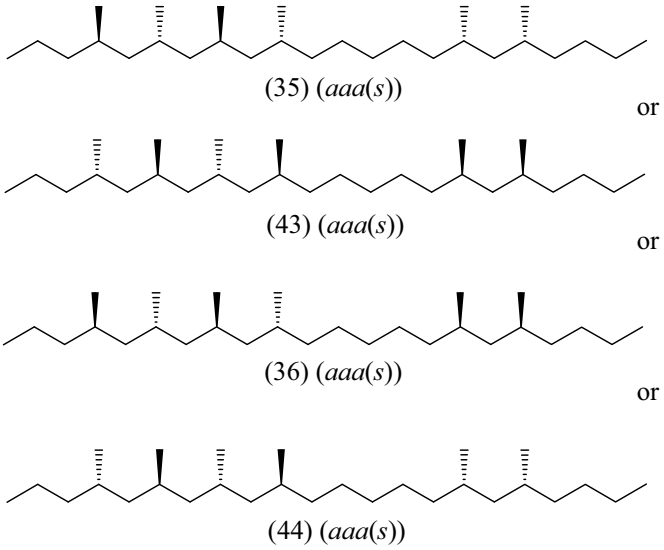


Figure 2 Possible structures of the natural lipid (7).

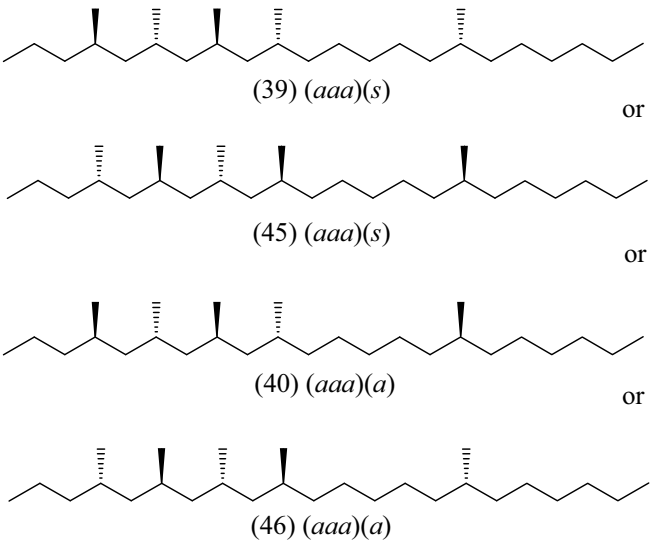
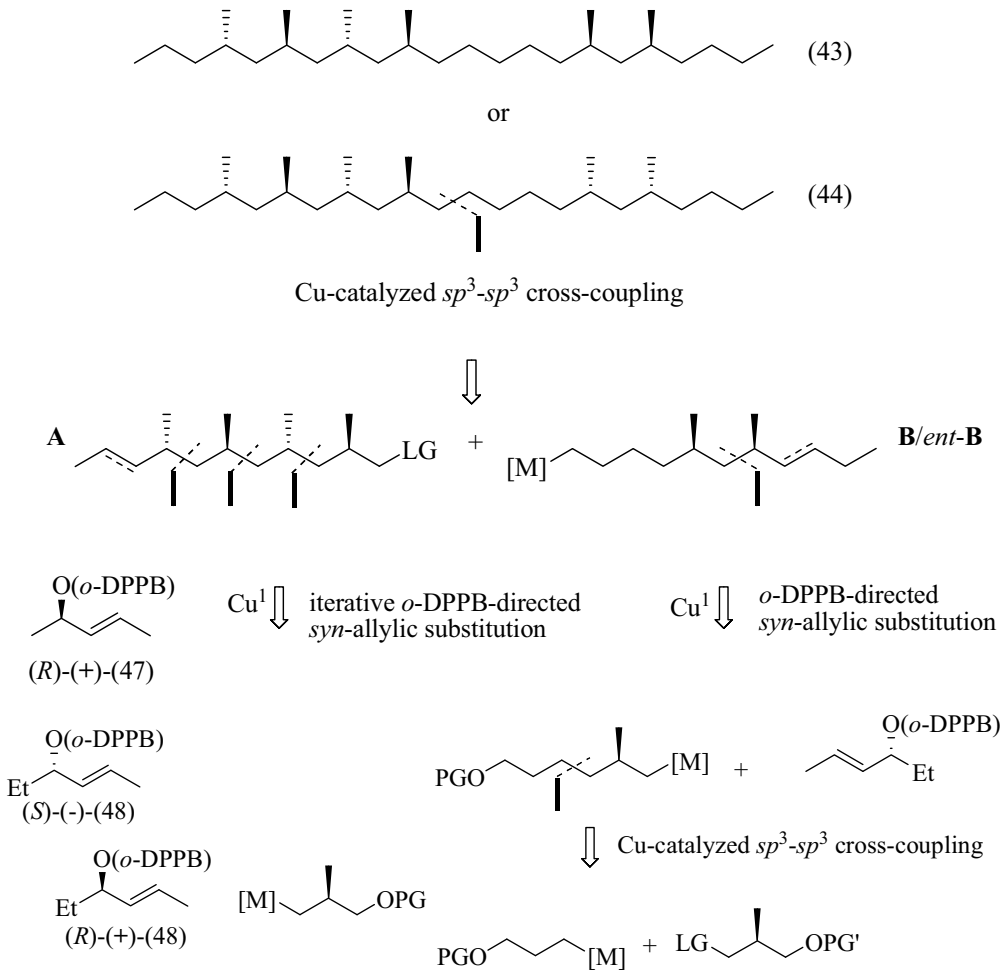


Figure 3 Possible structures of the natural lipid (8).

At this stage, a combined spectroscopic and another techniques have elucidated the relative *anti*-*anti*-*anti*-configuration of the four methyl bearing stereocentres in the tetrad unit of these natural products and the *syn* configuration within the methyl diad region. However the configurations of the all-*anti* tetrad relative to the *syn* diad, as well as the absolute configuration of these natural products were not established. This would require an enantiocontrolled synthesis utilizing the coupling of enantiopure tetramethyl- and dimethyl-substituted fragments [5].

1.3.2 Breit's total synthesis of diastereoisomers of lipids (43) and (44)

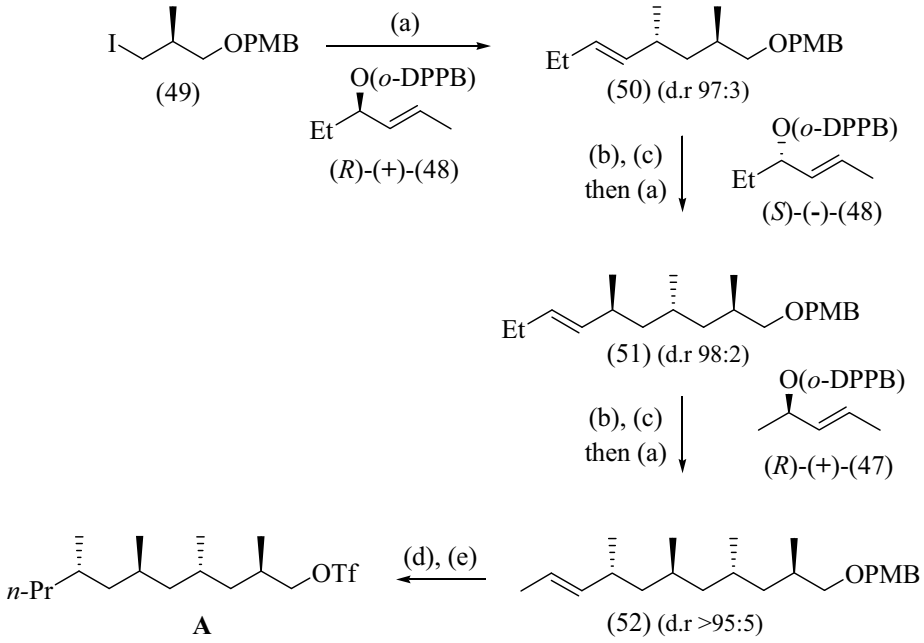
Breit and co-workers have published on the total synthesis of both diastereoisomers of (43) and (44) in enantiomerically pure form, enabling the determination of the relative and absolute configurations of the natural product [6,7]. The synthesis relied on recently developed copper-mediated and *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB)-directed *syn*-allylic substitution with Grignard reagents for iterative deoxypropionate synthesis [8,9]. The power of copper-catalyzed sp^3-sp^3 cross coupling was demonstrated for building block construction and as the fragment-coupling step in a convergent total synthesis as shown in Scheme 7.



Scheme 7 Retrosynthesis for lipids (43) and (44).
PG= protecting group, LG= leaving group, M= metal,
o-DPPB= *ortho*-diphenylphosphanylbenzoyl

The synthesis began with construction of the tetrad building block **A** (Scheme 8). Iodide (49), which was available in three steps from the Roche ester, was converted into a Grignard reagent and subjected to *o*-DPPB-directed *syn*-allylic substitution with allylic *o*-DPPB-ester (*R*)-(+)-(48) in the presence of 0.5 equivalent of copper bromide dimethylsulfide to give the dideoxypropionate (50) with a complete 1,3-chirality transfer. Two separate iterations consisting of three steps, alkene ozonolysis with a reductive workup with $NaBH_4$, transformation to the iodide and directed *syn*-allylic substitution with (*S*)-(-)-(48) and (*R*)-(+)-(47), respectively, furnished the tetradeoxypropionate (52) with all the carbon atoms and stereocenters

in place. Alkene hydrogenation and reductive cleavage of the *p*-methoxybenzyl ether occurred upon heterogenous catalytic hydrogenation to give building block A which was activated as the corresponding triflate prior to fragment coupling.

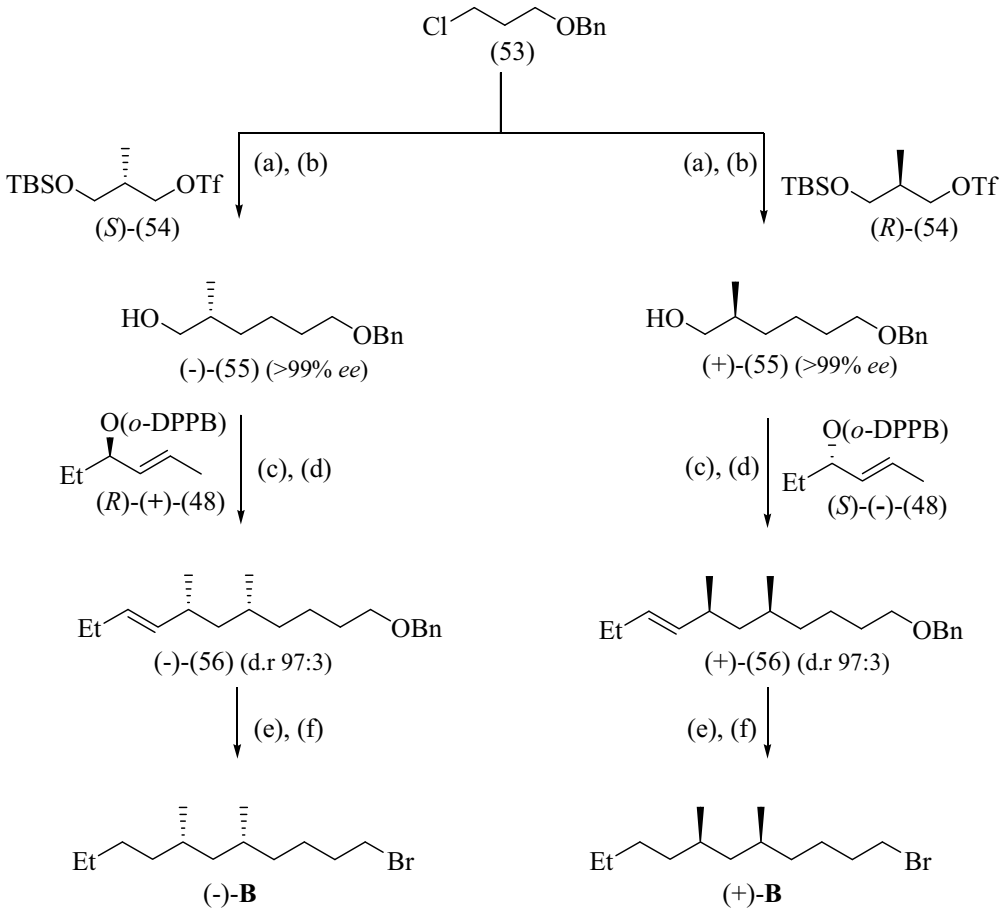


Scheme 8 Synthesis of tetradeoxypropionate building block **A**.

Reagents and conditions: (a) 2 *t*-BuLi, $MgBr_2.OEt_2$, then (*R*)-(48), (*S*)-(48) or (*R*)-(47), $CuBr.SMe_2$, Et_2O, 83%-85%; (b) O_3, $NaBH_4$, 95%; (c) Imidazole, PPh_3I_2, 92%; (d) PtO_2, H_2 (5 bar) then $Pd(OH)_2$, 98%; (e) Tf_2O, NEt_3, CH_2Cl_2, -78ºC, 97%.

Synthesis of the enantiomeric dideoxypropionate building blocks **B** commenced with the chloride (53) (Scheme 9). Triflates (*S*)-(54) and (*R*)-(54) underwent a copper catalyzed cross coupling at -20°C in the presence of 4 mol% of $[Li_2CuCl_4]$ with the Grignard reagent derived from the chloride (53) followed by desilylation of the crude coupling products with methanolic hydrogen chloride to give alcohols (-)-(55) and (+)-(55) respectively in 82% isolated yield over the two steps. A Mukaiyama redox condensation furnished the corresponding iodides, which were subjected for the directed *syn*-allylic substitution with (*R*)-(+)-(48) and (*S*)-(-)-(48), respectively, to furnish the dideoxypropionates (-)-(56) and (+)-(56) in

excellent yields with complete diastereoselectivities. A standard functional group manipulation thus led to the building blocks (-)-**B** and (+)-**B**.

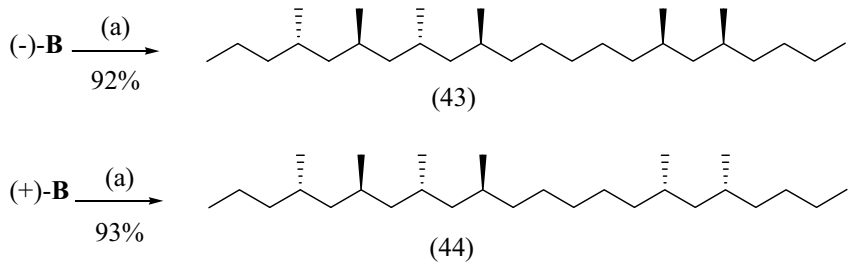


Scheme 9 Synthesis of the enantiomeric dideoxypropionate building blocks (-)-**B** /(+)-**B**.

Reagents and conditions: (a) Mg, THF, [Li_2CuCl_4] (4 mol%), then (*S*)-(54) or (*R*)-(54); (b) 5% HCl in MeOH, 82% over 2 steps; (c) PPh_3I_2, Imidazole, CH_2Cl_2, 93%; (d) 2 *t*-BuLi, $MgBr_2.OEt_2$ then (*R*)-(48) or (*S*)-(48), CuBr.SMe_2, Et_2O, 85%; (e) H_2, PtO_2, EtOAc, 12 h then H_2, Pd-C (10%) 24 h, 96%; (f) PPh_3, NBS, 97%.

The final coupling step (Scheme 10) employing a copper-catalyzed sp^3-sp^3 cross coupling of the Grignard reagent derived from (-)-**B** or (+)-**B** with triflate **A**. Addition of an ethereal solution of the triflate together with 4 mol% of the catalyst [Li_2CuCl_4] to an ethereal solution of the Grignard reagent derived form of **B** afforded

both distereoisomers (43) and (44) in an excellent yields. Comparison of ^{13}C NMR spectrum of synthetic and natural material showed a perfect match for diasteroisomer (43) [6,7]. Comparison of the optical rotation values of the natural and synthetic material determined the absolute configuration of the natural products of (43) and (44) as shown in Scheme 10.

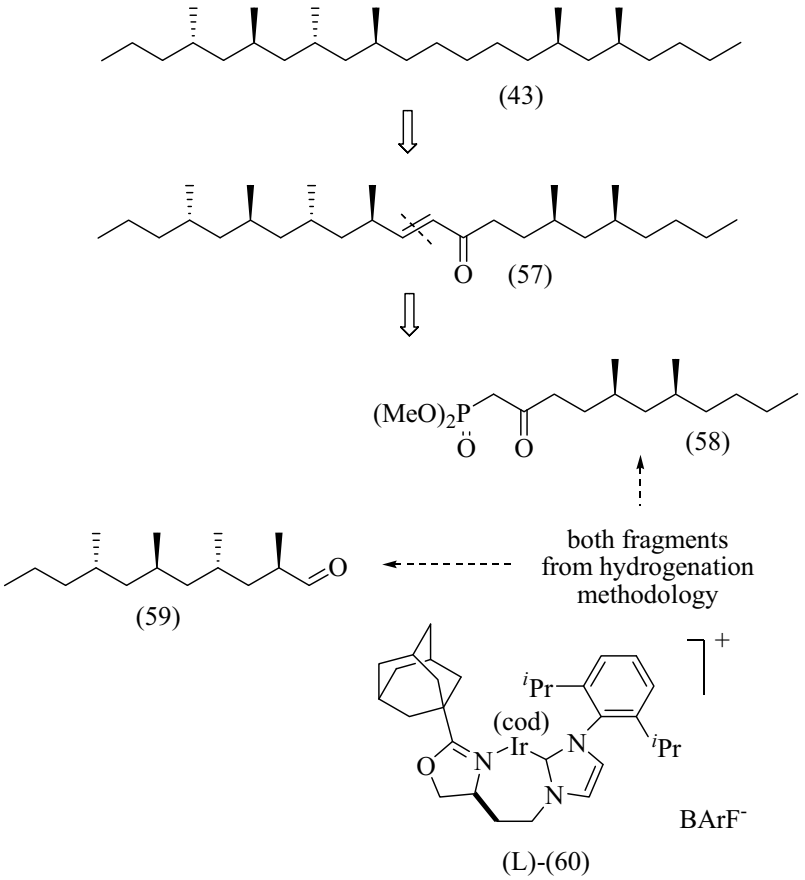


Scheme 10 Fragment coupling through Cu-catalyzed sp^3-sp^3 cross coupling.

Reagents and conditions: (a) Mg, Et_2O, $BrCH_2CH_2Br$ (0.4 equiv), $[Li_2CuCl_4]$ (4 mol%), then **A**.

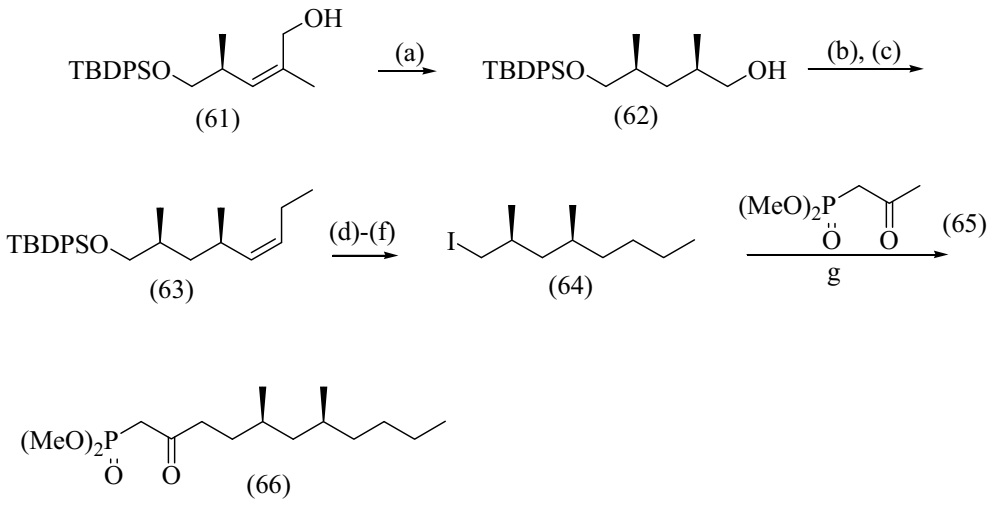
1.3.3 Burgess's total synthesis of lipid (43)

Burgess and co-workers [10] have developed a catalyst-controlled diastereoselective hydrogenation methodology for the syntheses of deoxypolyketide chirons. They have carried out considerable work on the used of carbene oxazoline complexes e.g. (L)-(60) on a broad range of substrates for which most other chiral catalysts are not effective [11]. A chiral analogue of Crabtree's catalyst, (L)-(60) was used in asymmetric hydrogenation of allylic alcohols and unsaturated esters with excellent diastereoselectivity [12]. Scheme 11 outlines the retrosynthetic approach towards a synthesis of lipid (43).



Scheme 11 Retrosynthetic analysis of lipid (43) according to Burgess.

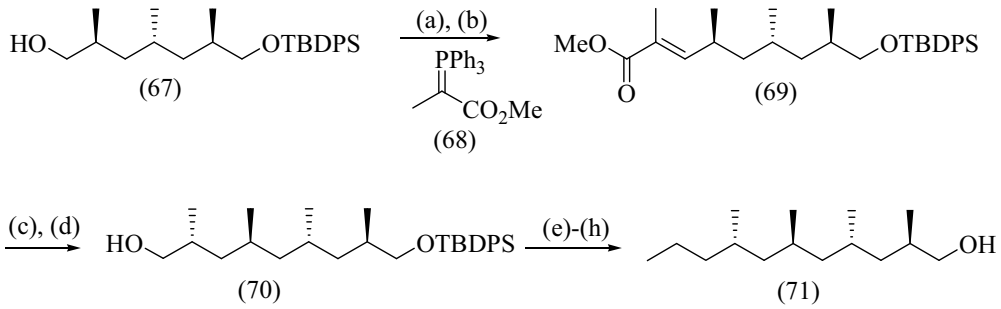
The allylic alcohol (61) was prepared in 87% yield over three steps from the commercially available Roche ester. Asymmetric hydrogenation of this *Z*-allylic alcohol with catalyst L-(60) favored the *syn*-product (62) [11]. The crude material formed in this step had a 34:1 *syn*- to *anti*-diastereomeric ratio as shown by GC analysis and 93% yield of 120:1 *syn*- to *anti*-product after chromatographic purification. Conversion of the alcohol (62) to the alkene (63) under Swern and Wittig conditions and subsequent reduction by heterogeneous hydrogenation produced the corresponding alkane which was desilylated and converted to the iodide (64). Alkylation of the dianion of keto-phosphonate (65) afforded keto-phosphonate (66) with the *syn* relative stereochemistry in 79% yield (Scheme 12).



Scheme 12 Synthesis of the eastern part of lipid (43).

Reagents and conditions: (a) 50 atm H_2, 0.2 mol% L-(60), CH_2Cl_2, 25ºC, 93%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78ºC, 10 min; (c) KHMDS, *n*-$PrPPh_3Br$, THF,-78ºC, 2h, 83%; (d) H_2, Pd-C, MeOH/ THF, 25ºC, 7 h, 99%; (e) TBAF, THF, 25ºC, 2 h; (f) PPh_3, I_2, imidazole, CH_2Cl_2, 25ºC, 30 min 86%; (g) (65), NaH then *n*-BuLi, 0ºC, 1 h, 79%.

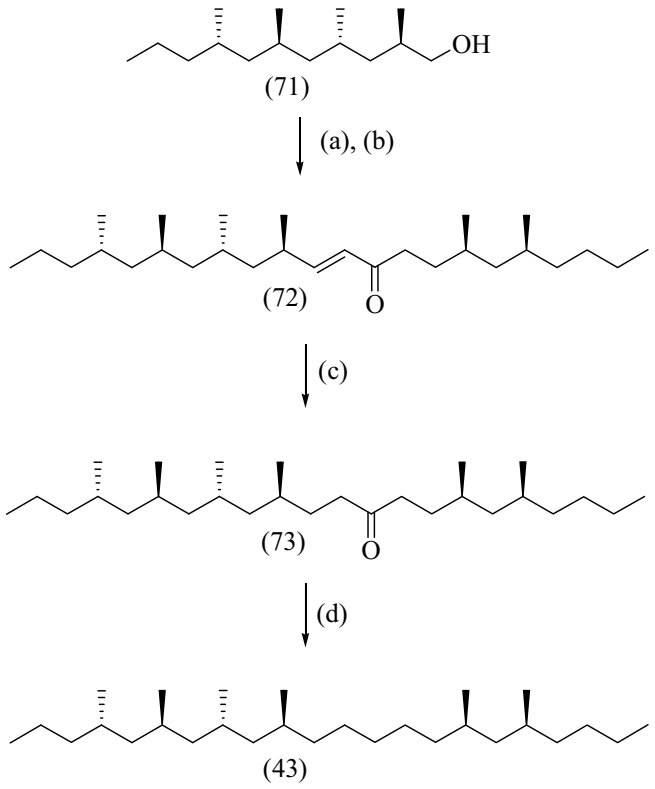
The western part of lipid (43) derived from aldehyde (59) contains a stereochemical tetrad. Alcohol (67) was prepared from the commercially available Roche ester. The *anti*-*anti*-stereochemical triad in the structure was obtained from the asymmetric hydrogenation using chiral analogue of Crabtree's catalyst [11,12]. Alcohol (67) was converted to the ester (69) in 80% yield, which was reduced using catalyst L-(60) with high stereoselectivity. The crude material was further reduced to alcohol (70) using di*iso*butylaluminium hydride. Oxidation of this alcohol followed by a Wittig reaction of the resultant aldehyde and heterogeneous hydrogenation followed by treatment with tetrabutylammonium fluoride resulted in desilylation to form the *anti*-*anti*-*anti*-tetramethyl intermediate (71) in 84% yield (Scheme 13).



Scheme 13 Synthesis of the western part of lipid (43).

Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, 25ºC, 30 min, 65%; (b) (68), PhMe, 80ºC, 12 h; (c) 50 atm H_2, 1 mol% L-(60); CH_2Cl_2, 25ºC, 4 h; (d) DIBAL-H, THF, 0ºC, 30 min, 80%; (e) TPAP, NMO, CH_2Cl_2, 25ºC, 30 min; (f) KHMDS, $EtPPh_3Br$, THF, -78ºC, 1 h; (g) H_2, Pd-C, MeOH/ THF, 25ºC, 7 h, 76%; (h) TBAF, THF, 25ºC, 1.5 h, 84%.

The synthesis of the target molecule (43) from the alcohol (71) using the aldehyde (59) and the phosphonate (66) was accomplished as shown in Scheme 14. The Horner-Wadsworth-Emmons coupling followed by heterogeneous hydrogenation of alkene (72) gave ketone (73). Reduction of the ketone tosylhydrazone using sodium cyanoborohydride gave lipid (43) in a good yield. The proton and ^{13}C NMR spectra of the synthetic product (43) were essentially identical to those reported in the literature by Kitching [3,5] and Breit [6,7].



Scheme 14 Completion of the synthesis of lipid (43).

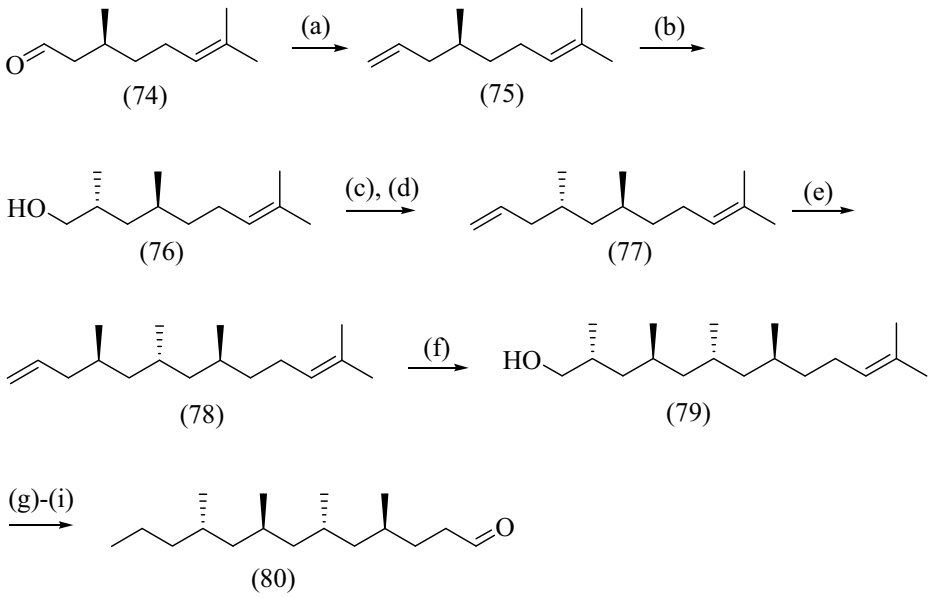
Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, 25ºC, 30 min; (b) $Ba(OH)_2$, then (66), wet THF, 25°C, 15 min, 86%; (c) H_2, Pd-C, MeOH/ THF, 25ºC, 4 h, 99%; (d) $TsNHNH_2$, $NaBH_3CN$, TsOH, DMF/ sulfolane, 110ºC, 2 h, 94%.

1.3.4 Negishi's total synthesis of lipid (43)

Negishi and co-workers have developed an efficient and enantio-face selective Zr-catalyzed asymmetric carboalumination (ZACA) reaction [13,14,15] which provides access to enantioselective carbon-carbon bond formation using terminal alkenes.

The terminal alkene (75) prepared from (*S*)-β-citronellal (74) using a simple Wittig reaction, reacted with Me_3Al in the presence of (-)-bis-(neomenthylindenyl)zirconium dichloride, (-)-$(NMI)_2ZrCl_2$ in dichloromethane at

23°C with oxidation of the carboalumination product with O_2 gave the alcohol (76) in a 60% yield. The purification of (76) was achieved by Amano PS lipase-catalyzed acetylation leading to higher recovery than that observed by chromatographic purification [13]. Installation of terminal olefin in (76) was achieved *via* a Pd-catalyzed vinylation of the primary iodide. Iteration of the Zr-catalyzed carboalumination of diene (77) followed by a Pd-catalyzed vinylation gave the terminal olefin (78) and subsequent iteration followed by quenching with O_2 gave end-differentiated deoxypropionate (79). The alcohol (79) was then subjected to standard reactions to give aldehyde (80) as shown in Scheme 15.

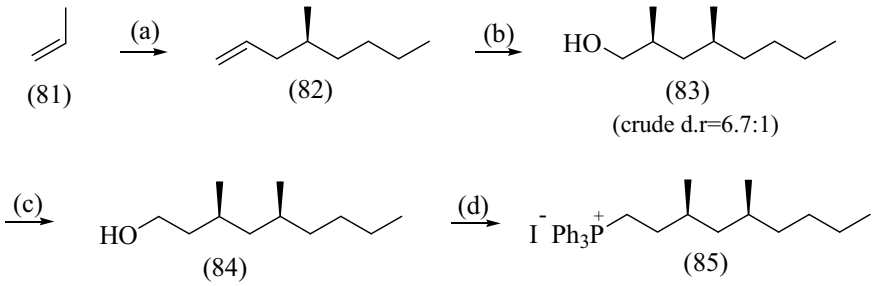


Scheme 15 Synthesis of the C1-C13 fragment.

Reagents and conditions: (a) CH_2=PPh_3, 95%; (b) (i) Me_3Al (2 equiv), (-)-$(NMI)_2ZrCl_2$ (4 mol%), CH_2Cl_2, 23°C, (ii) O_2, (iii) Amano PS lipase (30 mg/ mmol), vinyl acetate (5 equiv), CH_2Cl_2, 60%; (c) I_2, PPh_3; (d) (i) *t*-BuLi, Et_2O, -78°C, (ii) dry $ZnBr_2$, THF, (iii) CH_2=CHBr (3 equiv), $Pd(PPh_3)_4$ (2 mol%), 79% (over 2 steps); (e) (i) Me_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (3 mol%), CH_2Cl_2, (ii) evaporation of CH_2Cl_2 and Me_3Al, (iii) Dry $Zn(OTf)_2$ (1 equiv), DMF, 2 h, 70°C, (iv) Pd (DPEphos)Cl_2 (3 mol%), DIBAL-H (6 mol%), CH_2=CHBr (3 equiv), DMF, 70%; (f) (i) Me_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (4 mol%), CH_2Cl_2, 23°C, (ii) O_2, 45%; (g) TsCl, Et_3N; (h) EtMgBr, Li_2CuCl_4 (5%); (i) NMO (3 equiv), OsO_4 (1 %) then $NaIO_4$, 89% (over 3 steps).

The preparation of the *syn*-dimethylalkyl derivatives (83), (84) and (85) used a fully catalytic and reagent-controlled enantio-face selective ZACA route from

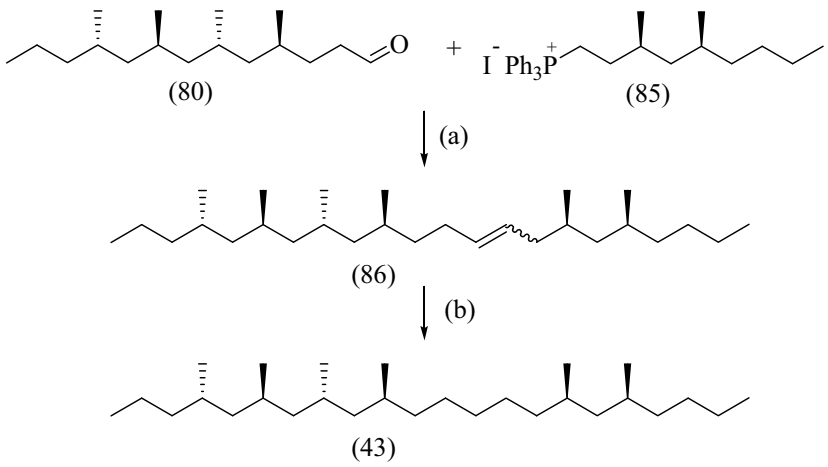
propene (81), as shown in Scheme 16. Transformation of (81) into the terminal olefin (82) set up a second stage asymmetric carboalumination in the presence of the same chiral Zr catalyst to give alcohol (83), which was highly enriched in the *syn* isomers, after isolation by chromatography. After hydroxyl group manipulations and a one carbon chain extension, the phosphonium salt (85) was prepared.



Scheme 16 Synthesis of the C14-C22 fragment.

Reagents and conditions: (a) (i) *n*-Bu_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (3 mol%), CH_2Cl_2, (ii) evaporation of CH_2Cl_2 and Me_3Al, (iii) dry $Zn(OTf)_2$ (1 equiv), DMF, 2 h, 70°C, (iv) Pd (DPEphos)Cl_2 (3 mol%), DIBAL-H (6 mol%), CH_2=CHBr (3 equiv), DMF, 67%; (b) (i) Me_3Al (2 equiv), (+)-$(NMI)_2ZrCl_2$ (4 mol%), CH_2Cl_2, 23°C, (ii) O_2, 48%; (c) (i) I_2, PPh_3, (ii) *t*-BuLi then HCHO, 83% (over 2 steps); (d) (i) I_2, PPh_3, (ii) PPh_3, toluene, 85% over 2 steps.

With the two key intermediates (80) and (85) as isomerically pure compounds, the final assembly of the target compound (43) was achieved in 85% yield by two steps *via* Wittig olefination and catalytic hydrogenation with H_2 over Pd-C (Scheme 17). The desired product (43) obtained exhibited ^1H and ^{13}C NMR spectra as well as an optical rotation which were in a good agreement with those reported previously [5,7,10].



Scheme 17 Final assembly of (43).

Reagents and conditions: (a) *n*-BuLi, THF; (b) H_2, Pd-C, 85% (over 2 steps).

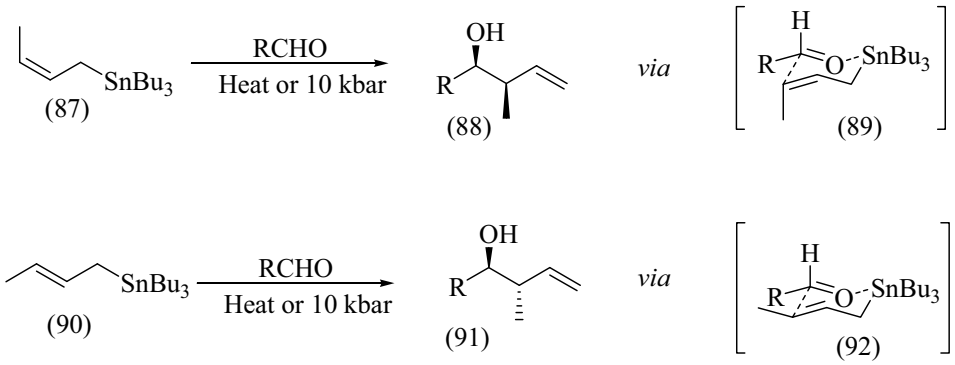
1.4 Remote Asymmetric Induction

Reactions leading to the control of the relative stereochemisty of two stereogenic centres are of great importance. Numerous reactions have been developed for effective 1,2- and 1,3-stereoinduction. As the separation of the two stereogenic centres extends further, stereoinduction becomes more difficult. This is especially the case for acyclic systems as they are intrinsically less ordered than their cyclic counterparts. In the area of acyclic stereocontrol there are now many excellent methods that give high 1,4-, 1,5-, 1,6- and 1,7-stereocontrol. This chapter is intended to review the highlights in this area for reactions that produce remote stereocontrol using the addition of an allyl-metal reagent to a carbonyl functionality to form a homoallylic alcohol with high enantio- and diastereocontrol [16]. A few representative examples of application of this chemistry in natural product synthesis are presented in the following chapter to show the diversity of this reaction.

1.5 Reactions of allylstannanes

1.5.1 Thermal reactions of alkylallylstannanes with aldehydes

The configurationally stable crotylstannanes have been shown to undergo highly diastereoselective reactions with aldehydes on heating to high temperatures [17]. The stereochemistry in thermal reactions of allylic tin derivatives generally depends upon the geometry of the but-2-enyl unit, as observed in ordinary allylic organometallic reactions. For example, as in Scheme 18, the (*Z*)-crotylstannane (87) produced the *syn*-homoallylic alcohol (88), while the (*E*)-isomer (90) afforded the *anti*-homoallylic alcohol (91) on heating with aldehydes [18]. The reaction of allylic trialkyltins with aldehydes also takes place at room temperature under neutral conditions by using the high-pressure technique (10 kbar in CH_2Cl_2 or Et_2O). The stereochemical outcome is the same as that in thermal reactions [19].

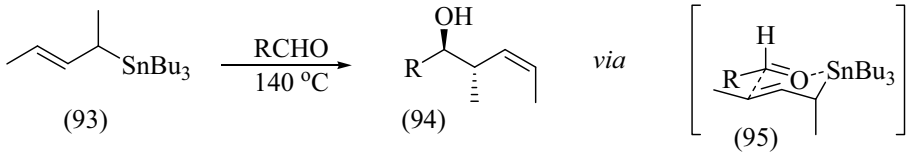


Scheme 18 Reaction of crotylstannanes with aldehyde on heating.

The stereoselectivities of these reactions are consistent with six-membered chair-like transition states (89) and (92). In these transition states, the metal is coordinated to the carbonyl oxygen and the larger R group of the aldehyde adopts an equatorial orientation. The attack at the carbonyl carbon is from the γ-position of the stannane double bond, with a concomitant allylic shift and migration of the tin to the

aldehyde oxygen. The trialkyltin group is then removed by hydrolysis on work-up [20].

The α-alkyl substituted crotylstannane (93) (*E*:*Z*-isomers, 90:10) produced the *anti*-homoallylic alcohol (94) containing a (*Z*)-double bond when heated with aldehyde [21]. The stereoselective origin of the reaction was interpreted in terms of the chair-like transition state (95) in which the methyl substituent α to tin, adopts an axial position (Scheme 19). No products arising from the (*Z*)-crotylstannane was isolated perhaps because of an unfavourable 1,3-diaxial interaction between an axial α-methyl group and the *cis*-disposed vinylic methyl group in the transition state analogous to (95).



(93) (94) (95)

Scheme 19 Reactions of α-alkyl crotylstannanes with aldehydes on heating.

A limitation to these thermal reactions of allylstannanes is the high temperatures required. This can lead to a competing self condensation reaction when primary alkyl aldehydes are used. Alternative procedures have been developed to overcome this problem. These include high pressure [19,22] photolysis [23] and more commonly, the use of a Lewis acid to activate the aldehyde, but this gave rise to different diastereoisomers.

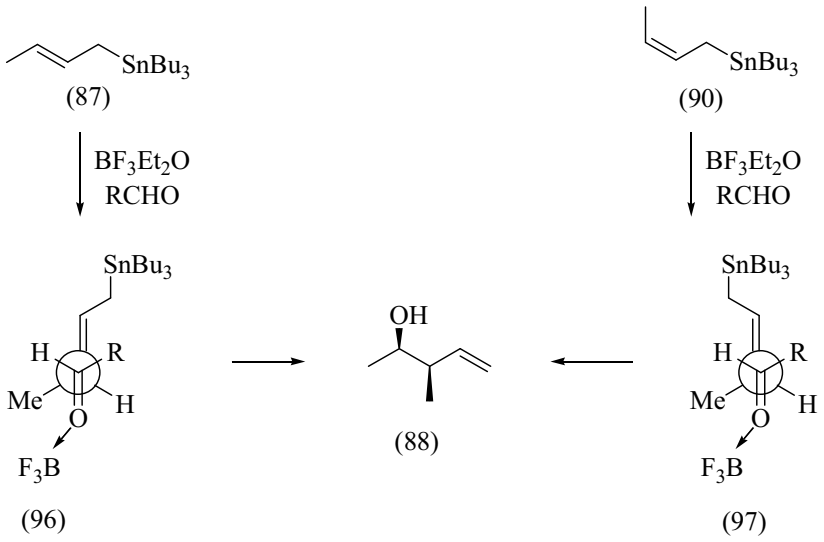
1.5.2 Lewis acid promoted reactions of alkylallylstannanes with aldehydes

Lewis acid activated reactions of alkylallylstannanes with aldehydes occur readily at low temperatures, typically at -78ºC. The structures of the products can be controlled by the choice of Lewis acid since there are two distinctly different reaction pathways available [24]. On the one hand, the transmetallation can take place between the Lewis acid and the allylstannane to form a more reactive allylmetal

species. Alternatively, the Lewis acid may coordinate to the carbonyl oxygen of the aldehyde, activating the carbonyl carbon to nucleophilic attack. Which process is preferred depends on the metal and/ or the Lewis acid used. Changing the Lewis acid can radically alter the regio- and stereochemistry of the products.

(*E*)- And (*Z*)-crotylstannanes (87) and (90) undergo stereoconvergent reactions with aldehydes in the presence of boron trifluoride diethyl etherate to give almost exclusively *syn*-homoallylic alcohol (88) [25]. This result is irrespective of the double-bond geometry of the crotylstannane (Scheme 20).

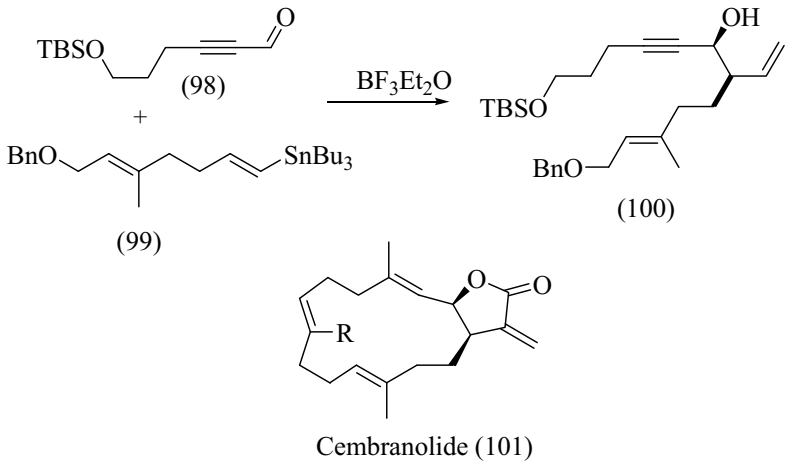
The *syn*-stereochemistry of these reactions cannot be explained by a conventional cyclic chair-like transition state. Instead, these reactions are believed to proceed *via* the open-chain, acyclic, transition states (96) and (97), in which the carbonyl oxygen is coordinated to the Lewis acid, thus preventing coordination by stannane [26]. Attack of the carbonyl group takes place from the γ–position of the stannane.



Scheme 20 Boron promoted reactions of crotylstannanes.

In connection with a synthesis of the cembranolide (101) [27], the boron trifluoride diethyl etherate mediated intermolecular reaction of the aldehyde (98)

with the allylstannane (99) was employed to form cembranolide precursor (100) as shown in Scheme 21.

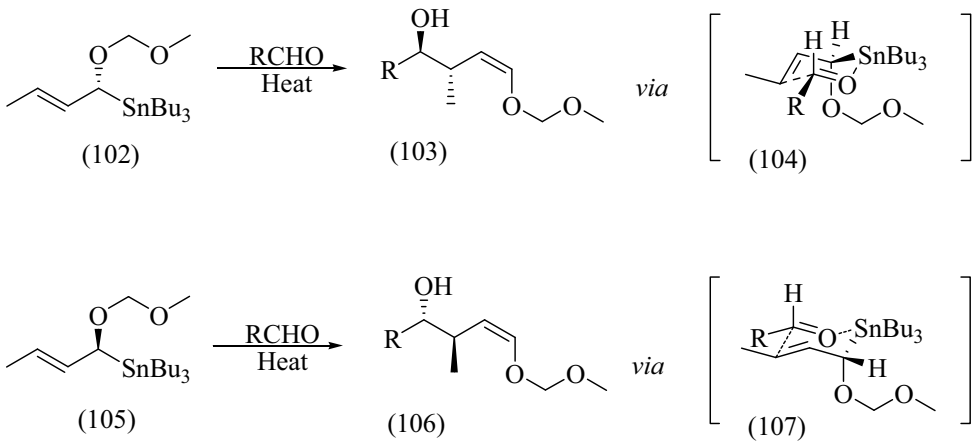


Scheme 21 An application of boron trifluoride diethyl etherate mediated reactions of allylstannanes.

1.5.3 α-Alkoxyallystannanes

The introduction of heteroelements into allylstannanes would be expected to enhance their applicability in synthesis. Reactions of alkoxyallylstannanes with aldehydes give rise to polyoxygenated products, and the oxygen in the substituent may influence the stereochemical outcome of reactions with aldehydes.

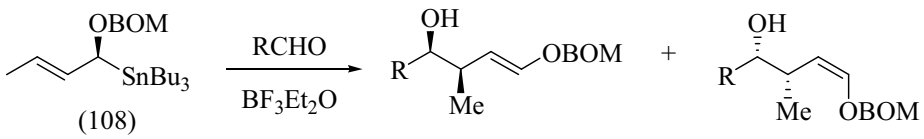
Thermal reactions of enantiomeric α-alkoxyallylstannanes (102) and (105) with aldehydes have been shown to give the *anti*-(*Z*)-enol ethers (103) and (106), respectively, [28] as shown in Scheme 22.



Scheme 22 Thermal reactions of α-alkoxy-(*E*)-allystannanes with aldehydes.

These products are believed to arise from the cyclic six-membered chair-like transition states, (104) and (107), in which the chiral α-alkoxyallylstannanes react with one face of the prochiral aldehyde with the alkoxy substituent α to tin adopting the axial orientation. This is consistent with the observation that α-alkoxy-(*Z*)-allylstannanes are much less reactive than the corresponding (*E*)-isomer [29]. The axial preference of the substituent α to tin would lead to severe 1,3-diaxial interactions in the transition state leading to products.

The addition of boron trifluoride diethyl etherate to the reactions of a chiral α-alkoxyallylstannane with an aldehyde reduces the reaction temperature required and change the stereochemical outcome (Scheme 23). For example, the reactions between the α-alkoxyallylstannane (108) and aliphatic aldehydes in the presence of boron trifluoride diethyl etherate gave rise predominantly to the *syn*-(*E*)-product (109) possibly *via* an open-chain antiperiplanar transition state [30]. When aromatic aldehydes were used, the *syn*-(*Z*)-product (110) was formed as the major product *via* a synclinal transition state. This may be due to differences in the structure of the aldehyde/ boron triflouride complexes [31].

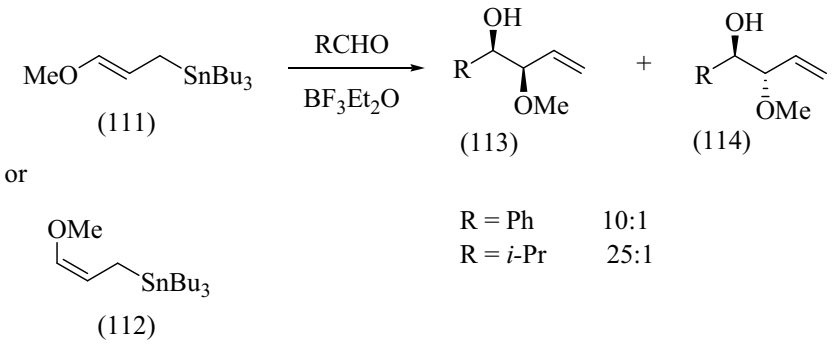


	syn-(*E*)	*syn*-(*Z*)
R = Alkyl	<1	>95
R = Aryl	80	20

Scheme 23 Boron trifluoride diethyl etherate promoted reactions of chiral α-alkoxyallylstannanes with aldehydes.

1.5.4 γ-Alkoxyallystannanes

The boron trifluoride diethyl etherate activated reactions of γ-alkoxyallystannanes of compounds (111) or (112) with aldehydes gave rise to mono-protected 1,2-diols (113) and (114) as shown in Scheme 24. The reactions afford predominantly *syn*-mono-protected diols (113), suggesting that an open chain antiperiplanar transition state is involved [32].

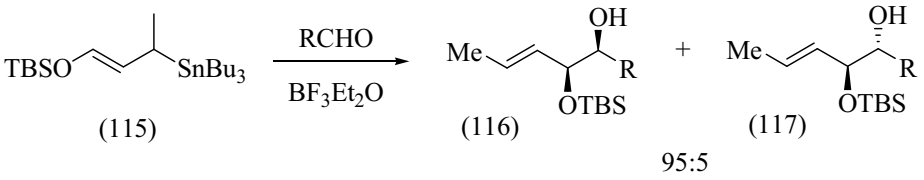


R = Ph 10:1
R = *i*-Pr 25:1

Scheme 24 Boron trifluoride diethyl etherate promoted reactions of γ-alkoxyallylstannanes with aldehydes.

γ-Alkoxyallystannanes with α-alkyl substituents have also been shown to undergo diastereoselective reactions with aldehydes in the presence of boron

trifluoride diethyl etherate. For example, as shown in Scheme 25, α-methyl-γ-alkoxyallylstannane (115) reacts with aldehydes possibly *via* an open-chain transition state to afford the *syn*-(*E*)-product (116) together with inseparable *anti*-(*E*)-isomer (117) [33].



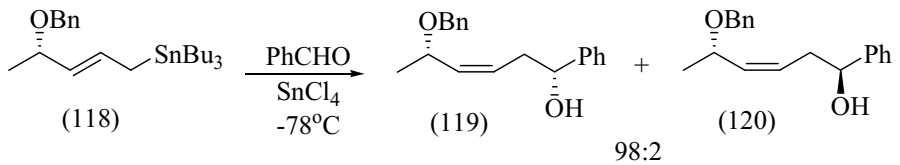
(115) (116) (117)

95:5

Scheme 25 Boron trifluoride diethyl etherate promoted reactions of α-methyl-γ-alkoxyallylstannanes with aldehydes.

1.5.5 δ-Alkoxyallystannanes

The δ-alkoxyallystannane (118) a 70:30 mixture of (*E*):(*Z*)-isomers has been prepared to investigate the influence of an oxygen substituted remote stereogenic centre on the diastereofacial selective reactions of allylstannanes with aldehydes [34,35]. Reaction of this compound with benzaldehyde in the presence of boron trifluoride diethyl etherate or at high temperature led to the formation of branched products. When tin(IV) chloride was reacted with (118) at -78°C followed after timing by the addition of benzaldehyde at this temperature, the linear homoallylic alcohol (119), containing a (*Z*)-double bond was formed with a *syn* (119) to *anti* (120) ratio of 98:2 (Scheme 26). This selectivity was observed to be general for a broad range of aldehydes [36,37].

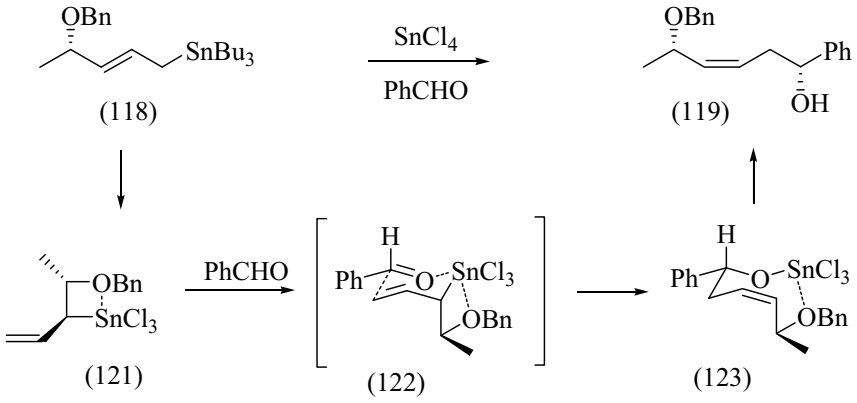


(118) (119) (120)

98:2

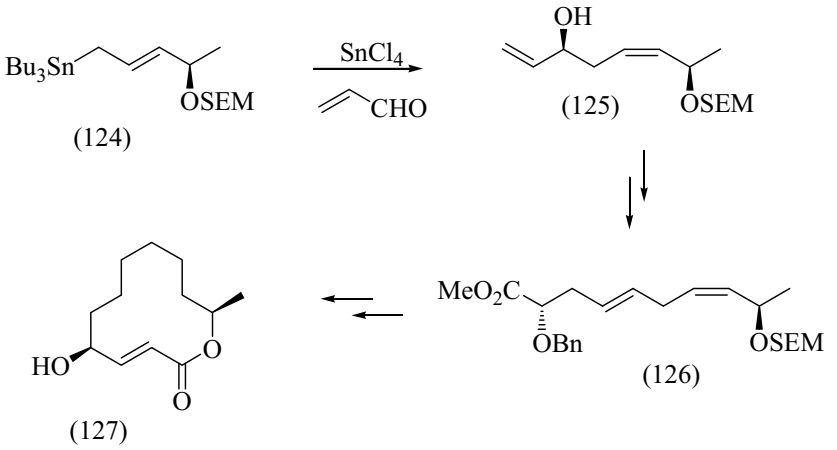
Scheme 26 Reaction of δ-alkoxyallylstannane (118) with $SnCl_4$ and aldehyde.

The formation of the 1,5-*syn*-(*Z*)-product from these reactions is consistent with the allyl(trialkyl)stannane (118) undergoing a stereoselective transmetallation with the tin(IV) chloride to form the allyl(trichloro)stannane (121), in which the methyl and vinyl group are *trans*-disposed [38,39]. This four-membered ring intermediate (121) is highly reactive towards aldehydes and is effectively configurationally stable due to the tin-oxygen interaction which prevents 1,3-isomerisation [40]. Recent work has shown that the proposed stereochemistry of (121) is correct, as treatment of (118) with tin(IV) chloride and an excess of phenylithium resulted in the trapping of this intermediate [41]. The reactions between the intermediate (121) and aldehydes proceed *via* a six-membered chair-like transition state (122) in which the bulky substituent α to tin is in the axial position [42] thus leading to the (*Z*)-double-bond (123). The configuration of the new chiral centre is controlled by the R group of the aldehyde which adopts an equatorial position, so determining which face of the prochiral aldehyde reacts as shown in Scheme 27.

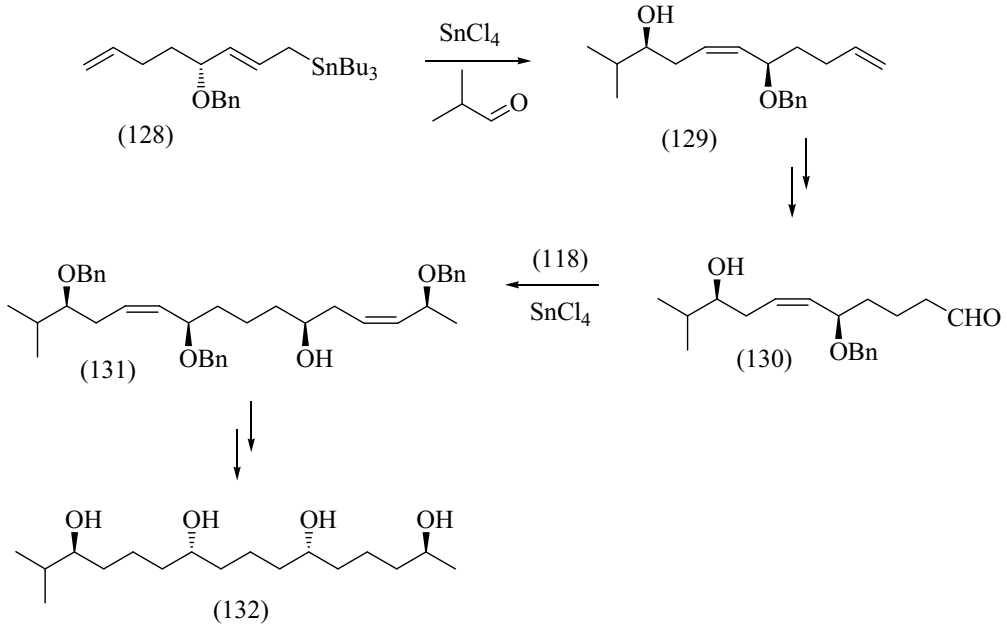


Scheme 27 The mechanism for formation of the *syn*-homoallylic alcohols (119).

Other δ-alkoxypent-2-enylstannanes have been prepared to investigate the applicability of this methodology. For example, the allylstannane (124) was used in a stereoselective total synthesis of patulolide C (127) *via* homoallylic alcohol (125) and ester (126) [36] (Scheme 28). Meanwhile, allylstannane (128) was used to synthesize stereoregular polyols such as compound (132) *via* homoallylic alcohols (129), (130) and (131) [37] (Scheme 29).



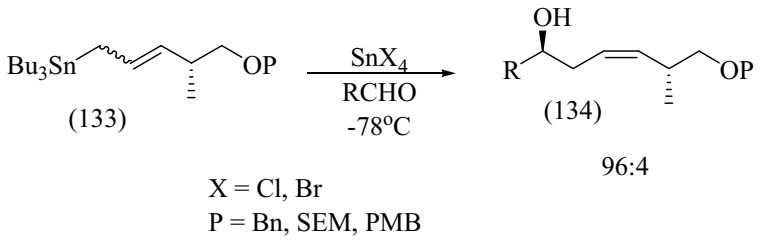
Scheme 28 Total synthesis of patulolide C (127) [36].



Scheme 29 Total synthesis of the stereoregular polyol (132) [37].

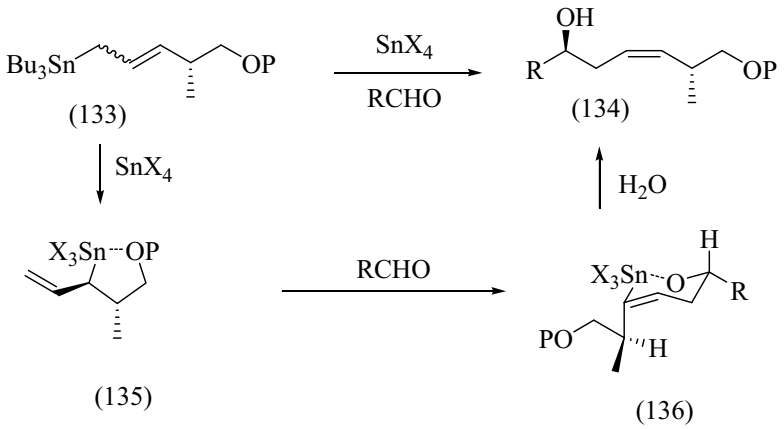
1.5.6 ε-Alkoxyallystannanes [43,44]

Reaction of the 5-substituted pent-2-enylstannanes (133) [35,45,46] with aldehydes at -78°C exhibited excellent 1,5-asymmetric induction after treatment with tin(IV) chloride or bromide (Scheme 30). The 1,5-*anti*- (*Z*)-homoallylic alcohol (134) was obtained as the major product of the reaction with 1,5-*anti*:1,5-*syn* of 96:4.



Scheme 30 Reaction of ε-alkoxyallystannanes (133) with SnX_4 and an aldehyde.

A transmetallation rapidly occurred on addition of the tin(IV) halide. During this process the Lewis acid is thought to be delivered to the double bond of the allylstannane stereoselectively following chelation to the oxygenated substituent. This gives rise to the five-membered oxastannane ring intermediate (135) where the vinyl and methyl groups are *trans*-disposed about the five-membered ring. The oxastannane then reacts with an aldehyde *via* a six-membered (136), chair-like transition state in which the substituent α to tin is in the axial position (Scheme 31).



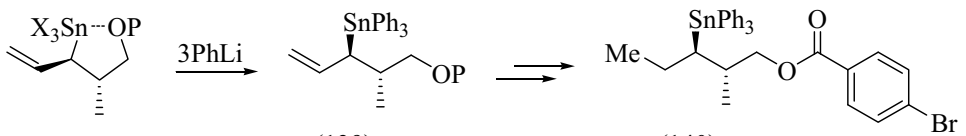
Scheme 31 Possible mechanism for formation of the *anti*-homoallylic alcohol (134).

In this reaction, there is a very high preference for the formation of *cis*-alkene irrespective of whether 1,5-, 1,6- or 1,7-induction is involved depending on the allylstannanes with heteroatom substituents at the 4-, 5- or 6-positions. If the oxygen substituent remains chelated to the tin during the reaction with aldehyde, an octahedral tin (137) is involved. However, if the aldehyde displace the oxygen substituent, the tin can remain as a trigonal bipyramid (138) during the reaction with the aldehyde (Scheme 32). From the thermal reaction of the α-substituted stannanes with aldehydes (see Scheme 22), there is a very strong preference to the group next to tin to adopt an axial position. This may well be the case here.

(137) (138)

Scheme 32 Possible transition structure for the reaction of allyltin trichloride (135) with aldehydes.

The intermediate allytin trichloride (135) (X=Cl) has been trapped by phenylithium to afford the 2,3-*anti*-triphenylalkyltin (139). The structure of major trapping product was established as 2,3-*anti*:2,3-*syn* in a ratio of 95:5 by X-ray diffraction of the *p*-bromobenzoate (140) [41,47] (Scheme 33).

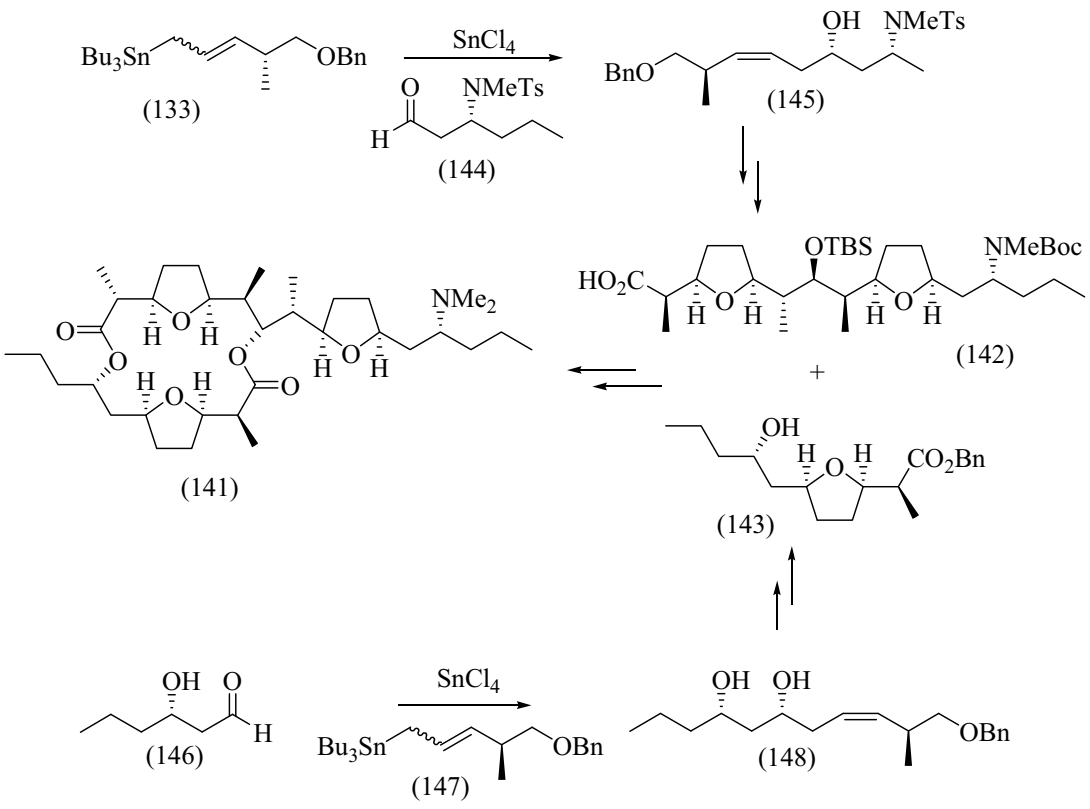


(135) (139) (140)

Scheme 33 Trapping the intermediate allyltin trichloride (135) with phenyllithium.

The usefulness of 1,5-asymmetric induction as a practical synthesis tool was further shown by the use of alkoxyallylstannane (133) in the total synthesis of

pamamaycin-607 (141) [48], which was synthesized by coupling of fragments (142) and (143). Fragment (142) was prepared by treating alkoxyallylstannane (133) with aldehyde (144) to afford the (*Z*)-1,5-*anti*-homoallylic alcohol (145). Alkoxyallylstannane (146) and aldehyde (147) were used to synthesize compound (143) *via* homoallylic alcohol (148) as shown in Scheme 34.



Scheme 34 Total synthesis of pamamycin-607 (148) [48].

1.6 Aspects of the chemistry of organobismuth compounds

1.6.1 Properties of bismuth metal [49] and organobismuth chemistry

Bismuth is the 83rd element in the periodic table and is the most metallic, the least abundant and the heaviest stable element in the nitrogen family. It is by far the

least toxic of the heavy metals and consequently an “ecofriendly” element. Natural bismuth consists of only one stable isotope, ^{209}Bi, with most of its compounds appearing colourless, unless they are attached to a chromophore. The bismuth atom usually utilizes its three *6p* electrons for use in bond formation and retains the two *6s* electrons as an inert pair, hence the oxidation state +3 is exhibited by bismuth in the majority of its compounds. Although it belongs to the group 15 family, the chemistry of bismuth differs greatly from the chemistry of the other lighter members such as phosphorus, arsenic and antimony. The decreasing availability of the diffuse *s* electrons makes the +5 oxidation state less stable when compared to the other elements. However, there are still a variety of organobismuth compounds that can contain the element in the +5 oxidation state.

Bismuth is uniquely characterised by its low toxicity and is non-carcinogenic. This is sharp contrast to closely located elements in the periodic table such as lead, antimony, arsenic and tin which are highly toxic with their use posing environmental hazards. Bismuth is used in a number of very different applications. Bismuth metal and several inorganic bismuth compounds are important as starting materials for industrial processes and they are commercially available at a low price. Currently, bismuth is used mainly in cosmetics, medicines and in medical applications. The majority of bismuth is consumed in a bismuth alloy, as the toxicity of lead has become more apparent in recent years. The alloy uses bismuth metal as a replacement for lead and has contributed to bismuth’s commercial importance. Bismuth forms stable complexes with polyhydrated carboxylic acids and phenols through bismuth-oxygen bonds and complex salts of this type are used as soothing agents for the treatment of digestive disorders, for outlining the alimentary tract during X-ray examinations, and treating skin injuries and infections.

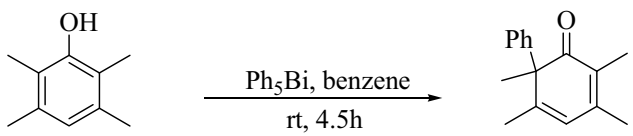
Accidental poisoning by bismuth compounds has been reported from the use of large doses during medical therapy rather than by exposure in the work place. The effects of acute intoxication of bismuth include gastro-intestinal disturbance, anorexia, headache and discolouration of the mucous membrane. Despite this, bismuth and its compounds do not appear to have been responsible for poisoning, either in the laboratory or in industry, and no strict limits have been set for bismuth in air, and drainage in industrialised countries.

1.6.2 Carbon-carbon bond formation with aryl compounds

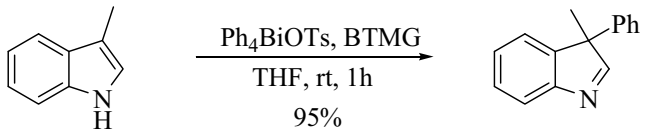
Since the beginning of the 1980s, the use of bismuth(III) derivatives as catalysts in organic synthesis has considerably increased. This new interest in bismuth compounds is justified by its friendly ecological behaviour. The usefulness of this element in organic synthesis was recognised when extensive work by the groups of Barton [50], Wada [51] and Suzuki [52] revealed the uniqueness and promising potential of bismuth as a reagent and catalyst for organic transformations. The present review focuses on some of the carbon-carbon bond forming reactions based on the use of metallic bismuth, inorganic bismuth salts and organobismuth compounds.

The arylation of organic materials remains a non-trivial issue for organic chemists. Using bismuth reagents, a wide range of functional groups can be arylated and in some cases, alkylated. The anionic chemistry associated with pentavalent bismuth has been extensively studied, showing that these derivatives are the reagent of choice for the arylation of compounds that containing a labile proton. Systematic studies have shown that *β*-dicarbonyl compounds, phenols, enolisable ketones and related compounds can be arylated with ease and often in good yields [53].

The *C*-arylation of phenolic compounds are usually conducted by a variety of tri- and tetra-aryl bismuth(V) derivatives under basic conditions in various solvents such as dichloromethane or tetrahydrofuran [54]. Similar *C*-arylation with pentaphenyl bismuth can be achieved under neutral conditions [55] (Scheme 35). For example, the reaction of alcohol (149) and indole (151) afforded dienone (150) and indole (152) in good yields. When compared with other arylbismuth(V) compounds, tetraarylbismuthonium salts require generally milder reaction conditions with shorter reaction times and are less likely to undergo oxidative side reactions [56].



(149) (150)

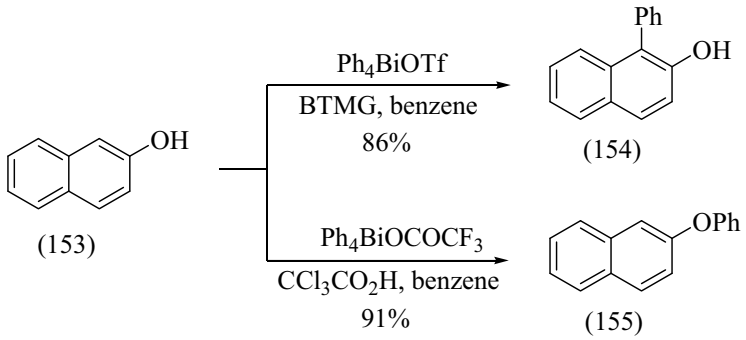


(151) (152)

Scheme 35 Representative arylation reaction using arylbismuth compounds. BTMG = 2-Benzyl-1,1,3,3-tetramethyl guanidene

The nature of the substituents on the aromatic rings in arylbismuth(V) reagents does not influence the yields of the arylated products, but it does appear to control the regioselectivity of the arylation, especially with phenols [57]. Phenols bearing an electron donating substituents are mostly *ortho C*-arylated, whereas phenols with electron withdrawing groups are predominantly or selectively *O*-arylated [58]. Other decomposition pathways are sometimes involved.

The *C*-arylation of 2-naphthol and 1,3-dicarbonyl compounds are readily performed with a variety of pentavalent organobismuth(V) reagents. The regioselectivity of phenylation, giving *O*- or *C*-phenylated products can be controlled by the choice of the organobismuth reagents under neutral, acidic or basic conditions [59]. For example, the reaction of 2-naphthol (153) with esters of tetraphenylbismuth under basic conditions favoured the *C*-phenylated product (154), while the *O*-phenylated product (155) becomes important under acidic conditions [60,61] (Scheme 36).

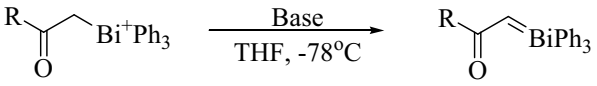


(153) (154) (155)

Scheme 36 Arylation of 2-naphthol under acidic and basic conditions. BTMG = 2-Benzyl-1,1,3,3-tetramethyl guanidene

1.6.3 Carbon-carbon bond forming reactions based on bismuthonium ylides

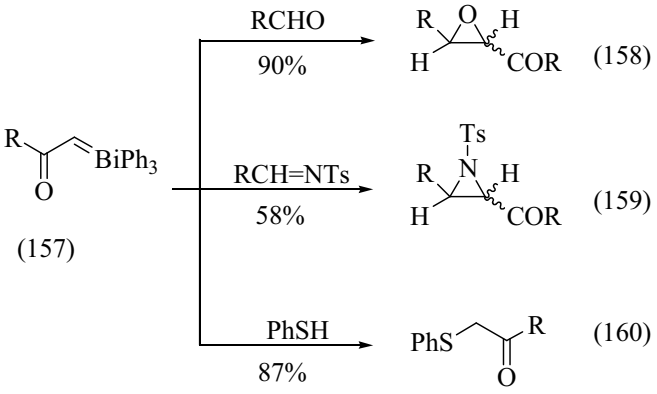
Ylide chemistry in carbon-carbon bond formation has been an active area of organic synthesis for a long time. Bismuthonium ylides have been known for many years, but their chemistry remains little explored. The first synthesis of stabilized bismuthonium ylides (157) was claimed by Lloyd *et al*. in 1967 [62]. Suzuki *et al*. isolated this ylide (R=*t*-Bu, Ph) in a crystalline form and its structure was characterised by X-ray analysis [63]. Treatment of an alkylbismuthonium salt (156) with potassium *t*-butoxide or lithium diisopropylamide at low temperatures gave expected ylide (157) as a yellow solution [64] (Scheme 37).



(156) (157)

Scheme 37 Synthesis of bismuthonium ylides (157).

These moderately stabilized bismuthonium 2-oxoalkylides (157) undergo reaction with a variety of aldehydes to give the corresponding α,β-epoxy ketones (158), but fail to react with ketones such as acetophenone and benzophenone [65]. On the other hand, these ylides readily react with activated imines and benzenethiol to give the corresponding α,β-aziridino (159) and α-phenylsulfanyl ketones (160) in good yields [65,66,67] (Scheme 38).

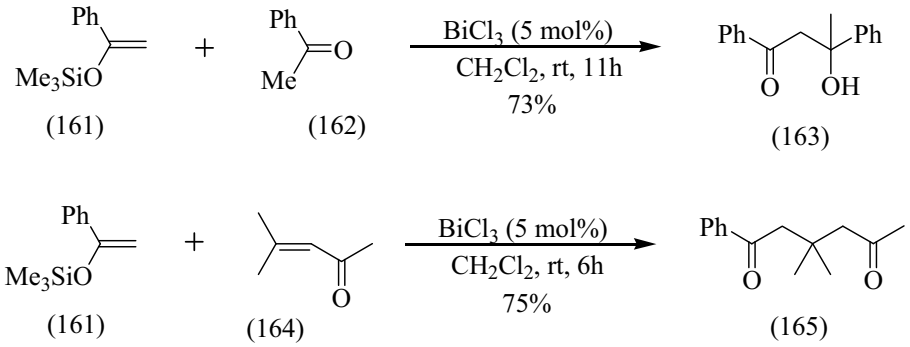


(157)

Scheme 38 Bismuthonium ylide reactions with aldehydes, imines and benzenethiol.

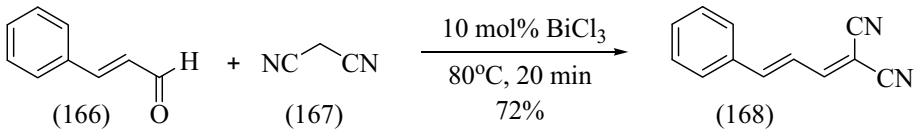
1.6.4 Bismuth(III) salt-catalysed carbon-carbon bond forming reactions

Bismuth(III) chloride is sometimes used as a soft Lewis acid catalyst for coupling and rearrangement reactions such as the Mukaiyama-aldol and the Michael reaction. In the presence of a catalytic amount of $BiCl_3$ (5 mol%), silyl enol ether (161) react smoothly with ketone (162) in dichloromethane at room temperature to give the corresponding aldol product (163) in good yield [68]. Similar reactions with silyl ketene acetals (161) give *β*-hydroxyketones (163) in moderate yield [69]. With *α*,*β*-unsaturated ketone (164), the Michael reaction takes place to afford the 1,5-dicarbonyl compound (165) [69] (Scheme 39). Cross aldolisation and Michael addition reaction are usually carried out using a stoichiometric amount of the bismuth promoter.



Scheme 39 $BiCl_3$ catalysed Mukaiyama-aldol and Michael type reactions.

The bismuth(III) chloride promoted Knoevenagel condensations of aldehydes with an active methylene compound produced olefinic products in good purity and high yields with no formation of Michael type addition products. This reaction can be carried out without complication under heterogeneous conditions using $BiCl_3$ as catalyst in the absence of solvent [70]. For example, the reaction of cinnamaldehyde (166) with malononitrile (167) afforded diene (168) in 72% yield (Scheme 40).



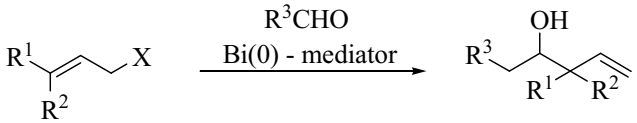
Scheme 40 A $BiCl_3$ catalysed Knoevenagel condensation.

1.6.5 Bi(0) promoted carbon-carbon bond forming reactions

The coupling reactions of organic halides and carbonyl compounds in the presence of a metal are fundamental procedures for making new carbon-carbon bonds [71]. Carbonyl allylation is an important synthetic transformation in organic and pharmaceutical chemistry because the homoallylic alcohols produced are valuable synthetic intermediates [72]. This type of functional group transformation has long been carried out using organometallic compounds such as Grignard reagents, organolithiums, organosilanes and organostannanes [73]. In recent years, however, an alternative approach involving a reductive allylation has become increasingly important. Here a combination of an allyl halide and a metal powder or a low valent metal halide is used for the *in situ* generation of the allylmetal species. This type of allylic carbonyl addition is called the Barbier-type allylation [71]. The Barbier reaction can be mediated by various metals including zinc [74], tin [75], indium [76] and manganese [77]. This methodology has attracted considerable attention since it can be carried out in aqueous media [72] or without solvent [78], sometimes with the assistance of dissolved salts, organic co-solvents or sonication to boost reactivity [72].

In 1985, Wada *et al*. reported that bismuth(0) can promote the Barbier-type allylation of aldehydes in dimethylformamide with high chemoselectivity over ketones [51]. Similar reactions were accomplished when bismuth(0) was generated *in situ* from a combination of bismuth(III) chloride and a variety of reducing agents such as zinc, iron, aluminium and magnesium [79], for example in allyl halide (169) system to afford homoallylic (170) (see Scheme 41 and Table 1). All allylations

proceed in high yields with high chemo-, regio- and stereo-selectivites from both aromatic and aliphatic aldehydes. Carboxylic acids, nitriles, esters, halides and alcohols were recovered unchanged under the allylation conditions [79]. The intermediate allylmetal species thus discriminated aldehydes from ketones and the carbonyl group from the carbonyl-conjugated double bonds. This reaction also proceeds smoothly in aqueous solvents and sometimes even catalytic amounts of $BiCl_3$ would achieve high yields [79].



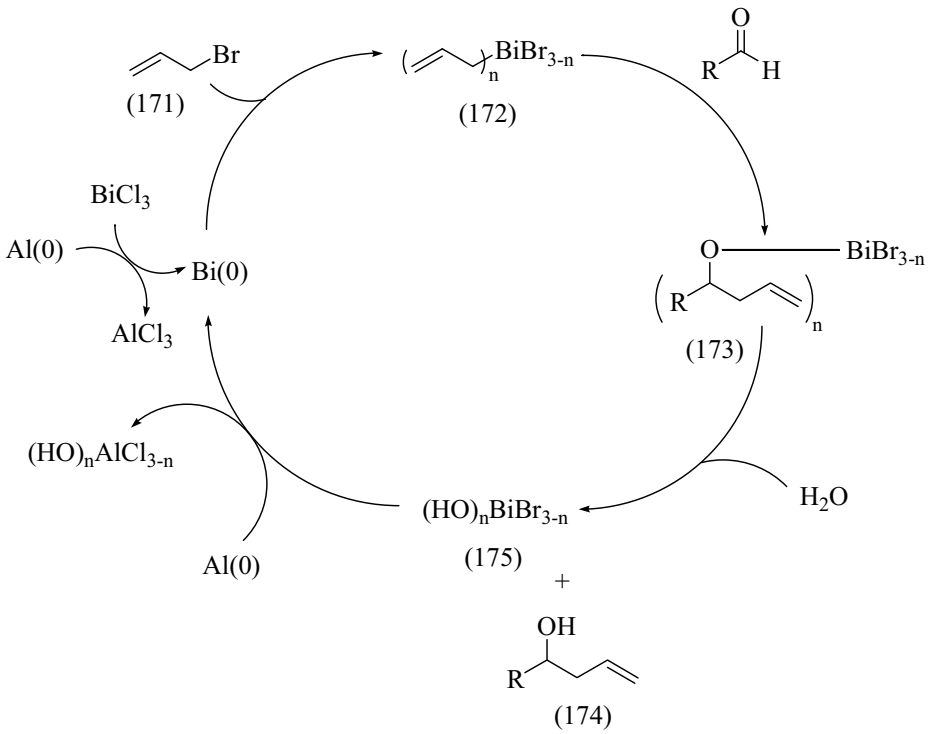
(169) (170)

Scheme 41 Reaction of allyl halide with aldehydes promoted by Bi(0)-mediator.

Table 1: Bismuth promoted allylation of aldehydes.

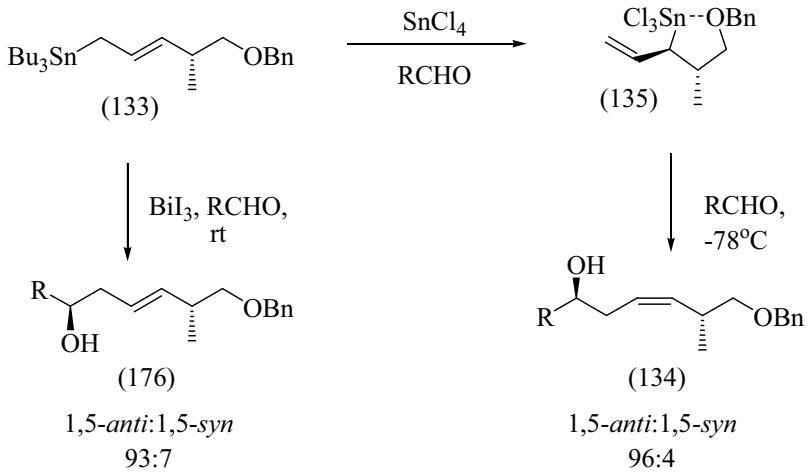
Bi-system	**Conditions**	**Yield, (%)**
$BiCl_3$-Al	THF/H_2O, rt, 10-22h	30 - 96
$BiCl_3$-Zn or Fe	THF, rt, 2-7h	45 - 99
$BiCl_3$-$NaBH_4$	THF, rt, 2-4h	74 - 96
$BiCl_3$-Mg	THF, rt, 2-7h	64 - 90
Bi(0)	DMF, rt, 2-12h	53 - 98

Although the reaction mechanism of the catalytic $BiCl_3$-aluminium mediated allylation was not properly investigated, the intermediate formation of allylbismuth species (172) through the oxidative addition of allylic halide (171) which react with aldehydes to give adduct (173) may be involved [79] (Scheme 42). The hydrolysis of these adduct (173) could then yield a homoallylic alcohol (174) and the bismuth(III) compound (175), which is reduced by Al(0), regenerating the Bi(0) catalyst [79].



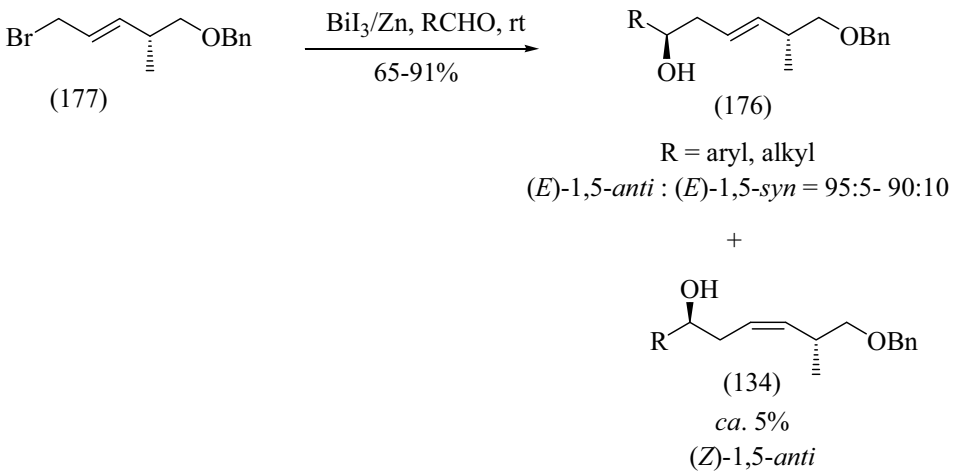
Scheme 42 Proposed mechanism of catalytic $BiCl_3$ mediated allylation of aldehydes.

Bismuth(III) iodide promoted reactions of the 5-subtituted pent-2-enylstannanes (133) with aldehydes in a mixed solvent of acetonitrile and dichloromethane gave the (3*E*)-1,5-*anti*-products (176) with useful stereoselectivity in a 93:7 ratio of the 1,5-*anti*:1,5-*syn* [80]. This product had the opposite configuration at the newly formed stereogenic centre from the major (3*Z*)-1,5-*anti* product (134) from the tin(IV) chloride promoted reactions of the pent-2-enylstannanes (133) [44] (see Scheme 43).



Scheme 43 Remote stereocontrol using organometal reagents.

The synthesis of 1,5-*anti*-substituted (*E*)-alkenols (176) using allylic organometallic reagents, but not involving allyl(trialkyl)stannanes, have been developed [80]. The reaction of the pent-2-enyl bromide (177) with "bismuth(0)," [78] prepared by reduction of bismuth(III) iodide using activated zinc powder, and aldehydes, gave (*E*)-alkenols in 65-91% yields and with *ca*. 95:5 stereoselectivity in favour of the 1,5-*anti*-(*E*)-isomers (176). The less polar, (3*Z*)-isomers (134) could be separated from the (3*E*)-isomers (176) by flash column chromatography [80]. These reactions of allylic bromide (177) mediated bismuth(III) iodide-zinc with aldehydes proceeded with stereochemistry which is complementary to that observed using 5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane (133) using bismuth(III) iodide, see Scheme 43, in that, the products were (*E*)-alkenes (176) with the same configuration at the newly formed stereogenic centres [80] (Scheme 44). The reaction of bromide (177) provides the tin-free 1,5-stereocontrol in good yield with a range of aldehydes.



Scheme 44 Remote stereocontrol using organobismuth reagents.

A synthesis of the synthetic intermediate (180) with *syn*-disposed 1,5-methyl bearing stereogenic centre has been reported [81]. The strategy relied on the application of organo-bismuth chemistry to affect a novel strategy based on remote stereocontrol. Analogous fragments are found in a range of natural products including terpenoids and lipids (178) found in *Archaea* bacteria and in vitamin E (179) [82] (Figure 4).

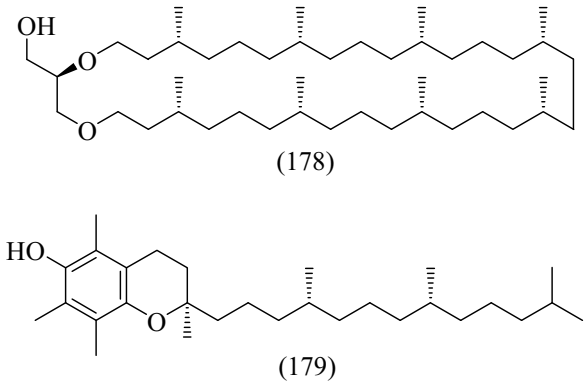
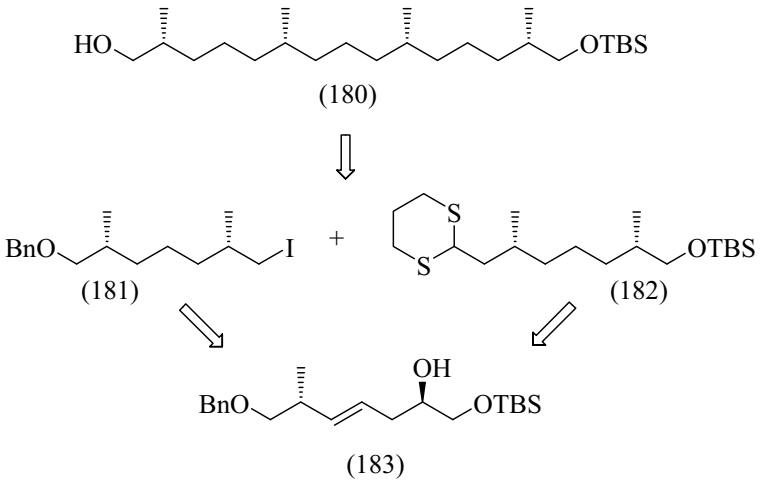


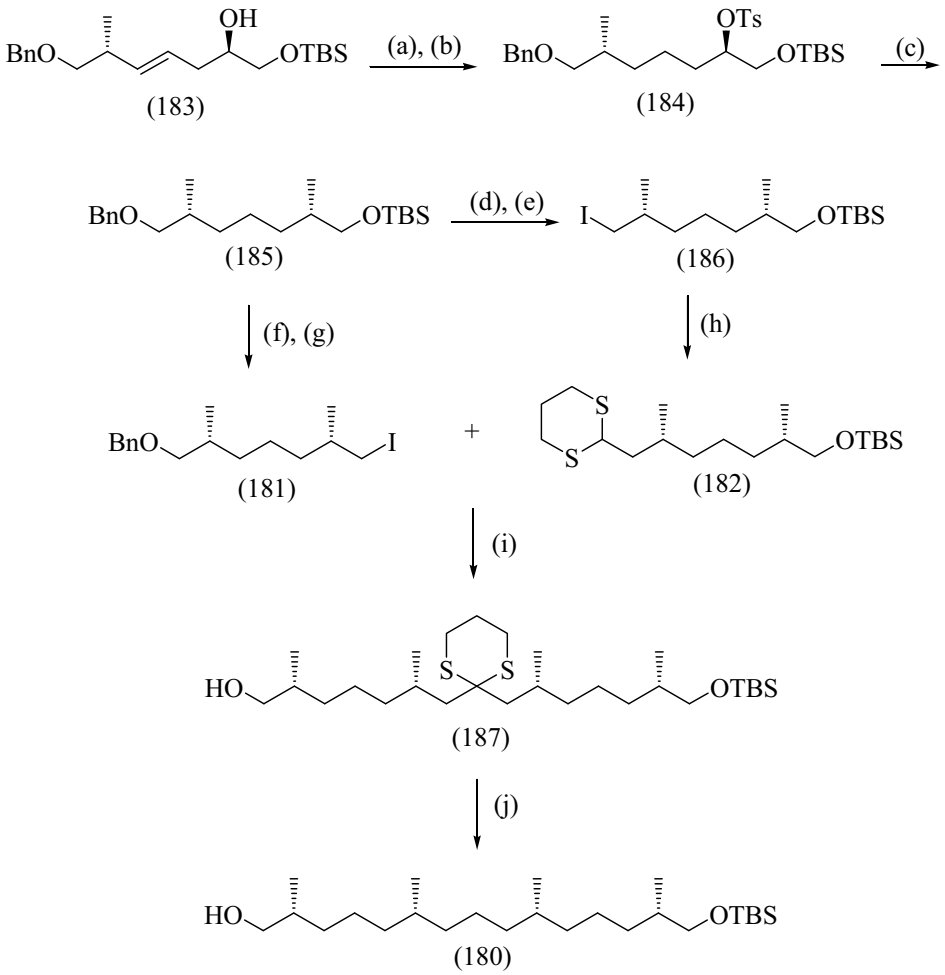
Figure 4 Representative terpenoids and lipids with *syn*-disposed 1,5-methyl substituents.

The synthesis of compound (180) was to involve a coupling of iodide (181) and dithiane (182) (Scheme 45), with the sulfur bonds and the benzyl protecting group being cleaved using Raney nickel in one step. Both iodide (181) and dithiane (182) were made from homoallylic alcohol (183), with reduction of the double-bond and displacement of the alcohol as its toluene *p*-sulfonate. Selective deprotection and functional group manipulation provided the iodide (181) and dithiane (182) [81].



Scheme 45 Retrosynthetic analysis of alcohol (180).

The synthesis of the alcohol (180) began with the bismuth(III) iodide/zinc-mediated reaction of bromide (177) and 2-(*t*-butyldimethylsilyloxy)ethanal which gave the 1,5-*anti*-adduct (183). This was reduced using diimide and esterified to give the toluene *p*-sulfonate (184). Reaction with a higher order cuprate reagent prepared from methyllithium and copper(I) cyanide in toluene as solvent gave the required *syn*-2,6-dimethyl-1-(*t*-butyldimethylsilyloxy)-7-benzyloxyheptane (185), which was taken through to the iodides (181) and (186) by selective deprotection and iodide formation. Sequential alkylation of dithiane (187) followed by reduction using Raney nickel then gave the monoprotected all *syn*-2,6,10,14-tetramethylpentadecane-1,15-diol derivative (180) [81] (Scheme 46).

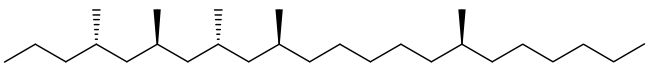


Scheme 46 Synthesis of open-chain compounds with 1,5-*syn*-oriented methyl groups.

Reagents and conditions. (a) $TsNHNH_2$, NaOAc, 92%; (b) TsCl, DMAP, CH_2Cl_2, rt, 90%; (c) MeLi (2 equiv), CuCN, toluene, 0°C, 5h then OsO_4 (cat), NMO, acetone, rt, 73%; (d) H_2/ Pd-C, EtOH, rt, 98%; (e) I_2, PPh_3, imidazole, THF, rt, 96%; (f) TBAF, THF, rt, 98%; (g) I_2, PPh_3, imidazole, THF, 94%; (h) *n*-BuLi, dithiane, 86%; (i) *n*-BuLi, HMPA, THF, -78°C, 78%; (j) Raney Ni, THF, rt, 94%.

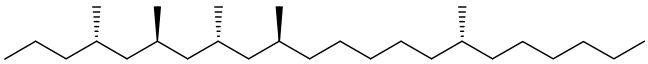
1.7 Aims of the project

It was proposed to extend the methodology for long range asymmetric induction using bismuth(III) iodide/zinc mediated reactions of allyl bromides with aldehydes. In the first place, the compatibility of this chemistry with a 2-methyl substituent in the allyl bromide has to be investigated. If successful the work has to be applied to complete stereoselective syntheses of open chain compound with 1,3,5-disposed methyl substituent and then extended to complete a synthesis of the insect lipid (45) notwithstanding that the full stereostructure of this natural product remains to be confirmed, *cf.* (45) (*aaa*)(*s*) or (46) (*aaa*)(*a*).



(45) (*aaa*)(*s*)

or



(46) (*aaa*)(*a*)