APPROACHES TO THE TOTAL SYNTHESIS OF A NOVEL DIARYLHEPTANOID

BY

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DECLARATION

I hereby certify that this work is a result of my own investigation, which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed…….
Nomandla Magnificent Vela

I hereby certify that this statement is correct

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November 2008

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TABLE OF CONTENTS

CHAPTER 4: EXPERIMENTAL

ABSTRACT

The total synthesis of a novel diarylheptanoid isolated from a South African medicinal plant, *Siphonochilus aethiopicus*, was investigated. *S. aethiopicus* (Indungulu in Zulu) is the only South African species of the Zingiberaceae plant family and is widely used in traditional medicine. One of the compounds isolated from this plant is a novel diarylheptanoid. Diarylheptanoids constitute a distinct group of natural plant metabolites characterized by two aromatic rings linked by a linear seven-carbon aliphatic chain, with varying functional groups on the aryl and the aliphatic chain. The target molecule for our synthesis contains two highly oxygenated aryl rings linked by an aliphatic chain with two stereogenic centres and a *trans*-alkene.

In this study we present our investigation of different strategies to a viable synthetic method that could provide material to supplement the relatively small quantity of product that can be isolated from the plant extract. The major challenges of this synthesis were to develop procedures for the preparation of the homobenzylic *trans*-alkene, the stereogenic centres and to attach the electron-rich aromatic rings to the aliphatic chain.

In this thesis the following aspects are described:

- Various types of olefination reactions (including Wittig, Julia and organometalic-mediated type of olefination reactions)
- Various types of alkylation reactions (including Grignard, Friedel-Crafts and organometalic-mediated type of alkylation reactions)
- Incorporation of the stereogenic centres (including asymmetric hydroxylation and use of chiral starting materials)

The synthesis will not only give a viable synthetic route to the target compound but is also versatile enough to allow the preparation of analogues.

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	Acetyl
AcOH	Acetic acid
H_3O^+ or H^+	Acid
aq	Aqueous
BT	*n*-alkyl Benzothiazole-sulfone
Bn	Benzyl
BnBr	Benzyl bromide
BzCl	Benzoyl chloride
BER	Borohydride exchange resin
br	Broadened (spectral)
$BuNH_2$	Butylamine
BuLi	Butyllithium
10-CSA	10-Camphorsulfonic acid
cat.	Catalytic or catalyst
COSY	Correlated spectroscopy
DMP	Dess-Martin periodinane
DCM	Dichloromethane
Et_2O	Diethyl ether
L-(+)-DET	L-(+)-Diethyl tartrate
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMS	Dimethyl sulfide
DEPT	Distortionless enhancement polarization transfer
d	Doublet (spectral)
dd	Doublet of doublets (spectral)
ESI-TOF	Electrospray ionization time-of-flight
EBV-EA	Epstein-Barrvirus early antigen
ETOH	Ethanol
ETSH	Ethanethiol
OEt	Ethoxy

ETOAc	Ethyl acetate
EDTA	Ethylenediaminetetraacetic acid
Glcp	Glucopyranosyl
Hz	Hertz
HMBC	Heteronuclear multiple quantum coherence
HSQC	Heteronuclear single quantum coherence
HMPA	Hexamethylphosphoramide
HRESIMS	High-resolution electrospray ionization mass spectrometry
h	hour (s)
HT	Human tumour
IR	Infrared
MeI	Iodomethane
i-Pr or Pr^i	Isopropyl
J	Coupling (spectral)
$LiAlH_4$	Lithium aluminium hydride
LCMS	Liquid chromatography-mass spectrometer
LHMDS	Lithium(bis(trimethylsilyl)amide
LDA	Lithium diisopropyl amide
lit.	Literature
MHz	MegaHertz
m/z	Mass-to-charge ratio
Mp	Melting point
Me	Methyl
OMe	Methoxy
MOM	Methoxymethyl
PMB	*para*-Methoxybenzyl
min	Minute (s)
mmol	millimole (s)
m	Multiplet (spectral)
S_NAr	Nucleophilic aromatic substitution reaction
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser effect
Ph	Phenyl

KHMDS	Potassium(bis(trimethylsilyl)amide
KO^tBu	Potassium *tert*-butoxide
KSC(S)-OEt	Potassium *O*-ethylxanthate
p	Para
ppm	Part (s) per million
PT	*n*-alkyl Phenyltetrazole sulfone
q	quartert (spectral)
s	Singlet (spectral)
sept	Septet (spectral)
sext	Sextet (spectral)
Red-Al	Sodium bis(2-methoxyethoxy)aluminium dihydride
TBAF or Bu_4NF	*tert*-Butylammonium fluoride
TBDMS or TBS	*tert*-Butyldimethylsilyl
TBDMSCl or TBSCl	*tert*-Butyldimethylsilyl chloride
TBDPS	*tert*-Butyldiphenylsilyl
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TBT	*tert*-Butyl tetrazole sulfone
TPA	Tetradecanoylphorbol-13-acetate
THF	Tetrahydrofuran
THP	Tetrahydropyran
THBP	2,4,5-Trihydroxybutyrophenone
TLC	Thin-layer chromatography
Et_3N	Triethylamine
TFA	Triflouroacetic acid
t	Triplet (spectral)
p-TsCl	*para*-Toluenesulfonyl chloride
v/v	volume per unit volume (volume-to-volume ratio)
UJ	University of Johannesburg
UKZN	University of KwaZulu-Natal

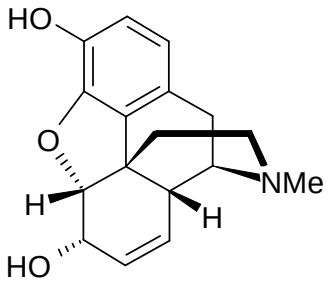
CHAPTER 1

INTRODUCTION

1.1 THE ROLE OF TOTAL SYNTHESIS IN NATURAL PRODUCT CHEMISTRY

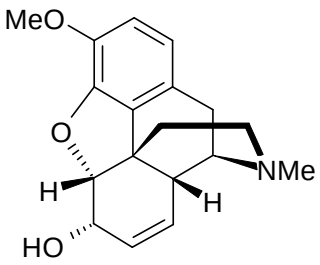
Natural products have been used by man since ancient times as remedies for diseases, spices, narcotics, dyes and as poisons for warfare and hunting. People have used traditional remedies without a scientific rationale, but with the experience that they can be highly effective if taken at therapeutic doses. Most of these natural products were used in crude forms and the active components were only isolated during and after the nineteenth century. The broad application of natural biologically active compounds as antimalarial, antitumour and antiviral drugs, amongst others, has stimulated organic chemists to develop methods for the syntheses of these compounds. The contribution of organic chemists lies not only in their ability to produce known substances for further study but more important, in their capacity to create new entities which may have enhanced activity.[1]

Morphine (**1**) can be used as a case study to illustrate how the activity of natural products can be enhanced or changed by synthetic chemists.

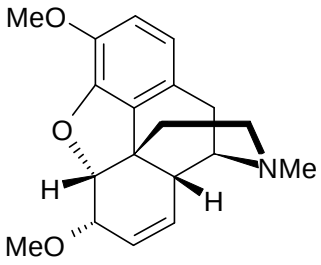


1

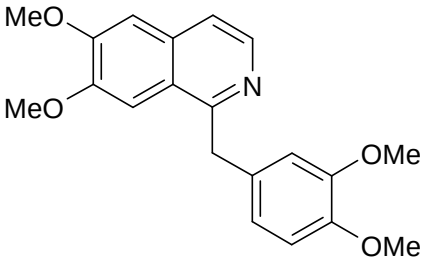
Morphine (**1**), first isolated from the opium poppy (*Papaver somniferum* and *P. setigrum*)[2] in 1803, is a strong analgesic. Opium is a sticky brown gum that hardens on standing that is obtained from *P. somniferum* by incision of the seed pot after the petals of the flower have dropped.[3] The sticky gum contains about twenty alkaloids including morphine (**1**), codeine (**2**), thebaine (**3**) and papaverine (**4**). Thebaine and papaverine are not analgesic but are precursors of several semi-synthetic opiate agonists.[3]



Codeine (**2**)



Thebaine (**3**)



Papaverine (**4**)

Initially, synthetic studies were aimed at the preparation of some natural opium alkaloid derivatives but later studies resulted in the preparation of morphine analogues with analgesic properties. Despite being a small molecule, morphine (**1**) has a complex structure containing five adjacent stereocenteres and five fused rings, two of which are heterocyclic. Minor modifications of morphine-like compounds often have a drastic influence on their activity. Methylation of the phenolic hydroxy group at C-3 reduces the efficacy of morphine (**1**) and drugs like codeine (**2**) and oxycodone (**6**) are mild morphine agonists while acetylation of both hydroxy groups of morphine increases the efficacy and yields heroin (**5**), which is a strong morphine agonist (Table 1.1). Partial agonist or antagonist properties are associated with replacement of the methyl substituent on the nitrogen atom with larger groups. For example, in the case of nalorphine (**9**) and naloxone (**10**), an allyl group replaced the methyl substituent on the nitrogen atom causing these compounds to be morphine antagonists.

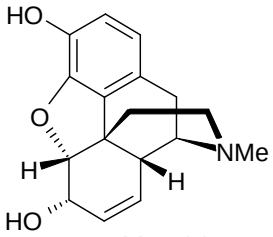
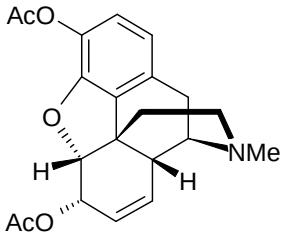
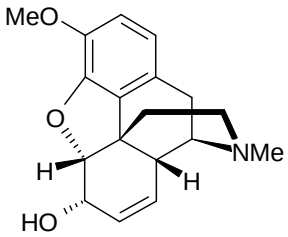
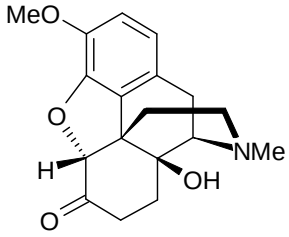
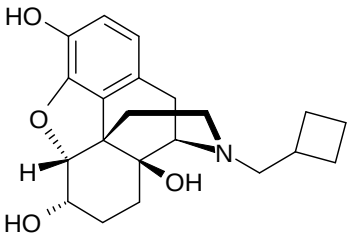
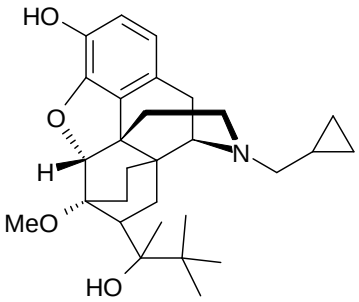
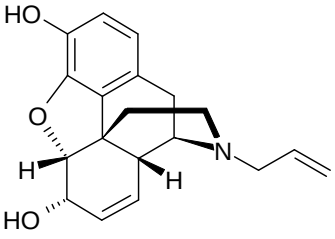
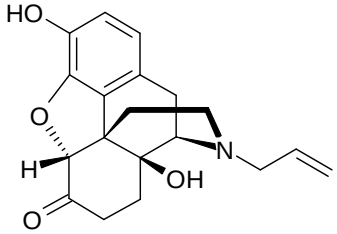
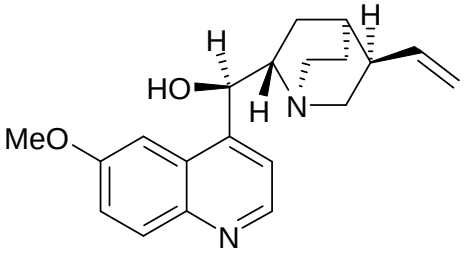
Strong Agonists	
 **Morphine** (**1**)	 **Heroin** (**5**)
Mild to Moderate Agonists	
 **Codeine** (**2**)	 **Oxycodone** (**6**)
Mixed Agonist-Antagonists	
 **Nalbuphine** (**7**)	 **Buprenorphine** (**8**)
Antagonists	
 **Nalorphine** (**9**)	 **Naloxone** (**10**)

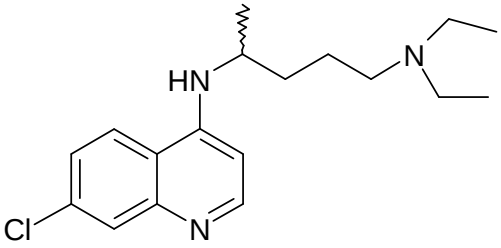
TABLE 1.1: Chemical structures of opioid analgesics and antagonists.

However, methylcyclopropane or methylcyclobutane as the substituent renders nalbuphine (**7**) and buprenorphine (**8**) as mixed agonist-antagonists. Also, substitution at the C-3 and C-6 hydroxy groups of morphine significantly alters the pharmacokinetic properties of these compounds. Heroin (**5**) is regarded as a much more potent and fast-acting drug than morphine (**1**), but without the respiratory depression effect. A possible reason may be that heroin (**5**) passes the blood-brain barrier much more rapidly than morphine (**1**) and once in the brain, it is hydrolysed back to morphine which is responsible for its activity.[3] It has been clearly illustrated that synthetic chemists have an ability to tweak the structure of a natural product like morphine to enhance its activity.

The development of antimalarial drugs also illustrates how the symbiosis between synthetic chemists and natural products can lead to new drugs. Quinine (**11**) is an antimalarial agent that was isolated from the *Cinchona* tree (originally found in the high altitudes of South America). As early as in the seventeenth century, Thomas Sydenman, a bachelor of medicine, prescribed a mixture of powdered bark of the *Cinchona* tree and syrup of cloves as a remedy for malaria.[2]



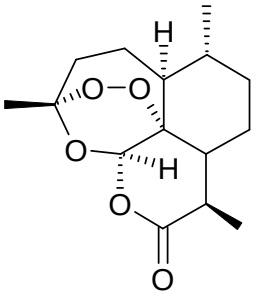
Quinine (**11**)



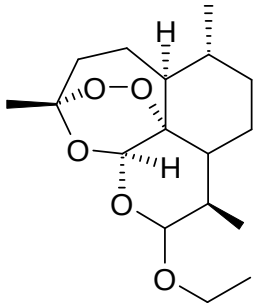
Chloroquine (**12**)

The first total synthesis of quinine (**11**) was disclosed by Woodward in 1944 and was a major advancement in the field of organic chemistry.[4] Quinine (**11**) was also used as a model for the preparation of resochin (chloroquine) (**12**) and sontochin (3-methylchloroquine). These compounds belong to a class of antimalarials called the 4-aminoquinolines.

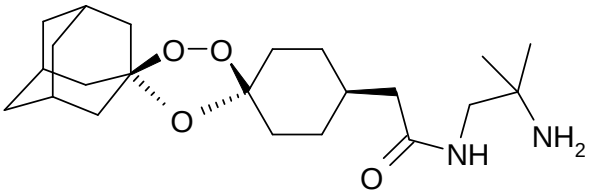
Artemisia annua (sweet wormwood) is known by Chinese herbalists as *Qinghao*. *Qinghao* extracts were shown to be as effective as chloroquine (**12**) and quinine (**11**) in clearing the malaria parasite.[5] The active principle in *A. annua* is artemisinin (**13**), a sesquiterpene peroxide. Although artemisinin is effective, it also breaks down quickly in the body and more stable analogues are needed. Molecules that contain a peroxide group have been developed from the artemisinin such as arte-ether (**14**). An attempt to improve the activity of artemisinin (**13**) led to the development of OZ277 (**15**), and is regarded to be more active than artemisinin (**13**). OZ277 has sufficient solubility to be administered orally, it has a longer lifetime in the plasma, stays active for longer time in the body and is less expensive to produce.[6]



Artemisinin (**13**)



Arte-ether (**14**)



OZ277 (**15**)

The examples presented above clearly illustrate the significance and richness of natural product synthesis. We close this brief outline with some words penned in 2003 by E.J. Corey:[7]

- How many challenging and worthy synthetic targets remain to be discovered?
- How many truly powerful and general new synthetic strategies and synthetic reactions remain to be discovered?

- Is there a prospect for the development of entirely new ways of planning or executing synthesis?

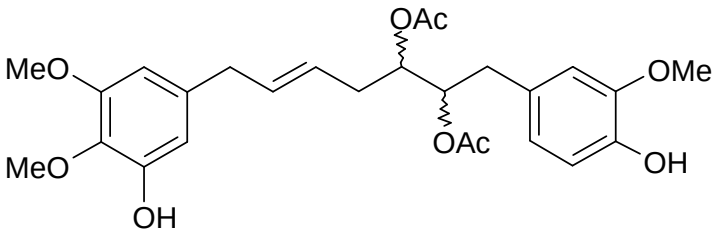
1.2 SOUTH AFRICAN NATURAL PRODUCTS

More than 30 000 species of higher plants are found in South Africa and that is about 10% of the total plant species of the world.[8] South Africa is also blessed with a wealth of traditional medicines and with a rich cultural diversity which is reflected by the healing practices that are performed in different parts of the country. In South Africa, a large part of the day-to-day medicine is still derived from plants and large volumes of plants or their extracts are sold in the informal and commercial sectors of the economy.

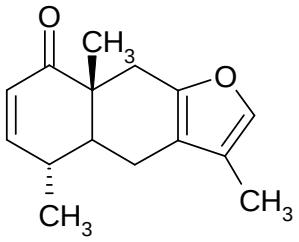
South Africa's contribution to world medicine includes Cape aloes (*Aloe ferox*, laxative and skin care preparations), rooibos tea (*Aspalathus linearis*, antioxidant activity), buchu (*Agathosma betulina*, diuretic and anti-inflammatory activities), devil's claw (*Harpagophytum procumbens*, anti-inflammatory activity), African potato (*Hypoxis hemerocallidea*, anticancer and anti-inflammatory activities) and ghaap (*Hoodia gordonii*, appetite-suppressant activity).[8]

1.3 AIM OF THIS STUDY

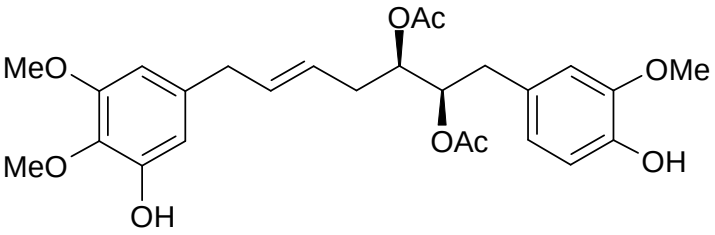
The aim of this study is to synthesise a novel diarylheptanoid isolated from a South African medicinal plant *Siphonochilus aethiopicus* B.L. Burtt (Zingiberaceae). *S. aethiopicus*, known as wild ginger or 'indungulu' in Zulu, is the only South African species of the Zingiberaceae (ginger) plant family. This rare African plant has been traditionally used for many ailments and is regarded as Africa's natural anti-inflammatory. [9,10,11] Two classes of compounds have been isolated from this plant, diarylheptanoids (*e.g.* **16**)[12] and sesquiterpenoids [*e.g.* siphonochilon (8,12-epoxy-2,7,11-eudesmatriene-1-one), **17**].[12,13] The relative and absolute stereochemistry of **16** has not been established conclusively.



Diarylheptanoid (**16**)



Siphonochilon (**17**)



(2*R*,3*R*,5*E*)-2,3-Diacetoxy-7-(3-hydroxy-4,5-dimethoxyphenyl)-1-(4-hydroxy-3-methoxyphenyl)-2-heptene (**18**)

In view of the importance of *S. aethiopicus* as a medicinal plant, we aim at synthesising diarylheptanoid **18**, as one of the possible structure of **16** with fixed relative and absolute stereochemistry. The availability of this compound will assist in assigning the absolute stereochemistry of **16** conclusively.

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CHAPTER 2

DIARYLHEPTANOIDS : A LITERATURE REVIEW

2.1 INTRODUCTION

The current state of knowledge of the chemistry (structure, and total synthesis) of diarylheptanoids, as well as their occurrence in the plant kingdom will be reviewed in this chapter. Diarylheptanoids are plant metabolites that have been isolated from various genera such as *Acer* (Aceraceae), *Platycarya strobilacea* (Juglandaceae), *Myrica gale* (Myricaceae) and *Centrolobium* (Leguminosae) but with the largest numbers occurring in *Alpinia*, *Curcuma* and *Zingiber* (Zingiberaceae) and *Alnus* and *Betula* (Betulaceae).[1] The common structural feature of diarylheptanoids is two aromatic rings linked by a linear seven-carbon aliphatic chain, with varying functional groups on the aryl and C_7-moieties (Fig. 2.1).

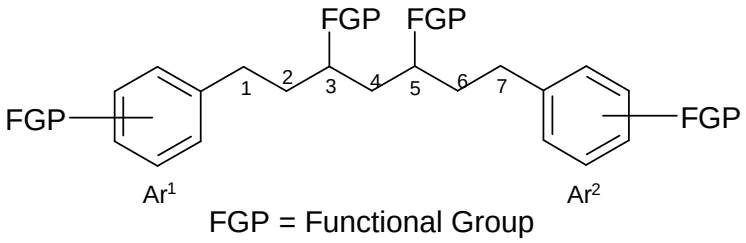
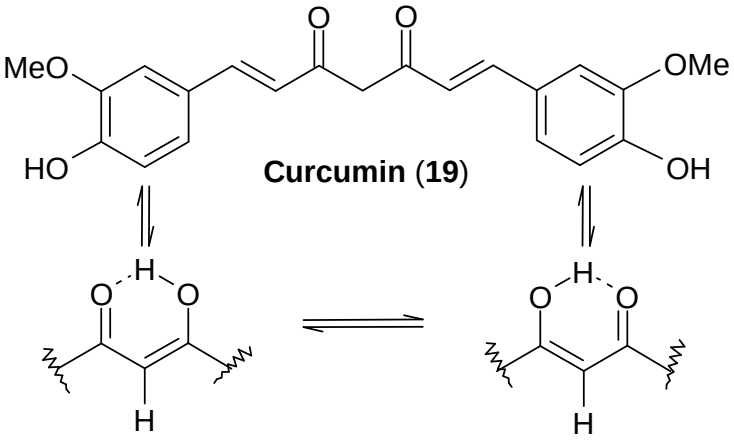


FIGURE 2.1: General structural feature of a diarylheptanoid.

Many diarylheptanoids possess biological activities such as anti-inflammatory, anti-hepatotoxic, antibacterial and antifungal activity.[2] For example, curcumin (**19**) isolated from rhizomes of *Curcuma longa* (Zingiberaceae) (Fig. 2.2) is responsible for the biological activity (anti-inflammatory, anticancer, hepatoprotective, antiallergic, cholesterol-lowering effects and anti-HIV) of this plant.[2] *C. longa*, also known as turmeric, is a tropical plant native to India and is cultivated in most tropical parts of the world including Africa, Madagascar as well as South and South-East tropical Asia.[3]

This plant has underground root-like stems and rhizomes which are commonly used as a spice but are also utilised for medicinal purposes in Indian Ayurvedic medicine.[4,5] Curcumin (**19**) is found in the enol form as shown below.



Curcumin (**19**)

Curcumin (**19**) in the enol forms

Tumeric plant, Photo: http://www.inmagine.com/agriculture-photos

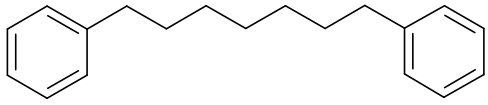
Tumeric rhizomes, Photo: http://www.inmagine.com/agriculture-photos

FIGURE 2.2: The tumeric plant and its rhizomes.

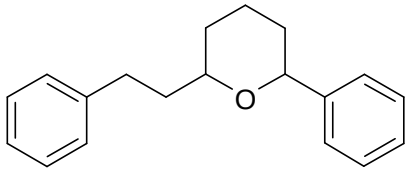
The constitution of this relatively simple and broadly-used compound was established in the nineteenth century, firstly by degradative reactions and later by synthesis.[2] Other well-known spices and medicinal plants which also belong to the Zingiberaceae plant family and contain chemical constituents with similar structures and biological effects to curcumin are ginger (*Zingiber officinale*), cardamom (*Elettaria cardamomum*, *Amomum subulatum*) and galangal (*Kaempferia galanga*, *Alpinia galanga*).[4]

2.2 CLASSIFICATION AND OCCURRENCE OF DIARYLHEPTANOIDS

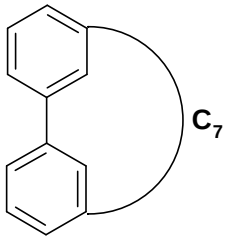
The diarylheptanoids can be sub-grouped into open chain linear (**20**) or cyclic (**21**, **22**, **23**) compounds (Fig. 2.3).[6] Oxidative coupling of the corresponding diarylheptanoids and their congeners may form the cyclic type that can be further divided into tetrahydropyrans (**21**) and cyclophanes, based on how the aromatic rings are linked through oxygen.[6] The latter group is further sub-grouped into *meta-meta* bridged biphenyls (**22**) and *meta-para* diphenyl ethers (**23**).[6] In addition to the above sub-groups, more complex diarylheptanoids (**24**), with the basic skeleton extended by fragments such as arylbutyl, chalcone or flavonoid moieties, have been isolated in the late nineties.[7]



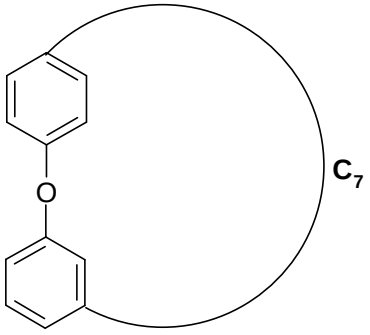
Diaryheptanoid (**20**)
Linear



Diaryheptanoid (**21**)
Tetrahydropyran

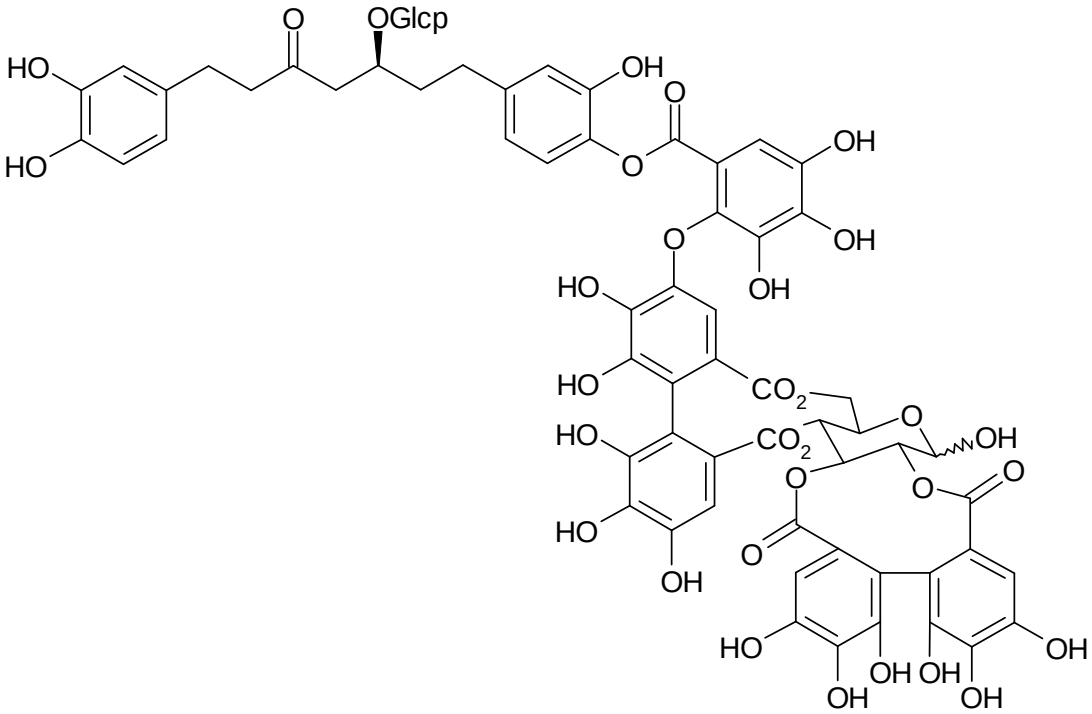


Diarylheptanoid (**22**)
Meta-meta bridged biphenyls



Diarylheptanoid (**23**)
Meta-para diphenyl ether

FIGURE 2.3: Classification of diarylheptanoids.



Glcp = Glucopyranosyl
Diaryheptanoid (**24**) Complex

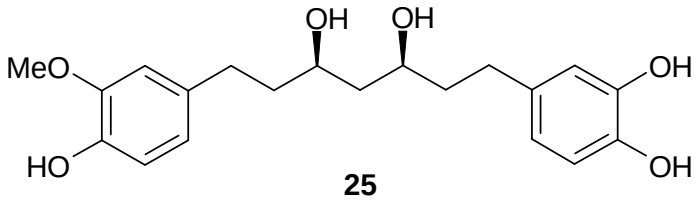
FIGURE 2.3 (continued): Classification of diarylheptanoids.

2.2.1 LINEAR DIARYLHEPTANOIDS

Curcumin (**19**), the first member of the linear diarylheptanoids that was discovered, was isolated in the eighteenth century.[2] It was not only the first linear diarylheptanoid to be described, but was also among the first natural organic compounds isolated in more or less pure state and was the only representative of the group until 1964. Numerous studies published associate the anti-inflammatory activity of curcumin (**19**) and its derivatives with presence of phenolic groups in the molecule, which are essential for the inhibition of prostaglandin and leucotriene biosynthesis.[1,2,8] On the other hand, some authors[9] suggested that the anti-inflammatory action is associated with the existence of the diene ketone system while others[10,11] also describe this system for antiparasitic activity as well.

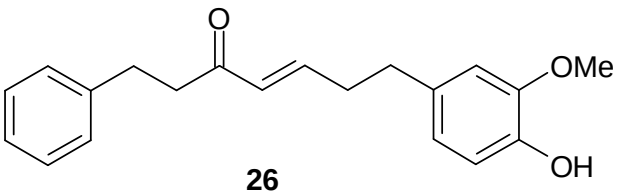
Recent investigations suggest that curcumin (**19**) has cancer-preventive properties as it inhibits expression of cyclooxygenase-2 in mouse skin treated with the tumour promoter (phorbol 12-myristate 13-acetate) through inactivation of the redox-sensitive eukaryotic transcription factor NF-$_{\kappa}$B.[12] To clarify structure-activity relationships of diarylheptanoids, curcumin and its congeners, called curcuminoids, and several linear diarylheptanoids from various plant species, have been isolated and investigated.[13]

Recently, a novel diarylheptanoid **25** was isolated from *Zingiber ottensii* (Zingiberaceae) which is cultivated in Malaysia and used in traditional medicine for its sedative effect. [14]

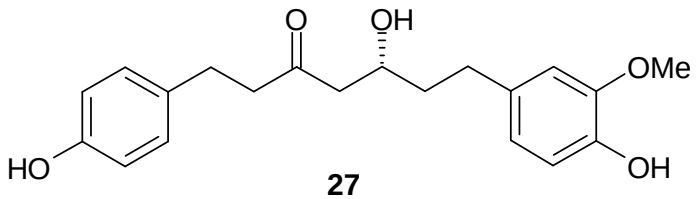


25

Diarylheptanoid **26** isolated from a Chinese medicinal herb, *Alpinia officinarum* (Zingiberaceae), inhibits nitric oxide production in lipopolysaccharide-activated mouse peritoneal macrophage.[15] In addition, a novel diarylheptanoid **27** has been also isolated from the same plant by Shin *et al.*[16] and found to have antiemetic activity.

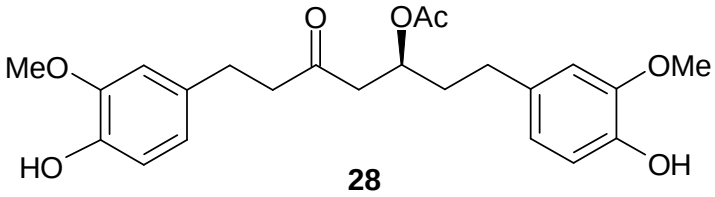


26



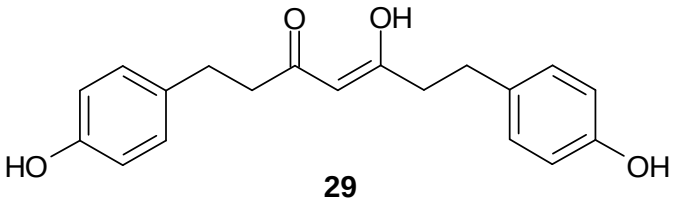
27

In the search for anti-cancer principles from ginger, diarylheptanoid **28** was isolated as a novel constituent of *Zingiber officinale* (Zingiberaceae) and was found to possess cytotoxic and apoptotic activity.[17]



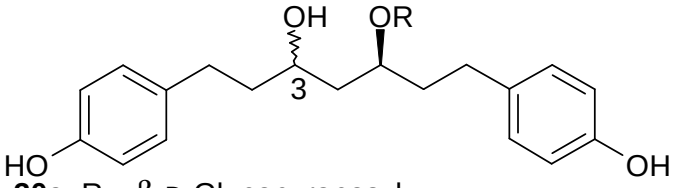
28

A potent inhibitor of collagen-induced, arachidonic acid-induced and adenoside diphosphate-induced platelet aggregation of human blood is diarylheptanoid **29** isolated from the seeds of *Alpinia blepharocalyx* (Zingiberaceae).[18]



29

The betulapalatosides **30a** and **30b** were identified in *Betula platyphylla var. japonica* (Betulaceae)[19] and both compounds are regarded to have hepatoprotective, superoxide scavenging, and antioxidant activities.

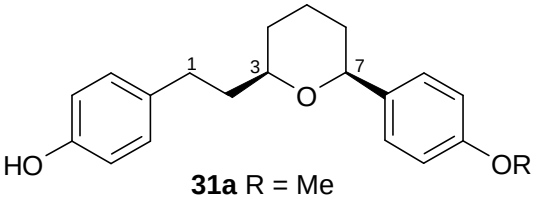


30a R = β-D-Glucopyranosyl
30b R = β-D-Glucopyranosyl-α -L-apiofuranosyl

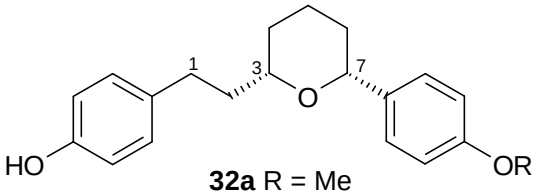
2.2.2 TETRAHYDROPYRANS

Centrolobium species (Leguminosae) are the source of the 2*H*-tetrahydropyran-type diarylheptanoids, such as the centrolobines **31a** and **31b**.

The laevorotatory enantiomers, (–)-**31a** and (–)-**31b**, occur in *Centrolobium paraense*, *C. sclerophyllum* and *C. tomentosum*, whereas the dextrorotatory enantiomers, (+)-**32a** and (+)-**32b**, are constituents of *C. robustum*.[6] A considerable confusion concerning the stereochemistry of these compounds resulted mainly from the fact that they occur naturally as both enantiomers. The centrolobin **31a** shows a strong antibacterial activity.[2]

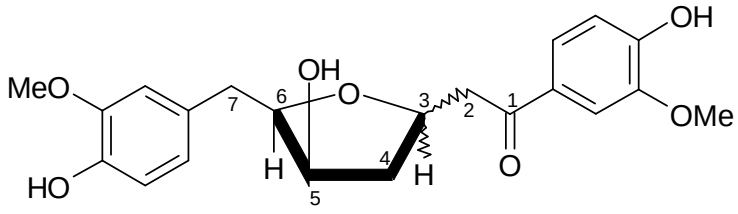


31a R = Me
31b R = H



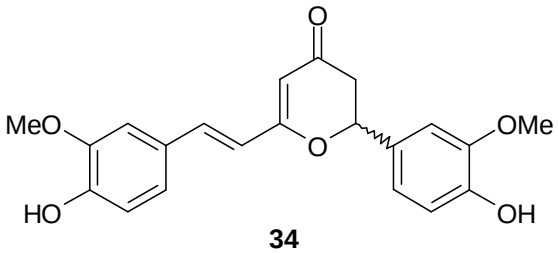
32a R = Me
32b R = H

Recently, the diarylheptanoids renealtin A (**33a**) and renealtin B (**33b**), featuring a trisubstituted tetrahydrofuran ring, have been isolated from the seeds of Brazilian medicinal plant *Renealmia exaltata* (Zingiberaceae).[20]

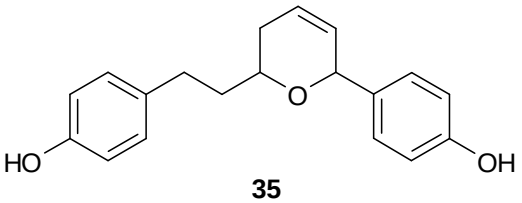


(**33a**) H-3α
(**33b**) H-3β

Cyclocurcumin (**34**) was isolated by Kiuchi *et al.*[21] as a novel constituent of the active (nematocidal activity against second stage larvae of dog ringworm) fraction of *Curcuma longa* and is a 2,6-disubstituted dihydro-2*H*-pyranyl-4-one. The structure of **34** was elucidated on the basis of spectral data and confirmed by partial synthesis from curcumin (**19**) (by an intramolecular Michael-type addition reaction).[2] As no specific rotation is indicated, the natural product is probably racemic. A good antileishmanial activity for diarylheptanoid **35**, isolated from *C. sclerophyllum*, was observed.[22]



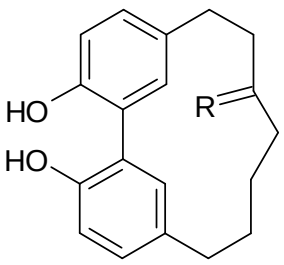
34



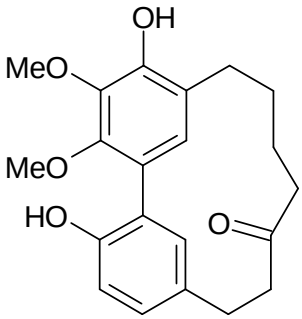
35

2.2.3 BIARYL-TYPE OF DIARYLHEPTANOIDS

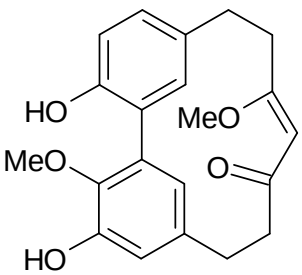
Acerogenin E (**36a**), is a biaryl-type diarylheptanoid originally isolated from *Acer nikoense* (Aceraceae).[23] This compound has also been isolated from *Betula platyphylla* (Betulaceae)[24], and its reduced analogue, acerogenin K (**36b**), was shown to be a constituent of *Acer nikoense*.[25] The tree is indigenous to Japan and has been used in folk medicine as a remedy for hepatic disorders and as an eyewash.[1] A cyclic diarylheptanoid (**37**) isolated from *Myrica rubra* (Myricaceae) has been proven to be the most active antitumour promoting agent among several tested cyclic diarylheptanoids.[26] Moreover, a novel biaryl-type diarylheptanoid, 6'-hydroxygaruganin V (**38**), has been recently isolated from *Garuga pinnata* (Burseraceae) by Ara *et al.*[27] The tree is indigenous to eastern part of Asia and is traditionally used to treat various diseases including asthma, opacity of cornea, and pulmonary infections.



36a R = O
36b R = H, OH



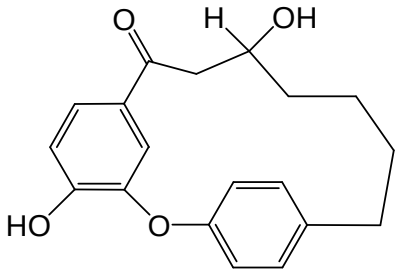
37



38

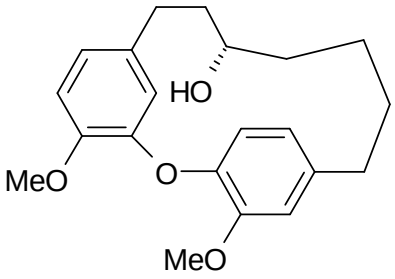
2.2.4 DIPHENYL ETHER-TYPE OF DIARYLHEPTANOIDS

Acer nikoense (Aceraceae) is also a source of novel diphenyl ether-type cyclophanes such as acerogenin M (**39**) recently isolated by Akihisa *et al.*[28] Evaluation of acerogenin M for the inhibitory effects on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice (1 μg/ear) showed a marked anti-inflammatory effect with a 50% inhibitory dose (ID_{50}) of 0.26-0.81 mg per ear. In addition, upon an evaluation against the Epstein-Barr virus early antigen (EBV-EA) activation induced by TPA exhibited moderate inhibitory effects against EBV-EA induction (IC_{50} values of 356-534 mol ratio/32 per mol TPA).

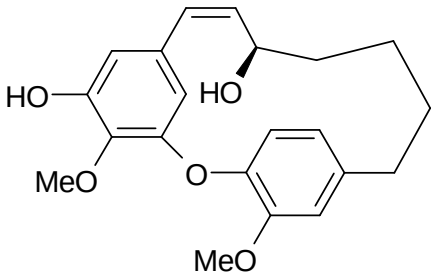


(**39**)

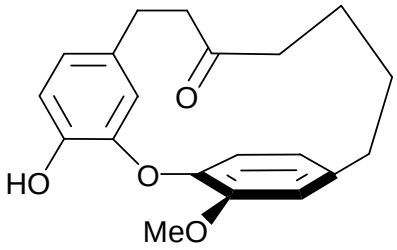
The platycarynols **40a** and **40b** were isolated from *Platycarya strobilacea*[29] (Juglandaceae) and from the inner bark of *Betula platyphylla*,[24] respectively, and their stereochemistry have been determined. The structure of (+)-galeon (**41a**) isolated from *Myrica gale var. tomentosa* was solved with the help of X-ray crystallographic analysis of the corresponding *p*-bromobenzoate by Nagai *et al.*[30], while earlier report revealed that (–)-galeon **41b** is also a constituent of this plant.[31] Recent findings suggest that (+)-galeon (**41a**) has a potent cytotoxic activity against selected cancer cell lines (human colon carcinoma and human lung carcinoma cell lines with IC_{50}'s ranging from 2 to 25 μg/mL).[32] The absolute stereostructures of both the (*R*)-(+)- and (*S*)-(–)-galeons **41a** and **41b** are depicted below.



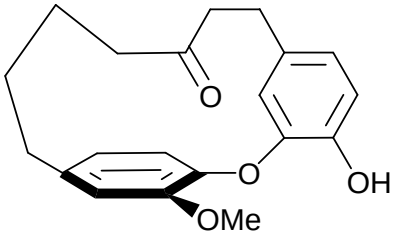
40a



40b



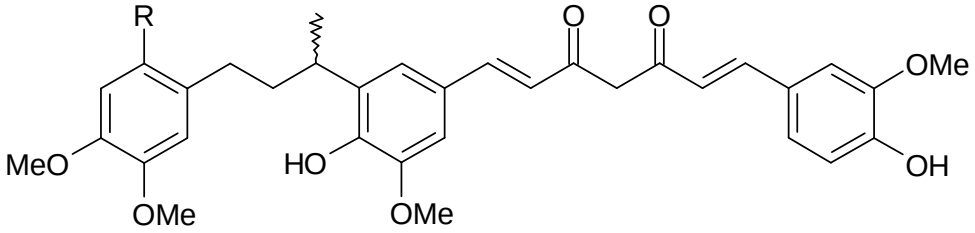
41a



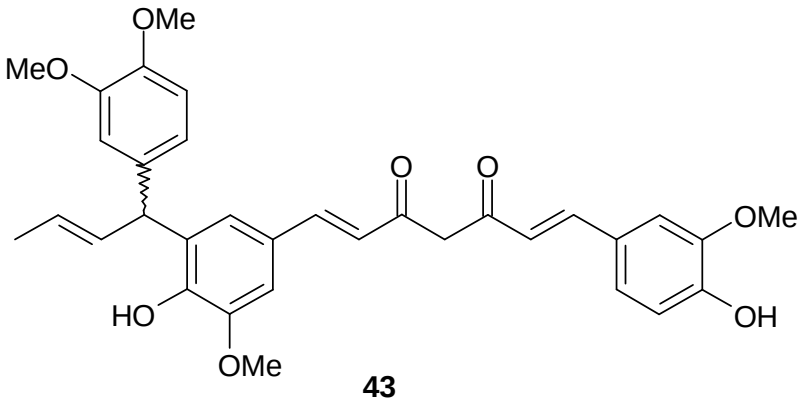
41b

2.2.5 COMPLEX DIARYLHEPTANOIDS

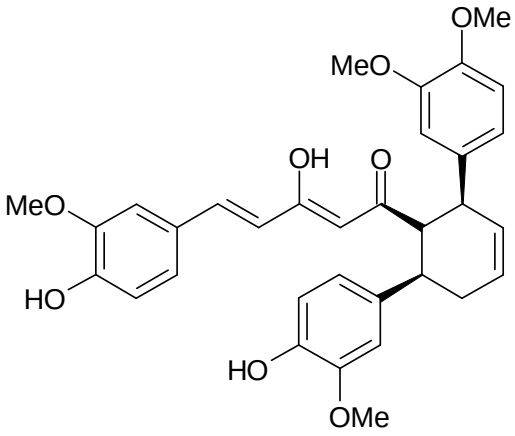
Masuda *et al.*[33] isolated a series of novel acyclic curcuminoids, the cassumins A (**42a**), B (**42b**) and C (**43**) together with the cyclic cassumunarins A (**44**), B (**45a**) and C (**45b**) from the rhizomes of the tropical ginger (*Zingiber cassumuna*).[34] Interestingly, the antioxidative and anti-inflammatory activities of these compounds were found to be significantly stronger than those of curcumin (**19**). Their formation is the result of an electrophilic aromatic substitution of curcumin (**19**) or of a cycloaddition reaction of curcumin (**19**).



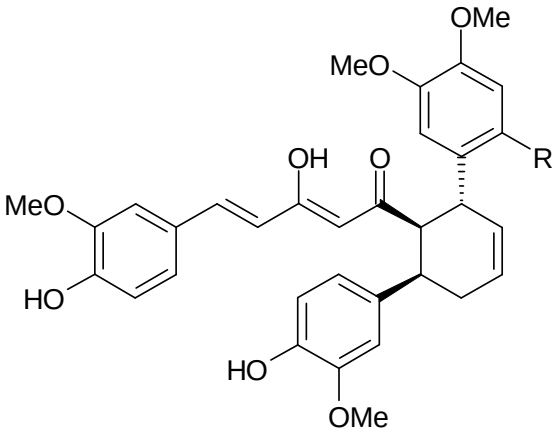
42a R = H
42b R = OMe



43

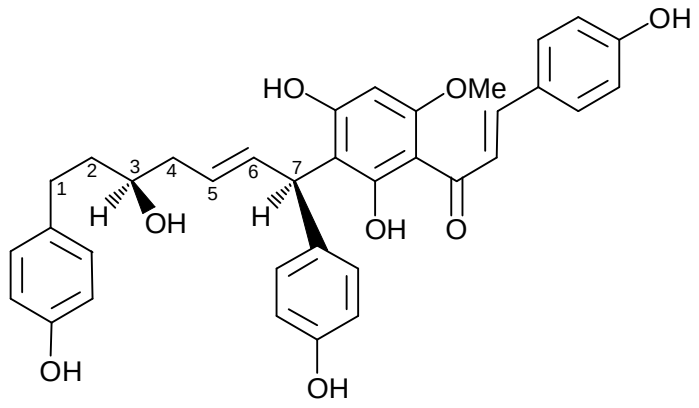


44

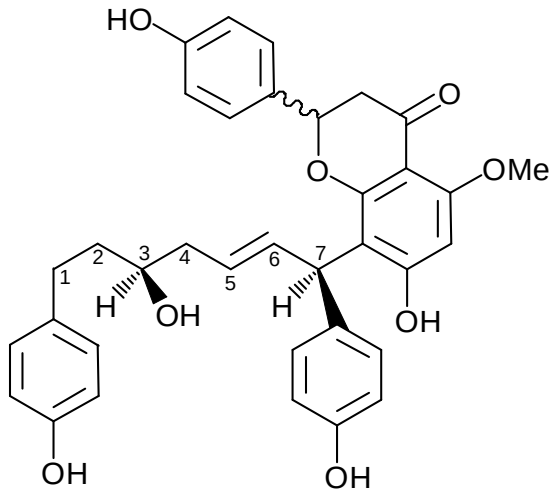


45a R = H
45b R = OMe

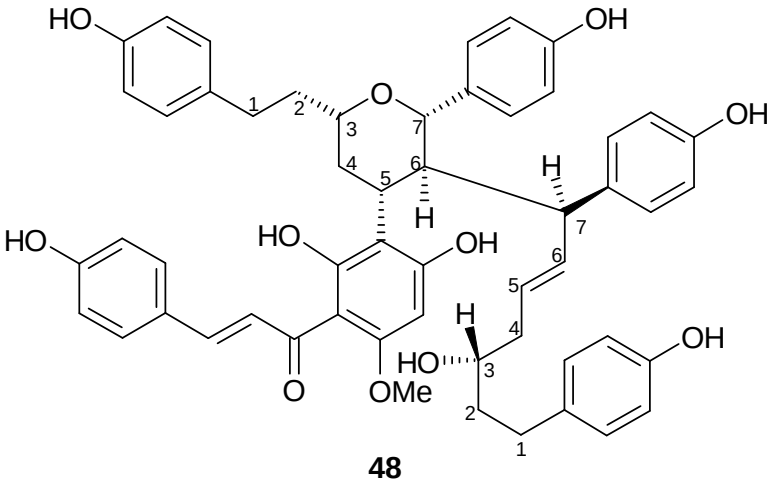
The most complex diarylheptanoids bearing a chalcone (**46**) or flavanone (**47**) moiety have been isolated from the seeds of *Alpinia blepharocalyx*[35] (Zingiberaceae) by Prasain[7,35] and his co-workers and showed inhibitory activity against nitric oxide production in activated murine macrophages. Another complex diarylheptanoid is blepharocalyxin E (**48**) recently isolated from *Alpinia blepharocalyx* (Zingiberaceae) showed a particular promise as a potential drug candidate for the treatment of human tumours, displaying *in vitro* inhibitory activity towards human fibrosarcoma HT-1080 carcinoma cells.[36]


OH
HO
OMe
1
2
3
4
5
6
7
H
OH
H
OH
O
OH
OH

46


HO
O
O
OMe
1
2
3
4
5
6
7
H
OH
H
OH
OH
OH

47


HO
OH
1
2
O
3
7
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5
6
H
H
OH
HO
HO
OH
6
5
H
4
HO
3
OH
O
OMe
2
1

48

These compounds combine the structural features of the aforementioned curcuminoids (intra- and intermolecular cyclisations, extension with non-diarylheptanoid moieties). To date numerous diarylheptanoids have been described and due to the complexity of the compounds, further structural revisions are in progress. Moreover, as there are many possible reactions with potential precursors, even more complex diarylheptanoids can be expected to be found in future investigations.[37] From the discussion above it can be seen that a wide variety of diarylheptanoids have been isolated from plants and that a large number of these compounds are associated with biological activities.

2.3 SYNTHESIS OF DIARYLHEPTANOIDS

2.3.1 SYNTHESIS OF LINEAR DIARYLHEPTANOIDS

Linear diarylheptanoids have relatively simple structures that can be easily accessed by today's synthetic methodologies. In this section, linear diarylheptanoids will be discussed according to the oxygenation level of the tether chain, namely, with one oxygen functional group, two oxygen functional groups and three oxygen functional groups, respectively (Fig. 2.4).

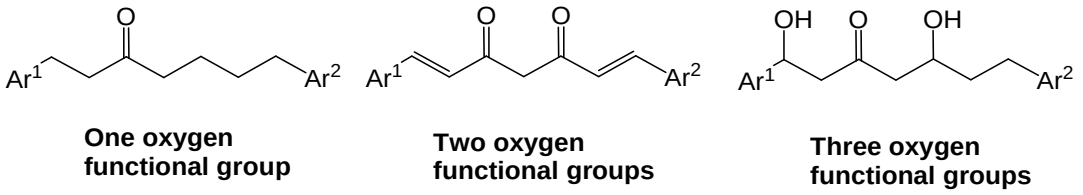
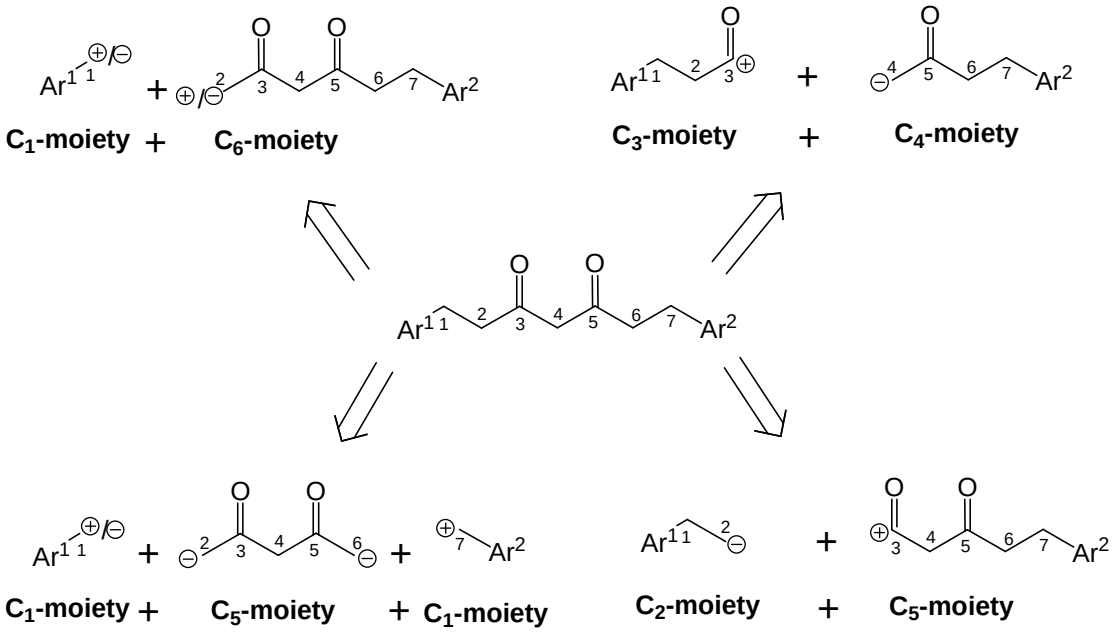


FIGURE 2.4: Incorporation of oxygen functions into the tether chain.

Retrosynthetic methodologies of linear diarylheptanoids may be classified according to the efficient ways to assemble the seven carbon aliphatic chain, namely, C_3-moiety + C_4-moiety strategy, C_1-moiety + C_6-moiety strategy, C_1-moiety + C_5-moiety + C_1-moiety strategy and C_2-moiety + C_5-moiety strategy, respectively (Scheme 2.1).

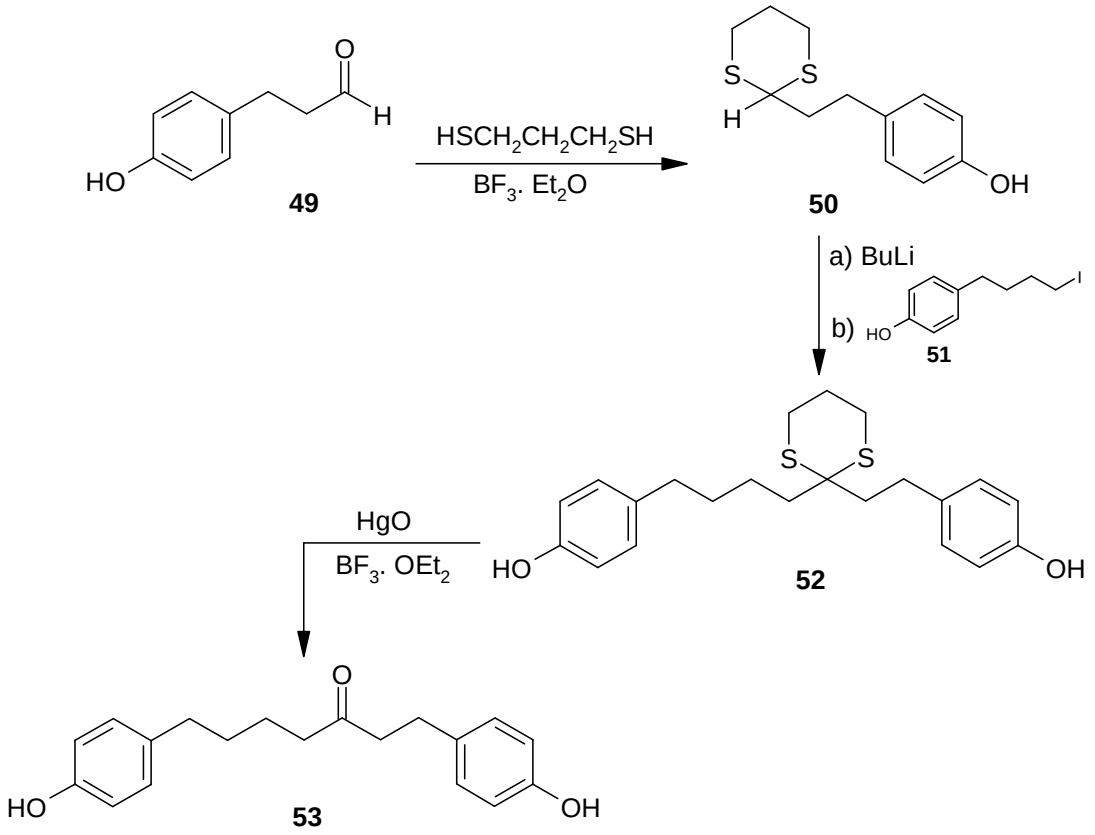
The assembly of these synthons can be accomplished using various types of reactions such as nucleophilic addition to an aldehyde, alkylation of a 1,3-dithiane (umpolung strategy), aldol condensation and other types of condensation and lastly Wittig-type reactions. A brief description of each synthesis will be presented accordingly.



SCHEME 2.1: Disconnection approach of linear diarylheptanoids.

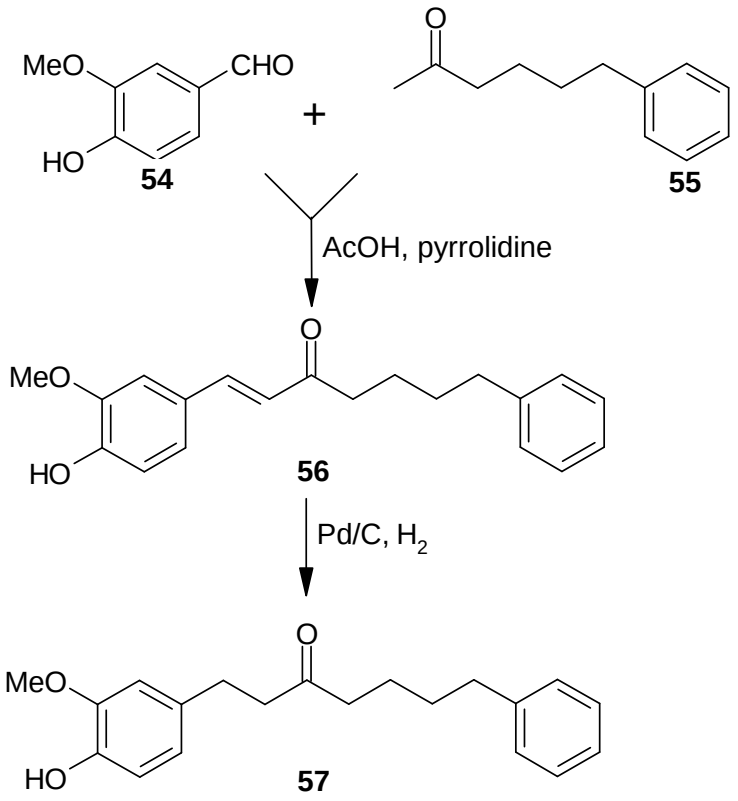
a) Diarylheptanoids with one oxygen functional group

For the synthesis of diarylheptanoid **53**, Whiting and his co-workers[38] developed an umpolung method based on dithiane chemistry (Scheme 2.2). Alkylation of lithiated dithiane **50** by iodide **51** gave **52** in 33% yield. Hydrolysis of the latter gave the diarylheptanoid **53** in 73% yield. The C_3-moiety + C_4-moiety strategy have been used in this synthesis.



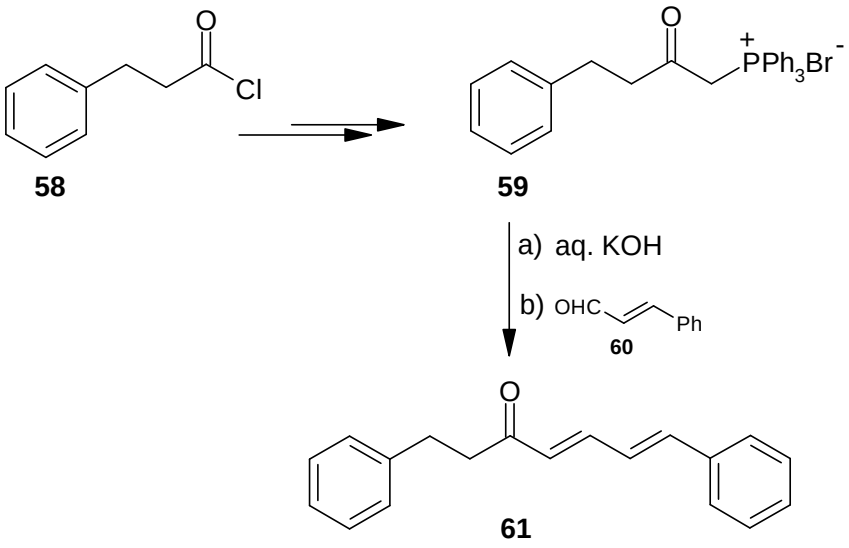
SCHEME 2.2

A Claisen-Schmidt reaction was employed for the synthesis of the two pungent principles of *Alpinia oxyphylla* (Zingiberaceae)[39], namely, yakuchinone A (**57**) and yakuchinone B (**56**) (Scheme 2.3).[40] Thus, condensation of vanillin (**54**) with 6-phenyl-2-hexanone (**55**) gave yakuchinone B (**56**) in 80% yield, and hydrogenation then gave yakuchinone A (**57**). This synthetic method is quite general and has been applied for the preparation of a number of analogues.[40] It was found that the presence of the phenolic hydroxy group was responsible for a high pungency, while unsaturation in the aliphatic chain tends to decrease the pungency. Yakuchinone A (**57**) is reported by Kiuchi *et al.*[41] as a potent inhibitor of prostaglandin synthase (IC_{50} = 0.51 μM) and 5-lipoxygenase and could be the main active compound of *A. oxyphylla*.



SCHEME 2.3

Diarylheptanoids containing a dienone moiety have been synthesised by a Wittig reaction between phosphorane **59** and cinnamaldehyde (**60**) in 56% yield (Scheme 2.4).[42] Recently, a novel diarylheptanoid containing a dienone moiety has been also synthesised in high yields by the Wittig-Horner reaction.[43]

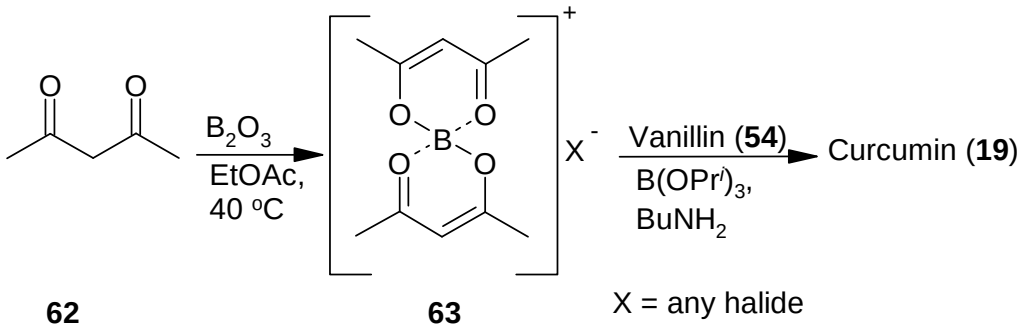


SCHEME 2.4

b) Diarylheptanoids with two oxygen functional groups

The first laboratory synthesis of 1,7-diarylheptanoids with two oxygen functional groups was that of curcumin (**19**) accomplished in 1918.[44] A practical industrial synthesis of curcumin (**19**) was needed due to its importance as food additives, dye, and its recently demonstrated chemopreventive effect. Such syntheses were developed by Pavolini[45] and later improved by Pabon[46] (Scheme 2.5).

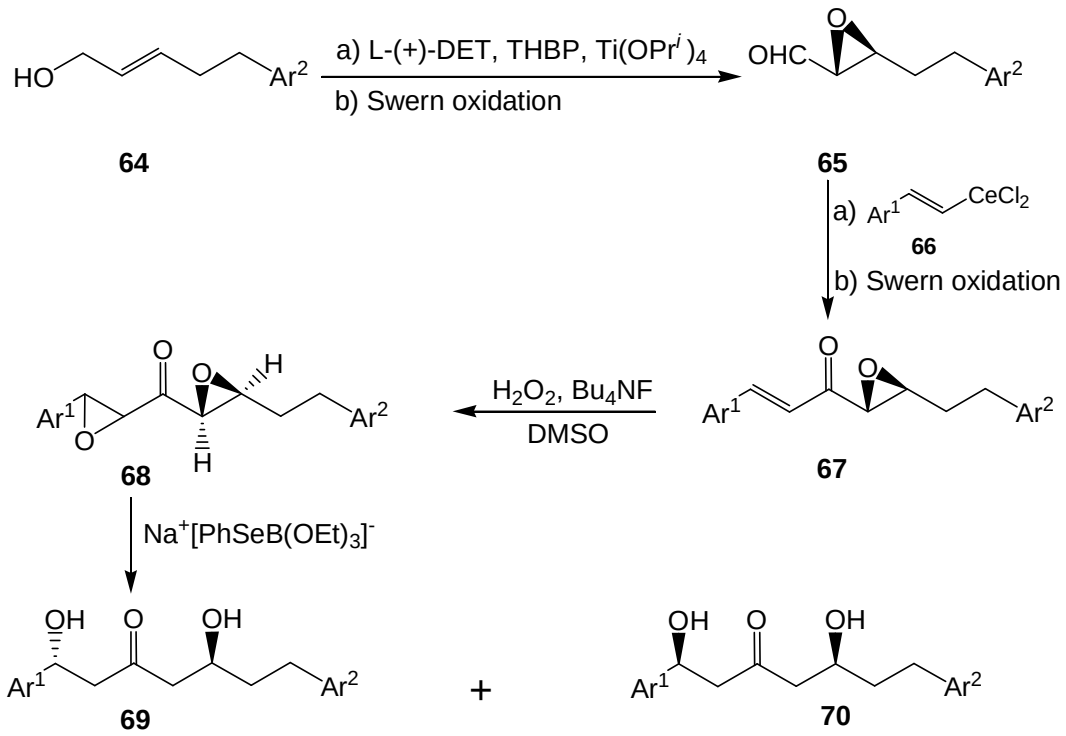
Reaction of vanillin (**54**) with 2,4-pentanedione (**62**), pretreated with boric anhydride, in the presence of triisopropylborate and butylamine gave curcumin (**19**) in 80% yield. In order to obtain a high yield of curcumin (**19**), the C-3 of 2,4-pentanedione had to be protected to avoid the undesired Knoevenagel condensation. This was achieved by reaction of 2,4-pentanedione with boric anhydride to produce the presumed boron complex **63**. The method is quite general and has been applied to the synthesis of other symmetrical natural and non-natural 1,7-diarylheptanoids.[47] Recently, the same method has been employed to synthesise a novel diarylheptanoid with anti-androgen activity.[48]



SCHEME 2.5

c) Diarylheptanoids with three oxygen functional groups

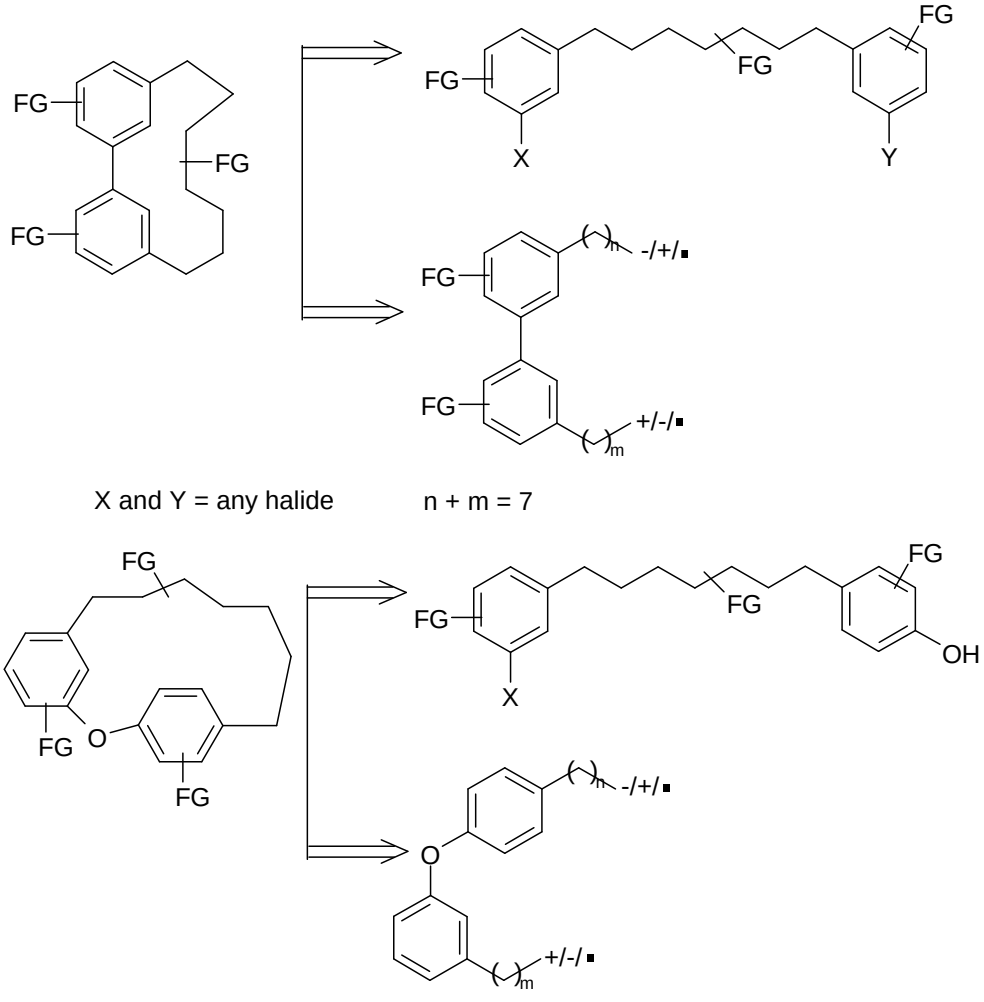
Some relatively rare linear diarylheptanoids contain three oxygen functional groups. Among the few examples of these diarylheptanoids are yashabushiketodiol A (**69**) and yashabushiketodiol B (**70**), which have been isolated from *Alnus sieboldiana*.[49] An enantioselective synthesis of these compounds was reported by Yoshikoshi *et al.*[50](Scheme 2.6).



SCHEME 2.6

2.3.2 SYNTHESIS OF CYCLIC DIARYLHEPTANOIDS

Macrocyclic compounds have attracted much attention by synthetic chemists due to their outstanding biological activity and the intrinsic challenges associated with their construction.[51] The central issue in planning the synthesis of a macrocyclic compound is the ring closure. The outcome of such a reaction depends on both the choice of a strategic bond and the reaction selected for its construction. Two obvious strategic bond disconnections for the synthesis of cyclic diarylheptanoids are outlined in Scheme 2.7. The one synthesis involves the formation of carbon-carbon bond at the tether chain, whereas the other strategy calls for the macrocyclisation *via* formation of an aryl-aryl or an aryl-aryl ether bond.



SCHEME 2.7: Disconnection approach of cyclic diarylheptanoids.

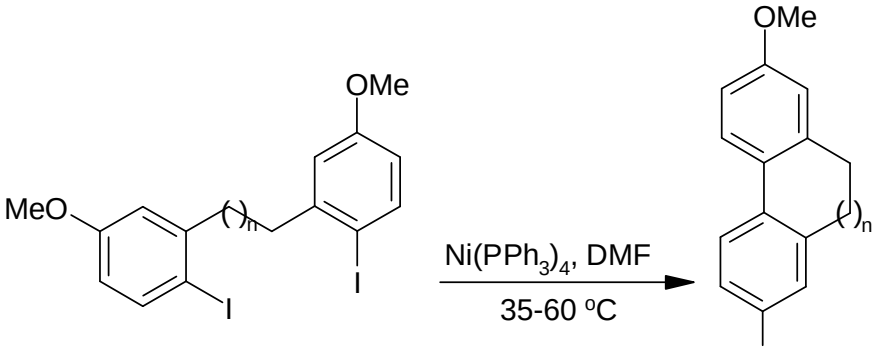
Recently, some new powerful ring closing methods have been developed in addition to the well-adopted macrolactonisation reactions.[52] These methods include intramolecular Ullmann reaction,[53] Prins cyclisation strategy,[54] intramolecular Wittig-type reactions,[55] intramolecular oxidative coupling,[56] intramolecular nucleophilic aromatic substitution reaction (S_NAr),[57] photocyclisation reaction,[58] asymmetric synthesis of tetrahydrofuran ring[20] and transition metal-catalysed reactions.[59] In the synthesis of macrocyclic diarylheptanoids, chemists do not only have to find the right way to perform the cyclisation but also need to control the atropisomerism and that become even more challenging.

2.3.2.1 Total synthesis of bridged biphenyl macrocycles

(a) Ring closure *via* aryl-aryl bond formation

(i) Nickel(0)-promoted intramolecular reductive coupling of arylhalide

The most powerful methods for the construction of biaryl unit using transition metal-catalysed cross-coupling reactions are the Suzuki, Stille, Ullmann and Negishi reactions.[60] Semmelhack[61] provides a significant contribution to the field by introducing the zerovalent nickel-promoted intramolecular coupling of an aryl halide (Scheme 2.8), though this cyclisation technology fails with sterically hindered *ortho*-disubstituted substrates.



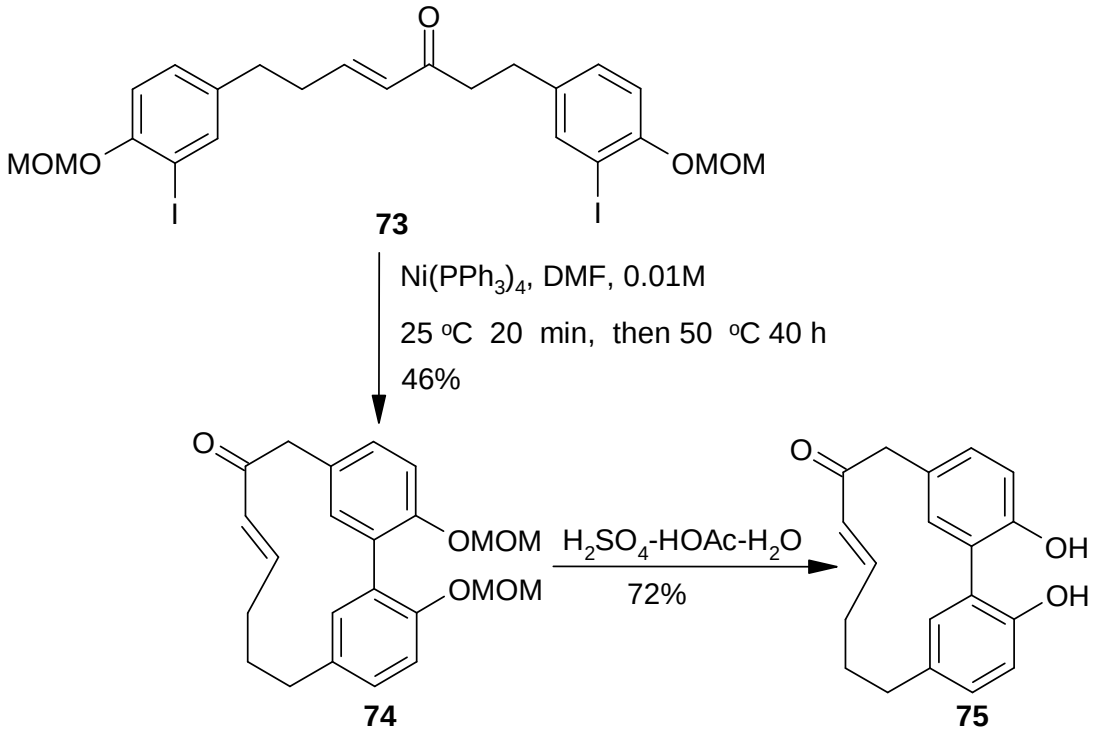
71

n = 1, yield 81%
n = 4, yield 85%
n = 5, yield 38%

72

SCHEME 2.8

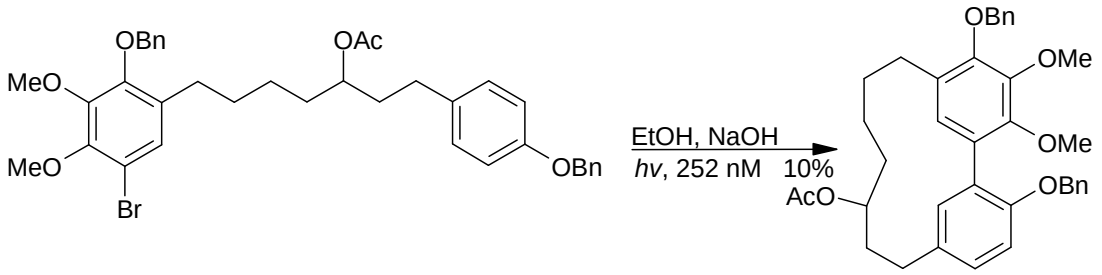
In addition to the above synthetic strategy of Semmelhack *et al.*[61], the total synthesis of alnusone (**75**) was developed (Scheme 2.9). Heating a solution of diiodide **73** in DMF in the presence of tetrakis(triphenylphosphine)nickel afforded the 13-membered *meta*,*meta*-bridged biphenylmacrocycle **74** in 46% yield. Deprotection of the MOM ethers under acidic conditions gave the natural alnusole (**75**) in 72% yield.



SCHEME 2.9

(ii) Photochemical aryl-aryl bond formation

An important technique for the construction of the biaryl bond is by photocyclisation of an appropriate aryl halide.[58] Whiting and Wood also applied this photolytically-induced radical cyclisation in the synthesis of dibenzylmyricanol (**77**) (Scheme 2.10).[62] Thus, irradiation of the bromide **76** in ethanolic sodium hydroxide for 30 min afforded the dibenzylmyricanol (**77**) in about 10% yield.

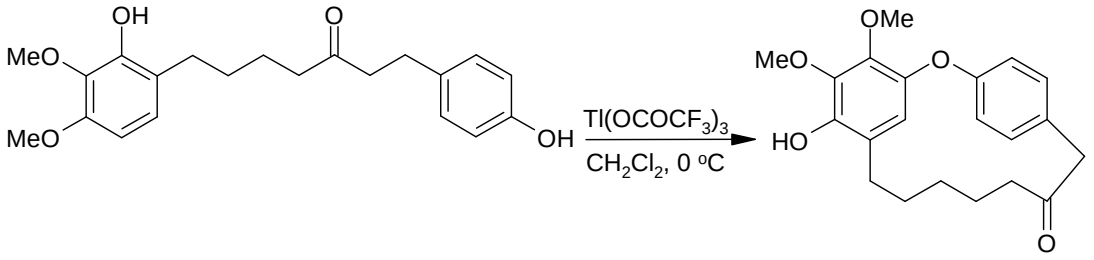


76 **77**

SCHEME 2.10

(iii) Intramolecular oxidative coupling

Oxidation of linear diarylheptanoid **78** has also been examined.[62] Utilisation of oxidising agents such as potassium hexacyanoferrate, silver oxide, manganese oxide, and vanadium oxychloride gave only tars, whereas thallium tris(triflouroacetate)-induced intramolecular C-O coupling afforded the 15-membered *m*,*p*-cyclophane **79** (Scheme 2.11).



78 **79**

SCHEME 2.11

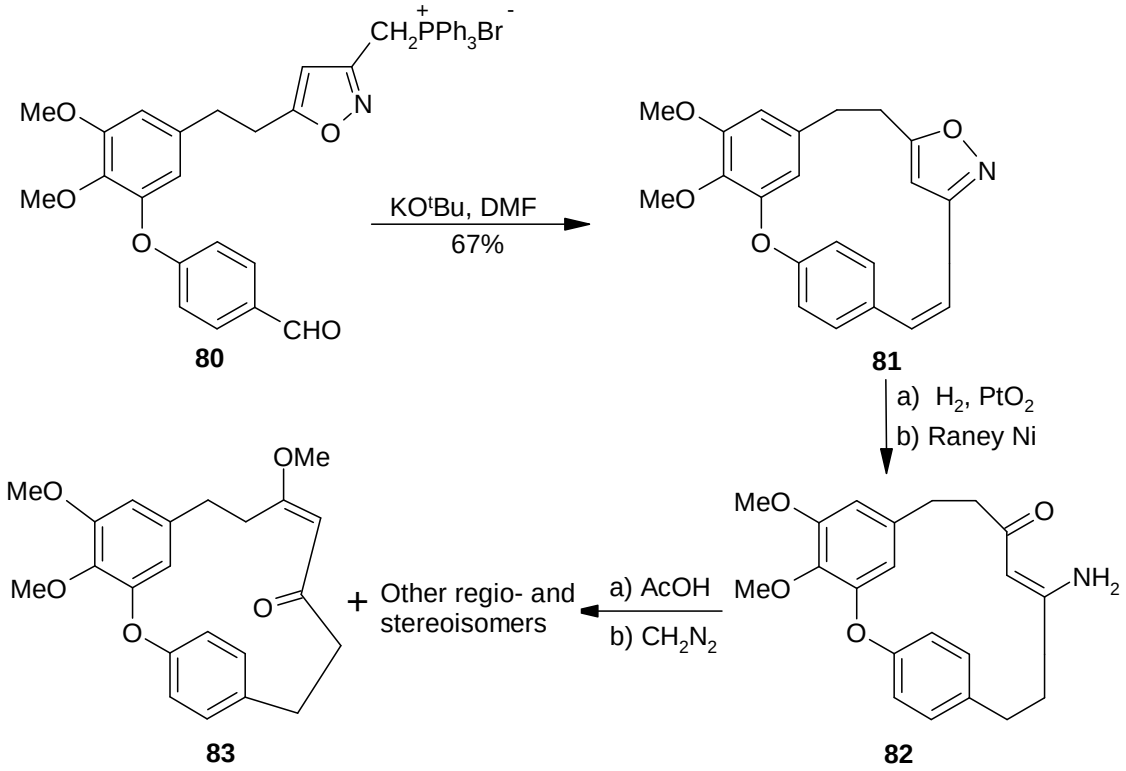
2.3.2.2 Total synthesis of *m*,*p*-cyclophanes

A long-standing problem is the synthesis of biaryl ethers with sensitive functionalities. Until recently, the classical Ullmann ether synthesis, using copper or copper salts, was regarded as less effective and required harsh conditions.[53] This was a result of the poor nucleophilicity of phenoxide and the low reactivity of aryl halides involved in the reaction.

An attempt to synthesise a biologically active (as an antibiotic) vancomycin complex has led to the development of a number of new powerful synthetic technologies such as cyclisation through aliphatic C-C bond formation and cyclisation through aryl-aryl ether bond formation.[63]

(a) Formation of macrocycle *via* formation of aliphatic C-C bond through intramolecular Wittig-type reaction

A developed synthesis of garuganin III (**83**), featuring the ring formation through aliphatic C-C bond formation using intramolecular Wittig reaction as a key, is outlined in Scheme 2.12.[64]



SCHEME 2.12

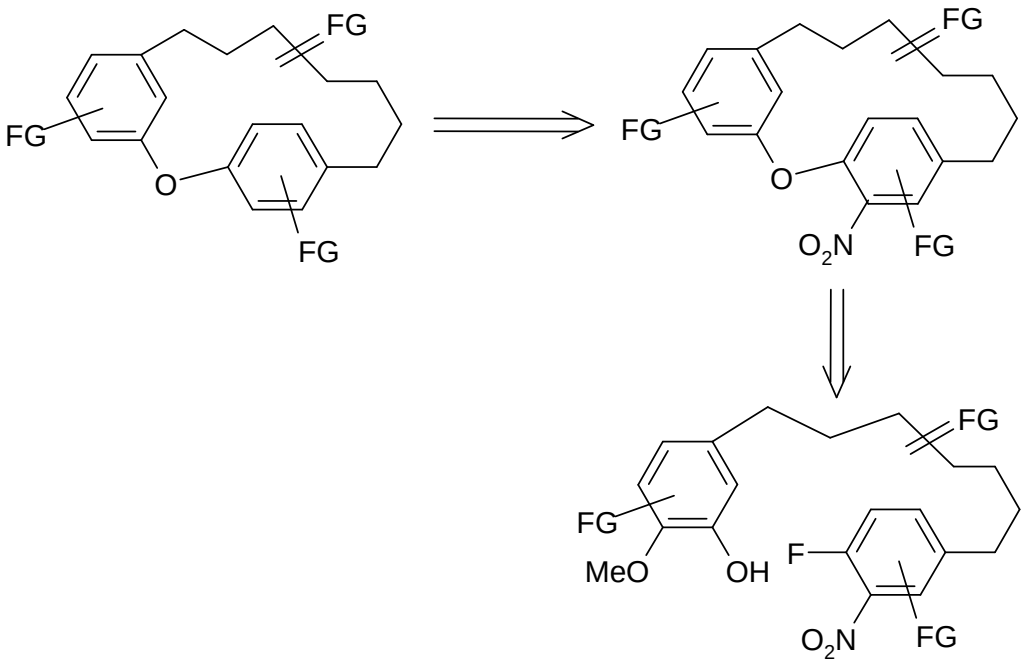
The addition of potassium *tert*-butoxide to a dilute solution of compound **80** in DMF produced macrocycle **81** in 67% yield.

Hydrogenation over platinum oxide doped with Raney nickel reduced simultaneously the olefin and the N-O bond leading to the enaminoketone **82**. Garuganin III (**83**) was isolated from a mixture of regio- and stereoisomers after acidic hydrolysis and methylation of the intermediate1,3-diketone.

(b) Ring formation *via* aryl-aryl ether bond formation

(i) Intramolecular S_NAr reaction

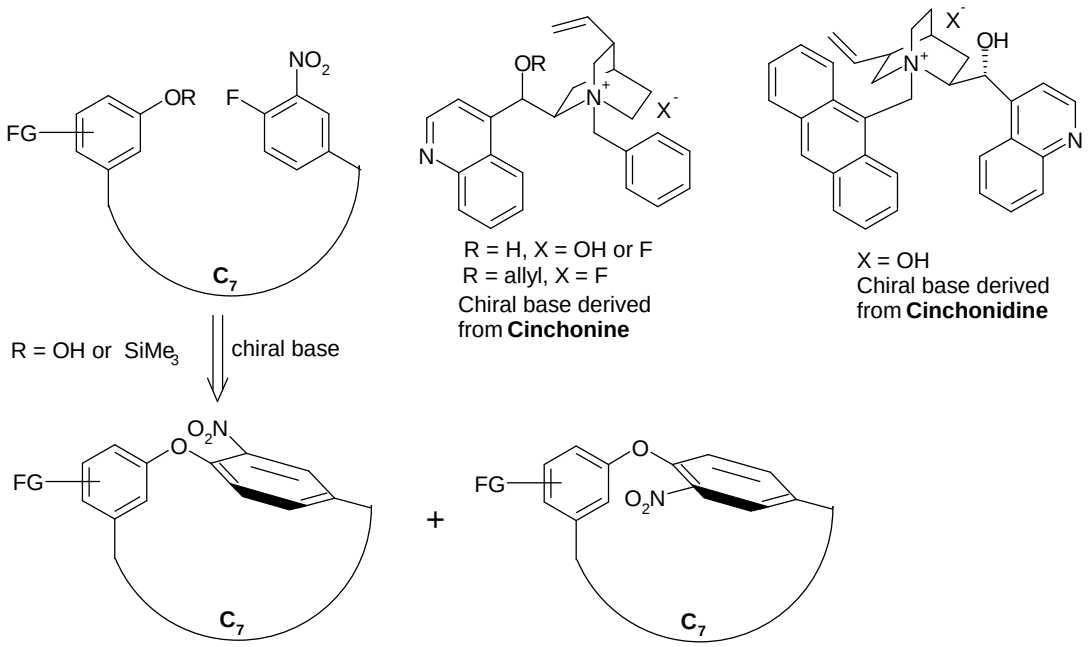
The investigation of the cyclisation of a linear diarylheptanoid through aryl-aryl ether bonds has resulted in the discovery of an efficient and unified synthesis of *m*,*p*-cyclophanes according to the general synthetic plan shown in Scheme 2.13.[57]



SCHEME 2.13: Retrosynthetic analysis of *m*,*p*-cyclophane.

Optically active natural products containing planar chiral cyclophane, such as (*R*)-(+)-galeon (**40a**) and (*S*)-(–)-galeon (**40b**) have been isolated and the enantioselective cyclisation leading to the planar chiral cyclophanes by intramolecular S_NAr was first designed by Zhu *et al.*[65]

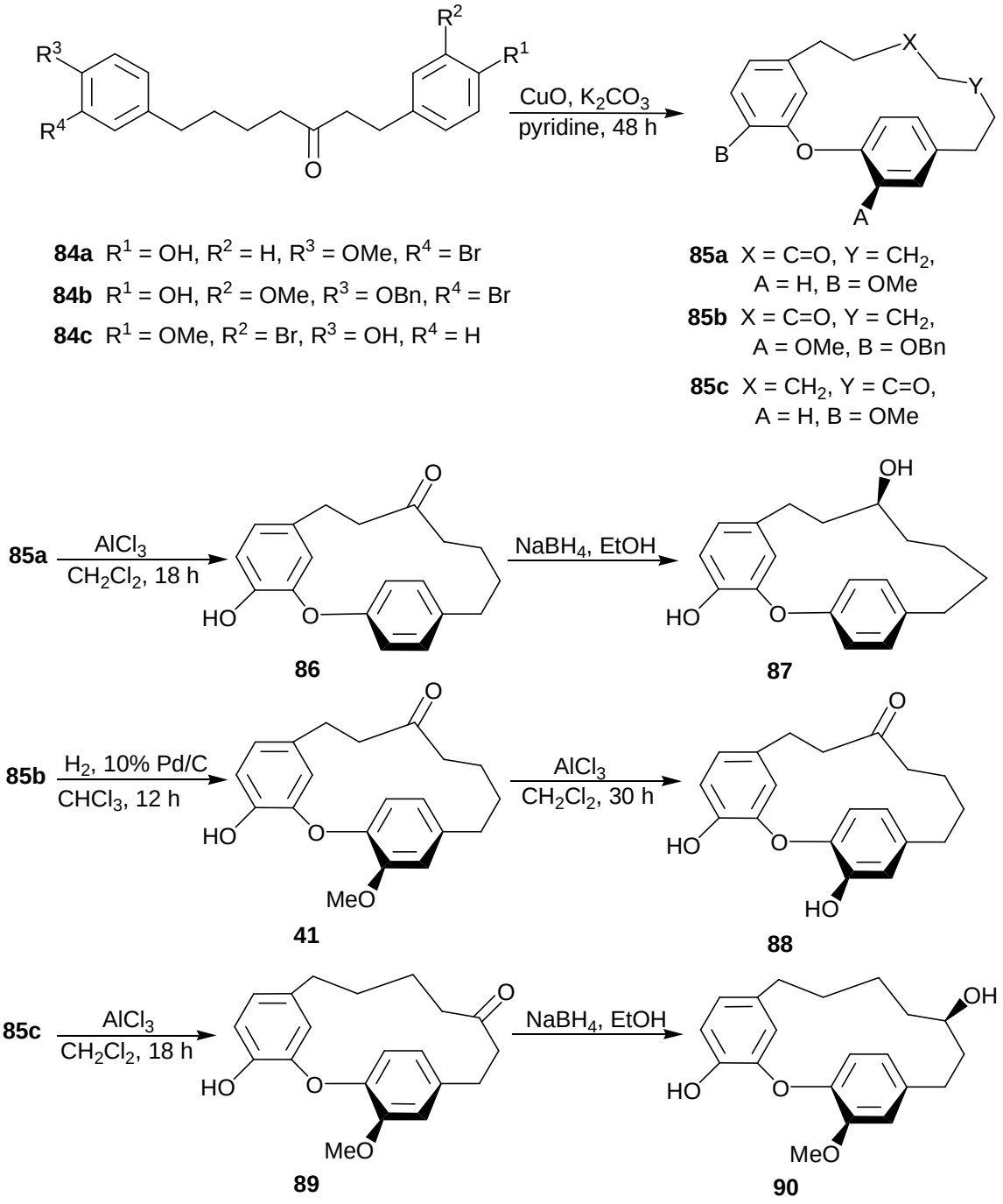
The mechanism of cyclisation was based on utilising an achiral linear diarylheptanoid with an *ortho* fluoro nitro aryl as to create a parallel planar chirality (Scheme 2.14). Potassium carbonate and caesium fluoride were previously used to promote cyclisation of the achiral linear diarylheptanoid and Zhu[65] found that tetrabutylammonium fluoride and tetrabutylammonium hydroxide were also able to promote the cyclisation as well. With these results Zhu and his co-workers investigated atropenantioselective cyclisation using chiral quaternary ammonium salts which were derived from cinchonine and cinchonidine.[65]



SCHEME 2.14: Atropenantioselective cycloetherification process.

(ii) Intramolecular Ullmann reaction

Parallel to the work of Islas-Gonzalez *et al.*[66] to synthesise acerogenin A (**90**) and acerogenin C (**89**) by implementation of an intramolecular S_NAr reaction, an Ullman ether synthesis has been recently employed by Jeong *et al.*[53] for the synthesis of these compounds (Scheme 2.15).



SCHEME 2.15

Their strategy employs a substituted diarylheptanoid **84** which was subjected to an Ullmann[67] reaction by using catalytic CuO/K_2CO_3 to yield the corresponding diphenyl ethers **85a, 85b** and **85c** in 49, 52 and 76% yield, respectively.

The *O*-demethylation of diarylheptanoids **85a** and **85c** by $AlCl_3$ afforded acerogenin L (**86**) and acerogenin C (**89**) in 86 and 89% yield, respectively. The selective cleavage of the benzyl ether of diarylheptanoid **85b** by catalytic hydrogenation quantitatively yielded the desired galeon (**41**) as a racemic mixture of rotamers, which was then subjected to *O*-demethylation by $AlCl_3$ to afford racemic pterocarine (**88**) in 88% yield. Similarly, reduction of acerogenin L (**86**) and acerogenin C (**89**) with $NaBH_4$ afforded the corresponding alcohols of acerogenin B (**87**) and acerogenin A (**90**), respectively.

Methods for the synthesis of natural diarylheptanoids have set a clear view of the constitution and chemical properties of diarylheptanoids which enhance their biological activity. This include the variation of the aryl end groups with either a free or protected phenolic hydroxy at both or either ends of the tether chain and incorporation of oxygen functions and other functional groups into the chain.

2.4 *SIPHONOCHILUS AETHIOPICUS*

Siphonochilus aethiopicus BL. Burtt (Zingiberaceae), commonly known as wild ginger or Natal ginger is regarded as one of the most important and threatened medicinal plants in South Africa.[68] The generic name *Siphonochilus* is derived from the Greek word *Siphono* meaning tube and *Chilus* meaning lip in reference to the shape of the flower while the species name *aethiopicus* means from Southern Africa. [69] The plant originated from southern tropical Africa (South of Malawi to the Eastern part of South Africa).[3] Wild ginger is a forest floor plant with aromatic rhizomatous roots, leaves that are deciduous and sprout annually from the underground stem in spring (Fig. 2.5).

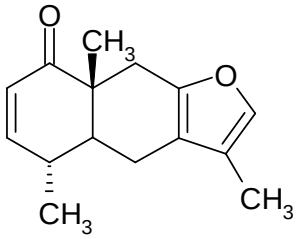
This South African wild ginger is highly prized for its medicinal value and as a result it has been over-harvested from the wild to a point just short of total extinction. The cone shaped rhizomes and fleshy roots are dug up and sold on the ‘muthi’ markets around the Country because the highly aromatic roots have a variety of medicinal and traditional uses.

The rhizomes and roots are chewed fresh to treat the following ailments: headache, influenza, mild asthma, sinusitis and sore throat, thrush, candidiasis, malaria and menstrual cramps.[70,71,72,73]

Photo: B-E van Wyk

FIGURE 2.5: *Siphonochilus aethiopicus*.

There is little information that gives insight on the chemical constituents of *S. aethiopicus*. The volatile oil contains sesquiterpene **17** of the furanoid type as the main component but large numbers of other terpenoids are present in the essential oil.[74]



Siphonochilon (**17**)

The terpenoids may be responsible for the reported beneficial effects of wild ginger in the treatment of colds and flu. Like many other volatile oils these should have a decongestant and antiseptic action, but further research is required. According to Viljoen *et al.*[75], the essential oil composition of the roots and rhizomes of *S. aethiopicus* obtained through hydrodistillation is reported to have the following major compounds, namely: 1,8-cineole, (*E*)-β-ocimene, *cis*-alloocimene, together with the recently reported furanoterpenoid, which is the major compound in both plant organs.

An interesting pharmacological report by McGaw *et al.*[76] in which the scientist tested a number of Zulu medicinal plants used in the treatment of pain and inflammation was published. In an assay considered to disrupt the inflammation process, ethanolic extracts of *Siphonochilus aethiopicus* were found to exhibit higher inhibitory activity than indomethacin, a standard pharmaceutical drug used as anti-inflammatory.

A screening of plants used by southern African traditional healers in the treatment of dysmenorrhoea for prostaglandin-synthesis inhibitors and uterine relaxing activity, has been reported by van Lindsey *et. al.*[77]. The highest activity was obtained with ethanolic extracts of *S. aethiopicus*.

Despite the importance of *S. aethiopicus* as medicinal plant of South Africa, there is a lack of knowledge of *S. aethiopicus* in some aspects which includes its pollination biology, genetics, chemical diversity and flowering initiation as stated in the literature.[70] Total synthesis of its natural occurring metabolites has not been covered yet and studies of this nature may be useful aspect that we aimed to reveal in our research.

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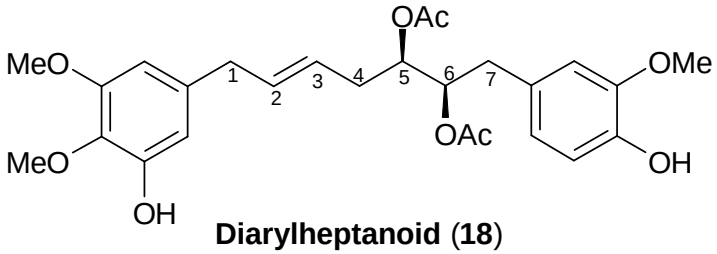
CHAPTER 3

SYNTHESIS OF THE LINEAR DIARYLHEPTANOID PRECURSORS

3.1 INTRODUCTION

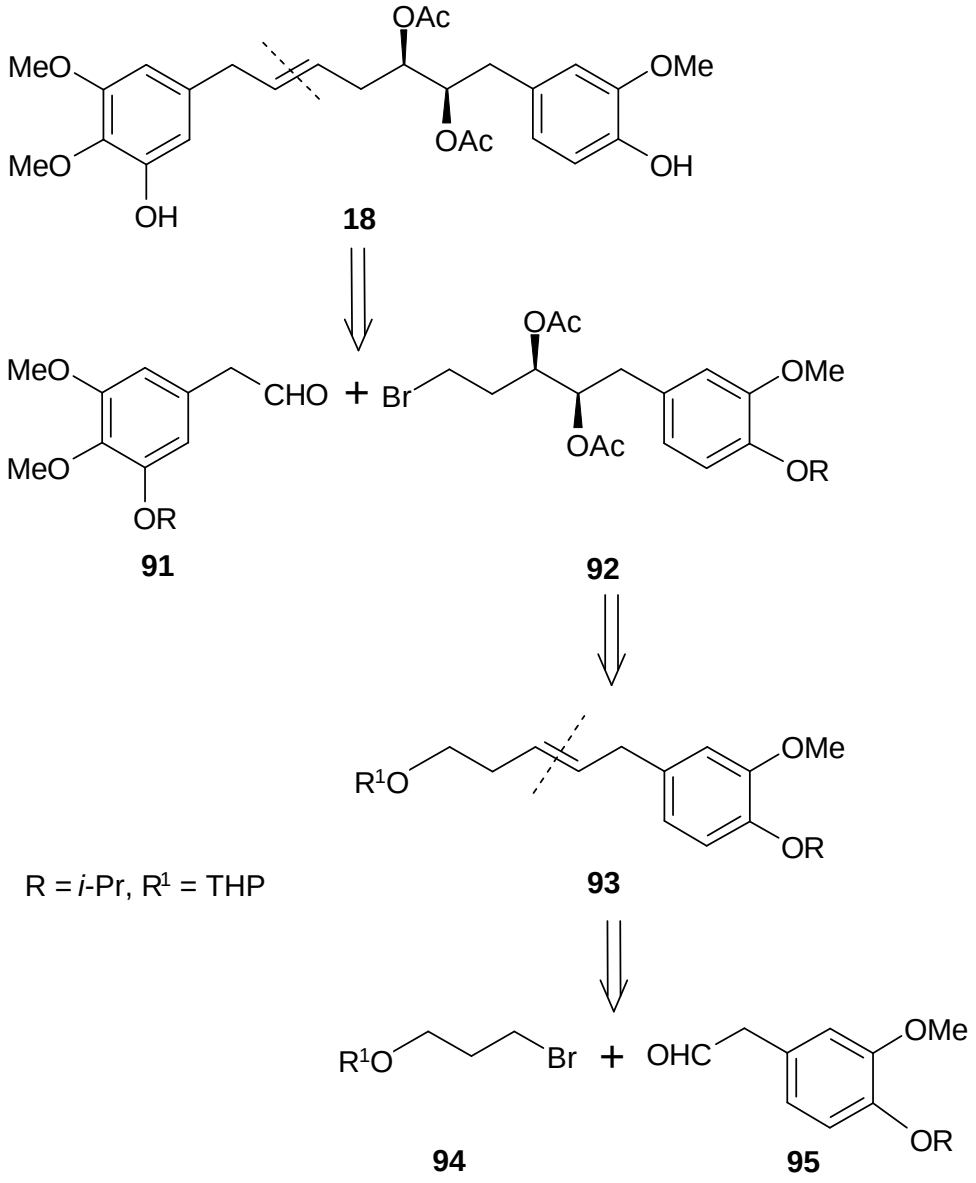
In the previous chapter, retrosynthetic methodologies of linear diarylheptanoids were classified according to the different ways to assemble the seven-carbon aliphatic chain, namely, the C_2-moiety + C_5-moiety strategy and C_1-moiety + C_6-moiety strategy were selected for this study in order to construct diarylheptanoid **18**, a specific stereoisomer of the novel diarylheptanoid **16** isolated from *Siphonochilus aethiopicus*. The assembly of these synthons could be accomplished using various types of reactions such as olefination reactions (including Wittig, Julia and organometallic-mediated type of olefination reactions) as well as alkylation reactions (including Grignard, Friedel-Crafts and organometallic-mediated type of alkylation reactions).



Diarylheptanoid (**18**)

Taking into account the stereochemistry in the seven-carbon aliphatic chain of the compound, incorporation of the stereogenic centres can be accomplished by asymmetric hydroxylation reaction or use of chiral starting materials to furnish these asymmetric centres. In this chapter, an investigation of two different routes that will provide a viable synthetic method is presented.

3.2 RETROSYNTHETIC ANALYSIS

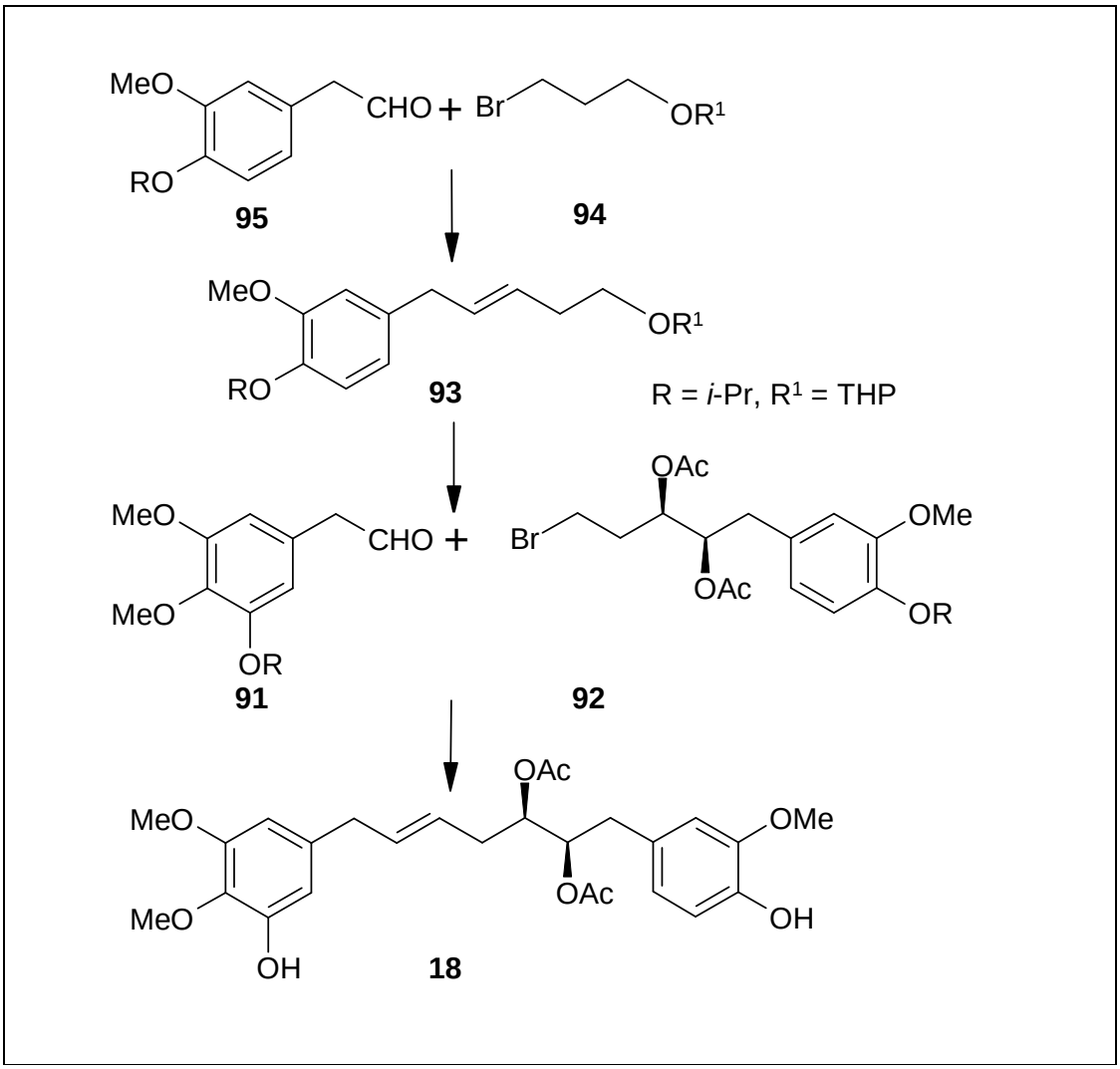


SCHEME 3.1

Structural analysis of the target compound reveals two electron-rich aromatic rings linked by a seven-carbon aliphatic chain with two stereogenic centres and a *trans*-alkene. The intended homobenzylic *trans*-alkene can be established using various ways of selective *E*-olefination that will be discussed in this chapter.

The chirality of the vicinal diols will be generated either by the use of chiral starting material with stereodefined vicinal diols or by asymmetric dihydroxylation. Another concern is the coupling of the highly oxygenated aryl rings to the aliphatic chain that can be introduced using various types of alkylation reactions to furnish the C-C bond formation.

Based on the retrosynthetic analysis outlined in Scheme 3.1, a synthetic strategy was developed as depicted in Scheme 3.2 which made use of a Wittig-type coupling planned to connect precursors **94** and **95**, and **91** and **92**.

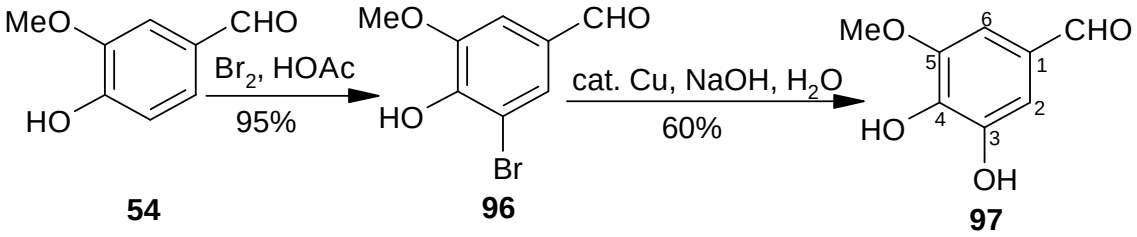


SCHEME 3.2

3.2.1 Synthesis of phenacetaldehydes 91 and 95

The first target was to obtain precursor **91**, which was required for the stereocontrolled olefination. Vanillin (**54**) was chosen as the readily available starting material (Scheme **3.3**).

A convenient method described by Yang *et al.*[1] was followed for the synthesis of 3-bromovanillin (**96**) in excellent yield of about 95%. Copper-catalysed base hydrolysis of 3-bromovanillin (**96**) was performed as described by Ellis and Lenger[2] to afford 3,4-dihydroxy-5-methoxybenzaldehde (**97**) in 60% yield.

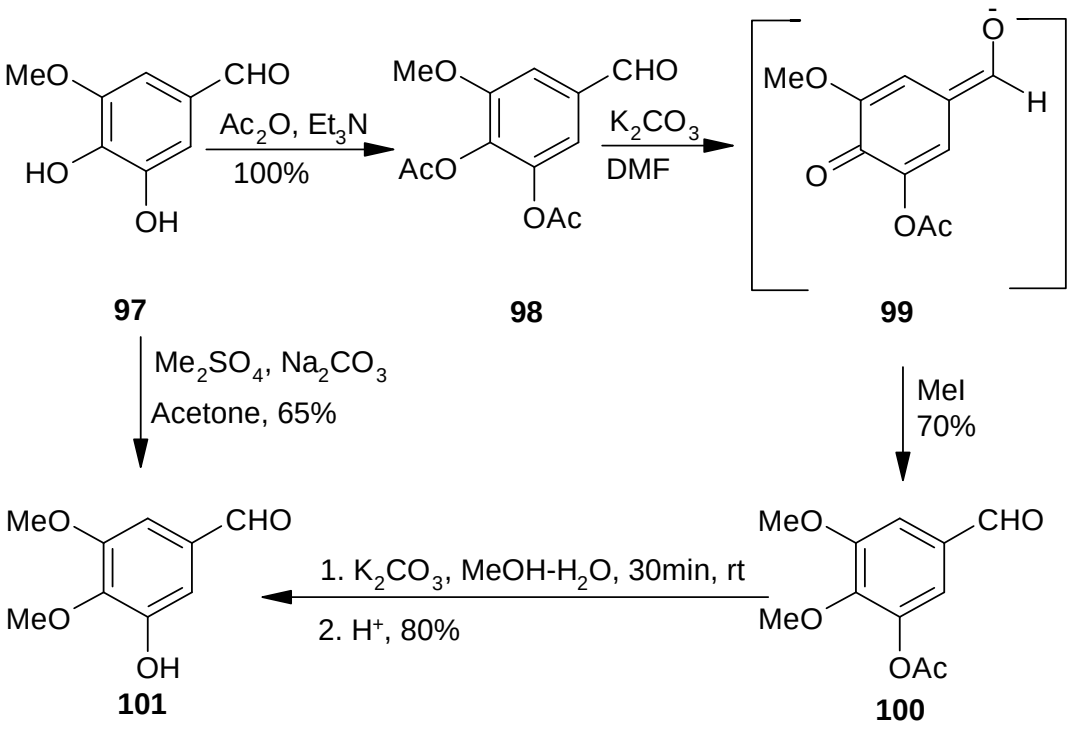


54 **96** **97**

SCHEME 3.3

The next step was the selective methylation of 3,4-dihydroxy-5-methoxybenzaldehyde (**97**) at the 4-position. The differentiation in the reaction rate between the two hydroxy groups of the compound **97** is not sufficient to get selective methylation at the 4-position in a reaction with K_2CO_3 and MeI, even though the presence of the *para* electron–withdrawing aldehyde function causes the 4-OH to be more reactive than the 3-hydroxy group. Therefore, a method developed by Zhu *et al.*[3,4]and Pearson and Bruhn[5] on selective protection of the 4-position of gallic acid was followed. The proposed pathway for this step is outlined in Scheme 3.4 (**97**→**98**→**99**→**100**).

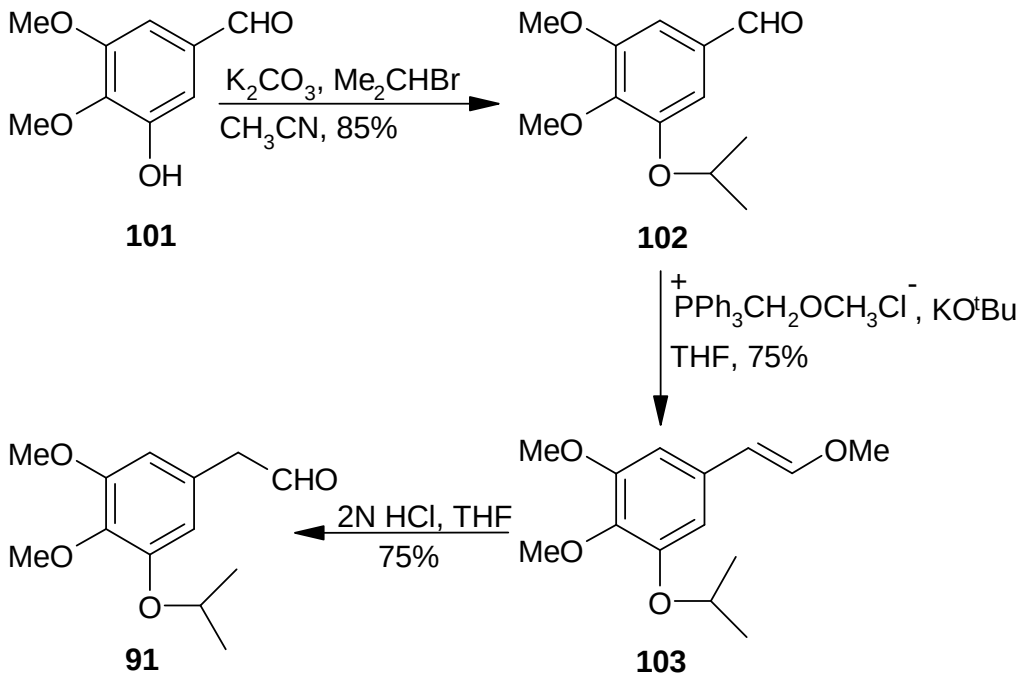
On the other hand, Ellis and Lenger[2] developed another method for the selective methylation at the 4-position where they utilised a weak base like Na_2CO_3 to abstract the reactive proton of the 4-OH followed by Me_2SO_4 as the source of methylation to furnish the desired product (Scheme 3.4).



SCHEME 3.4

The first reaction involved the heating of the di-acetate **98** in DMF at 40 ^{o}C in the presence of K_2CO_3 and MeI to give exclusively the 4-methoxylated compound **100**. The selectivity of this reaction may be explained by the trace of water present in the reaction medium that may selectively hydrolyse the reactive 4-acetyl group leading to the formation of the intermediate **99**, which is stabilised by the conjugation effect of the aldehyde function. Subsequent methylation gave the desired product **101** in 80% yield. Alternatively, when compound **97** was subjected to selective methylation in the presence of Na_2CO_3 and Me_2SO_4 the desired product was furnished in 65% yield along with the presence of the other regioisomeric by-product (4-hydroxy-3,5-dimethoxybenzaldehyde) in trace amounts and about 10% of the over-methylated by-product (3,4,5-trimethoxybenzaldehyde). The ^{1}H NMR spectrum of the di-methoxylated compound **101** displayed the expected signals including two methoxy groups (δ_H 3.82 and 3.91), the sharp singlet of the free hydroxy group (δ_H 6.36) and another sharp singlet of an aldehyde proton (δ_H 9.79).

A carbonyl signal (aldehyde), two methoxy signals and six aromatic carbon signals were observed in the ^{13}C NMR spectrum. The MS spectrum revealed an $[M+H]^+$ base peak of 183.1812 corresponding to the mass of the desired compound **101**. Subsequently, the free hydroxy group of compound **101** was protected as an isopropyl ether to eliminate the formation of side products when subjecting the compound to further synthetic steps. The protected compound **102** was homologated by the Wittig-reaction following a convenient method described by Treu and Jordis.[6] Subsequent hydrolysis of the enol ether **103**, isolated as the mixture of *cis*/*trans* isomers (67:33, *E*:*Z* ratio), gave **91** as the desired precursor (Scheme 3.5).

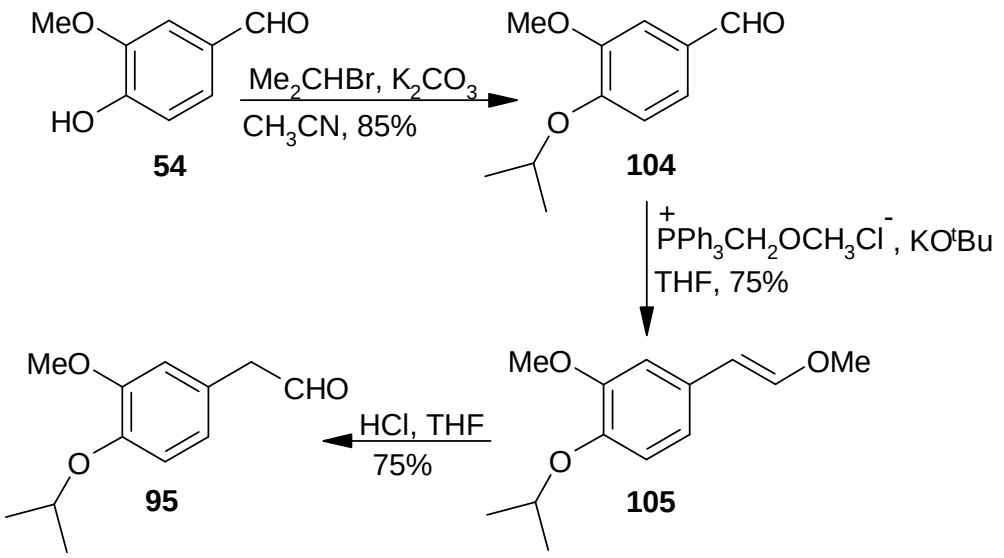


SCHEME 3.5

The structure of compound **91** was confirmed by ^1H NMR which displayed the expected signals including the aldehyde as a triplet (δ_H 9.71), isopropyl ether signals [δ_H 4.49 (CH) and 1.31 (2 x CH_3), α-CH_2 of acetaldehyde (δ_H 3.57) and the two methoxy signals (δ_H 3.83). In the ^{13}C NMR, all the expected signals were observed including the carbonyl peak of an aldehyde (δ_C 199.3) and the molecular formula of the compound was confirmed by MS.

The next step was to synthesise precursor **95**. Vanillin (**54**) was again chosen as the starting material for the synthesis (Scheme 3.6). Protection of the free hydroxy group of vanillin (**54**) as an isopropyl ether gave compound **104** in good yield. Subsequently, compound **104** was homologated by Wittig reaction followed by acid hydrolysis employing the above-mentioned method of Treu and Jordis[6] to furnish the desired precursor **95** in 75% yield.

The presence of the compound was confirmed by ^{1}H NMR which displayed the expected signals including the aldehyde as a triplet (δ_H 9.23), the isopropyl ether signals [δ_H 4.04 (CH) and 0.98 (2xCH_3)], the α-CH_2 of the acetaldehyde (δ_H 3.05) and the methoxy signals (δ_H 3.45). In the ^{13}C NMR all the expected signals were accounted for, including the distinct carbonyl peak of an aldehyde (δ_C 199.4).



SCHEME 3.6

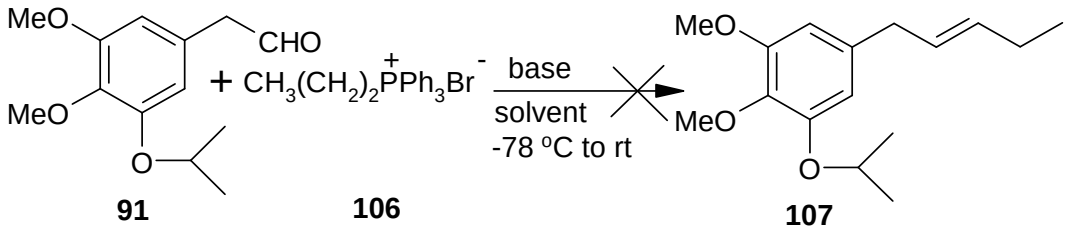
The synthesis of precursor **94** (see Scheme 3.2) was performed in a one-step reaction where the free hydroxy group of the readily available 3-bromopropanol was protected as the tetrahydropyranyl ether to obtain the desired compound **94** in 95% yield. The structure of **94** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

3.2.2 SELECTIVE *E*-OLEFINATION STRATEGIES

The next step was to develop a selective *E*-olefination reaction that could link two precursors in the construction of the target molecule. Different approaches followed towards the olefination reaction will be discussed in this section.

3.2.2.1 Wittig olefination

Initially, propyltriphenylphosphonium bromide (**106**) was used in a model reaction to develop reaction conditions for the Wittig reaction with precursor **91** (Scheme **3.7**). Though several attempts were made using different bases and reaction conditions, the desired olefination product was not obtained.

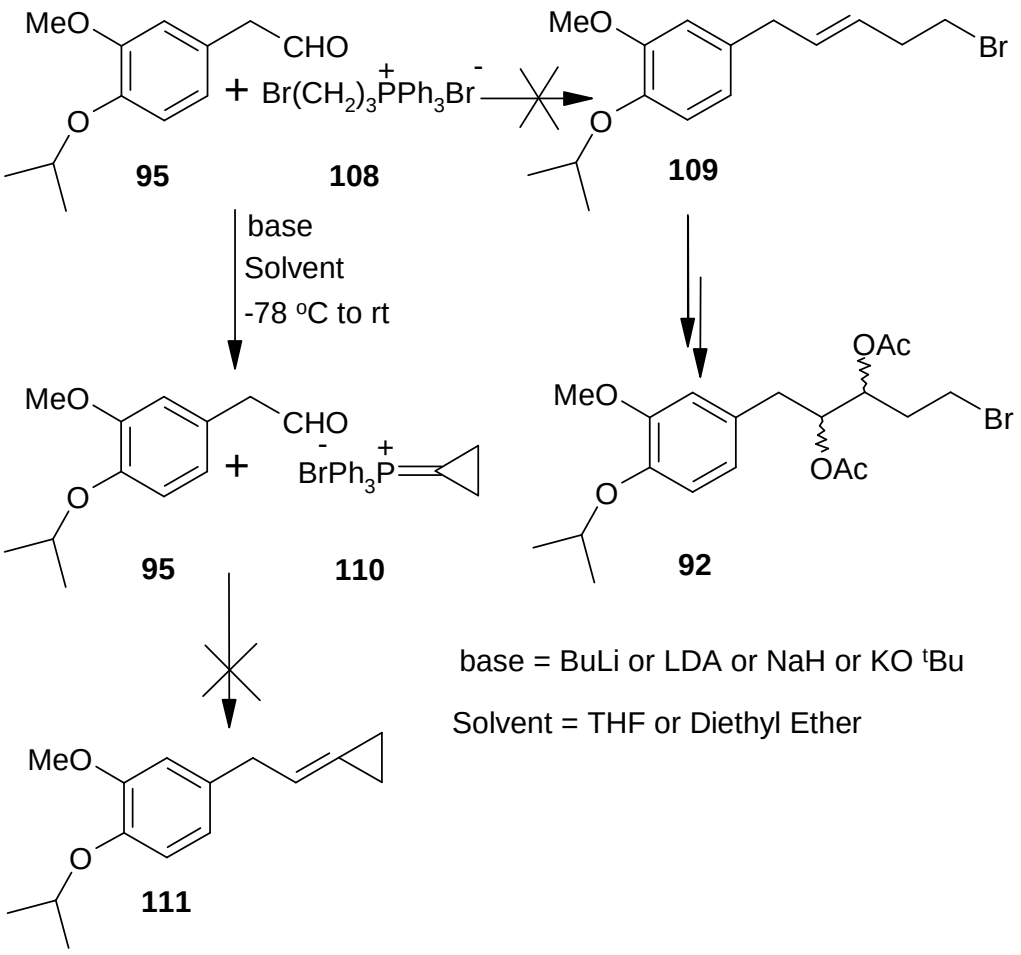


91 **106** **107**

base = NaH or KO^{t}Bu or BuLi or LDA
Solvent = THF or Ether

SCHEME 3.7

Another attempt to the Wittig reaction used the precursor **91** and the commercially available (3-bromopropyl)triphenylphosphonium bromide (**108**) with the intention to form compound **109** which, when subsequently subjected to further reactions, should furnish precursor **105** in a shorter way (Scheme 3.8). However, the desired alkene (**109**) was not obtained. Instead compound **108** underwent an intramolecular nucleophilic substitution reaction on successive treatment with two equivalents of base to furnish the cyclopropyltriphenylphosphonium salt (**110**) as described by Utimoto *et al.*[7] When compound **110** is subjected further to Wittig reaction conditions, it failed to furnish the desired olefination with precursor **91**.

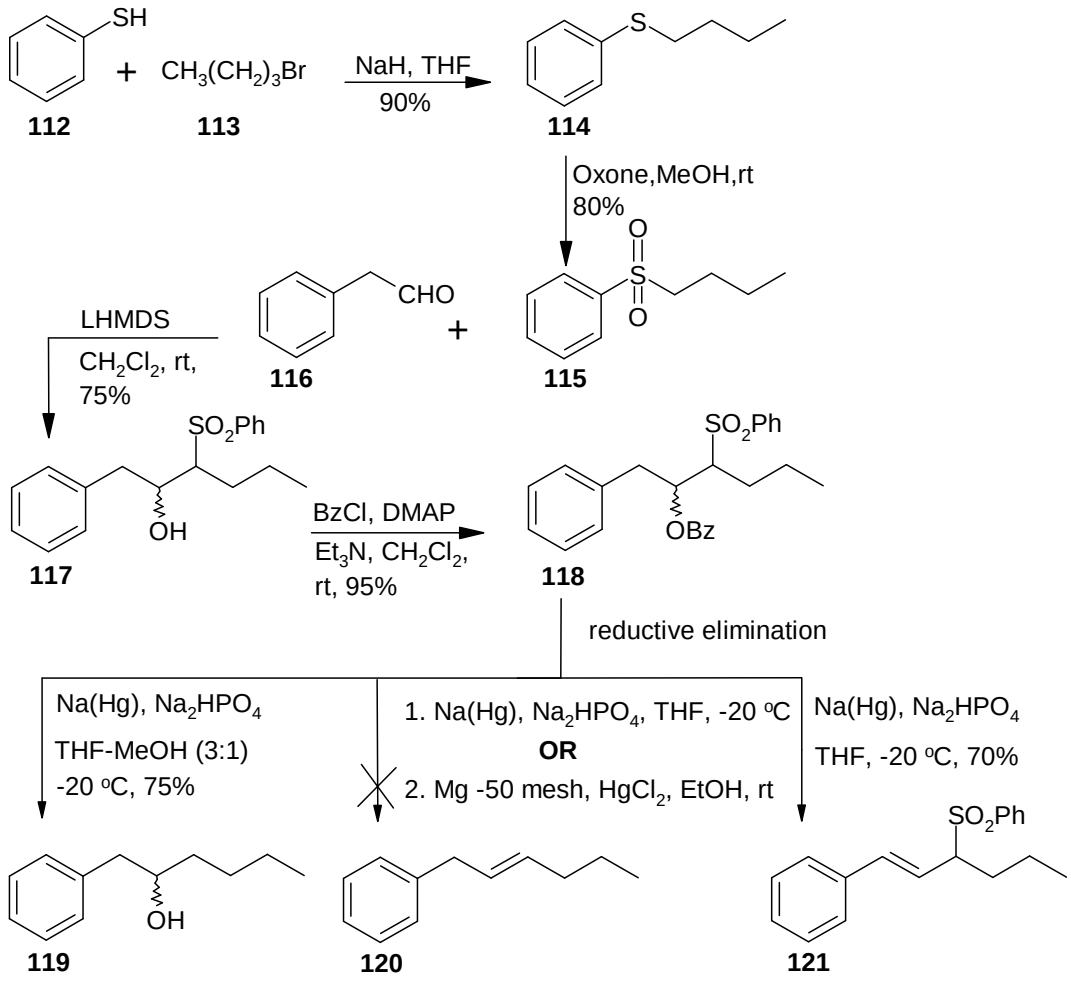


SCHEME 3.8

3.2.2.2 Julia olefination

It was therefore decided to carry out the preparation of the *trans*-alkene by Julia[8] olefination. A model reaction was utilised in an attempt to form an *E*-alkene by Julia olefination. This process began by the reaction between the sodium salt of benzenethiol (**112**) with butyl bromide (**113**) to form thioether **114** (Scheme 3.9). Subsequent oxidation of thioether **114** gave the sulfone **115** which was condensed with phenylacetaldehyde (**116**) in the presence of the base to furnish the diastereomers of β-hydroxy sulfones (**117**). Protection of the resultant hydroxy group with benzoyl chloride converted the mixture of alcohols into a mixture of β-benzoloxy sulfones (**118**).

The intended elimination reaction was performed on the mixture of β-benzoyloxy sulfones (**118**) using sodium amalgam but the reaction led to the formation of two undesired products (Scheme 3.9). Firstly, compound **119** was isolated when the reaction was performed using a solvent mixture of THF/MeOH (3:1) while compound **121** was isolated in 70% yield in the absence of methanol.



SCHEME 3.9

The presence of compound **119** shows the reductive cleavage of a sulfone functional group and hydrolysis of an ester functional group to yield the undesired alcohol. On the other hand, the formation of the undesired alkene **121** highlights the high reactivity of the benzylic protons. The structure of compound **119** was confirmed by the ^{1}H NMR spectrum which displayed the

proton signals of the CH with an attached hydroxy group as a doublet of triplet (δ_H 3.8), the expected aromatic protons signals and the aliphatic chain protons with the protons signals of the terminal CH_3 as triplet (δ_H 0.93). The ^{13}C NMR spectrum was in agreement with structure **119**. The distinctive carbon signal of a CH with an attached hydroxy group (δ_C 72.7), was present in the spectrum. Also, the structure of compound **121** was confirmed by ^{1}H NMR spectroscopy which reveals the presence of a *trans* double bond proton signals as doublet of doublet and a doublet [δ_H 5.88 (*J* = 15.6 and 9.6 Hz) and 6.24 (*J* = 15.6 Hz)]. The ^{13}C NMR spectrum of 121 was in agreement with the proposed structure.

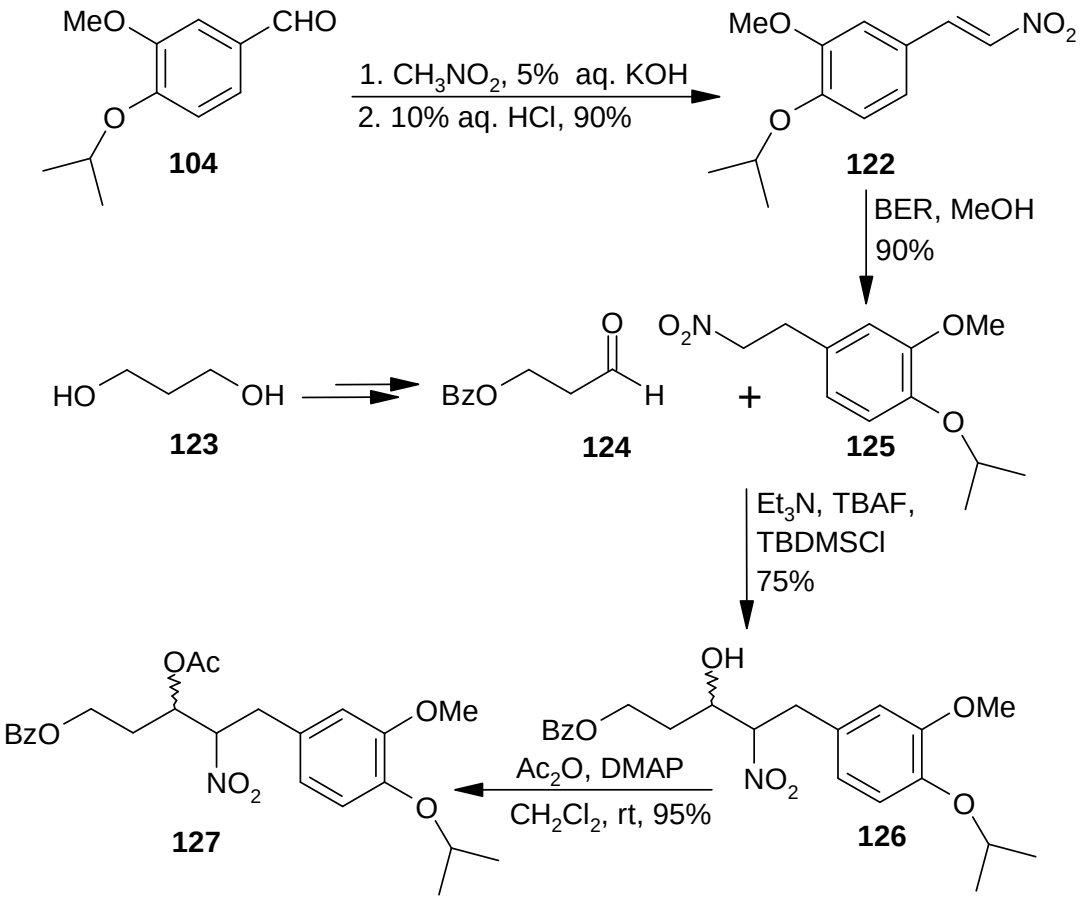
In another attempt to achieve this elimination, procedure described by Lee *et al*.[9] was followed whereby the substrate was treated with magnesium in ethanol. However, only starting material was recovered in this reaction.

3.2.2.3 β-Nitro xanthates as olefin precursors

Upon failing to perform elimination in the Julia reaction, other types of elimination procedures were investigated including radical elimination of nitrogen dioxide to form olefins. This approach reported by Zard[10] required β-nitro xanthates, which undergo elimination to give the corresponding olefins in good *E*-selectivity in the presence of a source of reactive radicals. The process begins with addition of potassium *O*-ethyl xanthate to α,β-unsaturated nitro compounds to give stable β-nitro xanthates which upon heating with lauroyl peroxide as source of reactive radical give the *trans*-alkene in good selectivity.[10] In order to ascertain the feasibility of this approach, compound **104** was transformed to the α,β-unsaturated nitro compound **122** by treatment with nitromethane and 5% KOH (Scheme 3.10).[11] Reduction of the α,β-unsaturated nitro compound **122** with borohydride exchange resin (BER) afforded the saturated nitro derivative **125** in 90% yield.[12,13]

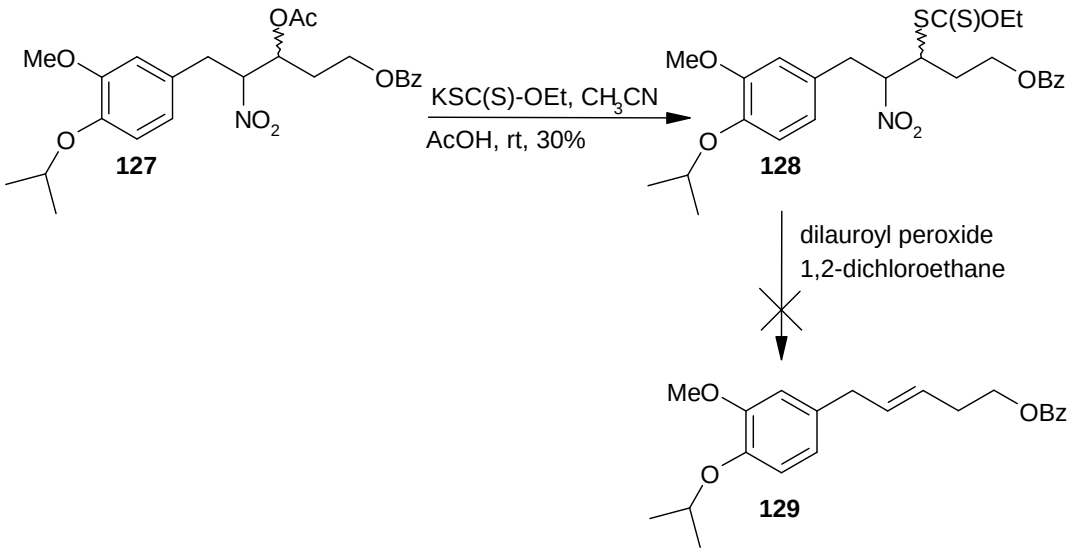
Addition of the nitro compound **125** to the aliphatic aldehyde **124** gave the β-hydroxy nitro compound **126** in good yield. 3-Benzoyloxypropanal (**124**) was obtained by selective protection of 1,3-propanediol followed by oxidation of the

free hydroxy group with Dess-Martin reagent. Acetylation of compound **126** yielded compound **127** in 95% yield.[14]



SCHEME 3.10

The next step was to prepare the β-nitro xanthate **128** from the acetylated adduct **127**. This compound was obtained in a very poor yield of about 30% as a mixture of diastereomers that were also observed by Zard.[10] Upon subjecting the β-nitro xanthate **128** to radical elimination using lauroyl peroxide as a reactive radical in refluxing 1,2-dichloroethane, no desired olefination was observed. The structure of the β-nitro xanthate **128** was confirmed by ^{1}H NMR and ^{13}C NMR with all the expected signals present. From the reactions described above, it is clear that the approach to a diarylheptanoid described in Scheme 3.2, is not feasible due to the extreme reactivity of the benzylic hydrogens and that other synthetic routes needed to be considered.



SCHEME 3.10 (continued)

3.3 THE ALTERNATIVE ROUTE TO THE CONNECTION OF PRECURSORS

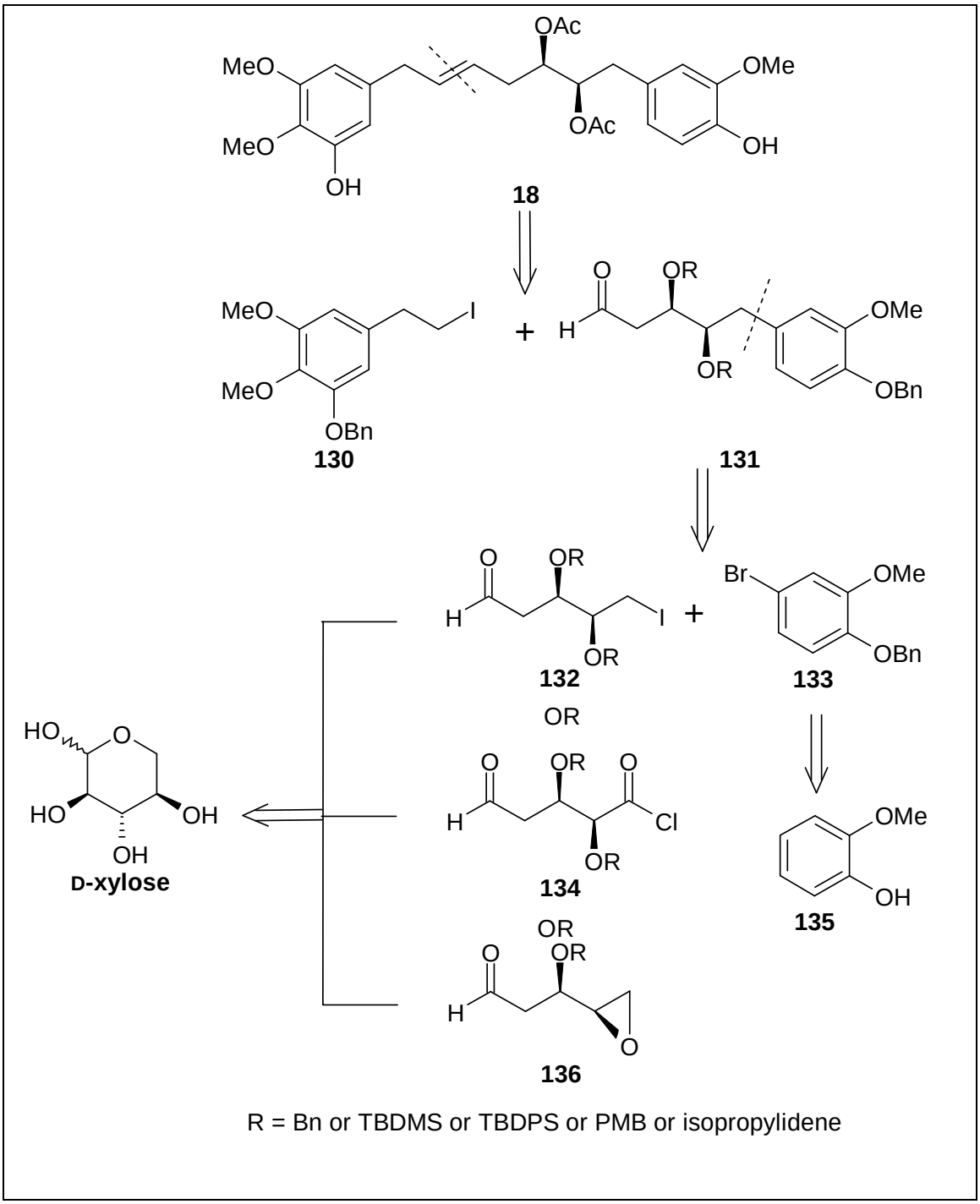
Upon failing to use the previous strategy as a way to link the fragments of the target molecule, another way of connecting the precursors was devised. In this strategy, the aldehyde functional group was positioned on the aliphatic chain as to avoid the highly reactive aryl-acetaldehyde bearing an α-carbon which may undergo self condensation. With this in mind, a strategy was developed to use carbohydrates as chiral starting materials. Carbohydrates are naturally-occurring organic compounds with readily available aldehyde functional group and gifted with a wealth of stereodefined attributes. Their advantage is that they are available in a variety of cyclic and acyclic forms, in a variety of chain length and lastly some of them are relatively cheap. The only disadvantage with them is that some are easily decomposed at certain elevated temperatures and need to be handled with care. Besides that, one can be able to modify their chains either by chain elongation or cleavage and to create or destroy asymmetric centres.

3.3.1 Retrosynthetic Analysis

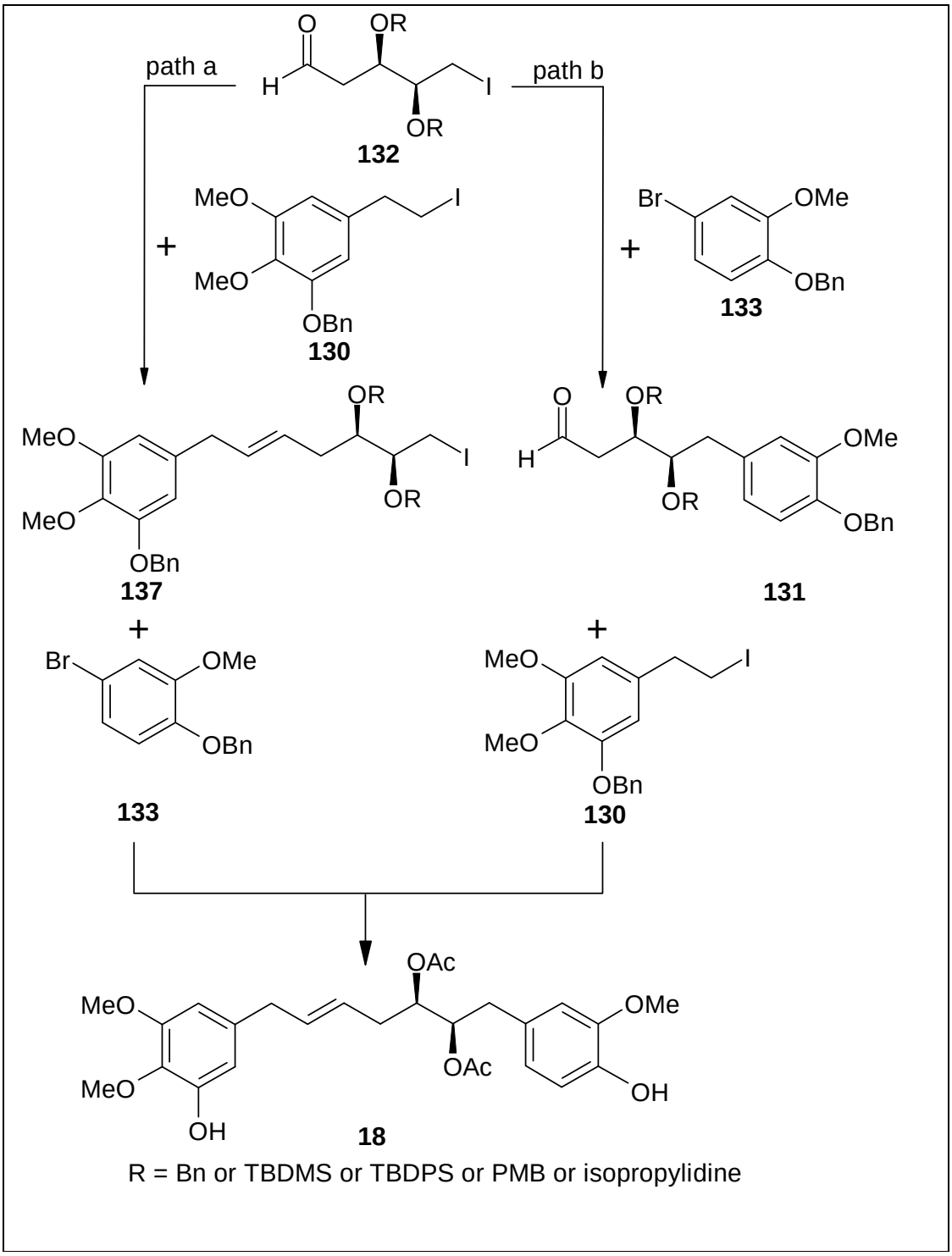
The alternative retrosynthetic analysis of the target molecule is based on two highly oxygenated aromatic rings that are linked to a 2-deoxypentose as the readily available aliphatic aldehyde (Scheme 3.11). The process will use the modified selective *E*-olefination methods to introduce the desired *trans*-alkene that will serve as the connection to the other side of the highly oxygenated aromatic ring. The modified olefination methods include an improved Julia olefination, an improved Wittig reaction and organometallic-mediated olefination reactions. Various C-C bond formation methods will be investigated in order to couple the other aromatic ring to the aliphatic chain. These various C-C coupling reactions are Friedel-Crafts acylation or alkylation, Grignard reaction and organometallic-mediated alkylation reactions.

In order to synthesise enantiomerically pure vicinal diols, the 2-deoxypentose was a key principle of the synthetic plan with an easy access to *erythro* and *threo* diols. The 2-deoxypentose was intended to serve not only as a chiral starting material but also as a locus for attaching the highly oxygenated aromatic rings. The 2-deoxypentose was prepared from D-xylose while D-arabinose and the readily available 2-deoxy-D-ribose were also investigated to elaborate the synthesis of other enantiomers.

The synthesis was planned as outlined in Scheme 3.12. Two pathways were investigated for the assembly of the precursors where path (a) begins the construction of the molecule with a selective *E*-olefination reaction while path (b) start with C-C bond alkylation reaction.


OAc
MeO
OMe
MeO
OAc
OH
OH
18
MeO
I
MeO
OBn
130
+
O
OR
H
OR
OMe
OBn
131
O
OR
H
I
OR
132
+
Br
OMe
OBn
133
HO
O
HO
OH
OH
D-xylose
OR
O
OR
O
H
Cl
OR
134
OMe
OH
135
OR
O
OR
H
O
136
R = Bn or TBDMS or TBDPS or PMB or isopropylidene

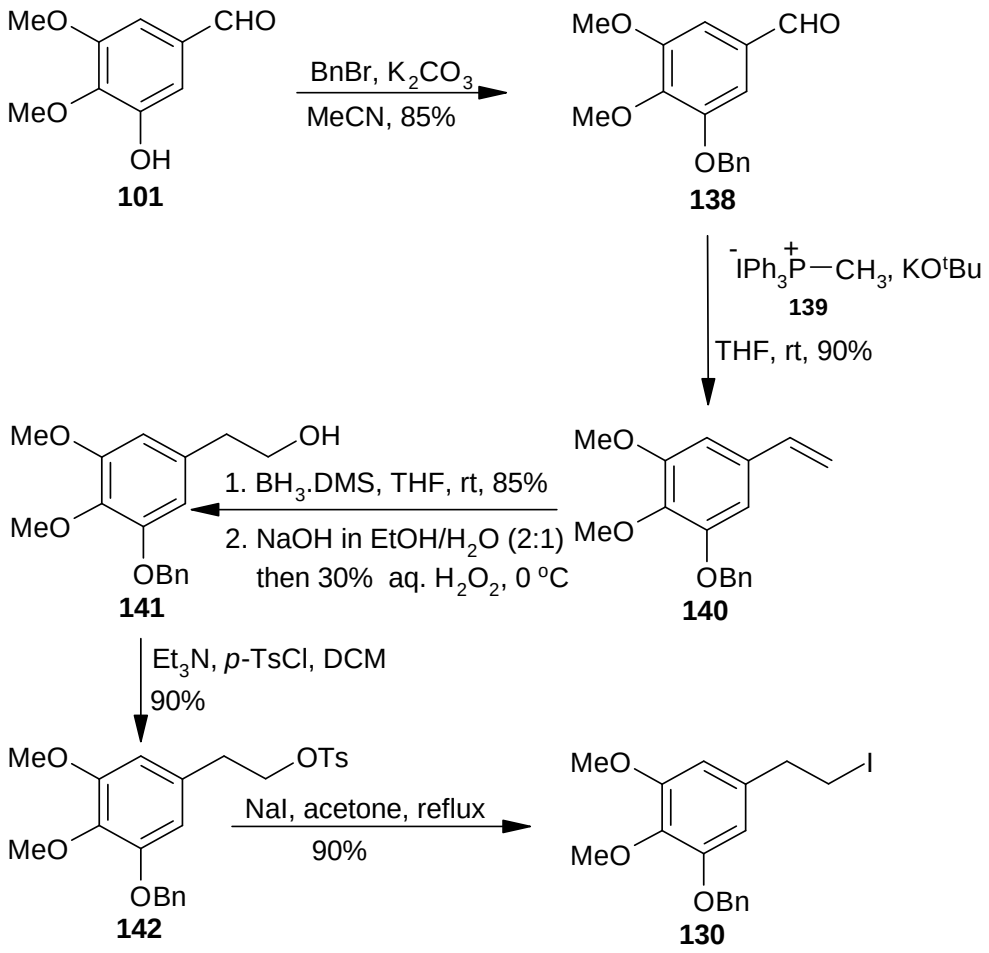
SCHEME 3.11


path a
path b
132
130
133
137
131
133
130
18
R = Bn or TBDMS or TBDPS or PMB or isopropylidine

SCHEME 3.12

3.3.2 Synthesis of precursors

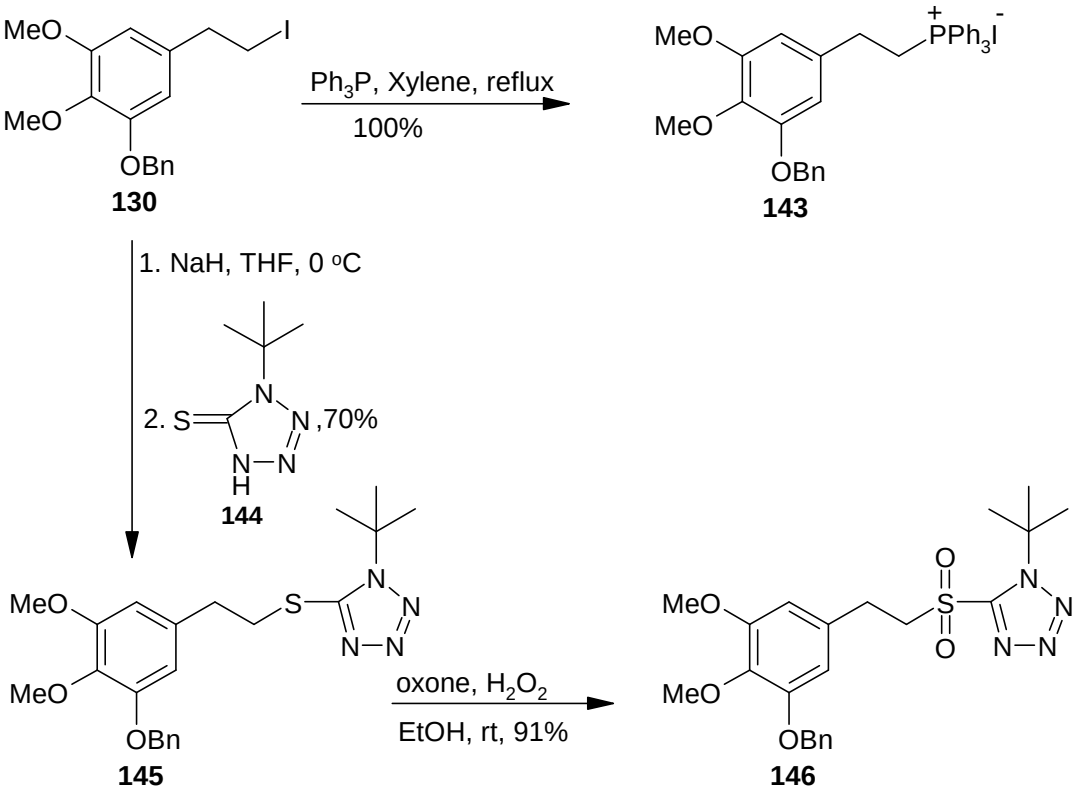
Synthesis of **130**, a coupling partner for chiral aliphatic aldehyde **132**, was prepared from **101** using a methodology developed by Fernandes *et al.*[15] The first step was the protection of the free hydroxy group of compound **101** as a benzyl ether to form **138** in 85% yield (Scheme 3.13). The subsequent Wittig olefination furnished compound **140** in 90% yield, which upon hydroboration/oxidation, afforded the alcohol **141** in quantitative yield. The primary hydroxy group of compound **141** was converted into the tosylate **142**, which underwent nucleophilic displacement with sodium iodide in refluxing acetone to obtain precursor **130** in quantitative yield.



SCHEME 3.13

The structure of compound **130** was confirmed by the ^{1}H NMR spectrum which reveals a $C\underline{H}_2$ signal shifted to a higher field by 0.89 ppm as compared to that of tosylate compound **142**, indicating replacement of the tosylate group. In the ^{13}C NMR spectrum all the expected signals were observed and the molecular formula of the compound was confirmed by MS.

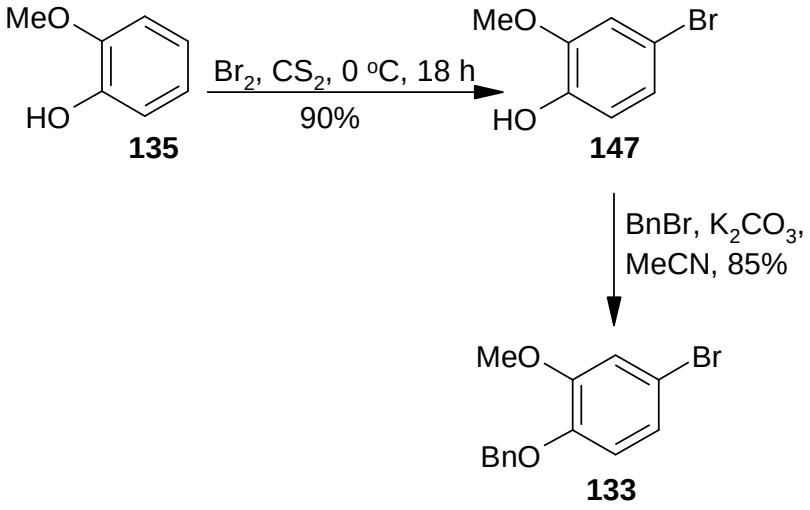
The next step was to convert **130** into useful coupling adducts, namely, Wittig reagent[16] **143** and Julia olefination adduct[17,18,19] **146** (Scheme 3.14). Firstly, compound **130** was converted into the essential Wittig reagent **143** that may undergo selective *E*-olefination as one of the fragment linkage methodologies. Compound **130** was reacted with excess triphenylphosphine in refluxing xylene to form the desired Wittig reagent **143** in almost 100% yield (Scheme 3.14). The presence of a phosphonium salt was confirmed by the high melting point. The solubility in different solvents also indicated that the precipitate consisted of the phosphonium salt.



SCHEME 3.14

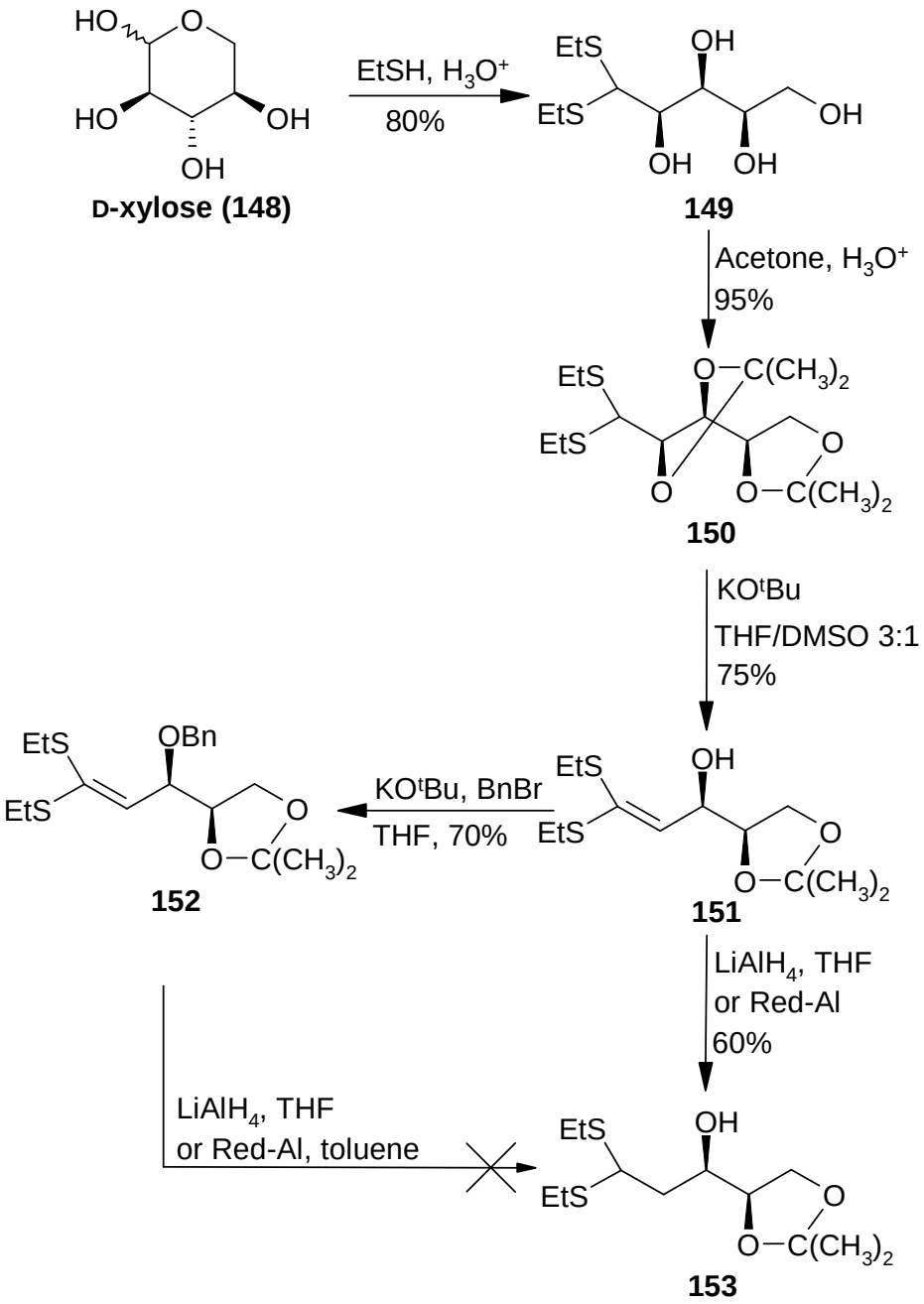
The Julia olefination adduct was also prepared from precursor **130** in a two-step reaction as illustrated in Scheme 3.14. The process begins with nucleophilic substitution of compound **130** with **144** to furnish the desired thioether **145** in a good yield which upon subsequent oxidation with oxone ($2KHSO_5.KHSO_4.K_2SO_4$) gave the desired Julia olefination adduct **146** in 91% yield. The presence of the compound was confirmed by the ^1H NMR spectrum which reveals a $C\underline{H}_2$ signal shift to a lower field by 0.29 ppm as compared to that of thioether **145** indicating oxidation of the thiol group. The ^{13}C NMR spectrum was in agreement with the proposed structure and the molecular formula of the compound was confirmed by high-resolution mass spectrometry.

Synthesis of precursor **133** was accomplished in a two-step reaction where the commercially available guaiacol (**135**) was subjected to selective bromination at the position *para* to the free hydroxy group to obtain the bromo guaiacol **147** in 90% yield (Scheme 3.15).[20] The position of the bromo substituent was confirmed by performing a NOE experiment. The results showed a clear NOE effect between the methoxy protons and the aromatic proton with a meta-coupling only, thereby confirming the position of the bromine. Compound **135** was further protected as a benzyl ether to obtain the desired precursor **133** in 95% yield.



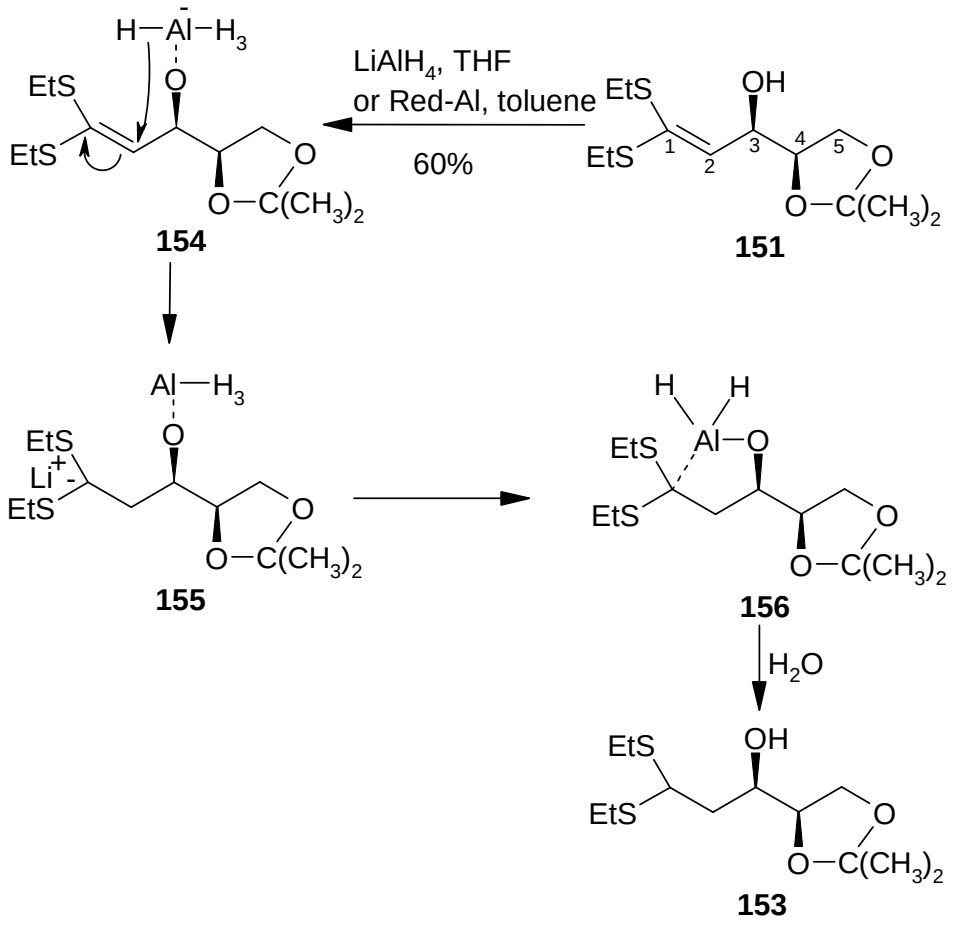
SCHEME 3.15

The chiral aldehyde **132** required for olefination reactions with the Wittig reagent **143** or Julia olefination adduct **146** was prepared from D-xylose (**148**) as outlined in Scheme 3.16. Thus, using literature precedent,[21,22,23] D-xylose (**148**) was first converted into known dithioacetal **149**, which was protected as the bis-acetonide **150** in 80% yield and 95% yield, respectively.



SCHEME 3.16

Base-promoted elimination led to dithioketene acetal **151** in 75% yield (Scheme 3.16). The free hydroxy group of dithioketene acetal **151** directed a hydride reduction to give the 2-deoxysugar derivative (**153**) in 60% yield. To determine whether the free C-3 hydroxy group of dithioketene acetal **151** is required for reduction of the compound, the 3-*O*-benzyl ether of the dithioketene acetal **151** was prepared to give compound **152**. Attempted reduction of this derivative **152** with lithium aluminium hydride failed. A simple mechanism of this $LiAlH_4$ reduction is outline in Scheme 3.17.

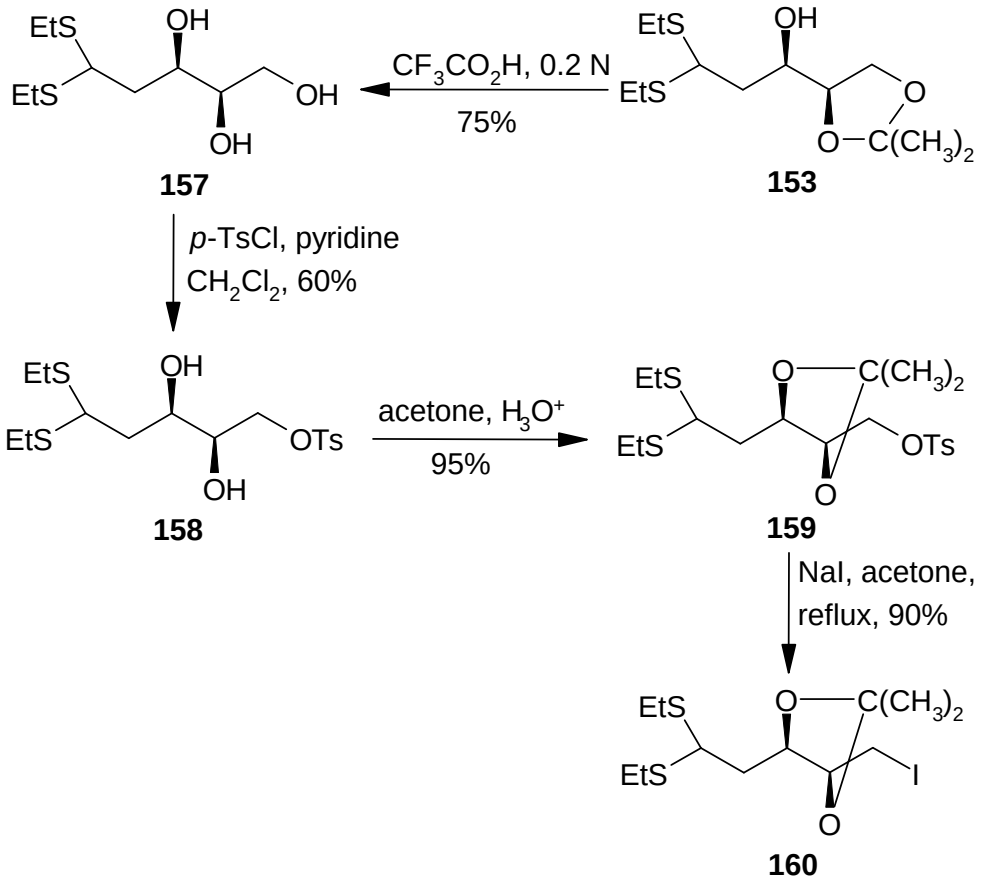


SCHEME 3.17

These results demonstrated that reduction proceeds *via* hydride transfer at C-2, with water serving as the proton donor at C-1.[24]

Because of the obligatory requirement for the free C-3 hydroxy group, the reaction is envisaged to proceed *via* directed hydride transfer through the alkoxyaluminium hydride salt **154** to yield the stabilised carbanion **155** or the cyclic alkoxy aluminium salt **156**. Hydrolysis of the latter salt during work-up would then result in the observed incorporation of the solvent hydrogen to obtain compound **153** in 60% yield.

The next step was the mild aqueous acid hydrolysis of 2-deoxysugar derivative **153** to yield the 2-deoxy-D-*threo*-pentose diethyl dithioacetal (**157**) in almost 75% yield (Scheme 3.18). The high solubility of compound **157** in water led to difficulties in extraction of the compound. Therefore, the water was removed by the additional of ethanol and the resulting azeotrope was removed under vacuum. This was to eliminate removal of water at elevated temperatures as this may lead to decomposition of the desired compound.

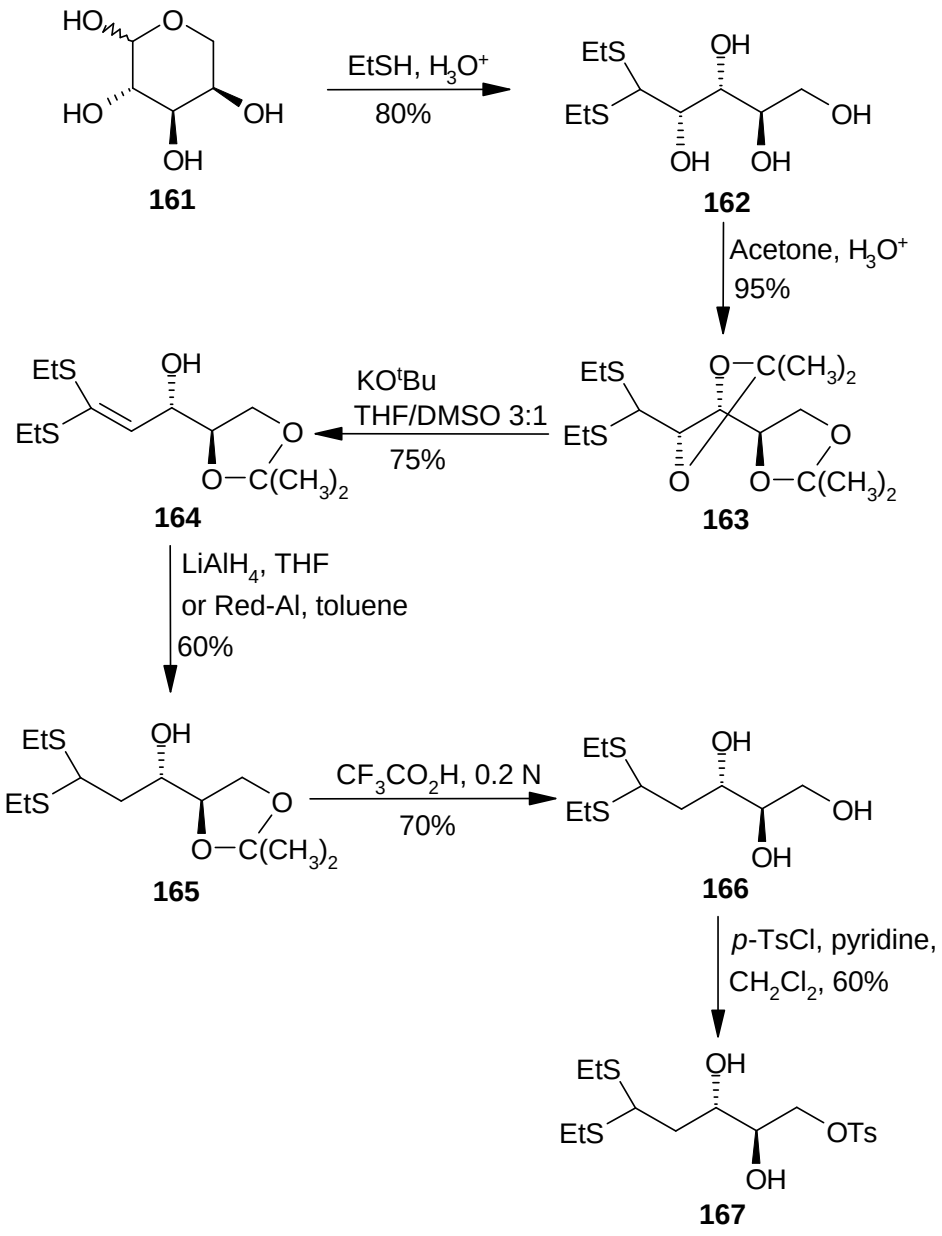


SCHEME 3.18

The primary hydroxy group of compound **157** was converted into the tosylate **158** in 60% isolated yield. Subsequent protection of **158** as the acetonide gave compound **159** which underwent nucleophilic displacement with sodium iodide in refluxing acetone to form **160** in 90% yield. The next step was to perform hydrolysis of the diethyl dithioacetal in order to obtain the desired aldehyde **132**. However, this step was postponed as it was planned to link the first two fragments through path b (Scheme 3.12) and the presence of an unprotected aldehyde would pose difficulties. The structures of all prepared sugar compounds were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy, and where required COSY, HSQC, HMBC and DEPT spectroscopy were employed to determine the position of substituents. Confirmation of the molecular formulae of these compounds was done on high-resolution MS.

The synthesis of 2-deoxy-D-*erythro*-pentose diethyl dithioacetal **157** was also investigated to give access to other enantiomers. The process used D-arabinose as the starting material[23,24,25] (**161**), which was converted to bis-acetonide **163** in 80% yield (Scheme 3.19). Treatment of the latter with potassium *tert*-butoxide followed by reduction of the intermediate ketene diethyl dithioacetal with $LiAlH_4$ or Red-Al as before, gave 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose (**165**) in 60% yield. Hydrolysis of the acetonide protecting group under similar conditions described above for the *threo* isomer gave the 2-deoxy-D-*erythro*-pentose (**166**) in 70% yield. The primary hydroxy group of compound **166** was converted into the tosylate **167** in 60% yield. The next two steps towards the synthesis of the required chiral aldehyde were suspended until the coupling conditions of the *threo* isomer were met.

In the preparation of the *threo* isomer **167** (Scheme 3.19), the structures of all prepared carbohydrate derivatives were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy, and where required COSY, HSQC, HMBC and DEPT spectroscopy were employed to determine the position of substituents. Confirmation of the molecular formulae of these compounds was obtained from high-resolution MS.

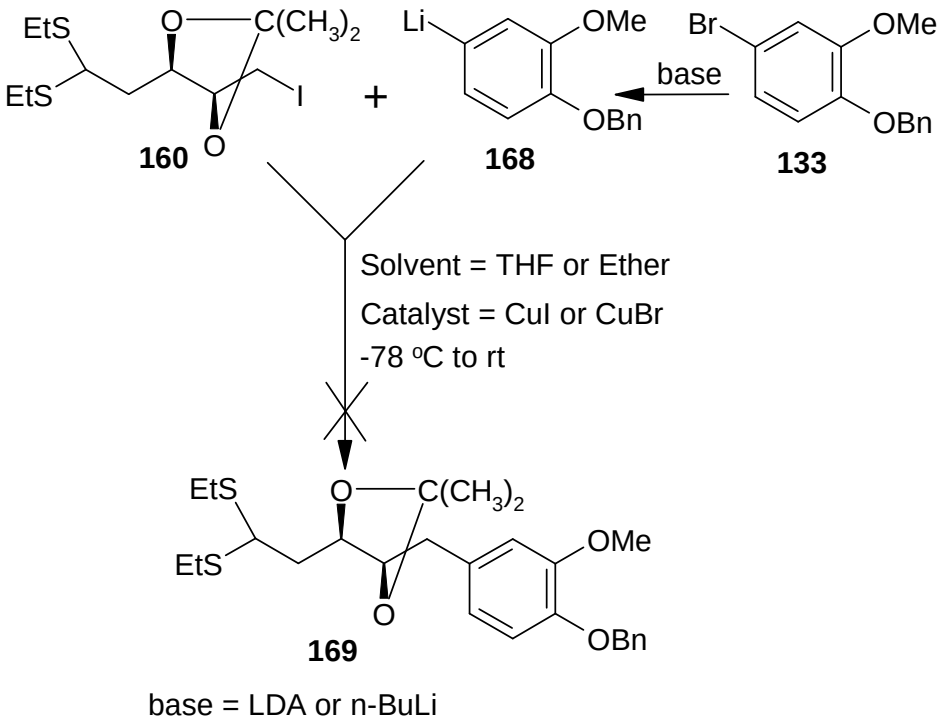


SCHEME 3.19

3.3.3 The assembly of precursors through path (b) (Scheme 3.12)

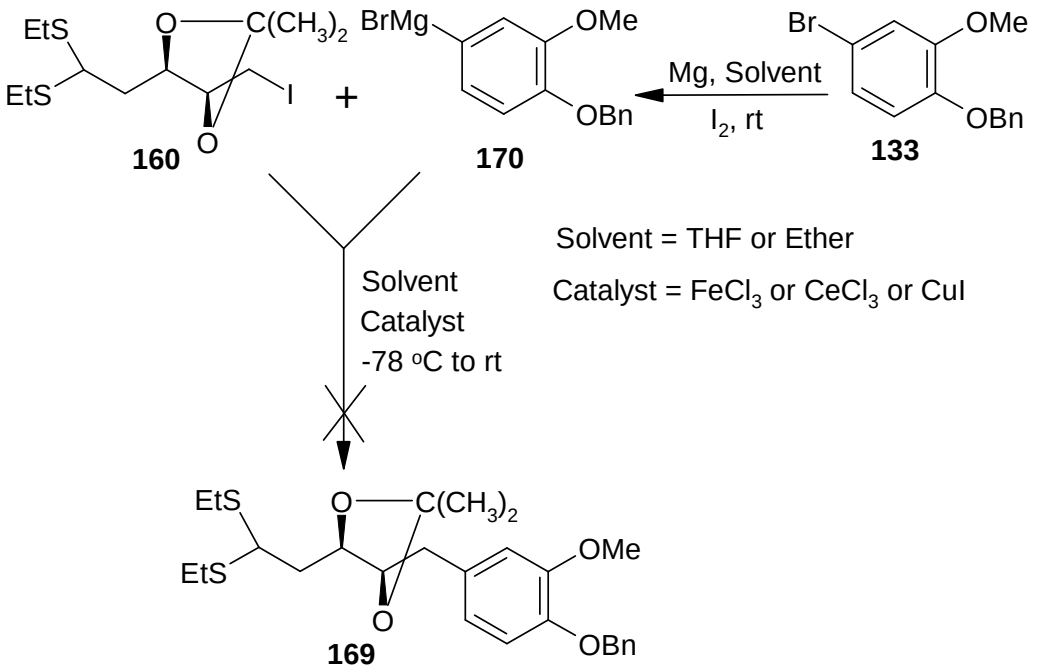
Various organometallic C-C bond forming reactions were investigated in an attempt to assemble the two precursors **133** and **160**. The first attempt was the reaction between the organolithium adduct **168**, prepared from compound **133**, and compound **160** (Scheme 3.20).

Several reaction conditions were investigated, which include different lithiating agents (n-BuLi, LDA, and Li metal), different solvents (THF and diethyl ether), different activating catalysts (CuI and CuBr) and lastly different temperatures (from -78 ^{o}C to room temperature) but the desired coupling was not accomplished.



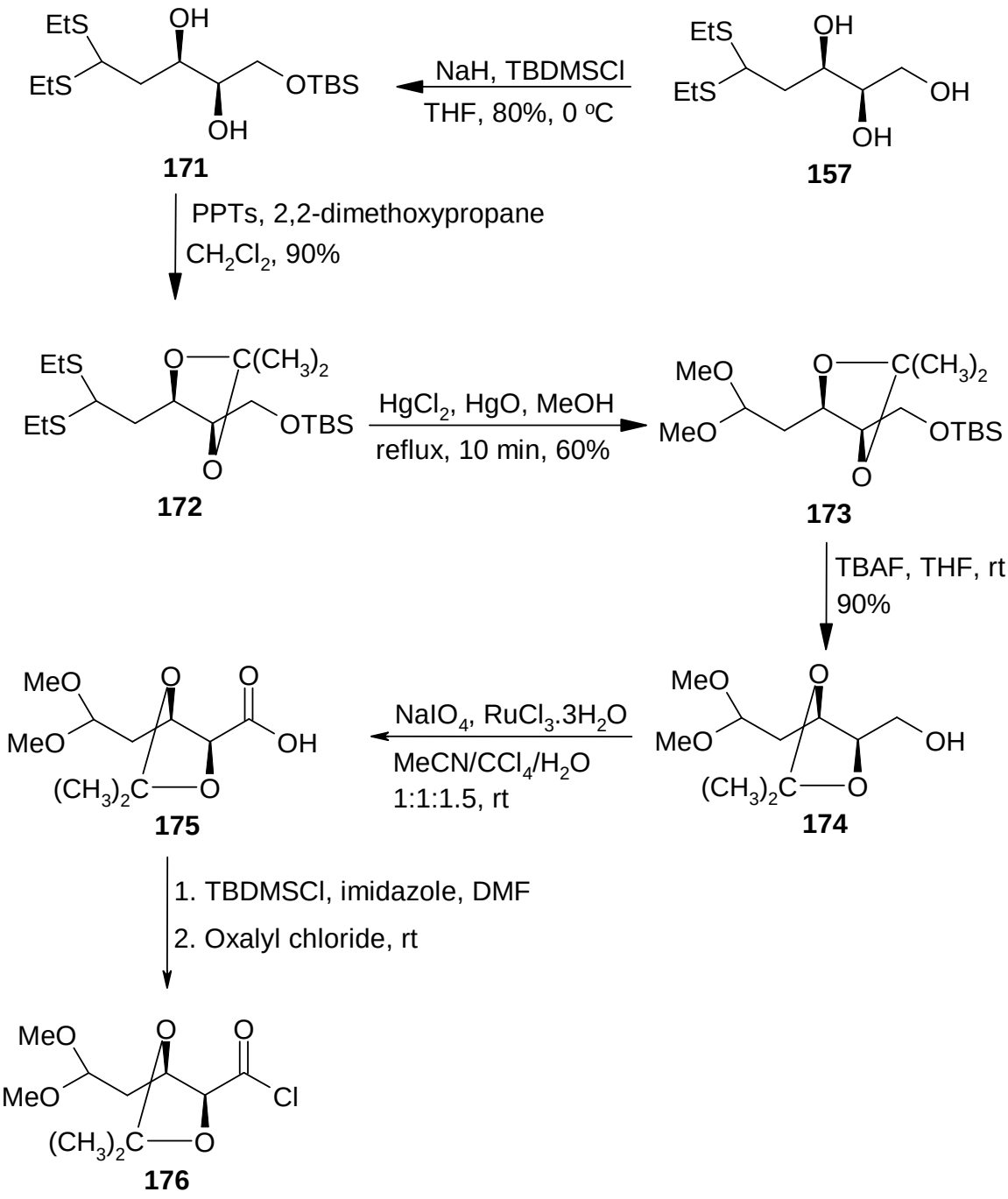
SCHEME 3.20

Another investigation involved the use of Grignard reagent **170** which was also prepared from **133** (Scheme 3.21). Similar reaction conditions were also investigated which include different solvents (THF and diethyl ether), different activating catalysts ($FeCl_3$, $CeCl_3$ and CuI) and lastly different temperatures (from -78 ^{o}C to room temperature and elevated temperature) but once again the desired product was not obtained. The failure of the coupling reactions can be attributed to the electron-rich aromatic compound. It is known that halogen-metal exchange can be slow for electron-rich aromatic substrates. Therefore, another useful way of connecting the two precursors was devised.



SCHEME 3.21

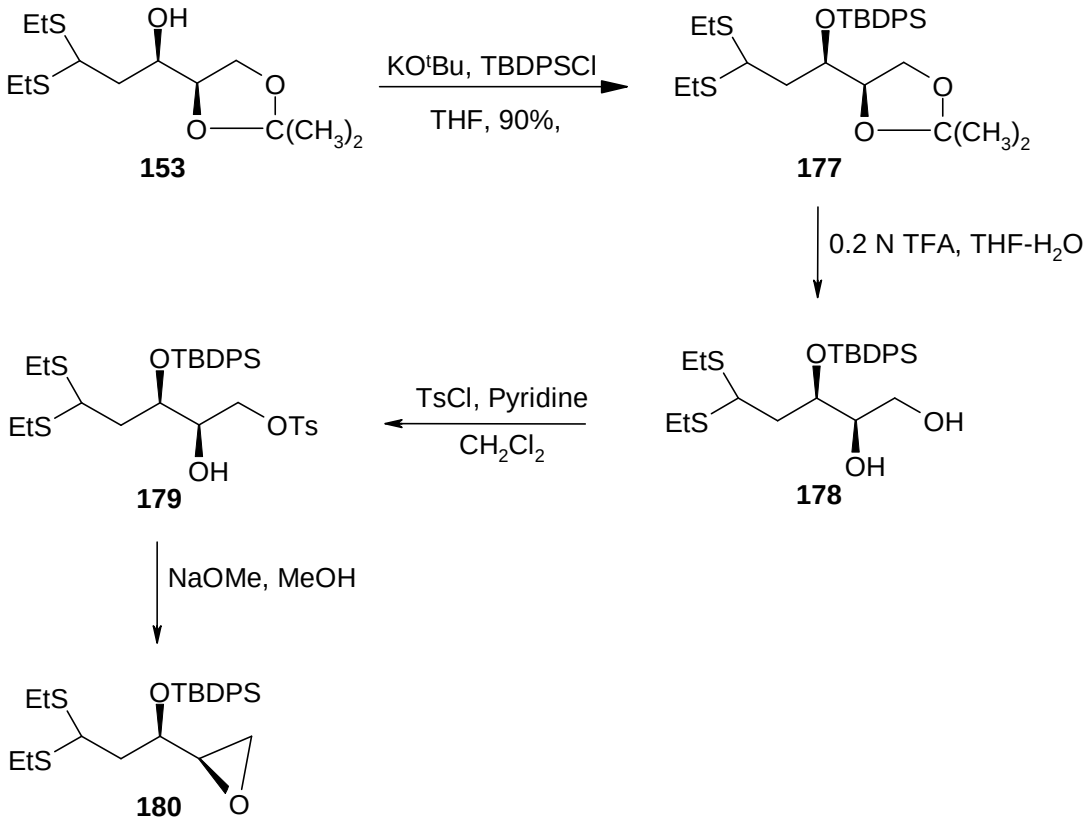
Transforming one terminal part of sugar moiety **160** into an acyl chloride which should be highly reactive under Friedel-Crafts acylating conditions could be a solution. The process began with 2-deoxy-D-*threo*-pentose diethyl dithioacetal (**157**), which upon selective protection of the primary alcohol gave the silylated compound **171** in 80% yield (Scheme 3.22). Subsequent protection of the diol as the acetonide gave compound **172** in good yield which upon conversion of its diethyl dithioacetal to dimethyl acetal furnish compound **173** also in reasonable yield. Removal of the silyl protecting group afforded compound **174** in 90% yield. The reaction worked well on small scale, but on larger scale (gram quantities), a much reduced yield was obtained. The next step planned was an oxidation of the primary alcohol to an acid, which could be transformed to the acyl chloride, but, due to limited amount of product **174**, those two steps were postponed until a model reaction has been evaluated.



SCHEME 3.22

The structures of all prepared sugar compounds were based on ^{1}H NMR and ^{13}C NMR spectroscopy. The molecular formulae of these compounds were confirmed by high-resolution MS.

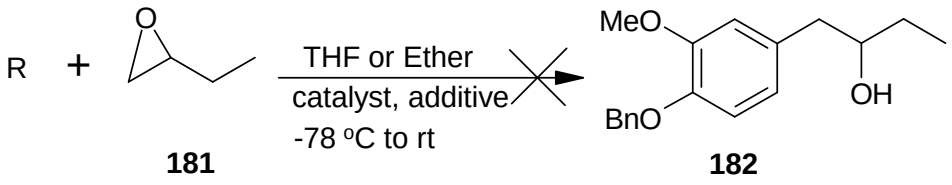
The problems encountered with the synthesis of the acylated terminal part of the carbohydrate, other alternative ways of transforming the terminal carbon into a reactive electrophile needed to be investigated. An reactive epoxide was considered as a viable precursor. The synthesis was planned is outlined in Scheme 3.23 where 2-deoxy-4,5-*O*-isopropylidene-D-threo-pentose diethyl dithio acetal (**153**) was utilised as starting material. The process began with the protection of compound **153** as its *tert*-butyl diphenylsilyl ether (**177**) in 90% yield. The identity of the compound was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy which reveals all the expected signals and the molecular formula of the compound was confirmed by MS.



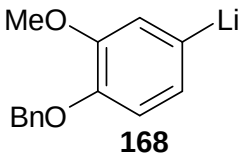
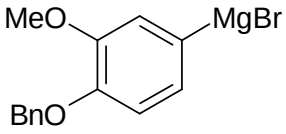
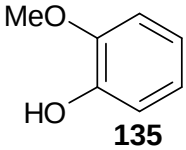
SCHEME 3.23

It was planned to perform mild hydrolysis of the acetonide group to yield compound **178** that could be subjected to a selective primary tosylation reaction. Treatment of the tosylated compound **179** with a base under methanolic solution should give the desired epoxide (**180**) (Scheme 3.23).

A model reaction was performed to study the reaction conditions for the ring-opening of epoxides, particularly with carbon-based nucleophiles (Scheme 3.24).[26,27,28,29]



181 **182**

Entry	R	catalyst	additive
1.	 **168**	$BCl_3.Et_2O$ $CeCl_3$	none none
2.	 **170**	$FeCl_3$ $CeCl_3$	N,N,N',N'-tetramethylene-diamine none
3.	 **135**	$AlCl_3$ $SnCl_4$	none CH_3NO_2

SCHEME 3.24

Lewis acid-catalysed epoxide ring-opening as well as the ferric chloride and cerium chloride-catalysed Grignard epoxide ring opening were investigated. Though the epoxides are known to be highly reactive to nucleophilic attack, in this reaction they reacted sluggishly and no efficient addition took place. The results of the model reaction are illustrated in Scheme 3.24.

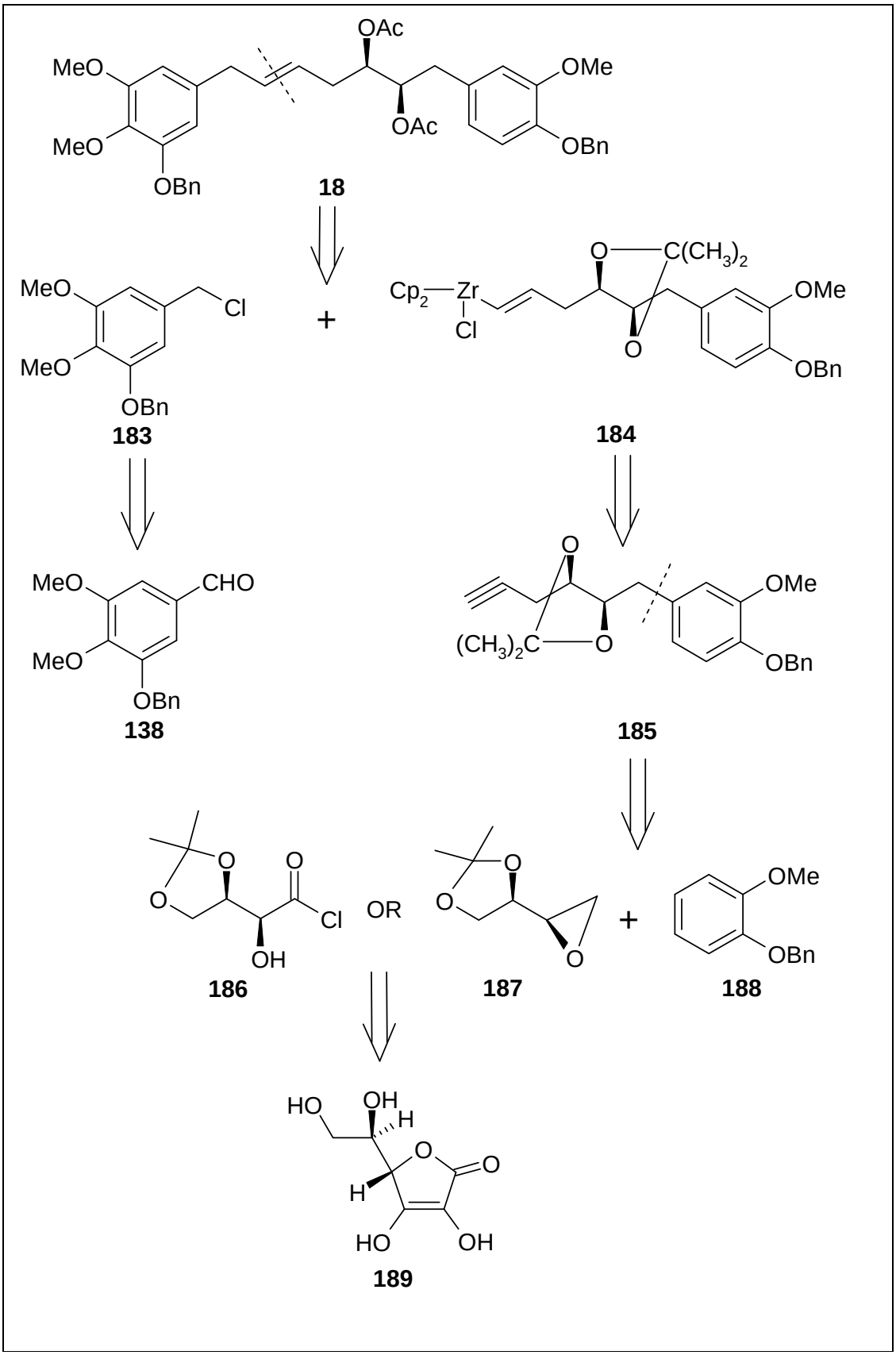
The assembling of the precursors through path (b) relied on having a reactive electrophile that could react with the aryl nucleophile. The failure to obtain

reactive electrophile led us to develop a practical route for large scale synthesis of these reactive electrophiles.

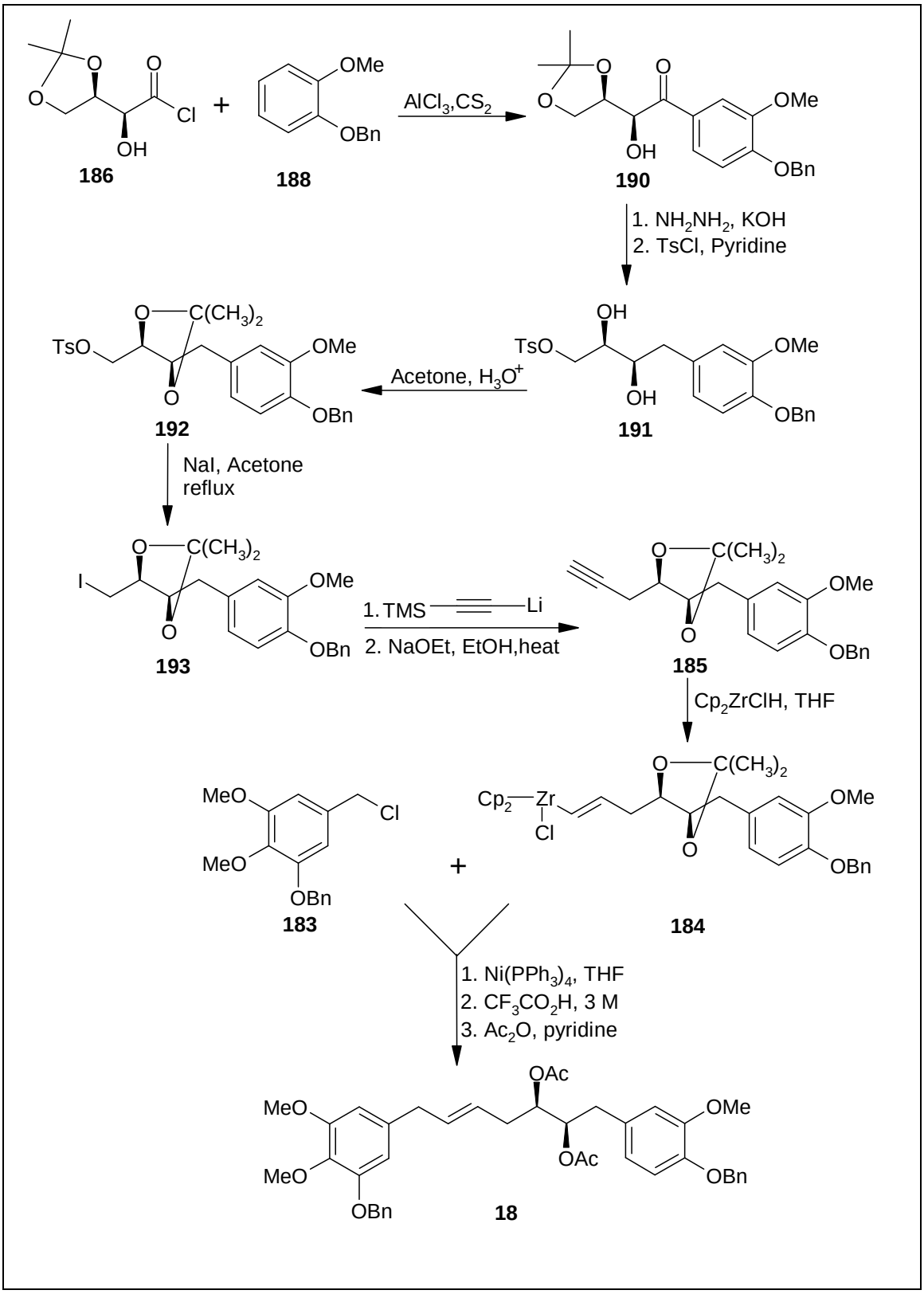
A great deal of effort had been devoted to the use of D-ascorbic acid as an alternative to the naturally occurring carbohydrate starting material. Looking at the synthetic strategies disclosed by Cho *et al*.[30] and Dahlgren *et al.*[31] it was considered that D-ascorbic acid (**189**) could be transformed into the reactive electrophiles **186** and **187** that were needed. With this in mind another retrosynthetic pathway was devised (Scheme 3.25), in which organometallic-mediated olefination reaction and alkylation reaction were the key steps.

Lipshutz *et al*.[32] devised a strategy of generating aromatics bearing a disubstituted allylic moiety with *E*-geometry by using the reaction between hydrozirconated terminal alkynes with benzylic chlorides at room temperature in the presence of catalytic amount of Ni(0). This method could be used to couple the benzylic chloride as it has been proven to be equally successful for both electron-rich and electron-poor benzylic chlorides.

Based on the retrosynthetic pathway (Scheme 3.25), the synthesis was planned as illustrated in Scheme 3.26 following a strategy of Lipshutz.[32] Firstly, it was planned to couple compound **186** and **188** by Friedel-Crafts acylation to yield compound **190**. Subjecting compound **190** to Wolff-Kishner reduction followed by selective protection of the hydroxy groups should provide compound **192**.


OAc
MeO
OMe
MeO
OAc
OBn
OBn
18
MeO
Cl
MeO
OBn
183
+
O
C(CH3)2
Cp2
Zr
Cl
O
OMe
OBn
184
MeO
CHO
MeO
OBn
138
O
OMe
(CH3)2C
O
OBn
185
O
O
O
Cl
OH
186
OR
O
O
O
187
+
OMe
OBn
188
HO
OH
H
O
O
H
HO
OH
189

SCHEME 3.25



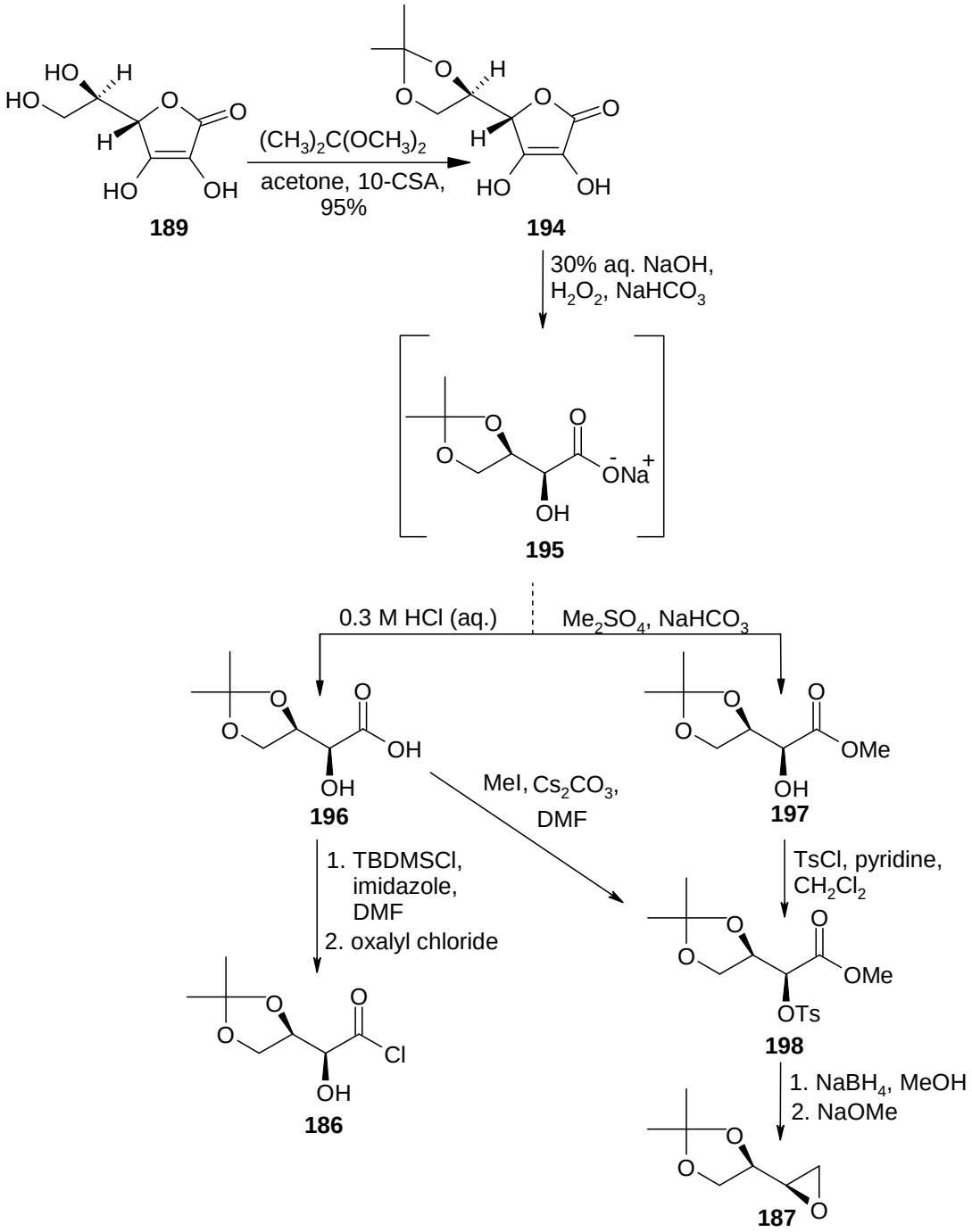
186 **188** **190** **192** **191** **193** **185** **183** **184** **18**

SCHEME 3.26

Substitution of the tosylate in **192** with iodide will form compound **193,** which can be extended further with two carbons by nucleophilic substitution with trimethylsilylethynyllithium followed by removal of the silyl group under basic conditions to yield the terminal alkyne **185**. The resulting alkyne **185** was to be treated with zirconocene chloride hydride in THF under argon atmosphere to form vinyl hydrozirconocene **184**. It was therefore intended to couple the vinyl hydrozirconocene **184** with benzylic chloride **183** using nickel as a catalyst in order to obtain the desired target molecule **18** after acetylation reaction.

Synthetic procedures[30,31] were followed for the synthesis of compound **186** as outlined in Scheme 3.27. D-Ascorbic acid was converted to its acetonide **194** in 95% yield. Oxidation of the latter with hydrogen peroxide produced threonic acid sodium salt (**195**) which was then transformed to methyl ester **197** with dimethyl sulfate and sodium bicarbonate in water. Methylation was attempted *in situ* without isolating the oxidation product **195** by slow addition of dimethyl sulfate to maintain the basic condition which is said to increase the yields according to literature[30] but the product **197** could not be isolated.

At this point, the known procedure[30] was slightly altered and an acidic workup attempted of threonic acid sodium salt (**195**) into its corresponding acid **196** as described by Dahlgren and his co-workers.[31] Difficulties arose in extracting the acid from the aqueous layer. This is due to the acetonide protecting group becoming susceptible to the mild acidic washings and cause compound **196** to have a large number of unprotected hydroxy groups. These conditions may cause compound **196** to have a higher solubility in water layer than in organic layer and posing difficulties in isolating it from aqueous layer. This led on to reconsider the synthesis of electrophiles using this method as difficulties arose on isolating the acid which is needed for further transformation into corresponding acyl chloride (**186**) and epoxide (**187**).

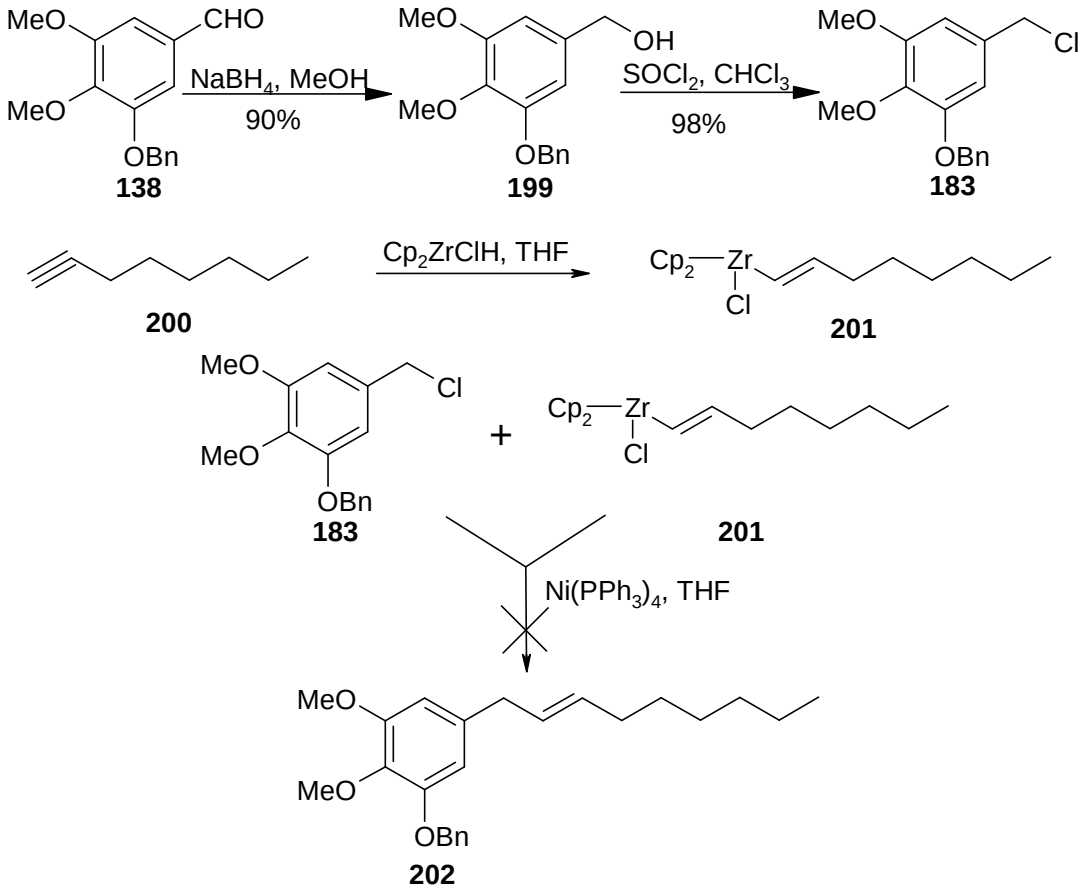


SCHEME 3.27

A model reaction was performed to illustrate the coupling conditions of the vinyl hydrozirconocene **184** with the benzylic chloride **183** (Scheme 3.28). The benzylic chloride **183** was prepared in two steps starting from compound **138**.

Thus, **138** was reduced to the corresponding benzyl alcohol using sodium borohydride in methanol and then treated with thionyl chloride to form the benzyl chloride (**183**) (Scheme 3.28).

1-Octyne (**200**) was the one of the readily available alkynes converted to its vinyl hydrozirconocene (**201**) as described by Lipshutz and his coworkers.[32] In an argon atmosphere, the freshly prepared vinyl hydrozirconocene (**201**) was subjected to a cross-coupling reaction *in situ* in the presence of catalytic amount of tetrakis(triphenylphosphine)nickel with benzylic chloride **183**. Though the reaction procedure seems to be simple and straightforward, the reaction conditions were complicated and because of the high moisture sensitivity associated with these organozirconocene compounds, after several attempts compound **202** was not isolated.

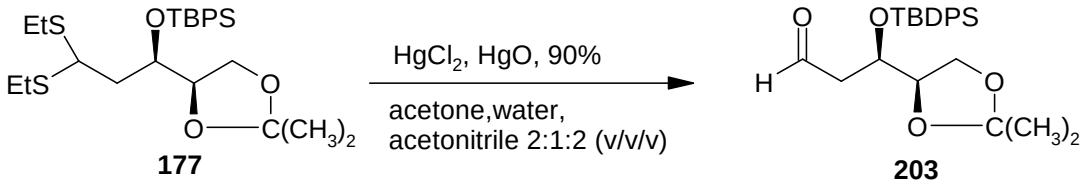


SCHEME 3.28

3.3.4 The assembly of precursors through path (a)

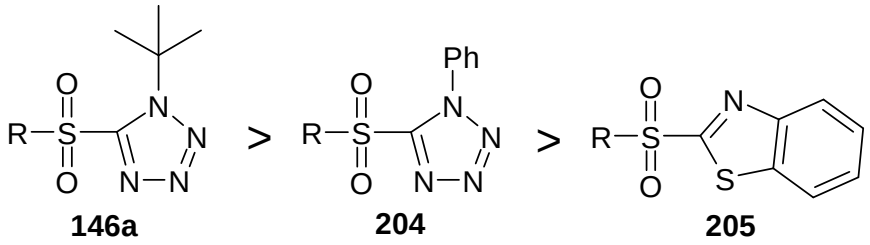
The synthetic pathway designed for path (a) (Scheme 3.12) is based on the *E*-olefination methodology to generate aromatics bearing a disubstituted allylic moiety of *E*-olefin geometry. Two olefination strategies were investigated namely, the improved Julia-Kocienski olefination[17] and the *E*-selective Wittig[33] reaction of nonstabilised ylides.

The process begins with converting compound **177** into a useful coupling agent for the olefination reaction. This was done by treating the compound **177** with mercuric oxide and mercuric chloride in a warm mixture of acetonitrile, acetone and water to obtain the desired aldehyde **203** in 90% yield (Scheme 3.29). The presence of the compound was confirmed by ^{1}H NMR spectroscopy which displays an aldehyde proton resonating at low field (δ_H 9.6) as a triplet. In the ^{13}C NMR all the expected signals were observed and the molecular formula of the compound was confirmed by MS.



SCHEME 3.29

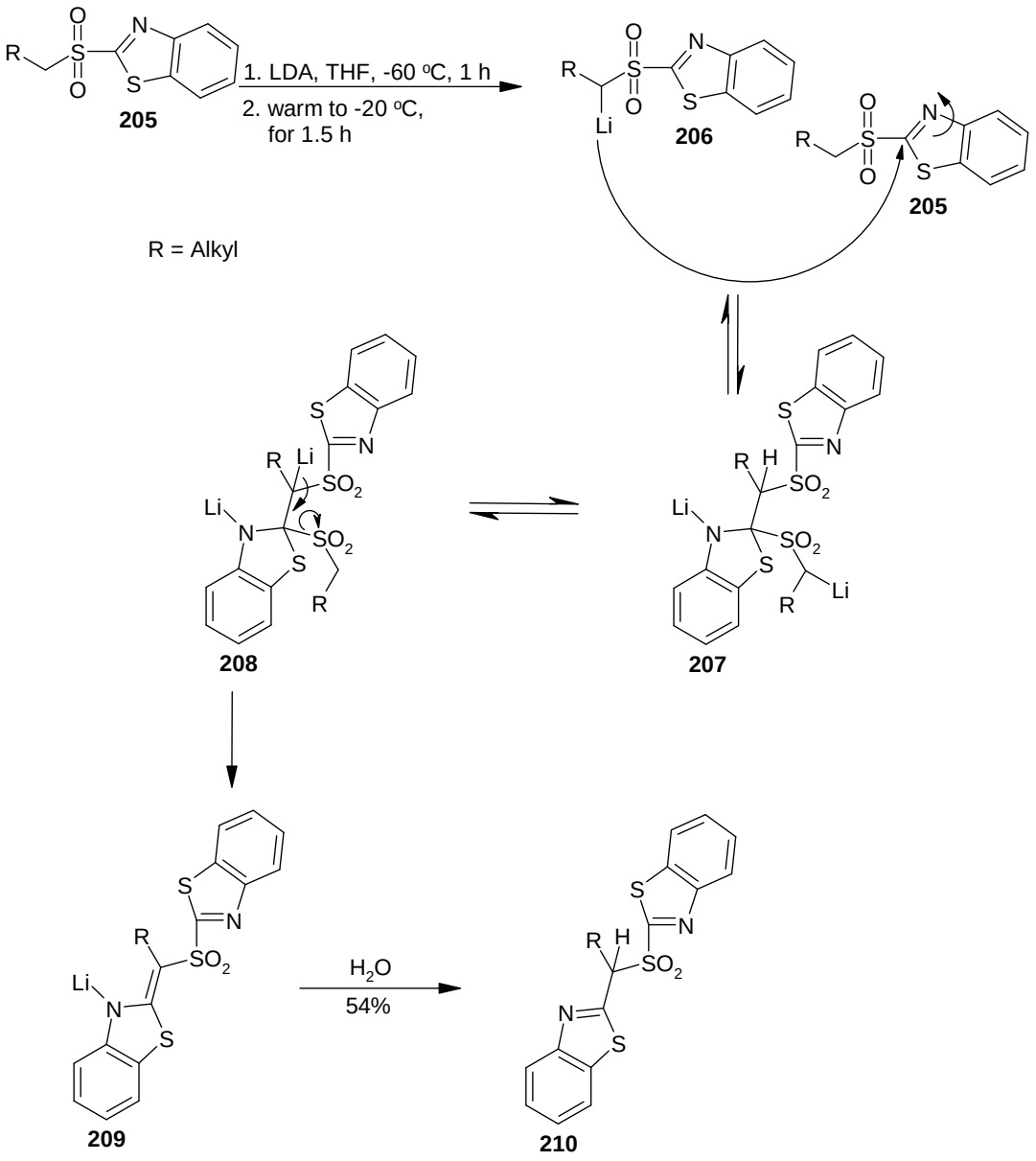
The improved Julia olefination is outlined in Scheme 3.31 where the *tert*-butyltetrazole (TBT) alkyl sulfone **146** was treated with a base to form a reactive nucleophile that can attack the threonic aldehyde (**203**) (Scheme 3.31). According to Aïssa *et al.*[17] and Kocienski *et al.*[18], *tert*-butyltetrazole (TBT)-alkyl sulfones (**146a**) are regarded as more stable than *n*-alkyl phenyltetrazole (PT) sulfones (**204**) and *n*-alkyl benzothiazole (BT) sulfones (**205**) as they are less prone to self-condensation reactions.[17]



R = Alkyl

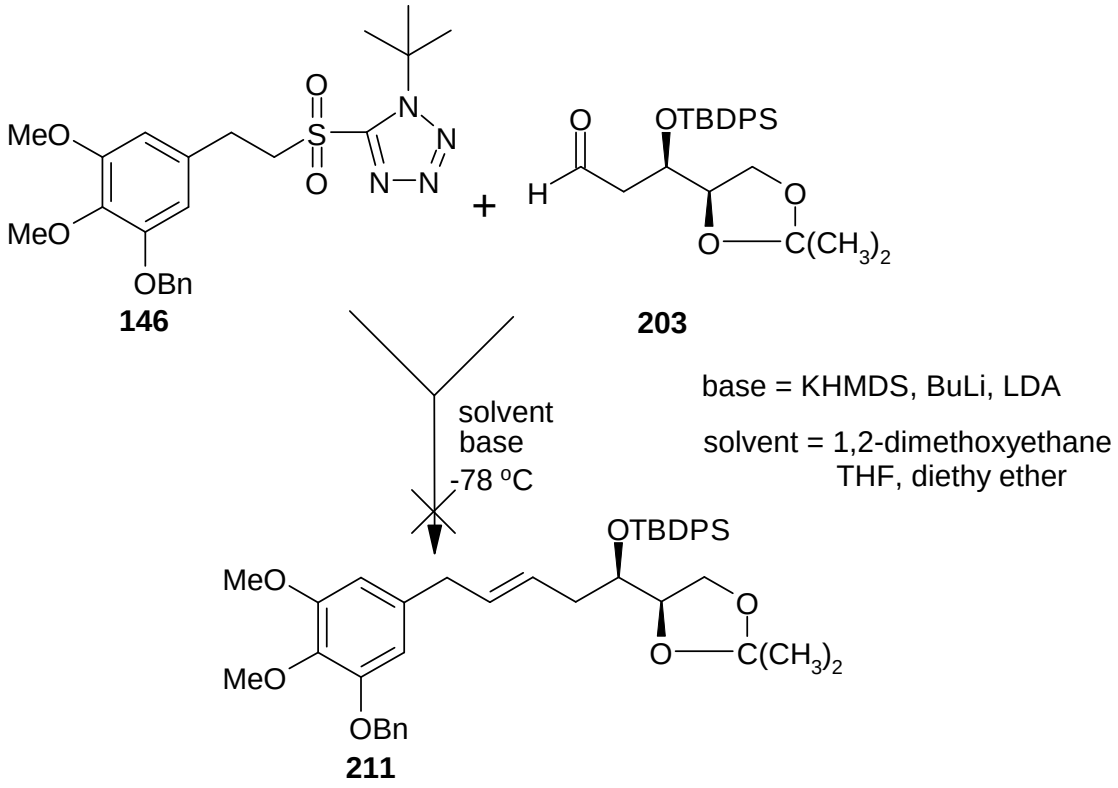
Even with sterically divergent substituents on the sulfone, self-condensation occurs even at low temperatures. The alkyl phenyltetrazole (PT) sulfones (**204**) is regarded as more stable than the alkyl benzothiazole (BT) sulfones (**205**) though they also decompose especially when a base like potassium bis(trimethylsilyl)amide (KHMDS) is used. The stability of the sulfones is enhanced by increasing the steric bulk of the substituent on the tetrazole ring hence the *tert*-butyltetrazole (TBT)-alkyl sulfones (**146**) is reasoned as the most stable sulfone.[18] The mechanism of the degradation of the *n*-alkyl benzothiazole (BT) sulfones (**205**) is outlined in Scheme 3.30. As described by Kocienski *et al.*[18] when the sulfone **205** is treated with lithium diisopropyl amide (LDA) in THF at -60 ^{o}C for 1 h followed by warming to -20 ^{o}C over 1.5 h, the condensation product **210** was obtained in 54% yield together with a further 7% of *n*-alkyl benzothiazole (BT) sulfones (**205**) (Scheme 3.30).

With this information in mind, *tert*-butyltetrazole (TBT)-alkyl sulfone (**146**) was utilised as Julia olefination reagent. Several attempts were made to synthesise the *E*-olefin **211** (Scheme 3.31). A number of different bases, solvent systems and different reaction temperatures were investigated. The desired olefin **211** was not obtained and instead the unreacted threonic aldehyde (**203**) was isolated.



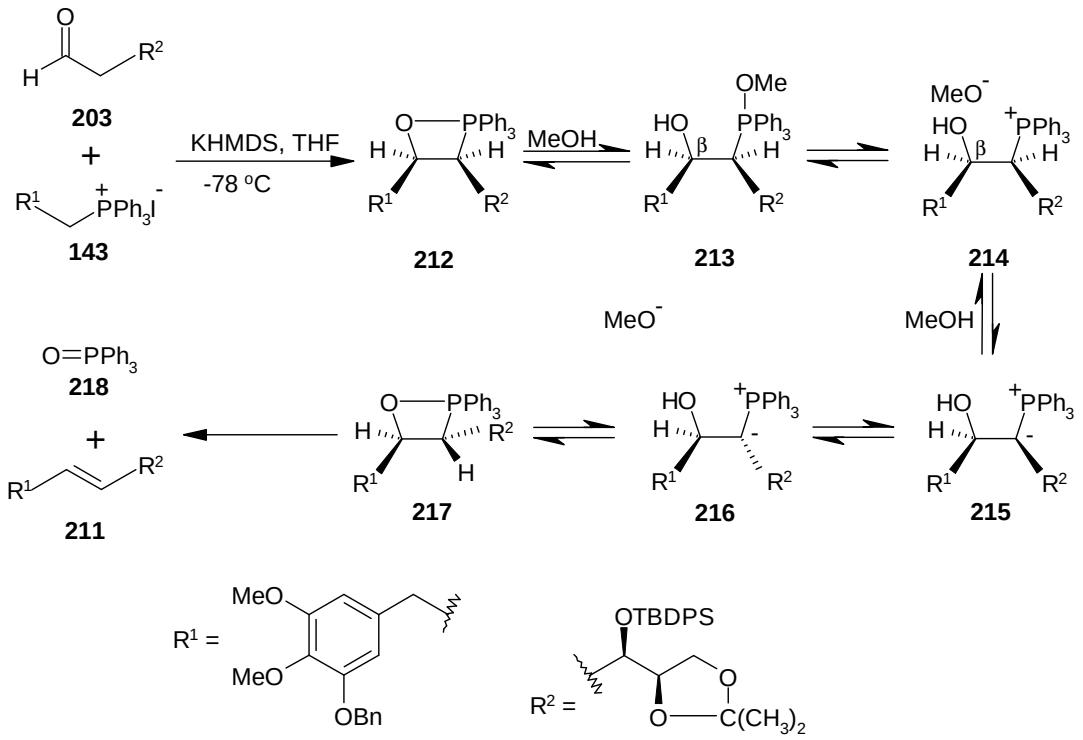
SCHEME 3.30

At this stage, it could not be concluded whether the (TBT)-alkyl sulfone (**146**) undergoes decomposition or self-condensation reactions (Scheme 3.31). When using Aïssa's[16a] alternate procedure for Julia-olefination which includes the use of Cs_2CO_3 and a mixture of THF/DMF at 70 ^{o}C, sulfone **146** decomposed. In the reaction, the starting material **146** was no longer observed (Scheme 3.31).



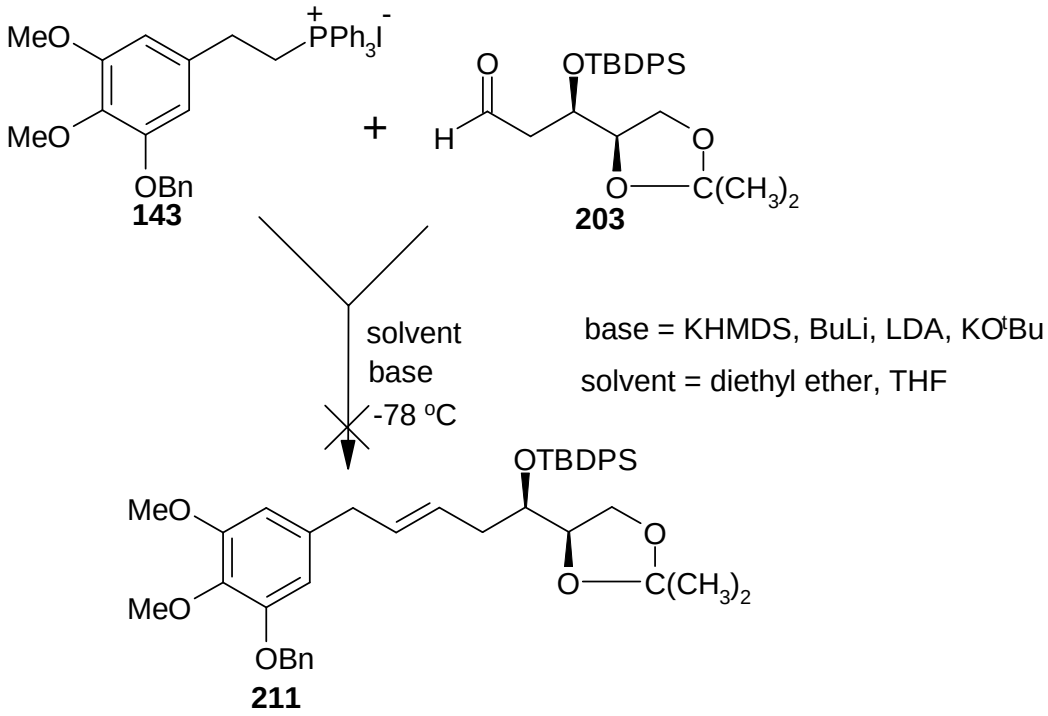
SCHEME 3.31

An *E*-selective Wittig reaction was attempted using a procedure described by Oh *et al.*[33] who demonstrated that *E*-alkenes could be produced as the major product by simply quenching the reaction with a large excess of methanol at -78 ^{o}C in the Wittig reaction with nonstabilised ylides of a linear alkyl chain. These conditions were found to work even under the salt-free conditions required by nonstabilised ylides for Wittig olefination reactions. Without the addition of methanol the usual *Z*-alkene will be obtained. The mechanism of enhanced selectivity for *E*-olefination is illustrated in Scheme 3.32. According to Oh *et al.*[33], the well-established oxaphosphetane intermediate **212** opens up under the salt free conditions with addition of methanol to give the acyclic intermediate **213** that is in equilibrium with the β-hydroxyphosphonium methoxide salt **214**. The betaine intermediate **216** is formed after the deprotonation step and the protonation step **217** would decompose to give the *E*-alkene product **211**.



SCHEME 3.32

With the above information in hand, a plan was to investigate the reaction described by Oh *et al.*[33] using unstabilised ylide **143** and aliphatic aldehyde **203** (Scheme 3.33). Several attempts were made using different bases, different solvents and different temperatures for screening the reaction conditions for reagents. No alkene formation was observed, even when the lithium salt was added. The problem may be associated with poor nucleophilicity of ylide **143** which may need an activator to speed up the reaction. To check the procedure, a Wittig reaction with benzyl bromide and benzaldehyde was performed, and no problems with these reagents were observed. Therefore, the failure of the reaction can be attributed to the low reactivity of phosphonium salt **143**.



SCHEME 3.33

3.4 CONCLUSION

Diarylheptanoids are natural products with a variety of biological activities and total synthesis of these compounds, which often occur in minute quantities in nature, is important. Two general strategies for executing the synthesis of diarylheptanoid **18** were investigated, namely: C_2-moiety + C_5-moiety and C_1-moiety + C_6-moiety as illustrated in Scheme 3.11 and 3.12.

The challenges were:

- To prepare suitable aromatic precursors.
- To prepare a linear fragment containing a diol with the required stereochemistry.
- To attach the linear fragment to the two aromatic precursors.

An achievement was to prepare the aromatic rings with the correct substitution pattern and to prepare the linear fragment with the required stereochemistry of the diol functionality. Carbohydrates were used as the starting material for the linear fragment. The advantages are that the pentose starting materials (D-xylose and D-arabinose) are available in both enantiomeric forms and these two pentoses gave access to both the *threo* and *erythro* stereochemistry of the diol. The last steps were the attachment of the linear chain to the aryl precursor and the formation of the *E*-alkene. Unfortunately, reaction conditions for these reactions could not be established. The electron-rich nature of both aromatic rings is responsible for the problems associated with these reactions and a substantial amount of research will be needed to solve this problem.

It is clear that organometallic-type reactions, which are often used for *Ar*-C coupling reactions, are very difficult with electron-rich aromatic rings. Friedel-Crafts reactions, which are enhanced by electron-rich aromatic rings, should be investigated for the arylation reaction. The formation of the *E*-alkene in the homobenzylic position from two bulky, relatively unstable precursors also needs further investigation. The solution may be to use a completely different approach such as a Grubbs metathesis reaction.

Although the final product was not prepared, significant advances towards the synthesis of this compound have been made.

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CHAPTER 4

EXPERIMENTAL

4.1 GENERAL EXPERIMENTAL PROCEDURES

4.1.1 PURIFICATION OF SOLVENTS AND REAGENTS

All the required chemicals or reagents were obtained from Fluka, Sigma-Aldrich or Merck and used without further purification unless otherwise specified. All solvents used for reactions and chromatography were purified and distilled prior to use. All reactions requiring anhydrous solvents were performed under a positive nitrogen pressure in oven-dried or flamed-out glass apparatus, unless otherwise mentioned. Anhydrous solvents were obtained from appropriate drying agents as follows:[1] tetrahydrofuran, diethyl ether, toluene and benzene were distilled under nitrogen from sodium wire and benzophenone; pyridine and dichloromethane were refluxed over calcium hydride; chloroform and carbon disulfide were refluxed over phosphorus(V) oxide. *N*,*N*-Dimethylformamide and acetone were stored over sodium and distilled. Dimethyl sulfoxide was dried over two consecutive batches of 4Å molecular sieves and then distilled under reduced pressure. When necessary, solvents were stored over activated molecular sieves (4Å) under a nitrogen atmosphere.

4.1.2 CHROMATOGRAPHY

Thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm silica gel plates (Merk silica gel 60 F_{254} or Machery-Nagel silica gel 60 UV_{254}). Normal and flash chromatography were performed using Merck Kieselgel 60 (230 - 400 mesh) and on columns with 4 cm or 1 cm diameters. Centrifugal chromatography was performed on a Harrison Research Chromatotron Model 7924T on glass plates coated with Merck silica gel 60 with particle size 0.040-0.063 mm, 2 - 4 mm thick.

The mobile phase comprised of different ratios of hexane - ethyl acetate. Detection of the developed TLC plate was accomplished using UV_{254} light or by using spraying reagents.

4.1.3 SPECTROSCOPIC AND PHYSICAL DATA

All melting points were obtained on a Reichert Kofler hot-stage microscope and are uncorrected.

Nuclear magnetic resonance spectroscopy (NMR) of the isolated compounds was performed on Varian Unity Inova 300 MHz or 500 MHz and Bruker Avance III 400 MHz or 500 MHz spectrometers. All NMR spectra were recorded at 25 ^{o}C (Varian) and 30 ^{o}C (Bruker) in deuterated solvents and the chemical shifts were referenced to the solvent shift. Where required, nuclear Overhauser effect (NOE), HMBC, HMQC, COSY and DEPT spectroscopy were employed to assign spectra and determine structures. Coupling constants were calculated as observed in the ^{1}H NMR spectrum. The following abbreviations are used for designated splitting patterns:

s	singlet	br	broadened
d	doublet	dd	doublet of doublets
t	triplet	ddd	doublet of doublet of doublets
q	quartet	m	multiplet

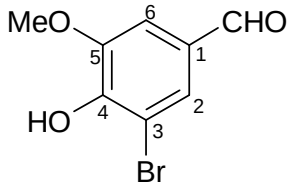
Mass spectra were obtained with a Waters LCT Premier mass spectrometer using both positive and negative electrospray ionisation. Optical rotations were measured in an appropriate spectroscopic grade solvent on a Perkin-Elmer 241 polarimeter and the measurements were obtained at the sodium (Na) D line (589 nm).

4.1.4 OTHER GENERAL EXPERIMENTAL PROCEDURES

The term “removal of solvent under reduced pressure” refers to the use of aspirator pressure (*ca*. 25 Torr) with a rotavapor at 40-50 ^{o}C. The term “*in vacuo*” refers to the removal of solvent by rotary evaporation, followed by removal of the residual solvent at oil pump pressure (*ca*. 0.1-1.0 Torr) at ambient temperature until constant mass was achieved.

4.2 SYNTHETIC PROCEDURES

4.2.1 Preparation of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (96)[2]



96

To a solution of vanillin (**54**) (1.00 g, 7 mmol) in glacial acetic acid (50 ml), bromine (1.05 g, 7 mmol) in glacial acetic acid (20 ml) was added dropwise at room temperature over a period of 1 h and stirred for 1 h at the same temperature. The reaction was quenched by addition of water (50 ml) and the resulting solid was filtered off. The crude product was recrystallised from ethanol to afford white crystals of **3-bromovanillin (96)** (0.95 g, 95%).

Mp: 163-164 ^{o}C from ethanol (lit.[2] 163-164 ^{o}C)

^{1}H NMR (300 MHz, DMSO-d_6) δ_H:

3.90 (3H, s, OCH_3), 7.41 (1H, d, *J*=1.8 Hz, H-6) and 7.71 (1H, d, *J*=1.8 Hz, H-2), 9.76 (1H, s, CHO), 10.60 (1H, s, OH).

^{13}C NMR (75 MHz, DMSO-d_6) δ_C:

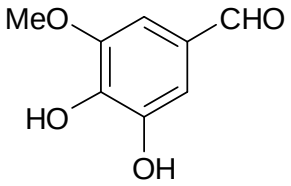
56.3 (OCH_3), 109.1 (C-6), 109.4, (C-2), 128.7 (C-3), 128.8 (C-1), 148.5 (C-4), 149.7 (C-5), 190.3 (CHO).

HRESIMS *m/z* $[M+H]^+$ 230.9669

(calc. for $C_8H_7\ ^{79}BrO_3$+H, 230.9657)

IR ν_{max} (cm^{-1}): 3229, 2717, 1672.

4.2.2 Preparation of 3,4-dihydroxy-5-methoxybenzaldehyde (97)[3]



97

3-Bromovanillin (**96**) (5.00 g, 22 mmol), sodium hydroxide (6.13 g, 153 mmol) and copper powder (0.03 g, 0.4 mmol) were stirred in 100 ml water. The reaction mixture was heated at reflux for 24-27 h. Sodium hydrogen phosphate (0.11 g, 0.6 mmol) was added during the last half hour of reflux. The reaction was then cooled to less than 50 ^oC, filtered to remove a precipitate of cupric hydrogen phosphate and acidified with 6 M HCl (9.6 ml). The reaction mixture was extracted with ethyl acetate (3 x 50 ml). The ethyl acetate extract was stirred with activated carbon and filtered. The filtrate was washed with saturated EDTA solution followed by brine (25 ml). The organic solution was then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was dissolved in boiling toluene (50 ml), treated with activated carbon, filtered and cooled to crystallise. The product, **3,4-dihydroxy-5-methoxybenzaldehyde (97)** (3.00 g, 60%) was afforded as brownish crystals.

Mp: 132-133 ^oC from toluene (*lit.*[3] 132-134 ^oC)

^{1}H NMR (300 MHz, DMSO-d_6) δ_H:

3.81 (3H, s, OCH_3), 6.99 (1H, d, *J*=1.2 Hz, H-6), 7.01 (1H, d, *J*=1.5 Hz, H-2), 9.48 (2H, 2xs, OH), 9.68 (1H, s, CHO).

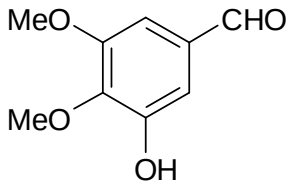
^{13}C NMR (75 MHz, d_6-DMSO) δ_C:

55.9 (OCH_3), 104.8 (C-6), 110.8 (C-2), 127.2 (C-1), 140.9 (C-5), 145.8 (C-3), 148.4 (C-4), 191.1 (CHO).

HRESIMS *m/z* $[M+H]^+$ 169.0504
(calc. for $C_8H_8O_4$+H, 169.0501)

IR ν_{max} (cm^{-1}): 3487, 2844, 1655.

4.2.3 Preparation of 3-hydroxy-4,5-dimethoxybenzaldehyde (101)[3,4]



101

Method : 1[4]

To a solution of 3,4-dihydroxy-5-methoxybenzaldehyde (**97**) (5.00 g, 29 mmol) in acetic anhydride (75 ml), triethyl amine (8 ml, 59 mmol) was added slowly at 0 ^{o}C. After stirring for 2 h at room temperature, the excess of acetic anhydride was destroyed by careful addition of EtOH (10 ml) at 0 ^{o}C. The reaction mixture was diluted with water and extracted with ethyl acetate, the organic phase was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude mixture was recrystallised from 70% ethyl acetate/hexane mixture to furnish compound **98** in 100% yield. To the acetylated compound **98** (5.0 g, 19 mmol) in DMF was added potassium carbonate (3.00 g, 19 mmol) and MeI (1.23 ml, 19 mmol). The resulting mixture was heated at 40 ^{o}C for 3 h. The inorganic salt was removed by filtration and the filtrate was diluted with ethyl acetate (20 ml) and cold water (20ml).

The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Compound **100** was obtained in 70% yield after recrystallisation from 90% heptane/ethyl acetate mixture. Then a solution of compound **100** (5.00 g, 22 mmol) in MeOH (100 ml) was added to a solution of potassium carbonate (16.00 g, 132 mmol) in water (50 ml). After stirring for 20 min at room temperature, the volatiles were evaporated and the aqueous solution acidified to pH of 2 and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was recrystallised from 90% heptane/ethyl acetate to furnish off-white crystals of **3-hydroxy-4,5-dimethoxybenzaldehyde (101)** (4.00 g, 80%).

Mp: 63-64 ^{o}C from 90% heptane/EtOAc (lit.[4] 64-65 ^{o}C)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

3.82 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.36 (1H, s, OH), 6.99 (1H, d, *J*=1.5 Hz, H-6), 7.07 (1H, d, *J*=1.2 Hz, H-2), 9.79 (1H, s, CHO).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

56.0 (OCH_3), 61.0 (OCH_3), 103.7 (C-6), 111.5 (C-2), 131.9 (C-1), 140.8 (C-5), 149.5 (C-4), 152.6 (C-3), 191.2 (CHO).

HRESIMS *m/z* $[M+H]^+$ 183.0650
(calc. for $C_9H_{10}O_4$+H, 183.0657)

IR ν_{max} (cm^{-1}): 3306, 2836, 1676.

Method : 2[3]

3,4-Dihydroxy-5-methoxybenzaldehyde (**97**) (5.00 g, 30 mmol), dimethyl sulfate (3 ml, 3.75 g, 30 mmol) and sodium carbonate (3.50 g, 29 mol) were stirred into acetone. The reaction mixture was heated at reflux for 4-6 h and then cooled to room temperature. The inorganic salts were removed by filtering, and then acetone was removed by concentrating *in vacuo* and replaced by toluene. The toluene solution was stirred at room temperature for 1 h and filtered to remove an insoluble tar. The product was extracted with a dilute sodium hydroxide solution. The aqueous layer was acidified with 3 M HCl to a pH of 1-2 and extracted with toluene. The organic layer was dried over anhydrous magnesium sulfate, then treated with activated carbon and filtered. The chromatographic purification on silica (elution with 70% hexane/ethyl acetate) followed by recrystallisation with toluene afforded off-white crystals of **3-hydroxy-4,5-dimethoxybenzaldehyde (101)** (3.00 g, 60%).

Mp: 63-64 ^{o}C from 90% heptane/EtOAc (lit.[4] 64-65 ^{o}C)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

3.82 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.36 (1H, s, OH), 6.99 (1H, d, *J*=1.5 Hz, H-6), 7.08 (1H, d, *J*=1.8 Hz, H-2), 9.79 (1H, s, CHO).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

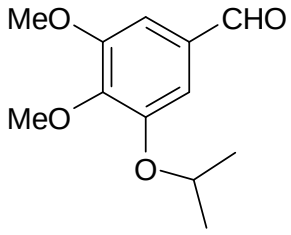
55 (OCH_3), 60. (OCH_3), 103.7 (C-6), 111.5 (C-2), 131.9 (C-1), 140.8 (C-5), 149.5 (C-4), 152.6 (C-3), 191.2 (CHO).

HRESIMS *m/z* $[M+H]^+$ 183.0650

(calc. for $C_9H_{10}O_4$+H, 183.0657)

IR ν_{max} (cm^{-1}): 3306, 2836, 1676.

4.2.4 Preparation of 3-isopropoxy-4,5-dimethoxybenzaldehyde (102)[5]



102

The 3-hydroxy-4,5-dimethoxybenzaldehyde (**101**) (1.00 g, 5 mmol), 2-bromopropane (1.50 ml, 2.00 g, 16 mmol) and K_2CO_3 (1.50 g, 10 mmol) were stirred in acetonitrile (30 ml) at 60 ^oC for 24 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in diethyl ether (50 ml) and washed with water (3 x 30 ml). The aqueous layer was extracted with diethyl ether (2 x 50 ml), the combined organic extracts were washed with water (2 x 50 ml) followed by brine (1 x 50 ml) and dried over anhydrous magnesium sulfate. The chromatographic purification on silica (elution with 80% hexane/ethyl acetate) afforded as a yellowish oil of **3-isopropoxy-4,5-dimethoxybenzaldehyde (102)** (0.85 g, 85%).

^1H NMR (300 MHz, $CDCl_3$) δ_H:

1.30-1.36 [6H, 2xs, OCH($C\underline{H}_3$)$_2$], 3.84-3.85 (3H, s, $CH_3\underline{O}$), 3.88-3.89 (3H, s, OCH_3), 4.58 [1H, sept, O$\underline{C}$H(CH_3)$_2$] 6.99 (1H, d, *J*=1.5 Hz, *Ar*-H_6), 7.08 (1H, d, *J*=1.8 Hz, *Ar*-H_2), 9.78 (1H, s, CHO).

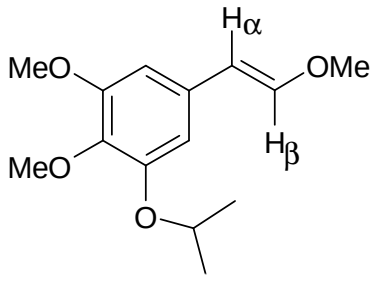
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

22.1 [OCH($\underline{C}H_3$)$_2$], 22.1 (OCH($\underline{C}H_3$)$_2$), 56.2 (OCH_3), 60.8 (OCH_3), 71.7 [O$\underline{C}$H(CH_3)$_2$], 105.9 (C-6), 110.50 (C-2), 131.5 (C-1), 143.8 (C-5), 151.7 (C-3), 153.8 (C-4), 190.9 (CHO).

HRESIMS *m/z* $[M+H]^+$ 225.1128
(calc. for $C_{12}H_{16}O_4$+H, 225.1120)

IR ν_{max} (cm^{-1}): 2727, 1689.

4.2.5 Preparation of 1-isopropoxy-2,3-dimethoxy-5-(2-methoxyvinyl)benzene (103)[5]



103

To a suspension of (methoxymethyl)triphenylphosphonium chloride (2.30 g, 65 mmol) in dry THF (20 ml), potassium *tert*-butoxide (1.00 g 85 mmol) was added at 0 ^{o}C and stirred for 15 min. The 3-isopropoxy-4,5-dimethoxy-benzaldehyde (**102**) (1.00 g, 44 mmol) was added and stirred for another 15 min. The reaction mixture was concentrated *in vacuo* and partitioned between water (10 ml) and diethyl ether (30 ml). The aqueous layer was extracted with diethyl ether (2 x 30 ml) and the combined organic layer was washed with water (2 x 30 ml) and brine (30 ml), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The purification on silica (elution with 90% hexane/ethyl acetate) afforded a yellowish oil of **1-isopropoxy-2,3-dimethoxy-5-(2-methoxyvinyl)benzene (103)** (0.75 g, 75%) as a mixture of *cis*/*trans* isomers (67%:33%, *E*:*Z* ratio).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.38 [6H, 2xs, OCH($C\underline{H}_3$)$_2$], 3.50-3.73 (9H, 3xs, 3xOCH_3), 4.04 [1H, sept, OC$\underline{H}$(CH_3)$_2$], 5.20 (1H, d, *J*=6.9 Hz, CH_α, *cis*), 5.56 (1H, d, *J*=13.2 Hz, CH_α, *trans*), 6.20 (1H, d, *J*=7.2 Hz, -CH_β, *cis*) 6.83 (1H, d, *J*=12.6 Hz, CH_β, *trans*), 6.26/6.80 (2H, 2xdd, *J*=1.8 Hz, *Ar*-H).

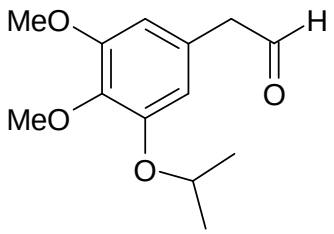
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

22.6 [OCH($\underline{C}H_3$)$_2$], 56.0 (OCH_3), 56.5 (OCH_3), 60.7 (OCH_3), 71.4 [2 X O$\underline{C}$H(CH_3)$_2$], 102.3 (CH_α) 105.0 (C-6), 105.5 (C-2), 105.6 (C-1), 106.4 (C-4), 109.5 (C-3), 147.3 (CH_β) 148.4 (C-5),

HRESIMS *m/z* $[M+H]^+$ 253.1441

(calc. for $C_{14}H_{20}O_4$+H, 253.1440)

4.2.6 Preparation of (3-isopropoxy-4,5-dimethoxyphenyl)acetaldehyde (91)[5]



91

The 1-isopropoxy-2,3-dimethoxy-5-(2-methoxy-vinyl)-benzene (**103**) (1.00 g, 4 mmol) was stirred in THF (20 ml) and 2 M HCl (5 ml) under argon and reflux for 3 h. The mixture was concentrated *in vacuo* and the residue was partitioned between water (10 ml) and diethyl ether (20 ml). The aqueous layer was extracted with diethyl ether (3 x 20 ml) and the combined organic layers were washed with water (2 x 10 ml), saturated $NaHCO_3$ (2 x 20 ml) and brine (10 ml), the organic layer dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a yellowish oil of **(3-isopropoxy-4,5-dimethoxyphenyl)acetaldehyde (91)** (0.75 g, 75%) after chromatographic purification on silica (elution with 90% hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.27-1.35 [6H, 2xs, OCH($C\underline{H}_3$)$_2$], 3.57 (2H, s, $C\underline{H}_2$CHO), 3.81-3.83 (6H, 2xs, OCH_3), 4.49 (1H, sept, OCH(CH_3)$_2$), 6.39 (2H, 2xs, *Ar*-H), 9.71 (1H, t, CHO).

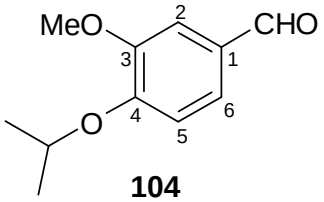
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

22.2 [OCH($\underline{C}H_3)_2$], 50.0 ($\underline{C}H_2CHO$), 56.1 (OCH_3), 60.6 (OCH_3), 71.5 [O$\underline{C}$H($CH_3)_2$], 106.5 (C-6), 110.6 (C-2), 126.9 (C-1), 141.8 (C-4), 151.8 (C-3), 153.8 (C-5), 199.3 (CHO).

HRESIMS *m/z* $[M+H]^+$ 239.1285
(calc. for $C_{13}H_{18}O_4$+H, 239.1283)

IR ν_{max} (cm^{-1}): 2789, 1670.

4.2.7 Preparation of 4-isopropoxy-3-methoxybenzaldehyde (104)[5]



104

Compound **104** was prepared according to the procedure described for the synthesis of compound **102** starting with vanillin (**54**) (2.00 g, 13 mmol). The residue was dissolved in diethyl ether (50 ml) and washed with water (3 x 30 ml). The aqueous layer was extracted with diethyl ether (2 x 50 ml), the combined organic extracts were washed with water (2 x 50 ml) followed by brine (1 x 50 ml) and dried over anhydrous magnesium sulfate. The chromatographic purification on silica (elution with 70% hexane/ethyl acetate) afforded as a colourless oil of **4-isopropoxy-3-methoxybenzaldehyde (104)** (1.70 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.37 [6H, 2xs, OCH($C\underline{H}_3)_2$], 3.86 (6H, s, OCH_3), 4.64 [1H, sept, O$\underline{C}$H($CH_3)_2$], 6.92 (1H, d, *J*=8 Hz, H-5), 7.37 (2H, dd, *J*=2.1 Hz, H-2 and H-6), 9.78 (1H, t, CHO).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

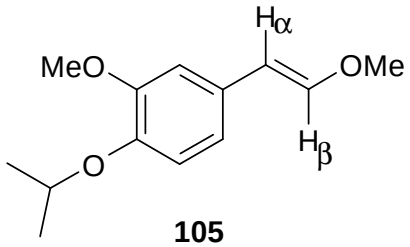
22.7 [OCH($\underline{C}H_3)_2$], 55.9 (OCH_3), 71.2 [O$\underline{C}$H($CH_3)_2$], 109.4 (C-2), 112.7 (C-5), 126.5 (C-6), 129.6 (C-1), 150.2 (C-3), 153.0 (C-4), 190.7 (CHO).

HRESIMS *m/z* $[M+H]^+$ 195.1022

(calc. for $C_{11}H_{14}O_3$+H, 195.1020)

IR ν_{max} (cm^{-1}): 2889, 1650.

4.2.8 Preparation of 1-isopropoxy-2-methoxy-4-(2-methoxyvinyl)benzene (105)[5]



105

Compound (**105**) was prepared according to the procedure described for synthesis of compound (**103**) starting with 4-isopropoxy-3-methoxy-benzaldehyde (**104**) (2.30 g, 2 mmol). The reaction mixture was concentrated *in vacuo* and partitioned between water (10 ml) and diethyl ether (30 ml). The aqueous layer was extracted with diethyl ether (2 x 30 ml) and the combined organic layer was washed with water (2 x 30 ml) and brine (30 ml), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The purification on silica (elution with 90% hexane/ethyl acetate) afforded a yellowish oil of **1-isopropoxy-2-methoxy-4-(2-methoxyvinyl)benzene (105)** (1.72 g, 75%) as a mixture of *cis*/*trans* isomers (67%:33%, *E*:*Z* ratio).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

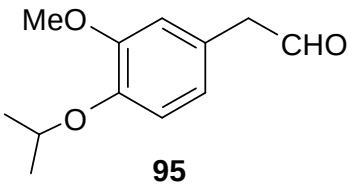
1.38 [6H, 2xs, OCH($C\underline{H}_3$)$_2$], 3.50 (3H, s, OCH_3 *cis*) 3.69 (3H, s, OCH_3 *trans*) 3.73 (3H, s, OCH_3), 4.41 [1H, sept, OC$\underline{H}$(CH_3)$_2$], 5.20 (1H, d, *J*=6.9 Hz, CH_α, *cis*), 5.56 (1H, d, *J*=13.2 Hz, C$\underline{H}_\alpha$, *trans*), 6.20 (1H, d, *J*=7.2 Hz, CH_β, *cis*) 6.83 (1H, d, *J*=12.6 Hz, CH_β, *trans*), 6.70 (1H, d, *J*=8 Hz, *Ar*-H_5), 6.83 (2H, 2xdd, *J*=1.8 Hz, *Ar*-$H_{2,6}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

22.1 [OCH($\underline{C}H_3$)$_2$], 55.8 (OCH_3 *cis*), 56.4 (OCH_3 *trans*), 60.5 (OCH_3), 71.6 (OCH(CH_3)$_2$), 104.8 (CH_α) 108.9 (C-2), 112.1 (C-5), 115.8 (C-6), 116.5 (C-1), 120.7 (C-4), 146.4 (CH_β) 147.6 (C-3).

HRESIMS *m/z* $[M+H]^+$ 223.1335
(calc. for $C_{13}H_{18}O_3$+H, 223.1333)

4.2.9 Preparation of (4-isopropoxy-3-methoxyphenyl)acetaldehyde (95)[5]



95

Compound **95** was prepared according to the procedure described for synthesis of compound **91** starting with 1-isopropoxy-2-methoxy-4-(2-methoxy-vinyl)-benzene (**105**) (2.00 g, 8 mmol). The mixture was concentrated *in vacuo* and the residue was partitioned between water (10 ml) and diethyl ether (20 ml).

The aqueous layer was extracted with diethyl ether (3 x 20 ml) and the combined organic layer washed with water (2 x 10 ml), saturated $NaHCO_3$ (2 x 20 ml) and brine (10 ml), the organic layer dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a yellowish oil of **(4-isopropoxy-3-methoxyphenyl)acetaldehyde (95)** (1.50 g, 75%) after purification on silica (elution with 90% hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.98 [6H, dt, OCH($C\underline{H}_3$)$_2$], 3.05 (3H, s, OCH_3), 3.45 (2H, d, *J*=2.2 Hz, $C\underline{H}_2CHO$), 4.04 [1H, sept, $OC\underline{H}(CH_3)_2$], 6.05 (1H, d, *J*=8 Hz, H-5), 6.55 (2H, dd, *J*=2.1 Hz, H-2 and H-6), 9.23 (1H, t, CHO).

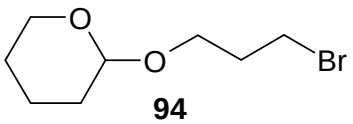
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

21.9 [OCH($\underline{C}H_3$)$_2$], 50.1 ($\underline{C}H_2CHO$), 56.00 (OCH_3), 70.8 [$OCH(CH_3)_2$], 106.3 C-2, 109.6 (C-5), 128.0 (C-6), 134.6 (C-1), 146.5 (C-4), 150.3 (C-5), 199.4 (CHO).

HRESIMS *m/z* $[M+H]^+$ 209.1179
(calc. for $C_{12}H_{16}O_3$+H, 209.1170)

IR ν_{max} (cm^{-1}): 2889, 1640.

4.2.10 Preparation of 2-(3-bromopropoxy)tetrahydropyran (94)[6]



94

To a stirred solution of the 3-bromopropanol (3 ml, 33 mmol) in dichloromethane was added *p*-toluenesulfonic acid (3.16 g, 33 mmol) under nitrogen atmosphere.

The mixture was cooled to below 10 ^{o}C and 3,4-dihydro-2H-pyran (3.6 ml, 39 mmol) was added slowly. Upon completion of the reaction by TLC monitoring for consumption of starting material, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (5 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml) and dried over anhydrous magnesium sulfate followed by concentration *in vacuo*. Purification of the residue on silica (elution with 90% hexane/ethyl acetate) afforded **2-(3-bromopropoxy)tetrahydropyran** (**94**) (4.39 g, 95%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.41-1.73 (6H, m, CH_2-THP), 1.99-2.04 (2H, m, $OCH_2C\underline{H}_2CH_2Br$), 3.38-3.44 (4H, m, $OC\underline{H}_2CH_2CH_2Br$ and $C\underline{H}_2$-THP), 3.74-3.77 (2H, m, $OCH_2CH_2C\underline{H}_2Br$), 4.49 (1H, m, C<u>H</u>-THP).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

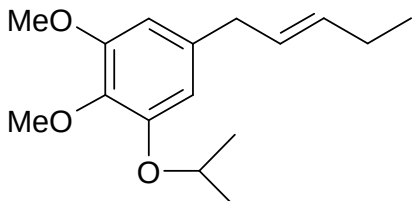
19.3, 25.3, 30.4, 64.6, 98.5 (5xC-THP), 30.5 ($OCH_2CH_2\underline{C}H_2Br$), 32.7 ($OCH_2\underline{C}H_2CH_2Br$), 61.9 ($O\underline{C}H_2CH_2CH_2Br$).

HRESIMS *m/z* $[M+H]^+$ 223.0330
(calc. for $C_8H_{15}{}^{79}BrO_2$+H, 223.0334)

4.2.11 Preparation of propyltriphenylphosphonium bromide (106)[7]

Triphenylphosphine (1.00 g, 4 mmol) was added to 1-bromopropane (0.35 ml, 0.47 g, 4 mmol) in benzene (50 ml) and the mixture was refluxed for 2 h until formation of the salt was complete. The reaction was cooled to room temperature and the salt was then filtered off and dried in high vacuum pressure (*ca*. 22 Torr) to obtain a pure white salt which upon recrystallisation from EtOH gave pure crystals of **propyltriphenylphosphonium bromide** (**106)** (0.50 g, 100%) with a melting point range of 233-237 ^{o}C (lit.[6] 235-238 ^{o}C).

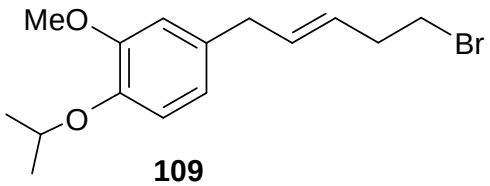
4.2.12 Attempted preparation of 1-isopropoxy-2,3-dimethoxy-5-pent-2-enylbenzene (107)[6]



107

To a suspension of propyltriphenylphosphonium bromide (**106**) (2.20 g, 8 mmol) in dry THF (20 ml) was added at 0 ^{o}C KO^{t}Bu (0.8 g, 8 mmol) and the mixture was stirred for 15 min. Then (3-isopropoxy-4,5-dimethoxy-phenyl)-acetaldehyde (**91**) (1.00 g, 4 mmol) in dry THF (5 ml) was added and the stirring was continued for another 15 min. The reaction mixture was concentrated *in vacuo* and partitioned between water (20 ml) and diethyl ether (30 ml). The aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined organic layer was washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo* to afford an orange yellow crude which was purified on silica (elution with 90% hexane/ethyl acetate) and no desired product was obtained.

4.2.13 Attempted preparation of 4-(5-bromopent-2-enyl)-1-isopropoxy-2-methoxybenzene (109)[6]

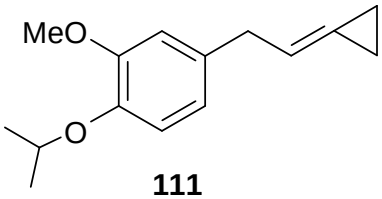


109

Compound **109** was prepared according to the procedure described for synthesis of compound **107** starting with a suspension of (3-bromopropyl)triphenylphosphonium bromide (**108**) (1.00 g, 2 mmol) in dry THF (20 ml) was added at 0 ^{o}C KO^{t}Bu (0,20 g, 2 mmol) and the mixture was stirred for 15 min.

Then (4-isopropoxy-3-methoxyphenyl)acetaldehyde (**95**) (0.20 g, 1 mmol) in dry THF (5 ml) was added and the stirring was continued for another 15 min. The reaction mixture was concentrated *in vacuo* and partitioned between water (20 ml) and diethyl ether (30 ml). The aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo* to afford an orange yellow crude which upon purification on silica (elution with 90% hexane/ethyl acetate), no desired product was obtained.

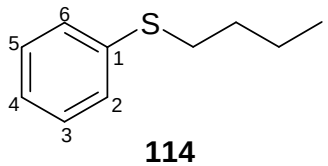
4.2.14 Attempted preparation of (2-cyclopropylidenethyl)-1-isopropoxy-2-methoxybenzene (111)[6]



111

Compound **111** was prepared according to the procedure described for synthesis of compound **109.** Cyclopropyltriphenylphosphonium bromide (1.00 g, 2 mmol) in dry THF (20 ml) [prepared from 2 equivalents of KO^{t}Bu (0,20 g, 2 mmol)] was added at 0 ^{o}C (4-isopropoxy-3-methoxy-phenyl)acetaldehyde (**95**) (0.20 g, 1 mmol) in dry THF (5 ml) and the mixture was stirred for 15 min. The reaction mixture was concentrated *in vacuo* and partitioned between water (20 ml) and diethyl ether (30 ml). The aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo* to afford an orange yellow crude which upon purificatio on silica (elution with 90% hexane/ethyl acetate), no desired (2-cyclopropylidenethyl)-1-isopropoxy-2-methoxybenzene (**111**) was obtained.

4.2.15 Preparation of butyl phenyl sulfide (114)[8]



114

To a suspension of NaH (2.82 g, 0.1 mmol) in dry THF under argon atmosphere at 0 ^{o}C, was added dropwise benzenethiol (**112**) (5 ml, 0.1 mmol) at 0 ^{o}C. The resulting solution was allowed to stir at room temperature for 3 h. Bromobutane (5 ml, 0.1 mmol) was added and the reaction mixture was allowed to stir for another 3 h with TLC monitoring for the consumption of the starting material. The reaction mixture was cooled to 0 ^{o}C and quenched with ice cold water. The resulting precipitate was filtered off and the solvent was removed *in vacuo*. The remaining aqueous layer was extracted with ethyl acetate (3 x 20 ml) and the organic phase was washed with water (20 ml) and brine (20 ml) followed by drying over magnesium sulfate and concentrated in *vacuo*. The chromatographic purification of the residue (elution with 90% hexane/ethyl acetate) afforded **butyl phenyl sulfide (114)** (3.80 g, 90%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

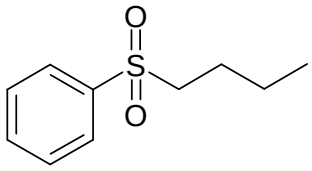
0.94 [3H, t, $S(CH_2)_3C\underline{H_3}$], 1.48 [2H, m, $S(CH_2)_2C\underline{H_2}CH_3$], 1.65 (2H, m, $SCH_2C\underline{H_2}CH_2CH_3$), 2.95 [2H, m, $SC\underline{H_2}(CH_2)_2CH_3$], 7.27-7.35 (5H, m, *Ar*-H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.6 [$S(CH_2)_3\underline{C}H_3$] 21.9 [$S(CH_2)_2\underline{C}H_2CH_3$], 31.2 ($SCH_2\underline{C}H_2CH_2CH_3$), 33.2 [$S\underline{C}H_2(CH_2)_2CH_3$], 125.4 (C-4), 126.6 (2C, C-2 and C-6), 128.7 (2C, C-3 and C-5), 136.9 (C-1).

HRESIMS *m/z* $[M+H]^+$ 167.0901
(calc. for $C_{10}H_{14}S$+H, 167.0904)

4.2.16 Preparation of (butane-1-sulfonyl)benzene (115)[8]



115

To a stirred solution of butyl phenyl sulfide (**114**) (4.00 g, 24 mmol) in methanol (30 ml) was added a solution of oxone (29.60 g, 48 mmol) in ice cold water of 0-10 ^{o}C (10 ml). After stirring for 3 h at temperature below 20 ^{o}C, the reaction was monitored by TLC for consumption of starting material and the mixture was concentrated *in vacuo*. The residue was partitioned between water (20 ml) and ethyl acetate (20 ml). The organic phase was washed with water (20 ml) and brine (20 ml) followed by drying over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 90% hexane/ethyl acetate) afforded colourless oil of **(butane-1-sulfonyl)benzene (115)** (3.20 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.97 [3H, t, $SO_2(CH_2)_3\underline{C}H_3$], 1.48 (2H, m, $SO_2(CH_2)_2\underline{C}H_2CH_3$), 1.65 (2H, m, $SO_2CH_2\underline{C}H_2CH_2CH_3$), 3.40 [2H, m, $SO_2\underline{C}H_2(CH_2)_2CH_3$], 7.35-7.80 (5H, m, *Ar*-H).

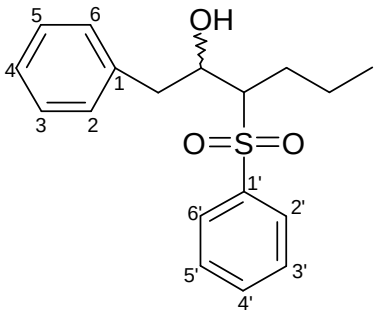
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.2 [$SO_2(CH_2)_3\underline{C}H_3$], 21.2 [$SO_2(CH_2)_2\underline{C}H_2CH_3$], 24.3 ($SO_2CH_2\underline{C}H_2CH_2CH_3$), 55.6 [$SO_2\underline{C}H_2(CH_2)_2CH_3$], 127.6 (2C, C-2 and C-6), 129.5 (2C, C-3 and C-5), 133.5 (C-4), 138.8 (C-1).

HRESIMS *m/z* $[M+H]^+$ 199.0800

(calc. for $C_{10}H_{14}O_2S$+H, 199.0803)

4.2.17 Preparation of 3-benzenesulfonyl-1-phenylhexan-2-ol (117)[8]



117

To a solution of (butane-1-sulfonyl)benzene (**115**) (1.00 g, 5 mmol) in dry dichloromethane under argon atmosphere was added dropwise a solution of lithium bis(trimethylsilyl)amide (LHMDS) (1.70 g, 10 mmol) in dichloromethane (5 ml) at room temperature. The solution was stirred for 10 min and the solution of phenylacetaldehyde (**116**) (0.6 ml, 5 mmol) in dichloromethane (3 ml) was added dropwise. The reaction mixture was stirred for 1 h at room temperature and the consumption of starting material was monitored by TLC and when the reaction is complete, the reaction mixture was added a solution of saturated aqueous NH_4Cl (10 ml) and the solvent was removed *in vacuo*. The residue was partitioned between water (20 ml) and diethyl ether (20 ml). The combined organic solvents were washed with saturated aqueous $NaHCO_3$ (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*.
The chromatographic purification of the residue (elution with 90% hexane/ethyl acetate) afforded a yellowish oil of **3-benzenesulfonyl-1-phenylhexan-2-ol (117))** (0.75 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.96 (3H, t, CH_3), 1.33-1.40 (2H, m, CH_2), 1.81-1.93 (2H, m, CH_2), 2.0 (1H, s, OH), 2.70-2.93 (2H, m, CH_2), 3.06 (1H, m, C<u>H</u>SO_2Ph), 4.20 (1H, m, C<u>H</u>OH), 7.08-7.93 (10H, m, *Ar*-H).

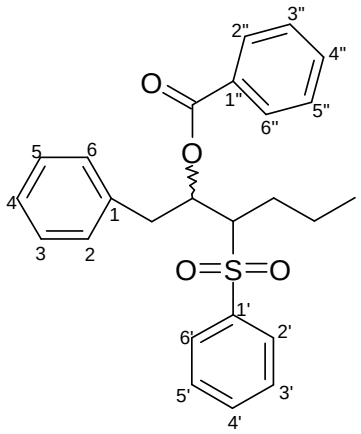
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.0 (CH_3), 19.8 (CH_2), 22.2 (CH_2), 39.8 (CH_2), 64.2 ($\underline{C}HSO_2Ph$), 67.8 ($\underline{C}HOH$), 125.0 (C-4), 126.5 (2C, C-2' and C-6'), 128.3 (4C, C-2, C-3, C-5 and C-6), 129.5 (2C, C-3' and C-5'), 133.5 (C-4'), 137.5 (C-1'), 138.5 (C-1).

HRESIMS *m/z* $[M+H]^+$ 319.1382
(calc. for $C_{18}H_{22}O_3S$+H, 319.1385)

IR ν_{max} (cm^{-1}): 3430.

4.2.18 Preparation of benzoic acid 2-benzenesulfonyl-1-benzylpentyl ester (118)[8]



118

The 3-benzenesulfonyl-1-phenyl-2-hexanol (**117**) (1.00 g, 3 mmol) in dichloromethane (20 ml) was treated with Et_3N (0.4 ml, 3 mmol), DMAP (0.4 g, 3 mmol) and benzoylchloride (0.4 ml, 3 mmol) and stirring was continued at room temperature for 20 h. The reaction was added saturated aqueous NH_4Cl (10 ml) and the solvent was removed *in vacuo*. The residue was partitioned between water (20 ml) and ethyl acetate (20 ml). The combined organic solvents were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

The chromatographic purification of the residue (elution with 90% hexane/ethyl acetate) afforded a yellowish oil of **benzoic acid 2-benzenesulfonyl-1-benzylpentyl ester (118)** (0.95 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.96 (3H, t, CH_3), 1.33-1.40 (2H, m, CH_2), 1.81-1.93 (2H, m, CH_2), 2.0 (1H, s, OH), 2.70-2.93 (2H, m, CH_2), 3.06 (1H, m, C<u>H</u>SO_2Ph), 4.20 (1H, m, C<u>H</u>OH), 7.08-7.93 (15H, m, *Ar*-H).

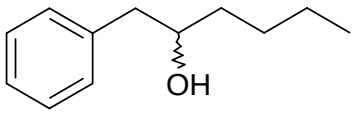
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.6 (CH_3), 20.6 (CH_2), 26.7 (CH_2), 36.5 (CH_2), 64.4 ($CHSO_2Ph$), 72.1 (CHOH), 121.4 (C-2'' and C-6''), 125.3 (C-4''), 125.7 (C-4), 126.7 (2C, C-2' and C-6'), 128.3 (4C, C-2, C-3, C-5 and C-6), 128.9 (2C, C-3'' and C-5''), 129.5 (2C, C-3' and C-5'), 133.5 (C-4'), 136.5 (C-1'), 137.7 (C-1), 153.1 (C-1'').

HRESIMS *m/z* $[M+H]^+$ 423.1650
(calc. for $C_{25}H_{26}O_4S$+H, 423.1652)

IR ν_{max} (cm^{-1}): 1620.

4.2.19 Preparation of 1-phenyl-2-hexanol (119)[9]



119

In a three-necked flask containing mercury (15 ml) under argon atmosphere was inserted piece of Na (1.00 g, 43 mmol) in ~0.20 g portions per 3 min time intervals.

After the amalgation is complete, the flask was cooled to -20 ^{o}C and a solution of benzoic acid 2-benzenesulfonyl-1-benzyl-pentyl ester (**118**) (1.00 g, 23 mmol) in a mixture of THF/MeOH (3:1, 20 ml) was transferred to the sodium amalgam via cannula followed by addition of Na_2HPO_4 (0.30 g, 23 mmol) in solution of 3:1 mixture of THF/MeOH (5 ml). The resulting mixture was stirred for 1 h at -20 ^{o}C followed by 2 h stirring at room temperature. The reaction was added with ice-cold water (10 ml) and elimination of the mercury residue was done by decanting the top solution. The resultant solution was extracted with diethyl ether (2 x 30 ml). The combined organic extracts were washed with aqueous NH_4Cl (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 80% hexane/ethyl acetate) afforded a yellowish oil of **1-phenyl-2-hexanol (119)** (0.75 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.93 (3H, t, CH_3), 1.34-1.58 (6H, m, 3xCH_2), 2.67-2.84 (2H, 2xdd, *J*=4.2 Hz and 8.4 Hz, CH_2), 3.80 (1H, m, C<u>H</u>OH), 7.25-7.33 (5H, m, *Ar*-H).

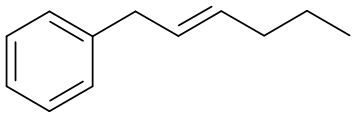
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.2 (CH_3), 22.8 (CH_2), 28.0 (CH_2), 36.6 (CH_2), 44.1 (CH_2), 72.7 (CHOH), 126.4 (C-4), 128.3 (4C, C-2, C-3, C-5 and C-6), 139.4 (C-1).

HRESIMS *m/z* $[M+H]^+$ 179.14452
(calc. for $C_{12}H_{18}O$+H, 179.14456)

IR ν_{max} (cm^{-1}): 3439.

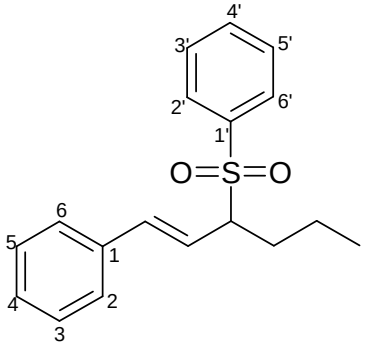
4.2.20 Attempted preparation of hex-2-enylbenzene (120)[10]



120

A mixture of benzoic acid 2-benzenesulfonyl-1-benzylpentyl ester (**118**) (1.00 g, 23 mmol), magnesium powder (-50 mesh) (80 mg, 23 mmol) and catalytic amount of $HgCl_2$ (0.12 g, 0.5 mmol) in dry ethanol (20 ml) were stirred for 2 h at room temperature. The reaction mixture was poured into cold (5 ^{o}C) 0.5 N HCl and extracted with diethyl ether (2 x 30 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (20ml), water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 80% hexane/ethyl acetate) afforded the starting material **benzoic acid 2-benzenesulfonyl-1-benzylpentyl ester** (**118**) in high yield without the presence of the desired compound (**120**).

4.2.21 Preparation of 3-benzenesulfonyl-1-phenyl-1-hexene (121)[9]



121

Compound (**121**) was prepared following exactly the same procedure and reagents [(mercury (15 ml), Na (1.00 g, 43 mmol), compound (**118**) (1.00 g, 23 mmol) and Na_2HPO_4 (0.30 g, 23 mmol)] utilised for the preparation of compound (**119**) but using only dry THF (20 ml) as the solvent.

The resulting mixture was stirred for 1 h at -20 ^{o}C followed by 2 h stirring at room temperature. The reaction was added with ice-cold water (10 ml) and elimination of the mercury residue was done by decanting the top solution. The resultant solution was extracted with diethyl ether (2 x 30 ml). The combined organic extracts were washed with aqueous NH_4Cl (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 80% hexane/ethyl acetate) afforded a yellowish oil of **3-benzenesulfonyl-1-phenyl-hexene (121)** (0.70 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.92 (3H, t, CH_3), 1.28-2.19 (4H, m, 2xCH_2), 3.61-3.68 (1H, m, $CHSO_2Ph$), 5.89 (1H, dd, *J*= 15.6 and 9.6 Hz, CH, *trans*), 6.24 (1H, d, *J*= 15.6 Hz, CH, *trans*), 7.23-7.80 (10H, m, *Ar*-H).

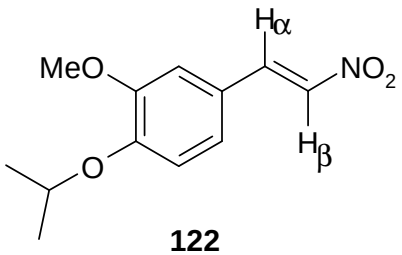
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.6 (CH_3), 20.0 (CH_2), 29.2 (CH_2), 29.4 ($CHSO_2Ph$), 121.2 (α-CH), 126.4 (β-CH), 126.6 (2C, C-2 and C-6), 126.8 (2C, C-2' and C-6'), 128.5 (C-4), 128.9 (C-3 and C-5), 130.5 (C-3' and C-5'), 135.4 (C-4'), 136.3 (C-1), 137.9 (C-1').

HRESIMS *m/z* $[M+H]^+$ 301.1274

(calc. for $C_{18}H_{20}O_2S$+H, 301.1278)

4.2.22 Preparation of 1-isopropoxy-2-methoxy-4-(2-nitrovinyl)benzene (122)[11]



122

To a solution of 4-isopropoxy-3-methoxybenzaldehyde (**104**) (1.00 g, 5 mmol) and nitromethane (1.3 ml, 30 mmol) in EtOH (25 ml) at 0 ^{o}C was added 5% aqueous potassium hydroxide solution (10 ml). After stirring for 1 h at the same temperature, the reaction mixture was poured into 15% aqueous HCl solution (20 ml) and a yellow precipitate formed which was filtered and dried *in vacuo*. The crude product was recrystallised from hexane to afford yellow crystals of **1-isopropoxy-2-methoxy-4-(2-nitrovinyl)benzene (122)** (0.90 g, 90%).

Mp: 90-93 ^{o}C from hexane

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.39 [6H, 2xs, OCH($C\underline{H}_3$)$_2$], 3.88 (3H, s, OCH_3), 4.63 [1H, sept, O$\underline{C}$H(CH_3)$_2$], 6.89 (1H, d, *J*=8.4 Hz, H-5) 6.99 (1H, d, *J*=2.4 Hz, H-2), 7.11 (1H, dd, *J*=2.1 Hz, H-6), 7.50 (1H, d, *J*=13.5 Hz, CH_α, *trans*) 7.94 (1H, d, *J*=13.5 Hz, CH_β, *trans*).

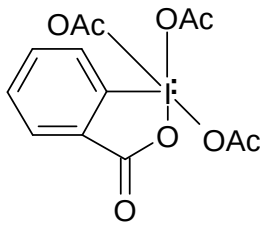
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

21.8 [OCH($\underline{C}H_3$)$_2$], 56.0 (OCH_3), 71.3 [O$\underline{C}$H(CH_3)$_2$], 109.8 (C-2), 111.0 (C-5), 114.1 (C-6), 122.5 (C-1), 124.5 (C-4), 135.0 (CH), 139.5 (CH), 150.4 (C-3).

HRESIMS *m/z* $[M+H]^+$ 239.1168
(calc. for $C_{12}H_{16}NO_4$+H, 239.1170)

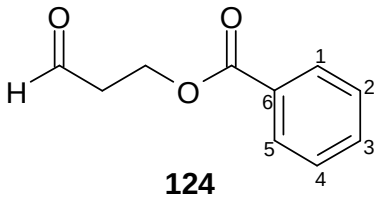
IR ν_{max} (cm^{-1}): 1625,1488.

4.2.23 Preparation of Dess-Martin periodinane[12]



Potassium bromate (15.00 g, 90 mmol) was added over a 0.5 h period to a vigorously stirred mixture of 2-iodobenzoic acid (17.00 g, 68 mmol) and sulfuric acid (146 ml, 0.7 M) at 55 ^{o}C. The mixture was warmed to 65 ^{o}C and stirred for 3.6 h. Then it was cooled to 0 ^{o}C, filtered off and washed with 1 L of water and ethanol (2 x 50 ml) to give 2-iodoxybenzoic acid in 98%. Then 2-iodoxybenzoic acid (5.00 g, 18 mmol) was stirred as slurry in acetic anhydride (17.00 g, 0.8 mol), acetic acid (70 ml) and heated to 100 ^{o}C. All the solids were dissolved approximately after 40 minutes and the solvent was removed under vacuum at room temperature until thick slurry remained. The slurry was filtered in an inert atmosphere and washed with diethyl ether (180 ml) to give the Dess-Martin periodinane (7.00 g, 87%) which was utilised without further purification.

4.2.24 Preparation of 3-oxopropyl benzoate (124)[13,14]



124

The compound was prepared in two steps, firstly selective protection of 1,3-propanediol followed by oxidation of the free hydroxy group. A solution of 1,3-propanediol (3.00 g, 42 mmol) in THF (5 ml) was added at 0 ^{o}C to a suspension of sodium hydride (2.39 g, 50 mmol) in THF(20 ml) and the mixture was stirred at room temperature for 1 h. Benzoyl chloride (5 ml, 42 mmol) in THF (5 ml) was slowly added at 0 ^{o}C to the mixture and continue stirring at room temperature for 2 h. The 10% potassium carbonate was added and the two-phase mixture was stirred at room temperature for 1 h. The mixture was extracted with diethyl ether (3 x 25 ml) and the combined organic extracts were washed with brine (25 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was subjected further to oxidation reaction without further purification.

A solution of crude material (1.00 g, 6 mmol) in dry dichloromethane (20 ml) was added Dess-Martin periodinane (4.00 g, 8 mmol) in dry dichloromethane (10 ml) and the mixture was stirred for 3 h at room temperature. The mixture was filtered off and the remaining organic filtrate was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 80% hexane/ethyl acetate) afforded a colourless oil of **3-oxopropyl benzoate (124)** (2.40 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

2.83 (2H, 2xt, $CHOC\underline{H_2}CH_2OBz$), 4.58 (2H, t, $CHOCH_2C\underline{H_2}OBz$), 7.33-7.96 (5H, m, *Ar*-H), 9.78 (1H, t, C<u>H</u>O).

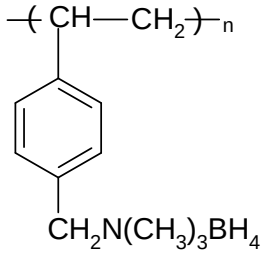
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

42.5 ($CHO\underline{C}H_2CH_2OBz$), 58.3 ($CHOCH_2\underline{C}H_2OBz$), 128.2 (2C, C-3 and C-5), 129.2 (2C, C-2 and C-6), 129.6 (C-1), 133.0 (C-4), 166.2 (CO_2Ar), 199.4 (CHO).

HRESIMS *m/z* $[M+H]^+$ 179.07178
(calc. for $C_{10}H_{10}O_3$+H, 179.07180)

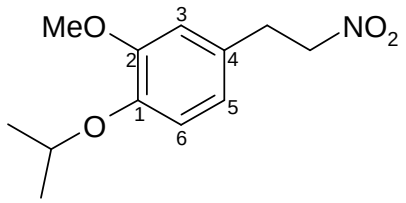
IR ν_{max} (cm^{-1}): 2773, 1643.

4.2.25 Preparation of borohydride exchange resin (BER)[15,16]



An aqueous solution of $NaBH_4$ (1 M, 200 ml) was stirred with wet chloride-form resin (Amberlite IRA 400) (40.00 g) for 1 h. The resulting resin was thoroughly washed with distilled water until free of excess $NaBH_4$. The borohydride exchange resin was then dried *in vacuo* at 60 ^oC for 6 h. The dried resin (40.00 g) was stored under nitrogen in a refrigerator.

4.2.26 Preparation of 1-isopropoxy-2-methoxy-4-(2-nitroethyl)benzene (125)[15]



125

To the solution of 1-isopropoxy-2-methoxy-4-(2-nitro-vinyl)-benzene (**122**) (1.00 g, 4 mmol) in mixture of methanol/dichloromethane (10:1, 20 ml) was added BER (1.5 g, 4 mmol). The reaction mixture was stirred at room temperature for 2 h. The resin was filtered off and the filtrate was concentrated *in vacuo*. The chromatographic purification of the residue (elution with 80% hexane/ethyl acetate) afforded a yellowish oil of **1-isopropoxy-2-methoxy-4-(2-nitroethyl)benzene (125)** (0.90 g, 90%).

^1H NMR (300 MHz, $CDCl_3$) δ_H:

1.30 [6H, 2xs, $OCH(C\underline{H}_3)_2$], 3.21 (2H, t, $C\underline{H}_2CH_2NO_2$), 3.80 (3H, s, OCH_3), 4.45 [1H, sept, $OC\underline{H}(CH_3)_2$], 4.55 (2H, t, $CH_2C\underline{H}_2NO_2$), 6.67 (2H, d, *J*=6.3 Hz, *Ar*-H), 6.80 (1H, d, *J*=9 Hz, *Ar*-H).

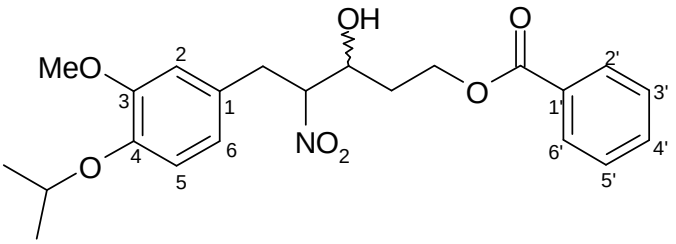
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

21.9 [$OCH(\underline{C}H_3)_2$], 32.9 ($\underline{C}H_2CH_2NO_2$), 55.8 (OCH_3), 71.3 [$O\underline{C}H(CH_3)_2$], 76.4 ($CH_2\underline{C}H_2NO_2$), 112.3 (C-2), 115.9 (C-5), 120.5 (C-6), 128.4 (C-1), 146.5 (C-4), 150.5 (C-3).

HRESIMS *m/z* $[M+H]^+$ 241.13266

(calc. for $C_{12}H_{18}NO_4$+H, 241.13269)

4.2.27 Preparation of 3-hydroxy-5-(4-isopropoxy-3-methoxyphenyl)-4-nitro-pentyl benzoate (126)[17,19]



126

To a solution of tetrabutylammonium fluoride (0.22 g, 0.8 mmol) in THF was added 1-isopropoxy-2-methoxy-4-(2-nitroethyl)benzene (**125**) (0.5 g, 2 mmol) at 0 ^oC. The 3-oxopropyl benzoate (**124**) (0.4 g, 2 mmol) and triethylamine (0.3 ml, 2 mmol) were added to the bright red solution. To this solution was added a solution of *tert*-butyldimethylsilyl chloride (0.5 g, 3 mmol) in THF (5 ml) at 0 ^oC. The reaction mixture was allowed to warm up to room temperature for 30 minutes. The mixture was filtered off and the remaining filtrate was diluted with water (20 ml) and extracted with diethyl ether (3 x 25 ml).

The combined organic layers were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 80% hexane/ethyl acetate) afforded a yellowish oil of **3-hydroxy-5-(4-isopropoxy-3-methoxyphenyl)-4-nitro-pentyl benzoate (126)** (0.30 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.29 [6H, 2xs, OCH(C<u>H</u>$_3$)$_2$], 1.98 (2H, m, CH_2), 3.18 (2H, m, CH_2), 3.74 (3H, s, OCH_3), 4.14 [1H, sept, OC<u>H</u>$(CH_3)_2$], 4.47 (3H, m, CH_2 and C<u>H</u>OH), 4.73 (1H, m, $CHNO_2$), 6.64 (2H, d, *J*=6.3 Hz, *Ar*-H), 6.71 (1H, d, *J*=9 Hz, *Ar*-H), 7.38-7.97 (5H, m, *Ar*-H).

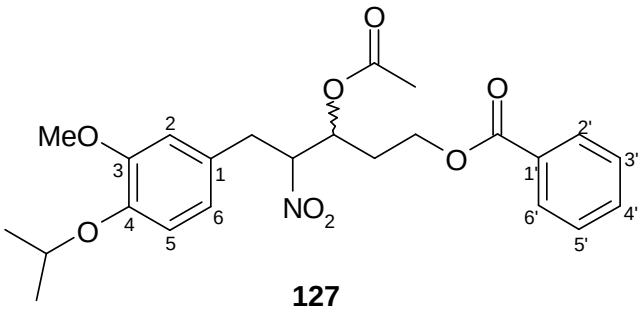
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

21.8 [OCH(<u>C</u>$H_3)_2$], 32.7 (CH_2), 35.7 (CH_2), 55.7 (OCH_3), 61.0 (CH_2), 68.7 (CHOH), 71.3 ($OCH(CH_3)_2$), 93.4 ($CHNO_2$), 112.5 (C-2), 115.7 (C-5), 120.9 (C-6), 123.8 (C-1), 128.4 (2C, C-3' and C-5'), 129.5 (2C, C-2' and C-6'), 130.5 (C-1'), 133.2 (C-4'), 146.9 (C-4), 150.3 (C-3).

HRESIMS *m/z* $[M+H]^+$ 419.19655
(calc. for $C_{22}H_{28}NO_7$+H, 419.19658)

IR ν_{max} (cm^{-1}): 3320, 16.30, 1456.

4.2.28 Preparation of 3-acetoxy-5-(4-isopropoxy-3-methoxyphenyl)-4-nitro-pentyl benzoate (127)[18,19]

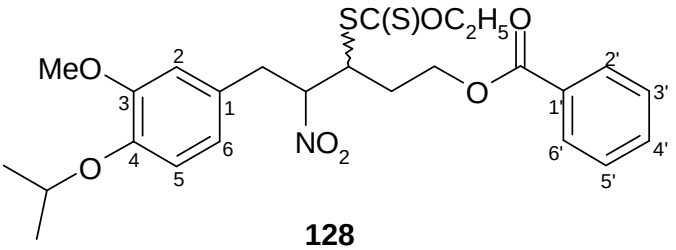


127

The 3-Hydroxy-5-(4-isopropoxy-3-methoxyphenyl)-4nitro-pentyl benzoate (**126**) (1.50 g, 4 mmol) was dissolved in dichloromethane (20 ml) and acetic anhydride (7 ml, 7 mmol) and DMAP (0.40 g, 4 mmol) were added sequentially at room temperature. After stirring for 2 h at the same temperature, the reaction was added water (20 ml) and extracted with dichloromethane (3 x 20 ml).

The combined organic layers were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The yellow solid of **5-3-acetoxy-5-(4-isopropoxy-3-methoxyphenyl)-4-nitro-pentyl benzoate (127)** (1.43 g, 95%) obtained and was utilised in the next step without further purification and characterisation.

4.2.29 Preparation of 3-ethoxythiocarbonylsulfanyl-5-(4-isopropoxy-3-methoxyphenyl)-4-nitropentyl benzoate (128)[19]



128

To a solution of 3-acetoxy-5-(4-isopropoxy-3-methoxyphenyl)-4-nitropentyl benzoate (**127**) (1.50 g, 3 mmol) in a 9/1 mixture of acetonitrile and acetic acid (20 ml) was added potassium *O*-ethylxanthate (0.60 g, 4 mmol) at 0 ^{o}C under nitrogen atmosphere. The reaction was stirred at room temperature until complete consumption of the starting material. The reaction was added a saturated solution of citric acid (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with water (20 ml), saturated solution of sodium hydrogen carbonate, brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 80% hexane/ethyl acetate) afforded a pale yellow oil of **3-ethoxythiocarbonylsulfanyl-5-(4-isopropoxy-3-methoxyphenyl)-4-nitropentyl benzoate (128)** (0.5 g, 30%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.20 (3H, t, CH_2CH_3), 1.32 (6H, 2xs, $OCH(CH_3)_2$), 1.99-2.31 [3H, m, CH_2 and C<u>H</u>SC(S)OEt], 3.18 (2H, m, CH_2), 3.83 (3H, s, OCH_3), 4.06 (2H, q, *J*=7.2 Hz and 7.5 Hz, CH_2CH_3), 4.14 [1H, sept, $OCH(CH_3)_2$], 4.48 (3H, m, $CHNO_2$ and CH_2), 6.85 (1H, d, *J*=8.4 Hz, *Ar*-H), 6.95 (1H, d, *J*=2.1 Hz, *Ar*-H), 7.00 (1H, dd, *J*=1.5 Hz and 1.8 Hz, *Ar*-H), 7.39-8.07 (5H, m, *Ar*-H).

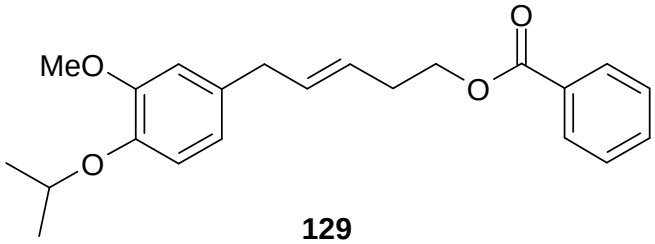
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.9 (CH_2CH_3), 21.8 [$OCH(CH_3)_2$] 29.3 (CH_2), 31.6 (CH_2), 35.6 [CHSC(S)OEt], 55.9 (OCH_3), 60.2 (CH_2CH_3), 62.7 (CH_2), 71.1 [$OCH(CH_3)_2$], 80.6 ($CHNO_2$), 111.2 (C-2), 114.5 (C-5), 120.9 (C-6), 123.8 (C-1), 128.3 (2C, C-3' and C-5'), 129.3 (C-1'), 130.0 (2C, C-2' and C-6'), 133.6 (C-4'), 149.0 (C-4), 150.4 (C-3), 171.5 [SC(S)OEt].

HRESIMS *m/z* $[M+H]^+$ 523.17251
(calc. for $C_{25}H_{32}NO_7S_2$+H, 523.17254)

IR ν_{max} (cm^{-1}): 1650, 1420.

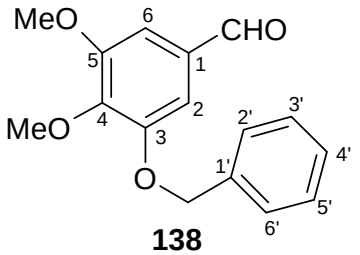
4.2.30 Attempted preparation of 5-(4-isopropoxy-3-methoxyphenyl)-3-pentenyl benzoate (129)[19]



129

To a solution 3-ethoxythiocarbonylsulfanyl-5-(4-isopropoxy-3-methoxyphenyl)-4-nitropentyl benzoate (**128**) (2.50 g, 5 mmol) in refluxing degassed 1,2-dichloroethane (25 ml) was added dilauroyl peroxide (DLP) (2.90 g, 7 mmol) under nitrogen atmosphere. The reaction was stirred at refluxed for 90 minutes and DLP (2.90 g, 7 mmol) was added once again. After a further 90 minutes at reflux, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water (20 ml) and dichloromethane (20 ml) and the aqueous layer was extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded the starting material **3-ethoxythiocarbonylsulfany-5-(4-isopropoxy-3-methoxyphenyl)-4-nitropentyl benzoate (128)** in high yield (2.3 g, 90%) without the presence of the desired compound (**129**).

4.2.31 Preparation of 3-benzyloxy-4,5-dimethoxybenzaldehyde (138)[20]



138

The 3-hydroxy-4,5-dimethoxybenzaldehyde (**101**) (2.00 g, 11 mmol), and K_2CO_3 (3.03 g, 22 mmol) were stirred in acetonitrile (30 ml) under argon. Benzyl bromide (1.60 ml, 2.25 g, 13 mmol) was added and the mixture heated at 60 ^{o}C for 12 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and washed with water (3 x 30 ml). The aqueous layer was extracted with ethyl acetate (2 x 50 ml), the combined organic extracts were washed with water (2 x 50 ml) solution followed by brine (1 x 50 ml) and dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a yellowish oil.

The chromatographic purification on silica (elution with 80% hexane/ethyl acetate) afforded **3-benzyloxy-4,5-dimethoxybenzaldehyde** (**138**) (1.7 g, 85%) as white solid.

Mp: 43-45 ^{o}C from hexane

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

3.90-3.95 (6H, 2xs, 2xOCH_3), 5.16 (2H, s, OCH_2Bn), 7.12 (1H, d, *J*=1.5 Hz, *Ar*-H), 7.16 (1H, d, *J*=1.5 Hz, *Ar*-H), 7.30-7.45 (5H, m, *Ar*-H), 9.81 (1H, s, CHO).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C:

56.1 (OCH_3), 71.1 (OCH_2Bn), 106.5 (C-6), 109.1 (C-2), 127.4 (2C, C-2' and C-6'), , 128.3 (2C, C-3' and C-5'), 129.9 (C-4'), 131.5 (C-1), 136.29 (C-4), 144.2 (C-1'), 152.5 (C-3), 153.7 (C-5), 190.9 (CHO).

HRESIMS *m/z* $[M+H]^+$ 273.1133

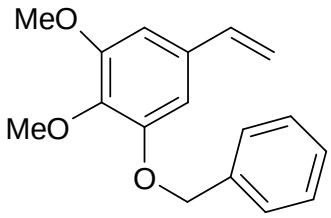
(calc. $C_{16}H_{16}O_4$+H, 273.1127)

IR ν_{max} (cm^{-1}): 1622.

4.2.32 Preparation of methyltriphenylphosphonium iodide (139)[7]

Triphenylphosphine (1.00 g, 4 mmol) was added to iodomethane (0.20 ml, 0.50 g, 4 mmol) in benzene (50 ml) and the mixture was refluxed for 2 h until formation of the salt. The reaction was cooled to room temperature and the salt was then filtered off and dried in high vacuum pressure (*ca*. 22 Torr) to obtain a pure white salt which upon recrystallisation from EtOH gave pure crystals of **methyltriphenylphosphonium iodide (139)** (0.50 g, 100%) with a melting point of more than 300 ^{o}C.

4.2.33 Preparation of 1-benzyloxy-2,3-dimethoxy-5-vinylbenzene (140)[21]



140

To a suspension of methyltriphenylphosphonium iodide (**139**) (3.00 g, 7 mmol) in dry THF (50 ml), potassium *tert*-butoxide (0.80 g, 7 mmol) was added at 0 ^{o}C and stirred for 15 minutes. Then the above mixture was added to a solution of 3-benzyloxy-4,5-dimethoxybenzaldehyde (**138**) (1.00 g, 4 mmol) in dry THF using a syringe. The combined mixture was stirred at room temperature for another 15 minutes. The consumption of starting material was monitored by TLC and when the reaction is complete, the mixture was concentrated *in vacuo* and partitioned between water and diethyl ether. The organic layer was washed with water (2 x 50 ml) followed by brine (1 x 50 ml), dried over magnesium sulfate and finally concentrated *in vacuo* to afford a yellowish oil. The chromatographic purification on silica (elution with 90% hexane/ethyl acetate) afforded **1-benzyloxy-2,3-dimethoxy-5-vinylbenzene** (**140**) (0.90 g, 90%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

3.88-3.89 (6H, 2xs, 2xOCH_3), 5.14 (2H, s, OCH_2Bn), 5.19 (1H, d, *J*=10.9 Hz, β_1-CH), 5.61 (1H, d, *J*=17.5 Hz, β_2-CH), 6.57-6.63 (1H, dd, *J*=10.8 Hz and 6.7 Hz, α-CH) 6.65-6.68 (2H, 2 x d, *J*=1.8 Hz, *Ar*-H), 7.30-7.47 (5H, m, *Ar*-H).

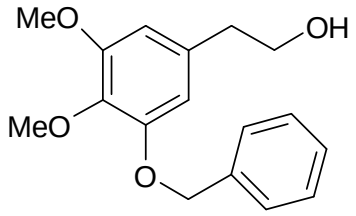
^{13}C NMR (125 MHz, $CDCl_3$) δ_C:

56.1 (OCH_3), 60.9 (OCH_3), 71.2 (OCH_2Bn), 103.7 (C-6), 105.8 (C-2), 113.2 (β-CH), 127.2 (2C, C-2' and C-6'), 127.8 (C-4'), 127.9 (2C, C-3' and C-5'), 133.2 (α-CH), 136.7 (C-1), 137.1 (C-4), 138.8 (C-1), 152.5 (C-3), 153.5 (C-5).

HRESIMS *m/z* $[M+H]^+$ 271.1333

(calc. for $C_{17}H_{18}O_3$+H, 271.1334)

4.2.34 Preparation of 2-[(3-benzyloxy)-4,5-dimethoxyphenyl]ethanol (141)[20]



141

To a solution of 1-benzyloxy-2,3-dimethoxy-5-vinylbenzene (**140**) (1.00 g, 3.6 mmol) in dry THF (50 ml) at 0 ^oC under argon atmosphere was added $BH_3.(CH_3)_2S$ (0.70 ml, 3.6 mmol, 5 M solution in diethyl ether) and stirred for 4 h at room temperature. The reaction flask was cooled to 0 ^oC and then a solution of NaOH (0.30 g, 7 mmol) in ethanol/water ratio 2:1 (20 ml) followed by hydrogen peroxide (0.30 ml, 11 mmol, 30% w/v solution in H_2O) were added dropwise over 30 minutes. The mixture was then allowed to stir at room temperature for 3 h. The product was taken up in ethyl acetate and the aqueous layer extracted twice with ethyl acetate (3 x 30 ml). The combined organic layers were washed with water (50 ml), brine (50ml), dried over magnesium sulfate and concentrated *in vacuo* to yield a crude product which upon chromatographic purification on silica (elution with 50% hexane/ethyl acetate) afforded **2-[(3-benzyloxy)-4,5-dimethoxyphenyl]ethanol** (**141**) (0.85 g, 85%) as colourless oil.

^1H NMR (500 MHz, $CDCl_3$) δ_H:

2.77 (2H, t, *J*=6.4 Hz, $C\underline{H_2}CH_2OH$), 3.81 (2H, t, *J*=6.4 Hz and 6.3 Hz, $CH_2C\underline{H_2}OH$), 3.86 (6H, 2xs, $2xOCH_3$), 5.13 (2H, s, OCH_2Bn), 6.45 (2H, 2xd, *J*=1.7 Hz and 1.8 Hz, *Ar*-H), 7.31-7.44 (5H, m, *Ar*-H).

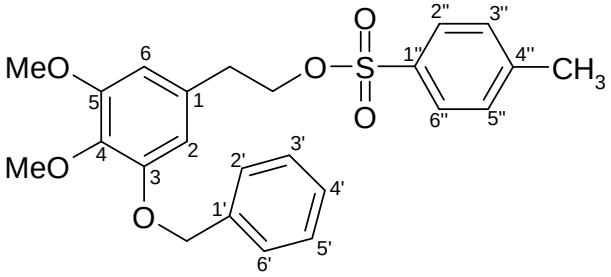
^{13}C NMR (125 MHz, $CDCl_3$) δ_C:

39.4 ($\underline{C}H_2CH_2OH$), 56.1 (OCH_3), 60.9 (OCH_3), 63.5 ($CH_2\underline{C}H_2OH$), 71.1 (OCH_2Bn), 106.3 (C-6), 108.3 (C-2), 127.3 (2C, C-6' and C-2'), 127.9 (C-4'), 128.5 (2C, C-3' and C-5'), 134.0 (C-1), 137.2 (C-4), 137.4 (C-1'), 152.4 (C-3), 153.5 (C-5).

HRESIMS *m/z* $[M+H]^+$ 289.1451
(calc. for $C_{17}H_{20}O_4$+H, 289.1440)

IR ν_{max} (cm^{-1}): 3410.

4.2.35 Preparation of 3-(benzyloxy)-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate (142)[20]



142

To a solution of 2-[(3-benzyloxy)-4,5-dimethoxyphenyl]ethanol (**141**) (1.00 g, 4 mmol) in dry CH_2Cl_2 (30 ml) at 0 ^oC under argon atmosphere was triethyl amine (0.60 ml, 4 mmol) followed by *para*-toluenesulfonyl chloride (0.80 g, 4 mmol) and the reaction mixture was stirred at room temperature for 30 minutes to 2 h. Upon completion of the reaction by TLC monitoring for consumption of starting material, the reaction mixture was quenched with aqueous HCl (5 ml, 5 M).

The resulting aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue on silica (elution with 70% hexane/ethyl acetate) afforded **3-(benzyloxy)-4,5-**

dimethoxyphenethyl 4-methylbenzenesulfonate (**142**) (0.90 g, 90%) as a white solid.

Mp: 35-37 ^{o}C from hexane

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

2.41 (3H, s, OTs-CH_3), 2.84-2.87 (2H, t, *J*=6.9 Hz and 8.05 Hz, C$\underline{H_2}$$CH_2$OTs), 3.79-3.84 (6H, 2xs, 2xOCH_3), 4.17-4.20 (2H, t, *J*=7.05 Hz and 6.9 Hz, CH_2C$\underline{H_2}$OTs), 5.05 (2H, s, OCH_2Bn), 6.31-6.36 (1H, 2xd, *J*=1.7 Hz and 1.6 Hz, *Ar*-H), 7.26 (1H, d, *J*=2.9 Hz, *Ar*-H), 7.27-7.44 (5H, m, *Ar*-H).

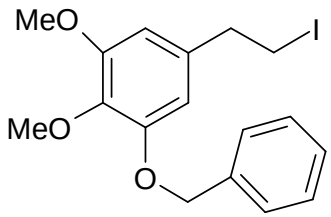
^{13}C NMR (125 MHz, $CDCl_3$) δ_C:

21.6 (OTs-CH_3), 35.9 ($\underline{C}H_2CH_2$OTs), 56.0 (OCH_3), 60.9 (OCH_3), 70.5 ($CH_2\underline{C}H_2$OTs), 71.1 (OCH_2Bn), 106.2 (C-6), 108.1 (C-2), 127.3 (2C, C-2' and C-6'), 127.8 (2C, C-3' and C-5'), 127.9 (2C, C-2'' and C-6''), 128.5 (2C, C-3'' and C-5''), 129.7 (C-4'), 130.2 (C-1''), 131.8 (C-1), 132.9 (C-4), 137.1 (C-4''), 137.2 (C-1'), 144.7 (C-3), 152.3 (C-5).

HRESIMS *m/z* $[M+Na]^+$ 465.1083

(calc. for $C_{24}H_{26}O_6$+Na, 465.1080)

4.2.36 Preparation of 1-benzyloxy-5-(2-iodoethyl)-2,3-dimethoxybenzene (130)[22]



130

A solution of 3-(benzyloxy)-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate (**142**) (1.00 g, 2 mmol) in acetone (50 ml) containing NaI (1.70 g, 11 mmol) was refluxed for 24 h. Upon completion of the reaction by TLC monitoring for consumption of starting material, the reaction mixture was cooled to room temperature and precipitated sodium *para*-toluenesulfonate was filtered off. The filtrate was concentrated *in vacuo*. The residue was partitioned between water (50 ml) and chloroform (25 ml). The organic layer was washed with aqueous $Na_2S_2O_3$ (50 ml), water (50 ml) and brine (50 ml) followed by drying over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue on silica (elution with 80% hexane/ethyl acetate) afforded **1-benzyloxy-5-(2-iodoethyl)-2,3-dimethoxybenzene (130)** (0.90 g, 90%) as white solid.

Mp: 60-63 ^{o}C from hexane

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

2.84-2.87 (2H, t, *J*=8 Hz $C\underline{H_2}CH_2I$), 3.29 (2H, t, *J*=8 Hz, $CH_2C\underline{H_2}I$), 3.85-3.86 (6H, 2xs, $2xOCH_3$), 5.13 (2H, s, OCH_2Bn), 6.41 (1H, d, *J*=1.8 Hz, *Ar*-H), 6.44 (1H, d, *J*=1.8 Hz, *Ar*-H), 7.31-7.45 (5H, m, *Ar*-H).

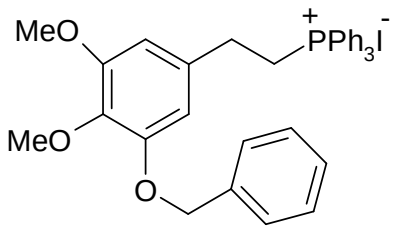
^{13}C NMR (125 MHz, $CDCl_3$) δ_C:

5.3 ($CH_2\underline{C}H_2I$), 40.7 ($\underline{C}H_2CH_2I$), 56.1 (OCH_3), 60.9 (OCH_3), 71.2 (OCH_2Bn), 105.8 (C-6), 107.7 (C-2), 127.3 (2C, C-2' and C-6'), 127.9 (C-4'), 128.5 (2C, C-3' and C-5'), 136.2 (C-1), 137.1 (C-4), 137.9 (C-1'), 152.4 (C-3), 153.5 (C-5).

HRESIMS *m/z* $[M+H]^+$ 399.0452

(calc. for $C_{17}H_{19}IO_3$+H, 399.0457)

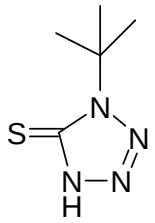
4.2.37 Preparation of 1-benzyloxy-2,3-dimethoxyphenethyltriphenylphosphonium iodide(143)[23]



143

To a solution of 1-benzyloxy-5-(2-iodoethyl)-2,3-dimethoxybenzene (**130**) (1.00 g, 2 mmol) in xylene (50 ml) was added triphenylphosphine (1.30 g, 5 mmol) and the reaction mixture was refluxed under argon for 24 h or until the formation of the salt. Then the solution was cooled to 50 ^{o}C and filter the solution to afford the milky white solid of **1-benzyloxy-2,3-dimethoxyphenethyltriphenylphosphonium iodide** (**143)** (1.00 g, 100%) after successive drying in high vacuum (*ca*. 22 Torr). The salt was utilised without further purification and characterisation.

4.2.38 Preparation of 1-*tert*-butyl-1,4-dihydrotetrazol-5-thione (144)[24,25]

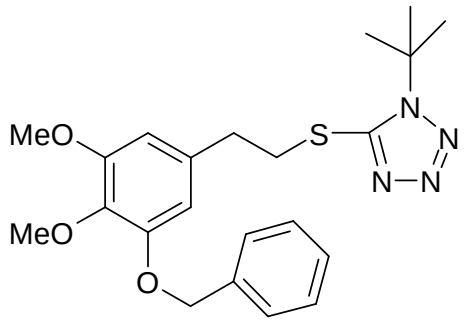


144

To a solution of NaN_3 (5.60 g, 86.8 mmol) in warm water (27 ml) was added *tert*-butyl isothiocyanate (10.00 g, 86.8` mmol) as an *i*-PrOH (21 ml) solution *via* dropping funnel over a period of 30 minutes. At the end of the addition, the mixture was refluxed for 16 h, then cooled in ice-bath and concentrated HCl (13 ml) was added carefully. The mixture was concentrated under reduced pressure and stored at 0 ^{o}C for overnight.

The yellow solid obtained was filtered off and washed once with ice-cooled water, then dried under high vacuum pressure (*ca*. 22 Torr) to obtain a pale yellow powder of **1-*tert*-butyl-1,4-dihydrotetrazol-5-thione (144)** (10.00 g , 100%) with a melting point of 88-90 ^{o}C (lit.[10] 90-92 ^{o}C) from cyclohexane. The salt was utilised without further purification and characterisation.

4.2.39 Preparation of 5-[2-(3-benzyloxy-4,5-dimethoxyphenyl)-ethylsulfanyl]-1-*tert*-butyl-4,5-dihydro-1*H*-tetrazole (145)[24]



145

A solution of 1-*tert*-butyl-1,4-dihydrotetrazol-5-thione (**144**) (1.00 g, 6.7 mmol) in anhydrous THF (5 ml) was added *via* a canula at 0 ^{o}C into a suspension of NaH (0.30 g, 8 mmol) in anhydrous THF (20 ml). After an hour stirring at 0 ^{o}C, 1-benzyloxy-5-(2-iodo-ethyl)-2,3-dimethoxy-benzene (**130**) (2.70 g, 6.7 mmol) in anhydrous THF (5 ml) was added *via* with a syringe. The mixture was stirred overnight at room temperature. Upon completion of the reaction by TLC monitoring for consumption of starting material, the reaction mixture was cooled to 0 ^{o}C and quenched with ice cold water. The resulting precipitate was filtered off and the solvent was removed *in vacuo*. The remaining aqueous layer was extracted with ethyl acetate (3 x 20 ml) and the organic phase was washed with water (20 ml) and brine (20 ml) followed by drying over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 70% hexane/ethyl acetate) afforded **5-[2-(3-benzyloxy-4,5-dimethoxyphenyl)-ethylsulfanyl]-1-*tert*-butyl-4,5-dihydro-1*H*-tetrazole (145)** (0.90 g, 90%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:

1.73, [9H, s, $C(CH_3)_3$], 3.06 (2H, t, *J*=7.4 Hz and 7.8 Hz, $C\underline{H_2}CH_2S$), 3.60 (2H, t, *J*=7.8 Hz and 7.4 Hz, $CH_2C\underline{H_2}S$), 3.87 (6H, s, 2xOCH_3), 5.14 (2H, s, OCH_2Bn), 6.49 (1H, d, *J*=1.7 Hz, *Ar*-H), 6.54 (1H, d, *J*=1.7 Hz, *Ar*-H), 7.28-7.48 (5H, m, *Ar*-H).

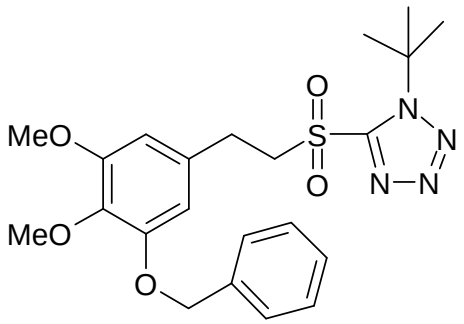
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:

28.7 [$C(CH_3)_3$], 34.9 ($\underline{C}H_2CH_2S$), 35.8 ($CH_2\underline{C}H_2S$), 56.2 [$\underline{C}(CH_3)_3$], 60.9/61.0 (2xOCH_3), 71.3 (OCH_2Bn), 106.2 (C-6), 108.1 (C-2), 127.4 (2C, C-2' and C-6'), 127.9 (C-4'), 128.1 (SCN_2), 128.5 (C-3'), 128.5 (C-5'), 134.9 (C-1), 137.2 (C-4), 137.7 (C-1'), 152.4 (C-3), 153.5 (C-5).

HRESIMS *m/z* $[M+H]^+$ 429.1963

(calc. for $C_{22}H_{28}N_4O_3S$+H, 429.1960)

4.2.40 Preparation of 5-[2-(3-benzyloxy-4,5-dimethoxyphenyl)-ethanesulfonyl]-1-*tert*-butyl-4,5-dihydro-1*H*-tetrazole (146)[24]



146

A solution of oxone (0.12 g, 0.2 mmol) in H_2O_2 (2 ml) was added at 0 ^{o}C to a stirred solution of 5-[2-(3-benzyloxy-4,5-dimethoxyphenyl)-ethylsulfanyl]-1-*tert*-butyl-4,5-dihydro-1*H*-tetrazole (**145**) (1.00 g, 2.3 mmol) in ethanol (25 ml). The mixture was stirred for few hours at room temperature.

Upon completion of the reaction by TLC monitoring for consumption of starting material, the mixture was concentrated *in vacuo*. The residue was partitioned between water (20 ml) and dichloromethane (20 ml). The organic phase was washed with water (20 ml) and brine (20 ml) followed by drying over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 70% hexane/ethyl acetate) afforded **5-[2-(3-benzyloxy-4,5-dimethoxyphenyl)-ethanesulfonyl]-1-*tert*-butyl-4,5-dihydro-1*H*-tetrazole (146)** (0.91 g, 91%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:

1.87, [9H, s, $C(CH_3)_3$] 3.14 (2H, t, *J*=7.6 Hz and 7.5 Hz, $C\underline{H_2}CH_2SO_2$), 3.84 - 3.94 (8H, s and m, 2x$OC\underline{H_3}$ and $CH_2C\underline{H_2}SO_2$), 5.14 (2H, s, OCH_2Bn), 6.52 (1H, d, *J*=7 Hz, *Ar*-H), 6.56 (1H, d, *J*=7 Hz, *Ar*-H), 7.28-7.52 (5H, m, *Ar*-H).

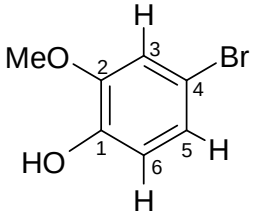
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:

29.8 ($\underline{C}H_2CH_2SO_2$), 30.2 [$C(\underline{C}H_3)_3$], 54.5 [$\underline{C}(CH_3)_3$], 56.3 ($CH_2\underline{C}H_2SO_2$), 60.9/64.1 (2xOCH_3), 71.3 (OCH_2Bn), 106.2 (C-6), 108.1 (C-2), 127.3 (SO_2CN_2), 127.3 (2C, C-2' and C-6'), 127.9 (C-4'), 128.5 (2C, C-3' and C-5'), 133.2 (C-1), 137.0 (C-4), 137.3 (C-1'), 152.7 (C-3), 153.8 (C-5).

HRESIMS *m/z* $[M+H]^+$ 461.1855`

(calc. for $C_{22}H_{28}N_4O_5S$+H, 461.1859)

4.2.41 Preparation of 4-bromo-2-methoxyphenol (147)[26]



147

A mixture of bromine (5.4 ml, 105 mmol) in carbon disulfide (5 ml) was added dropwise to the solution of guaiacol (**135**) (11.2 ml, 105 mmol) and carbon disulfide (30 ml). The solution was stirred at 0 ^{o}C for 18 h, and then partitioned between water (20 ml) and carbon disulfide (20 ml). The organic extracts were washed with water (3 x 20 ml), brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 70% hexane/ethyl acetate) afforded **4-bromo-2-methoxyphenol (147)** (11.38 g, 90%) as a brownish oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

3.87 (3H, s, OCH_3), 5.61 (1H, s, OH), 6.81 (1H, d, *J*=10 Hz, H-6), 6.97 (1H, d, *J*=2.2 Hz, H-3), 7.99 (1H, dd, *J*=2.2 Hz, H-5).

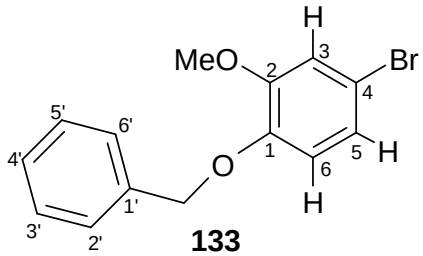
^{13}C NMR (175 MHz, $CDCl_3$) δ_C:

56.1 (OCH_3), 71.2 [O<u>C</u>H(CH_3)$_2$], 114.1 (C-4), 115.7 (2C, C-3 and C-6), 124.1 (C-5), 144.8 (C-1), 147.2 (C-2).

HRESIMS *m/z* $[M+H]^+$ 203.0720
(calc. for C_7H_7 $^{79}BrO_2$+H, 203.0723)

IR ν_{max} (cm^{-1}): 3509.

4.2.42 Preparation of 1-benzyloxy-4-bromo-2-methoxybenzene (133)[20]



133

The 4-Bromo-2-methoxyphenol (**147**) (1.00 g, 5 mmol) and anhydrous potassium carbonate were added to acetonitrile (20 ml) under nitrogen atmosphere.

Benzyl bromide (0.7 ml, 6 mmol) was added and the mixture was heated for 20 h at 50 ^{o}C. After cooling, the mixture was filtered to remove inorganic material and the filtrate was concentrated *in vacuo*. The residue was partitioned between water (20 ml) and chloroform (20 ml). The aqueous layer was extracted with chloroform (3 x 20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 80% hexane/ethyl acetate) afforded **1-benzyloxy-4-bromo-2-methoxybenzene (133)** (0.85 g, 85%) as a white solid.

Mp: 40-46 ^{o}C from hexane

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:

3.89 (3H, s, OCH_3), 5.18 (2H, s, OCH_2Bn), 6.77 (1H, d, *J*=8.5 Hz, H-6), 6.99 (1H, dd, *J*=2.8 Hz, H-3), 7.03 (1H, d, *J*=2.8 Hz, H-5), 7.31-7.49 (5H, m, *Ar*-H).

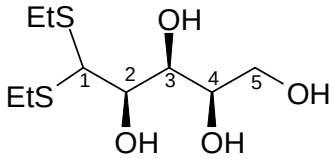
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:

56.2 (OCH_3), 71.2 (OCH_2Bn), 113.4 (C-4), 115.3 (C-6), 115.5 (C-3), 127.3 (2C, C-2' and C-6'), 127.5 (C-4'), 128.0 (2C, C-3' and C-5'), 136.8 (C-1'), 147.4 (C-1), 150.6 (C-2).

HRESIMS *m/z* $[M+H]^+$ 293.0190

(calc. for $C_{14}H_{14}{}^{79}BrO_2$+H, 293.0177)

4.2.43 Preparation of D-xylose diethyl dithioacetal (149)[27,28,29]



149

To a stirred solution of D-xylose (**148**) (10.00 g, 67 mmol) in 6 M hydrochloric acid (100 ml) was added dropwise ethyl mercaptan (10 ml, 135 mmol) over 20 minutes. The mixture was stirred for 2,5 h at room temperature, diluted with water (10 ml) and neutralised with 25% ammonium hydroxide solution (5 ml). The aqueous solution was extracted twice with petroleum ether (20 ml) and the organic phase containing excess of ethane thiol being discarded. Concentration of the aqueous phase under vacuum gave a crystalline residue which was suspended in a mixture of acetone and ethyl acetate (30 ml, 2:1 ratio). The resulting suspension was filtered over a layer of celite and the insoluble mineral material was washed with acetone.

The collected filtrate was concentrated *in vacuo* to obtain syrup (8.00 g, 80%) which crystallised on standing in the cold. The **D-xylose diethyl dithioacetal (149)** was utilised without further purification.

Mp: 39–42 ^{o}C from hexane (*lit.*[27]. 40–43 ^{o}C)

^{1}H NMR (300 MHz, DMSO-d_6) δ_H:

1.16 (6H, t, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H}_3$), 2.08 (1H, s, OH), 2.56-2.66 (4H, m, 2x$SC\underline{H}_2CH_3$), 3.56-4.00 (6H, m, CH-1, CH-2, CH-3, CH-4 and CH_2-5), 4.29/4.42 (2H, 2xs, OH), 4.721 (1H, s, OH).

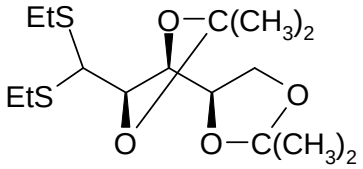
^{13}C NMR (75 MHz, d_6-DMSO) δ_C:

14.3 (2x$SCH_2\underline{C}H_3$), 24.1/25.0 (2x$S\underline{C}H_2CH_3$), 54.7/63.6/70.5/73.3/73.5 (CH-1, CH-2, CH-3, CH-4 and CH_2-5).

HRESIMS *m/z* $[M-H]^-$ 255.0737
(calc. for $C_9H_{20}O_4S_2$-H, 255.0725)

IR ν_{max} (cm^{-1}): 3328.

4.2.44 Preparation of 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (150)[27,28,29]



150

To a suspension of D-xylose diethyl dithioacetal (**149**) (6.00 g, 23 mmol) in anhydrous acetone (100 ml) at 0 ^{o}C was added concentrated sulfuric acid (1 ml). The resulting solution was warmed to room temperature and was stirred for 16 h and then neutralised by addition of calcium hydroxide (4.00 g). The precipitated solid was removed by filtration and washed with acetone (50 ml). The filtrate was concentrated *in vacuo* to leave brown oil which was taken up in diethyl ether and washed with a saturated solution of sodium bicarbonate (50 ml), and then brine (50 ml). The organic extract was dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue on silica (elution with 90% hexane/ethyl acetate) afforded **2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (150)** (5.70 g, 95%) as a yellowish oil.

$[\alpha]_D^{25}$ -64° (*c* 2.6, acetone) [lit.[27,28,29] -67.0° (*c* 2.8, acetone)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.07-1.12 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H_3}$), 1.19-1.28 [12H, 4xs, 2x$OC(C\underline{H_3})_2$] 2.52-2.63 (4H, m, 2x$SC\underline{H_2}CH_3$), 3.74 (2H, m, CH_2-5), 3.87-4.19 (4H, m, CH-1, CH-2, CH-3, CH-4).

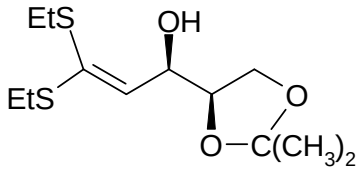
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.9/14.0 (2x$SCH_2\underline{C}H_3$), 24.4/24.8/25.2/25.7/26.7/26.9 (2x$S\underline{C}H_2CH_3$ and 2x$OC(\underline{C}H_3)_2$), 52.5/65.4/74.7/78.1/79.7(CH-1, CH-2, CH-3, CH-4, CH-5), 108.9/109.4 (2x$O\underline{C}(CH_3)_2$).

HRESIMS *m/z* $[M+H]^+$ 337.1502

(calc. for $C_{15}H_{28}O_4S_2$+H, 337.1507)

4.2.45 Preparation of 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diethyl dithioacetal (151)[27,28,29]



151

To a solution of potassium *tert*-butoxide (3.00 g, 27 mmol) in tetrahydrofuran (70 ml) and dimethyl sulfoxide (25 ml) at rt was added dropwise over 15 minutes a solution of 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diethyl dithioacetal (**150**) (4.5 g, 13 mmol) in tetrahydrofuran (5 ml). The mixture was stirred for 1hr and was poured on to ice (500 g). The aqueous mixture was extracted with chloroform (3 x 25 ml), and the combined extracts were washed with cold water (3 x 20 ml), dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* followed by chromatography of the residual oil on silica (elution with 80% hexane/ethyl acetate) afforded **2-deoxy-4,5-*O*-isopropylidene-D-*threo* pent-1-enose diethyl dithioacetal (151)** (2.25 g, 75%) as a pale yellow oil.

$[\alpha]_D^{25}$ -50.5° (*c* 2.4, $CHCl_3$) [lit.[27,28,29] -48.5° (*c* 2.4, $CHCl_3$)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.14-1.19 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H_3}$), 1.28-1.37 [6H, 2xs, $OC(C\underline{H_3})_2$], 2.60-2.85 (5H, m, 2x$SC\underline{H_2}CH_3$ and OH), 3.69-3.87 (2H, 2xdd, *J*=8.1 Hz and 8.4 Hz, CH_2-5), 3.99 (1H, dd, *J*=6.6 Hz, CH-4), 4.68 (1H, m, CH-3), 5.81 (1H, d, *J*=8.1 Hz, CH-2).

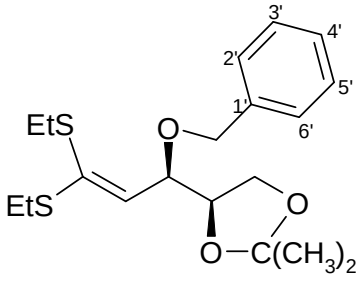
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

13.6/14.8 (2x$SCH_2\underline{C}H_3$), 25.1/26.4/26.8/27.3 [2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$], 65.5 (CH-5), 70.4 (CH-4), 78.6 (CH-3), 109.6 [$O\underline{C}(CH_3)_2$], 132.5 (CH-2), 135.7 (CH-1).

HRESIMS *m/z* $[M-H]^-$ 277.0941
(calc. for $C_{12}H_{22}O_3S_2$-H, 277.0932)

IR ν_{max} (cm^{-1}): 3474.

4.2.46 Preparation of 3-*O*-(benzyl)-2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diethyl dithioacetal (152)[27,28,29]



152

Potassium *tert*-butoxide (0.50 g, 4 mmol) was added in one portion to a stirred solution of 2-deoxy-4,5-*O*-isopropylidene-D-*threo* pent-1-enose diethyl dithioacetal (**151**) (1.00 g, 4 mmol) in THF (30 ml) at -20 ^oC for 1 h, and then catalytic amount of tetrabutylammonium iodide (0.1 g, 0.4 mmol) followed by a solution of benzyl bromide (0.5 ml, 4 mmol) in THF (5 ml) were added. The suspension was allowed to warm to room temperature and stirring was continued for 15 h. Saturated ammonium chloride solution (15 ml) was added and the solvent removed *in vacuo*. The residue was portioned between ethyl acetate (20 ml) and water (20 ml) and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

The chromatography of the residual oil on silica (elution with 80% hexane/ethyl acetate) afforded **3-*O*-(benzyl)-2-deoxy-4,5-*O*-isopropylidene-D-*threo*pent-1-enose diethyl dithioacetal (152)** (0.70 g, 70%) as a pale yellow oil in 70% yield.

$[\alpha]_D^{25}$ +40.5° (*c* 2.4, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

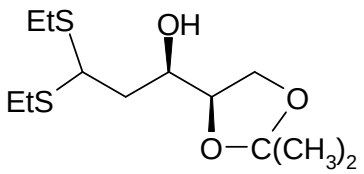
1.21-1.27 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H_3}$), 1.36/1.41 [6H, 2xs, $OC(CH_3)_2$] 2.69-2.91 (4H, m, 2x$SC\underline{H_2}CH_3$), 3.77/3.94 (2H, 2xdd, *J*=1.8 Hz and 15.3 Hz, CH_2-5), 4.22 (1H, dd, *J*=6.6 Hz and 19.7 Hz, CH-4), 4.49/4.62 (2H, 2xd, *J*=12.2 Hz, CH_2Bn), 4.71 (1H, dd, *J*=2.7 Hz and 15.7 Hz, CH-3), 5.84 (1H, d, *J*=9.2 Hz, CH-2), 7.24-7.36 (5H, m, *Ar*-H).

^{13}C NMR (175 MHz, $CDCl_3$) δ_C:

14.0/15.2 (2x$SCH_2\underline{C}H_3$), 25.4/26.4/27.0/27.5 [2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$], 65.7 (CH-5), 70.5 (CH-4), 77.8 (CH-3), 109.7 [$O\underline{C}(CH_3)_2$], 127.4 (C-4'), 127.7 (2C, C-2' and C-6'), 128.2 (2C, C-3' and C-5'), 131.2 (CH-2), 137.5 (CH-1), 138.5 (C-1').

HRESIMS *m/z* $[M+H]^+$ 313.0941
(calc. for $C_{15}H_{20}O_3S_2$+H, 313.0948)

4.2.47 Preparation of 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (153)[27,28,29]



153

Method : 1[27,28,29]

To a stirred suspension of lithium aluminium hydride (0.20 g, 4mmol) in tetrahydrofuran (30 ml) at 0 ^{o}C was added a solution of 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diethyl dithioacetal (**151**) (1.00 g, 4 mmol) in tetrahydrofuran (5 ml) over 20 min. After the addition was complete the mixture was allowed to warm to room temperature and was stirred for a further 3.5 h. Residual lithium aluminium hydride was quenched by sequential addition of water (2 ml), 15% aqueous sodium hydroxide (2 ml) and water (7 ml). The resulting mixture was filtered through a layer of celite, and the collected solid was washed with ethyl acetate. The filtrate was washed with brine and dried over magnesium sulfate. Removal of the solvent *in vacuo* followed by chromatography of the residual oil on silica (elution with 80% hexane/ethyl acetate] afforded **2-deoxy-4,5-*O*-isopropylidene-D-*threo* pentose diethyl dithioacetal (153)** (0.60 g, 60%) as colourless oil.

$[\alpha]_D^{25}$ +24°(*c* 3.9, $CHCl_3$) [lit.[27,28,29] +25.6°(*c* 5.0, $CHCl_3$)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.10 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2 x $SCH_2C\underline{H}_3$), 1.20-1.28 [6H, 2xs, $OC(CH_3)_2$], 1.54-1.85 (2H, m, CH_2-2), 2.39-2.58 (4H, m, 2x$SC\underline{H}_2CH_3$), 2.77 (1H, d, *J*=5.7 Hz, OH), 3.55-3.90 (4H, m, CH-3, CH-4 and CH_2-5), 3.95 (1H, 2 x d, *J*=4.2 Hz and 3.9 Hz, C<u>H</u>-1).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.1/14.2 (2x$SCH_2\underline{C}H_3$), 23.5/24.0/25.0/26.2 [2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$], 39.7 (CH_2-2), 47.2/65.6/69.1/78.5 (CH-1, CH-3, CH-4 and CH_2-5), 109.0 [$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M-H]^-$ 279.1090
calc. for $C_{12}H_{24}O_3S_2$-H, 279.1089)

IR ν_{max} (cm^{-1}): 3447.

Method : 2[27,28,29]

A solution of Red-Al (1 ml, 4 mmol, 3.4 M solution in toluene) was added a cold solution (0 ^{o}C) of purified 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diethyl dithioacetal (**151**) (1.00 g, 4 mmol) in dry toluene (10 ml) in the course of 15 min. After an hour stirring at 0 ^{o}C, the reaction was quenched with 15% aqueous sodium hydroxide solution. The reaction mixture was diluted with ether (50 ml) and the aqueous phase was discarded. The organic phase was washed with water (30 ml), brine (30 ml), and then dried over magnesium sulfate. The chromatography of the residue on silica (elution with 70% hexane/ethyl acetate) afforded **2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (153)** (0.90 g, 90%) as a colourless oil.

$[\alpha]_D^{25}$ +24° (*c* 3.9, $CHCl_3$) [lit.[27,28,29] +25.6° (*c* 5.0, $CHCl_3$)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.10 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H}_3$), 1.20-1.28 [6H, 2xs, $OC(CH_3)_2$], 1.54-1.85 (2H, m, CH_2-2), 2.39-2.58 (4H, m, 2x$SC\underline{H}_2CH_3$), 2.77 (1H, d, *J*=5.7 Hz, OH), 3.55-3.90 (4H, m, CH-3, CH-4 and CH_2-5), 3.95 (1H, 2xd, *J*=4.2 Hz and 3.9 Hz, CH-1).

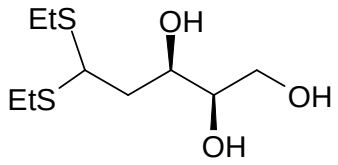
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.1/14.2 (2x$SCH_2\underline{C}H_3$), 23.5/24.0/25.0/26.2 [2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$], 39.7 (CH_2-2), 47.2/65.6/69.1/78.5 (CH-1, CH-3, CH-4 and CH_2-5), 109.0 [$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M-H]^-$ 279.1090
(calc. for $C_{12}H_{24}O_3S_2$-H, 279.1089)

IR ν_{max} (cm^{-1}): 3447.

4.2.48 Preparation of 2-deoxy-D-*threo*-pentose diethyl dithioacetal (157)[28]



157

The 2-deoxy-4,5-*O*-isopropylidene-D-*threo* pentose diethyl dithioacetal (**153**) (1.00 g, 4 mmol) was hydrolysed for 24 h in triflouroacetic acid (15 ml, 0.01 M) at 4 ^{o}C. Upon completion of the reaction by TLC monitoring for consumption of starting material, the acidic mixture was diluted by addition of water (10 ml) and the solution was evaporated to dryness by removal of the solvent *in vacuo*. The resulting **2-deoxy-D-*threo*-pentose diethyl dithioacetal (157),** (0.75 g, 75%) as a sticky brown gum was utilised without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ_H:

0.95-1.00 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2xSCH$_2$C<u>H$_3$</u>), 1.52-1.67 (2H, m, CH$_2$-2), 2.31-2.44 (4H, m, 2xSC<u>H$_2$</u>CH$_3$), 3.08-3.59 (4H, m, CH-3, CH-4, CH$_2$-5), 3.80-3.85 (1H, m, CH-1), 4.15 (3H, s, 3 x OH).

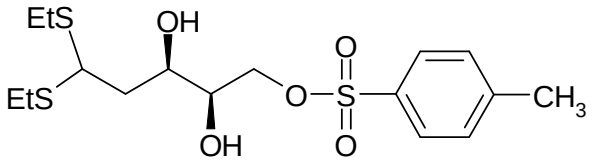
^{13}C NMR (75 MHz, DMSO-d_6) δ_C:

14.7 (2xSCH$_2$<u>C</u>H$_3$), 23.2/24.0 (2xS<u>C</u>H$_2$CH$_3$), 47.9 (CH$_2$-2), 62.7/67.2/68.1/74.1 (CH-1, CH-3, CH-4 and CH$_2$-5).

HRESIMS *m/z* [M-H]$^-$ 239.0782
(calc. for $C_9H_{20}O_3S_2$-H, 239.0776)

IR ν_{max} (cm^{-1}): 3328.

4.2.49 Preparation of 2-deoxy-5-*O*-tosyl-D-*threo*-pentose diethyl dithioacetal (158)[22]



158

To a solution of 2-deoxy-D-*threo*-pentose diethyl dithioacetal (**157**) (1.00 g, 4 mmol) in dry dichloromethane (10 ml) was added pyridine (0.3 ml, 4 mmol) and cooled the resulting solution to 0 ^{o}C. A solution of p-toluenesulfonyl chloride (0.9 g, 5 mmol) in dry dichloromethane (5 ml) was added dropwise for 15 min. The mixture was then stirred at room temperature overnight and diluted with dichloromethane (30 ml), washed with aqueous sodium bicarbonate (30 ml) and water (30 ml). The organic phase was dried over magnesium sulfate, concentrated in to syrup which upon chromatography of the residue on silca (elution with 70% hexane/ethyl acetate) afforded **2-deoxy-5-*O*-tosyl-D-*threo*-pentose diethyl dithioacetal (158)** (0.60 g, 60%) as a white solid.

Mp: 690–73 ^{o}C from 98% hexane/ethylacetate

$[\alpha]_D^{25}$ +89.7° (*c* 0.9, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.96 (6H, 2xt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H_3}$), 1.48-1.86 (2H, m, CH_2-2), 2.17 (3H, s, CH_3-tosyl), 2.25-2.50 (4H, m, 2x$SC\underline{H_2}CH_3$), 3.12-3.87 (5H, m, CH-1, CH-3, CH-4 and CH_2-5), 7.09 (2H, dd, *J*=8 Hz, *Ar*-H), 7.53 (2H, dd, *J*=8 Hz, *Ar*-H).

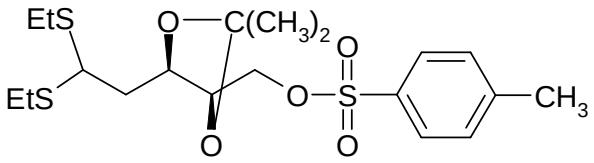
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.2 (2x$SCH_2\underline{C}H_3$), 21.3 (CH_3-Tosyl), 23.6/24.0 (2x$S\underline{C}H_2CH_3$), 39.2/47.6/68.4/70.9/71.2 (CH-1, CH-2, CH-3, CH-4 and CH_2-5), 127.7 (2C, C-2' and C-6'), 129.7 (2C, C-3 and C-5), 132.1 (C-4'), 144.8 (C-1).

HRESIMS *m/z* $[M+H]^+$ 339.0411
(calc. for $C_{12}H_{18}O_5S_3$+H, 339.0413)

IR ν_{max} (cm^{-1}): 3426.

4.2.50 Preparation of 2-deoxy-3,4-*O*-isopropylidene-5-*O*-tosyl-D-*threo*-pentose diethyl dithioacetal (159)[27,28,29]



159

To a suspension of 2-deoxy-5-*O*-tosyl-D-*threo*-pentose diethyl dithioacetal (**158**) (1.00 g, 3 mmol) in anhydrous acetone (100 ml) at 0 ^oC was added concentrated sulfuric acid (1 ml). The resulting solution was warmed to room temperature and was stirred for 16 h. The acidic mixture was neutralised by addition of calcium hydroxide (4.00 g). The precipitated solid was removed by filtration and washed with acetone (50 ml). The filtrate was concentrated *in vacuo* to leave brown oil which was taken up in diethyl ether and washed with a saturated solution of sodium bicarbonate (50 ml), and then brine (50 ml). The organic extract was dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue on silica [elution with 90% hexane/ethyl acetate) afforded **2-deoxy-3,4-*O*-isopropylidene-5-O-tosyl-D-*threo*-pentose diethyl dithioacetal (159)** (0.95 g, 95%) as a yellowish oil.

$[\alpha]_D^{25}$ -30.7° (*c* 2.4, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

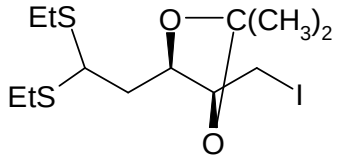
1.17 (6H, 2xt, *J*=7.5 Hz, 2x$SCH_2C\underline{H}_3$), 1.03/1.28 [6H, 2xs, $OC(CH_3)_2$], 1.77-2.03 (2H, m, CH_2-2), 2.46-2.65 (4H, m, 2x$SC\underline{H}_2CH_3$), 3.78 (2H, m, CH_2-5), 3.88 (1H, dd, *J*=4.2 Hz, CH-4), 4.02 (1H, dd, *J*=5.1 Hz, CH-3), 4.16 (1H, m, CH-1).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.2/14.3 (2x$SCH_2\underline{C}H_3$), 21.4 (CH_3-tosyl), 23.6/24.2 [$OC(\underline{C}H_3)_2$], 26.5/27.1 (2x$S\underline{C}H_2CH_3$), 39.8/47.6/68.9/75.3/76.9 (CH-1, CH-2, CH-3, CH-4, and CH_2-5), 109.6 [$O\underline{C}(CH_3)_2$], 127.8 (2C, CH-2' and CH-6'), 129.7 (2C, *C*H-3' and CH-5'), 132.3 (CH-4), 144.9 (CH-1).

HRESIMS *m/z* $[M+H]^+$ 379.0725
(calc. for $C_{15}H_{22}O_5S_3$+H, 379.0728)

4.2.51 Preparation of 2-deoxy-3,4-*O*-isopropylidene-5-iodo-D-*threo*-pentose diethyl dithioacetal (160)[22]



160

The 2-deoxy-3,4-*O*-isopropylidene-5-*O*-tosyl-D-*threo*-pentose diethyl dithioacetal (**159**) (1.00 g, 2 mmol) was dissolved in anhydrous acetone and sodium iodide (1.7 g, 12 mmol) was added. The mixture was refluxed for 20 h until the reaction is complete. The mixture was then cooled, precipitated sodium *p*-toluenesulfonate was filtered off, and the filtrate concentrated to dryness. The residue was partitioned between water (30 ml) and chloroform (30 ml).

The organic layer was washed with aqueous sodium sulfite (20 ml) and water (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*.
The chromatography of the residue on silica (elution with 90% hexane/ethyl acetate) afforded **2-deoxy-5-iodo-D-*threo*-pentose diethyl dithioacetal (160)** (0.90 g, 90%) as a colourless oil.

Mp: 69–73 ^{o}C from 98% hexane/ethylacetate

$[\alpha]_D^{25}$ -89.7° (*c* 0.9, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

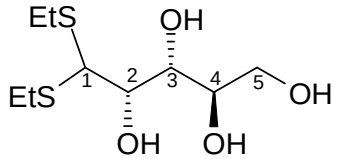
1.21 (6H, 2xt, *J*=7.5 Hz, 2x$SCH_2C\underline{H}_3$), 1.33/1.37 [6H, 2xs, $OC(CH_3)_2$], 1.93-2.08 (2H, m, CH_2-2), 2.48-2.71 (4H, m, 2x$SC\underline{H}_2CH_3$), 3.19 (2H, d, *J*=5.7 Hz, CH_2-5), 3.70 (1H, dd, *J*=6Hz, CH-4), 3.93 (1H, dd, *J*=5 Hz, CH-3), 4.11 (1H, m, CH-1).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

5.5 (CH_2-I), 14.3 (2x$SCH_2\underline{C}H_3$), 23.6/24.4 [$OC(\underline{C}H_3)_2$], 27.3/27.5 (2x$S\underline{C}H_2CH_3$), 40.6/47.8/78.7/79.5 (CH-1, CH-2, CH-3, CH-4), 109.3 [$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M+H]^+$ 334.9653
(calc. for $C_8H_{15}IO_2S_2$+H, 334.9655)

4.2.52 Preparation of D-arabinose diethyl dithioacetal (161)[30,31]



161

To a solution of D-arabinose (**161**) (20.00 g, 0.1 mol) in 6 M hydrochloric acid (200 ml) was added dropwise ethyl mercaptan (10 ml, 0.1 mol) over 20 minutes. After being stirred for 2.5 h, the mixture was cooled to 0 ^{o}C and filtered. The collected solid was washed with cold water (200 ml) and air-dried to give **D-arabinose diethyl dithioacetal (162)** (12.00 g, 60%) as colourless plates.

Mp: 120–123 ^{o}C from hexane (lit.[28,31] 124–126 ^{o}C)

$[\alpha]_D^{25}$ +70.5° (*c* 1.2, MeOH)

^{1}H NMR (300 MHz, d_6-DMSO) δ_H:

1.05 (6H, t, *J*=7.2 Hz and 7.5 Hz, 2xSCH$_2$C<u>H</u>$_3$), 2.08 (1H, OH) 2.56-2.66 (4H, m, 2xSC<u>H</u>$_2$CH$_3$), 3.56-4.00 (6H, m, CH-1, CH-2, CH-3, CH-4 and CH$_2$-5), 4.29-4.42 (1H, 2xs, OH), 4.72 (1H, s, OH).

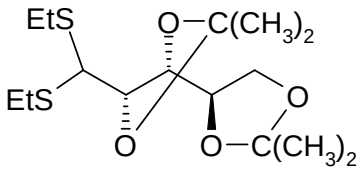
^{13}C NMR (75 MHz, d_6-DMSO) δ_C:

14.3 (2xSCH$_2$<u>C</u>H$_3$), 24.1/25.0 (2xS<u>C</u>H$_2$CH$_3$), 54.7/63.6/70.5/71.4/71.7 (CH-1, <u>C</u>H-2, CH-3, CH-4 and CH$_2$-5).

HRESIMS *m/z* $[M-H]^-$ 255.0737
(calc. for $C_9H_{20}O_4S_2$-H, 255.0725)

IR ν_{max} (cm^{-1}): 3310.

4.2.53 Preparation of 2,3:4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (163)[30,31]



163

To a suspension of D-arabinose diethyl dithioacetal (**162**) (4.00 g, 20 mmol) in anhydrous acetone (100 ml) at 0 ^{o}C was added concentrated sulfuric acid (1 ml). The resulting solution was warmed to room temperature and was stirred for 16 h. The acidic mixture was neutralised by addition of calcium hydroxide (4.00 g). The precipitated solid was removed by filtration and washed with acetone (50 ml). The filtrate was concentrated *in vacuo* to leave brown oil which was taken up in diethyl ether and washed with a saturated solution of sodium bicarbonate (50 ml), and then brine (50 ml). The organic extract was dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue on silica (elution with 90% hexane/ethyl acetate) afforded **2,3:4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (163)** (3.20 g, 80%) as a yellowish oil.

$[\alpha]_D^{25}$ +82.5° (*c* 1.2, MeOH) [lit.[28,31] +83.3° (*c* 1.4, MeOH)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

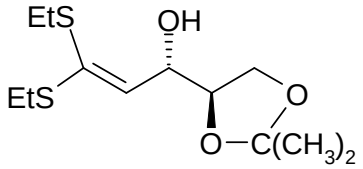
1.12-1.19 (6H, t, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H}_3$), 1.22-1.32 [12H, 4xs, 2x$OC(CH_3)_2$] 2.56-2.68 (4H, m, 2x$SC\underline{H}_2CH_3$), 3.82-4.20 (6H, m, CH-1, CH-2, CH-3, CH-4 and CH_2-5).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.2 (2x$SCH_2\underline{C}H_3$), 24.7/24.9/25.1/26.5/26.9/27.2 [2x$S\underline{C}H_2CH_3$ and 2x$OC(\underline{C}H_3)_2$], 52.2/67.6/76.9/78.9/84.4 (CH-1, CH-2, CH-3, CH-4, CH_2-5), 109.5/109.9 [2x$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M+H]^+$ 337.1504
(calc. for $C_{15}H_{28}O_4S_2$+H, 337.1507)

4.2.54 Preparation of 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (164)[30,31]



164

To a solution of potassium *tert*-butoxide (1.50 g, 13 mmol) in tetrahydrofuran (70 ml) and dimethyl sulfoxide (25 ml) at rt was added dropwise over 15 minutes a solution of 2,3:4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (**163**) (3.00 g, 9 mmol) in tetrahydrofuran (5 ml). The mixture was stirred for 1 h and was poured on to ice (500 g). The aqueous mixture was extracted with chloroform (3 x 25 ml), and the combined extracts were washed with cold water (3 x 20 ml), dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* followed by chromatography of the residual oil on silica (elution with 90% hexane/ethyl acetate) afforded **2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (164)** (2.46 g, 82%) as a pale yellow oil.

$[\alpha]_D^{25}$ +62.5° (*c* 0.9, $CHCl_3$) [lit.[28,31] +49.2° (*c* 0.9, $CHCl_3$)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.11-1.17 (6H, t, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H}_3$), 1.25-1.32 [6H, 2xs, $OC(CH_3)_2$] 2.58-2.80 (5H, m, 2x$SC\underline{H}_2CH_3$ and OH), 3.76-3.88 (2H, 2xdd, *J*=8.1 Hz and 8.4 Hz, CH_2-5), 4.02-4.08 (1H, td, *J*=6.6 Hz, CH-4), 4.74-4.79 (1H, m, CH-3), 5.82 (1H, d, *J*=8.1 Hz, CH-2).

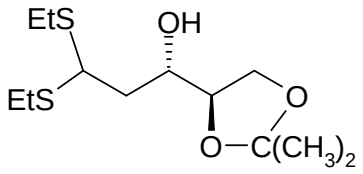
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.7/14.8 (2x$SCH_2\underline{C}H_3$), 25.0/26.1/26.7/27.2 [2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$], 65.0 (CH-5), 69.3 (CH-4), 77.8 (CH-3), 109.1 [$O\underline{C}(CH_3)_2$], 133.1 (CH-2), 134.1 (CH-1).

HRESIMS *m/z* $[M+H]^+$ 279.1085
(calc. for $C_{12}H_{22}O_3S_2$+H, 279.1089)

IR ν_{max} (cm^{-1}): 3228.

4.2.55 Preparation of 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (165)[25]



165

Method : 1[30,31]

To a stirred suspension of lithium aluminium hydride (0.20 g, 4 mmol) in tetrahydrofuran (30 ml) at 0 ^oC was added a solution of 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (**164**) (1.00 g, 4 mmol) in tetrahydrofuran (5 ml) over 20 min. After the addition was complete the mixture was allowed to warm to room temperature and was stirred for a further 3.5 h. Residual lithium aluminium hydride was quenched by sequential addition of water (2 ml), 15% aqueous sodium hydroxide (2 ml) and water (7 ml). The resulting mixture was filtered through a layer of celite, and the collected solid was washed with ethyl acetate. The filtrate was washed with brine and dried over magnesium sulfate. Removal of the solvent *in vacuo* followed by chromatography of the residual oil on silica (elution with 80% hexane/ethyl acetate) afforded **2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (165)** (0.60 g, 60 %) as a colourless oil.

$[\alpha]_D^{25}$ -7.7°(*c* 1.4, $CHCl_3$) [lit.[28,31] -7.8°(*c* 1.3, $CHCl_3$)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.14-1.18 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2\underline{C}H_3$), 1.24-1.31 [6H, 2xs, $OC(CH_3)_2$] 1.74-1.90 (2H, m, CH_2-2), 2.45-2.85 (5H, m, 2x$SC\underline{H_2}CH_3$ and OH), 3.81-4.00 (5H, m, CH-1, CH-3, CH-4 and CH_2-5).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.2/14.3 (2x$SCH_2\underline{C}H_3$), 23.4/24.1/25.0/26.3 (2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$), 38.8 (CH_2-2), 47.9/65.4/69.4/78.2 (CH-1, CH-3, CH-4 and CH_2-5), 109.0 [$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M+H]^+$ 281.1244
(calc. for $C_{12}H_{24}O_3S_2$+H, 281.1246)

IR ν_{max} (cm^{-1}): 3215.

Method : 2[28]

A solution of Red-Al (1 ml, 4 mmol, 3.4 M solution in toluene) was added a cold solution (0 ^{o}C) of purified 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (**164**) (1.00 g, 4 mmol) in dry toluene (10 ml) in the course of 15 min. After an hour stirring at 0 ^{o}C, the reaction was quenched with a 15% aqueous sodium hydroxide solution. Work-up and chromatograph of the residue (elution with 70% hexane/ethyl acetate) afforded **2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (165)** (0.60 g, 60 %) as a colourless oil.

$[\alpha]_D^{25}$ -7.7° (*c* 1.4, $CHCl_3$) [lit.[28,31] -7.8° (*c* 1.3, $CHCl_3$)]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.14-1.18 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H_3}$), 1.24-1.31 [6H, 2xs, $OC(CH_3)_2$] 1.74-1.90 (2H, m, CH_2-2), 2.45-2.85 (5H, m, 2x$SC\underline{H_2}CH_3$ and OH), 3.81-4.00 (5H, m, CH-1, CH-3, CH-4 and CH_2-5).

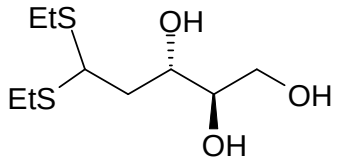
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.2/14.3 (2x$SCH_2\underline{C}H_3$), 23.4/24.1/25.0/26.3 [2x$S\underline{C}H_2CH_3$ and $OC(\underline{C}H_3)_2$], 38.8 (CH_2-2), 47.9/65.4/69.4/78.2 (CH-1, CH-3, CH-4 and CH_2-5), 109.0 [$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M+H]^+$ 281.1244
(calc. for $C_{12}H_{24}O_3S_2$+H, 281.1246)

IR ν_{max} (cm^{-1}): 3215.

4.2.56 Preparation of 2-deoxy-D-*erythro*-pentose diethyl dithioacetal (166)[28]



166

The 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pentose diethyl dithioacetal (**165**) (1.00 g, 4 mmol) was hydrolysed for 24 h in triflouroacetic acid (15 ml, 0.01 M) at 4 ^{o}C. The acidic mixture was neutralised by addition of water (10 ml) and the solution was evaporated to dryness by removal of the solvent *in vacuo*. The resulting **2-deoxy-D-*erythro*-pentose diethyl dithioacetal (166)** (0.70 g, 70%) was isolated as a sticky milky-white gum and was utilised without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ_H:

1.09-1.14 (6H, dt, *J*=7.2 Hz and 7.5 Hz, 2xSCH$_2$C<u>H$_3$</u>), 1.68-1.89 (2H, m, CH$_2$-2), 2.42-2.58 (5H, m, 2xSC<u>H$_2$</u>CH$_3$), 3.15-3.58 (5H, m, CH-1, CH-3, CH$_2$-5 and OH), 3.99-4.03 (1H, dd, *J*=3 Hz, CH-4), 4.42 (2H, s, 2xOH).

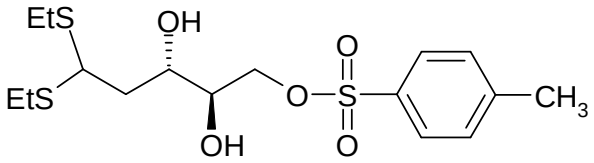
^{13}C NMR (75 MHz, DMSO-d_6) δ_C:

14.2/14.3 (2xSCH$_2$<u>C</u>H$_3$), 22.6/23.6 (2xS<u>C</u>H$_2$CH$_3$), 47.4 (<u>C</u>H$_2$-2), 63.1/66.8/68.4/74.7 (CH-1, CH-3, CH-4 and CH$_2$-5).

HRESIMS *m/z* $[M-H]^-$ 239.0782
(calc. for $C_9H_{20}O_3S_2$-H, 239.0776)

IR ν_{max} (cm^{-1}): 3388.

4.2.57 Preparation of 2-deoxy-5-*O*-tosyl-D-*erythro*-pentose diethyl dithioacetal (167)[22]



167

To a solution of 2-deoxy-D-*erythro*-pentose diethyl dithioacetal (**166**) (1.00 g, 4 mmol) in dry dichloromethane (10 ml), pyridine (0.3 ml, 4 mmol) was added and the resulting solution cooled to 0 ^{o}C. A solution of *p*-toluenesulfonyl chloride (0.9 g, 5 mmol) in dry dichloromethane (5 ml) was added dropwise for 15 min. The mixture was then stirred at room temperature overnight and diluted with dichloromethane (30 ml), washed with aqueous sodium bicarbonate (30 ml) and water (30 ml).

The organic phase was dried over magnesium sulfate, concentrated in to syrup which upon chromatography of the residue on silca (elution with 70% hexane/ethyl acetate) afforded **2-deoxy-5-*O*-tosyl-D-*erythro*-pentose diethyl dithioacetal (167)** (0.60 g, 60%) as a white solid.

Mp: 89–92 ^{o}C from 98% hexane/ethylacetate

$[\alpha]_D^{25}$ +90.7° (*c* 0.9, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.12 (6H, 2xt, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H}_3$), 1.17-1.23 (2H, m, CH_2-2), 2.42 (3H, s, CH_3-tosyl), 2.46-2.75 (4H, m, 2x$SC\underline{H}_2CH_3$), 3.70-4.46 (5H, m, CH-1, CH-3, CH-4 and CH_2-5), 7.30 (2H, dd, *J*=8 Hz, *Ar*-H), 7.69 (2H, dd, *J*=8 Hz, *Ar*-H).

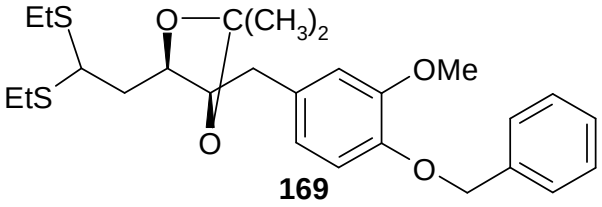
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

14.3 (2x$SCH_2\underline{C}H_3$), 21.6 (CH_3-Tosyl), 23.6/24.3 (2x$S\underline{C}H_2CH_3$), 38.9/47.7/67.1/67.9/80.7 (CH-1, CH-2, CH-3, CH-4 and CH_2-5), 127.9 (2C, C-2' and C-6'), 129.9 (2C, C-3 and C-5), 132.0 (C-4'), 145.2 (C-1).

HRESIMS *m/z* $[M+H]^+$ 339.0411
(calc. for $C_{12}H_{18}O_5S_3$+H, 339.0413)

IR ν_{max} (cm^{-1}): 3248.

4.2.58 Attempted preparation of 5-(4-benzyloxy-3-methoxybenzene)-2,5-dideoxy-D-*erythro*-pentose diethyl dithioacetal (169) [32,33,34,35]



169

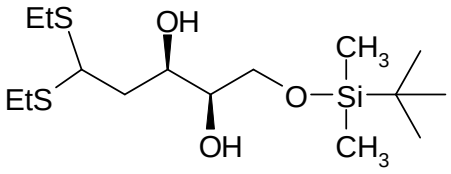
Method : 1[32]

To a solution of 1-benzyloxy-4-bromo-2-methoxybenzene (**133**) (1.00 g, 3 mmol) in either anhydrous THF or diethyl ether (20 ml) cooled to -78 ^{o}C was added dropwise via a syringe n-butyllithium (4 ml, 7 mmol, 1.6 M in hexane) or LDA (2.5 ml, 7 mmol) or *tert*-butyllithium (4 ml, 7 mmol, 1.7 M in pentane) over a period of 20 minutes. The solution was allowed to warm to room temperature for 30 minutes, dropped back to -78 ^{o}C and a catalytic amount of either cuprous iodide (0.3 g, 2 mmol) or cuprous bromide (0.2 g, 2 mmol) in solution of either THF or diethyl ether (5 ml) was added. Then a solution of 2-deoxy-3,4-O-isopropylidene-5-iodo-D-*threo*-pentose diethyl dithioacetal (**160**) (1.14 g, 3 mmol) in either THF or diethyl ether (5 ml) at the same temperature dropwise over 10 minutes. After stirring at -78 ^{o}C for an additional 2 h followed by stirring at room temperature for 1 h, the mixture was treated with saturated solution of ammonium chloride (10 ml). The phases were separated and the aqueous phase is extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate, filtered off and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded an oil in absentia of the desired product.

Method : 2[33,34,35]

To a stirred solution of 2-deoxy-3,4-O-isopropylidene-5-iodo-D-*threo*-pentose diethyl dithioacetal (**160**) (1.14 g, 3 mmol) in either anhydrous THF or diethyl ether (20 ml) and catalytic amount of either cuprous iodide (0.3 g, 1 mmol) or iron (III) chloride (0.2 g, 1 mmol) or cerium (III) chloride (0.4 g, 1 mmol) was added dropwise at 0 ^{o}C (1-benzyloxy-2-methoxyphenyl)-4-magnesium bromide (**170**) [freshly prepared from refluxing 1-benzyloxy-4-bromo-2-methoxybenzene (0.9 g, 3 mmol) with magnesium turnings (0.4 g, 15 mmol), catalytic amount of iodine (0.08 g, 0.3 mmol) in either dry THF or diethyl ether (5 ml)]. After stirring overnight at room temperature followed by refluxing for 5 h, the reaction mixture was added at room temperature saturated solution of ammonium chloride (10 ml) and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate, filtered off and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded an oil in absentia of the desired product.

4.2.59 Preparation of 5-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-*threo*-pentose diethyl dithioacetal (171)[36]



171

To a solution of 2-deoxy-D-*threo*-pentose diethyl dithioacetal (**157**) (1.00 g, 4 mmol) in dry THF (5 ml) was added to a suspension of sodium hydride (0.2 g, 4 mmol) in dry THF (15 ml) and the mixture was stirred at room temperature for 2.5 h. *Tert*-butyldimethylsilyl chloride (0.6 g, 4 mmol) in dry THF (5 ml) was added and the mixture was stirred at room temperature until the consumption of the starting material.

The reaction was added aqueous potassium carbonate (20 ml) and the mixture was extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate, filtered off and concentrated *in vacuo*. The chromatography of the residue (elution with 80% hexane/ethyl acetate) afforded a colourless oil of **5-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-*threo*-pentose diethyl dithioacetal (171)** (0.80 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

0.04 [6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$], 0.86 [9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$], 1.21 (6H, t, *J*=7.2 Hz and 7.5 Hz, 2x$SCH_2C\underline{H_3}$), 1.79-2.10 (2H, m, CH_2-2), 2.50-2.79 (6H, m, 2x$SC\underline{H_2}CH_3$ and 2xOH), 3.44 (1H, dd, *J*=3.9 Hz and 4.8 Hz, CH-4), 3.68 (2H, m, CH_2-5), 4.00 (2H, m, CH-3 and CH-1).

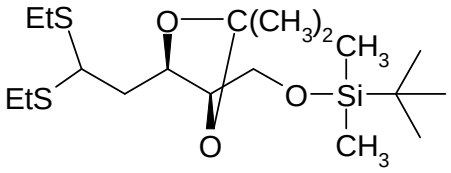
^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

-5.5 [$Si(\underline{C}H_3)_2C(CH_3)_3$], 14.4 (2x$SCH_2\underline{C}H_3$), 18.1 [$Si(CH_3)_2\underline{C}(CH_3)_3$], 23.9/24.2 (2x$S\underline{C}H_2CH_3$), 25.8 [$Si(CH_3)_2C(\underline{C}H_3)_3$], 40.0 (CH-2), 47.8 ($CH_2$-5), 65.4 (CH-4), 69.8 (CH-3), 73.1 (CH-1).

HRESIMS *m/z* $[M+H]^+$ 299.1180
(calc. for $C_{11}H_{26}O_3S_2Si$+H, 299.1187)

IR ν_{max} (cm^{-1}): 3428.

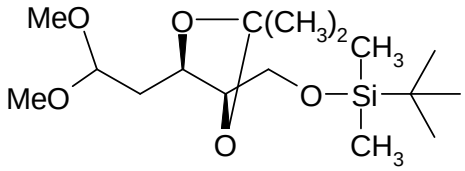
4.2.60 Preparation of 5-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (172)[37]



172

To a stirred solution of 5-*O*-*tert*-butyldimethylsilyloxy-2-deoxy-D-*threo*-pentose diethyl dithioacetal (**171**) (0.50 g, 1 mmol) and 2,2-dimethoxypropane (0.3 ml, 2 mmol) in dry dichloromethane (10 ml) was added a catalytic amount of pyridinium *para*-toluenesulfonate (0.1 g, 0.4 mmol). The mixture was stirred at room temperature until the consumption of the starting material. The reaction was added saturated aqueous sodium hydrogen carbonate (20 ml) and the mixture was extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate, filtered off and concentrated *in vacuo*. The crude of **5-*O*-*tert*-butyldimethylsilyloxy-2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (172)** (0.45 g, 90%) was obtained and was utilised in the next step without further purification.

4.2.61 Preparation of 5-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose dimethylacetal (173)[28]



173

The 5-*O*-*tert*-butyldimethylsilyloxy-2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (**172**) (1.00 g, 3 mmol) was dissolved in warm solution of anhydrous methanol (50 ^{o}C) (20 ml) and yellow mercuric oxide (2.20 g, 8 mmol) in anhydrous methanol (5 ml) was added to the hot vigorously stirred mixture over a period of about 2 minutes. The stirring was continued for 15 minutes in refluxing methanol. The solids were removed by hot filtration and washed with warm methanol and the combined filtrate and washings were concentrated under reduced pressure into syrup containing small amounts of mercuric oxide. The traces of mercuric oxide were dissolved in dichloromethane and filtered. The filtrate was washed with water (20 ml), 10% potassium iodide (2 x 20 ml), brine (20 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded a colourless oil of **5-*O*-*tert*-butyldimethylsilyloxy-2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose dimethylacetal (173)** (0.60 g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

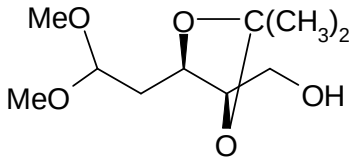
0.02 [6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$], 0.85 [9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$], 1.34 [6H, 2xs, $OC(CH_3)_2$], 1.76-1.94 (2H, m, CH_2-2), 3.29 (6H, s, 2xOCH_3), 3.68 (3H, m, CH_2-5 and CH-4), 3.93 (1H, m, CH-3), 4.56 (1H, dd, *J*=3.3 Hz and 3.6 Hz, CH-1).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

-5.5 [$Si(\underline{C}H_3)_2C(CH_3)_3$], 18.3 [$Si(CH_3)_2\underline{C}(CH_3)_3$], 25.9 [$Si(CH_3)_2C(\underline{C}H_3)_3$], 26.9/27.3 [$OC(\underline{C}H_3)_2$], 36.7 (CH-2), 52.8 ($OCH_3$), 63.5 ($CH_2$-5), 75.2 (CH-4), 80.9 (CH-3), 101.9 (CH-1), 108.6 [$O\underline{C}(CH_3)_2$].

HRESIMS *m/z* $[M+H]^+$ 335.2269
(calc. for $C_{16}H_{34}O_5Si$+H, 335.2271)

4.2.62 Preparation of 2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose dimethylacetal (174)[38]



174

To a solution of 2-deoxy-5-*O*-*tert*-butyldimethylsilyloxy-3,4-*O*-isopropylidene-D-*threo*-pentose dimethylacetal (**173**) (0.50 g, 1.5 mmol) in THF (20 ml) was added tetra-n-butylammonium fluoride (4.5 ml, 4.5 mmol, 1 M solution in THF) and the mixture was stirred at room temperature until the consumption of the starting material. The mixture was concentrated *in vacuo*, partitioned between water (20 ml) and ethyl acetate (20 ml) and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried over anhydrous magnesium sulfate, filtered off and concentrated *in vacuo*. The chromatography of the residue (elution with 80% hexane/ethyl acetate) afforded a colourless oil of **2-deoxy-3,4-*O*-isopropylidene-D-*threo*-pentose dimethylacetal (174)** (0.45 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H:

1.39 [6H, s, OC($C\underline{H}_3$)$_2$], 1.87 (3H, t, *J*=6 Hz, CH_2-2 and OH), 3.32 (6H, 2xs, 2xOCH_3), 3.61 (1H, 2xd, *J*=5.4 Hz, C$\underline{H}$-4), 3.76 (2H, 2xd, *J*=4.5 Hz, CH_2-5), 3.95 (1H, sept, CH-3), 4.55 (1H, t, *J*=5.4 Hz and 5.7 Hz, CH-1).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C:

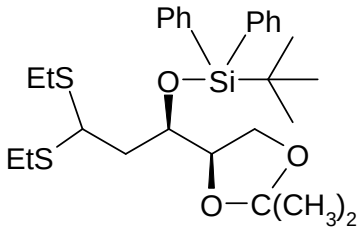
26.9/27.2 [OC($\underline{C}H_3$)$_2$], 36.5 (CH-2), 52.9/53.5 (OCH_3), 64.2 (CH_2-5), 74.3 (CH-4), 78.7 (CH-3), 101.9 (CH-1), 109.3 [O$\underline{C}$(CH_3)$_2$].

HRESIMS *m/z* $[M+H]^+$ 221.1399

(calc. for $C_{10}H_{20}O_5$+H, 221.1401)

IR ν_{max} (cm^{-1}): 3442.

4.2.63 Preparation of 3-*O*-*tert*-butyldiphenylsilyl-2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (177)[31]



177

To a stirred solution of 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (**153**) (2.00 g, 7 mmol) in THF at -20 ^{o}C under nitrogen, was added potassium *tert*-butoxide (0.96 g, 9 mmol). The mixture was stirred at the same temperature for 1 h under nitrogen atmosphere. Then a solution of *tert*-butylchlorodiphenylsilane (2 ml, 9 mmol) in THF (3 ml) was added dropwise. The solution was allowed to warm to 15 ^{o}C over 6 h and was stirred for 16 h. The solvent was removed and the residue was partitioned between ethyl acetate (20 ml) and water (20 ml). The aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 80% hexane/ethyl acetate) afforded a colourless oil of **3-*O*-*tert*-butyldiphenylsilyloxy-2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (177)** (1.8 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:

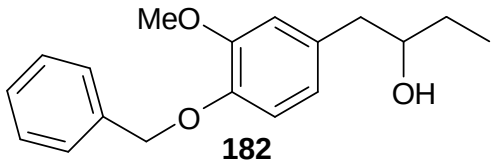
1.10 [9H, s, $Si(Ph)_2C(C\underline{H_3})_3$], 1.17 (6H, t, *J*=7.2 Hz and 7.5 Hz, $2xSCH_2C\underline{H_3}$), 1.33 [6H, s, $OC(C\underline{H_3})_2$], 2.01 (1H, m, CH_2-2), 2.44 (4H, m, $2xSC\underline{H_2}CH_3$), 2.59 (1H, m, CH_2-2), 3.84-3.97 (3H, m, CH_2-5 and CH-4), 4.15 (1H, dd, *J*=3.3 Hz and 3.6 Hz, CH-1), 4.17 (1H, sept, CH-3), 7.39-7.77 (10H, m, *Ar*-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C:

14.4 (2x$SCH_2\underline{C}H_3$), 19.5 [$Si(Ph)_2\underline{C}(CH_3)_3$], 23.0/23.9 (2x$S\underline{C}H_2CH_3$), 26.2/26.6 [$OC(\underline{C}H_3)_2$], 27.1 [$Si(CH_3)_2C(\underline{C}H_3)_3$], 38.8 (CH-2), 48.0 ($CH_2$-5), 65.2 (CH-4), 71.6 (CH-3), 76.8 (CH-1), 109.2 [$O\underline{C}(CH_3)_2$], 127.5 (2C, C-3' and C-5'), 127.5 (2C, C-3'' and C-5''), 129.6 (C-2' and C-6'), 129.6 (C-2'' and C-6''), 133.9 (C-4'), 134.8 (C-4''), 136.0 (C-1'), 136.0 (C-1'').

HRESIMS *m/z* $[M+H]^+$ 519.8570
(calc. for $C_{28}H_{42}O_3S_2Si$+H, 519.8573)

4.2.64 Attempted preparation of 1-(4-benzyloxy-3-methoxyphenyl)-2-butanol (182)[21,33,34,39,40]



182

Method : 1[39,40]

To a solution of n-butyllithium ((2 ml, 3.7 mmol, 1.6 M in hexane) in anhydrous THF (10 ml) at -78 ^oC was added 1-benzyloxy-4-bromo-2-methoxy-benzene (**133**) (1.00 g, 3.4 mmol) in THF (5 ml). The reaction mixture was stirred for 90 minutes with warming up to -20 ^oC gradually. Then the mixture was cooled down to -78 ^oC, treated with a solution of 1,2-epoxybutane (0.3 ml, 3.4 mmol) in THF (2 ml) followed by addition of boron triflouride etherate (0.5 ml, 3.7 mmol) or cerium choride (0.8 g, 3.4 mmol) and the mixture was continuously stirred at -78 ^oC for 2 h before being added a saturated solution of ammonium chloride (10 ml). The mixture was warmed to room temperature, added water (20 ml) and extracted with ethyl acetate (3x 20 ml). The combine organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded a yellowish oil with the presence of the starting materials and absence of the desired product **182**.

Method : 2[33,34]

To a solution of Grignard reagent **170** (13 ml, 26 mmol, 0.5 M) [prepared from activated magnesium (0.40 g, 17 mmol) and 1-benzyloxy-4-bromo-2-methoxy-benzene (**133**) (1.00 g, 3.4 mmol) in refluxing THF (20 ml)] was added N',N',N',N'-tetramethylene-diamine (0.3 ml, 20.4 mmol) and 1,2-epoxybutane (**181**) (1.8 ml, 20.4 mmol) and the mixture cooled to -78 ^{o}C. Then a 0.1 M solution of iron (iii) chloride in THF (0.5 ml, 5%) was added at the same temperature. The resulting solution was warmed up and stirred for 30 minutes at 0 ^{o}C. Alternately to the prepared Grignard reagent **170** (13 ml, 26 mmol, 0.5 M) was added cerium (iii) chloride (6.50 g, 26 mmol) and 1,2-epoxybutane (**181**) (1.8 ml, 20.4 mmol) at -78 ^{o}C. The mixture was warmed to room temperature and stirred for 2 h. A saturated solution of ammonium chloride (10 ml) was added to the reaction mixture followed by ethyl acetate (20 ml) and water (20 ml) and separated the two layers.

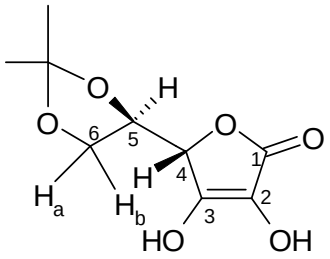
The aqueous phase was extracted with ethyl acetate (3 x 20 ml) and the combine organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded a yellowish oil with the presence of the starting materials and absence of the desired product **182**.

Method : 3[21]

To a stirring solution of guaiacol (**135**) (1 ml, 9 mmol) in dry dichloromethane (20 ml) under argon atmosphere at 0 ^{o}C was added tin (iv) chloride (1.2 ml, 11 mmol). The reaction mixture was stirred for 45 minutes at room temperature. The 1,2-epoxybutane (**181**) (0.9 ml, 11 mmol) was added in small portions to the suspension, followed by nitromethane (3 ml).

The mixture was stirred for 10 h at room temperature and then quenched with cold water (10 ml) and ethyl acetate (20 ml) and separated the two layers. The aqueous phase was extracted with ethyl acetate (3 x 20 ml) and the combine organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded a yellowish oil with the presence of the starting materials and absence of the desired product **182**.

4.2.65 Preparation of 5,6-*O*-isopropylidene-D-ascorbic acid (194)[41,42]



194

To a suspension of D-ascorbic acid (**189**) (1.00 g, 5.6 mmol) in acetone was added 2,2-dimethoxypropane (1.2 ml, 9.7 mmol) and catalytic amount of 10-camphorsulfonic acid (CSA) (0.07 g, 0.3 mmol). The mixture was stirred for 1 h at room temperature after which the reaction was quenched with addition of triethylamine (0.04 ml, 0.3 mmol). The solvent was removed by filtration and the remaining solid was washed with cold acetone and dried under vacuum to give the crude white solid. The chromatography of the residue (elution with 99% ethyl acetate/acetic acid) afforded a white crystals of **5,6-*O*-isopropylidene-D-ascorbic acid (194)** (0.95 g, 95%).

Mp: 195-198 ^{o}C (lit.[32] 218-219 ^{o}C)

^{1}H NMR (500 MHz, D_2O) δ_H:

1.32 [6H, s, $OC(CH_3)_2$], 4.12 (1H, dd, *J*=5 Hz, CH_b-6), 4.26 (1H, dd, *J*=7.2 Hz, CH_a-6), 4.53 (1H, dtd, *J*=2.3 Hz, CH-5), 4.86 (1H, d, *J*=2.3 Hz, CH-4).

^{13}C NMR (125 MHz, D_2O) δ_C:

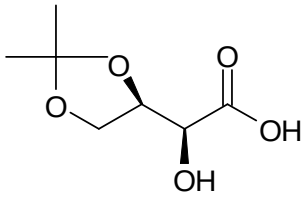
24.1/25.0 [OC($\underline{C}H_3)_2$], 65.2 (C-6), 73.1 (C-5), 76.0 (C-4), 111.0 [O$\underline{C}(CH_3)_2$], 118.0 (C-2), 155.8 (C-3), 173.6 (C-1).

HRESIMS *m/z* $[M+H]^+$ 231.0879

(calc. for $C_{10}H_{14}O_6$+H, 231.0881)

IR ν_{max} (cm^{-1}): 3418, 1640.

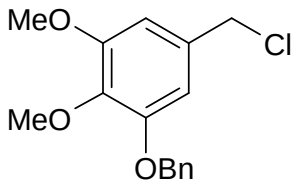
4.2.66 Attempted preparation of 3,4-*O*-Isopropylidene-D-threonic acid (196)[42]



196

To a solution of 5,6-*O*-isopropylidene-D-ascorbic acid (**194**) (1.00g, 4.6 mmol) and distilled water (25 ml) was added aqueous 30% NaOH (30 ml) and the reaction mixture was stirred to become a clear solution. To the clear solution was added sodium hydrogen carbonate (1.00 g, 12 mmol) and hydrogen peroxide (0.3 ml, 9 mmol, 35% v/v) dropwise and the resulting mixture was stirred for further 1 h at room temperature. The temperature was slowly raised to 40 ^oC and after 4 h, activated carbon (2.6 g) and catalytic amount of 10% palladium on activated carbon (0.15g) were added and the mixture was heated at 85 ^oC until a negative peroxide test was obtained. The resulting suspension was filtered and the aqueous HCl (100 ml, 0.3 M) was added until pH equals to three was reached. Then several attempts were made to extract the product (**196**) from aqueous phase using dichlromethane (4 x 20 ml) and ethyl acetate (4 x 20 ml). The combined organic phases were pooled, dried over magnesium sulfate and concentrated *in vacuo* to obtain a yellowish oil which upon characterisation reveals no presence of the desired threonic acid (**196**).

4.2.67 Preparation of 1-benzyloxy-5-chloromethyl-2,3-dimethoxybenzene (183)[43]



183

The compound **183** was synthesised in two steps *in situ*. To an ice-cold solution of 3-benzyloxy-4,5-dimethoxybenzaldehyde (**138**) (1.00 g, 4 mmol) in ethanol was added sodium borohydride (0.3 g,9mmol) in portions. The solution was stirred for 1.5 h at room temperature and the excess reagent was destroyed by addition of 10% aq. HCl (10 ml). The volatiles were removed and the product was partitioned between water (20 ml) and ethyl acetate (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combine organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield crude colourless oil in almost 90% yield. The crude residue (1.00 g, 4 mmol) in anhydrous chloroform (5 ml) was added dropwise to a solution of anhydrous chloroform (10 ml) and thionyl chloride (0.3 ml, 4.4 mmol) and the solution was stirred at room temperature for 1.5 h. The Then ice-cold water (15 ml) was added to the reaction and extracted with chloroform (3 x 20 ml). The combine organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 80% hexane/ethyl acetate) afforded a yellowish oil of **1-benzyloxy-5-chloromethyl-2,3-dimethoxybenzene (183)** (0.98 g, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H:

3.84 (6H, 2xs, 2xOCH_3), 4.51 (2H, s, $C\underline{H_2}Cl$), 5.23 (2H, s, OCH_2Bn),6.59 (2H, s, *Ar*-H), 7.30-7.45 (5H, m, *Ar*-H).

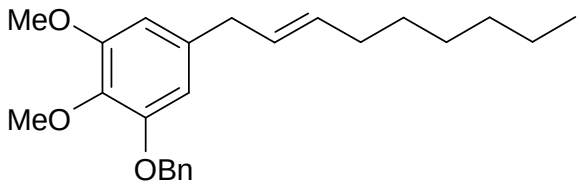
^{13}C NMR (125 MHz, $CDCl_3$) δ_C:

56.0 (2xOCH_3), 60.7 (CH_2Cl), 71.8 (OCH_2Bn), 107.5 (C-6), 109.8 (C-2), 1279 (2C, C-2' and C-6'), 128.9 (2C, C-3' and C-5'), 130.9 (C-4'), 132.5 (C-1), 137.29 (C-4), 144.2 (C-1'), 144.5 (C-3), 148.7 (C-5).

HRESIMS *m/z* $[M+H]^+$ 293.0958

(calc. $C_{16}H_{17}ClO_3$+H, 293.0960)

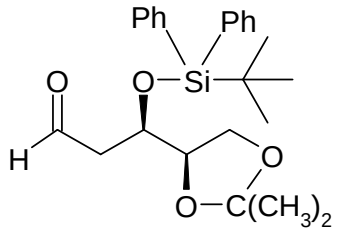
4.2.68 Attempted preparation of 1-benzyloxy-2,3-dimethoxy-5-non-2-enylbenzene (202)[43]



202

Firstly compound **201** was prepared in situ in a separate flask. A suspension of octyne (**200**) (0.1 ml, 0.55 mmol) and zirconocene chloride hydride (0.10 g, 0.55 mmol) in anhydrous THF (2 ml) were stirred under argon in the dark until a clear solution is obtained for about 30 minutes. In a separate flask, the benzyl chloride (**183**) (0.13 g, 0.4 mmol) was added to a solution of $Ni(PPh_3)_4$ (0.1 g, 0.55 mmol) [prepared from n-BuLi (0.01 ml, 0,55 mmol, 1.6 M solution in hexane) added in a suspension of $Ni(PPh_3)_2Cl_2$ (0.02 g, 0.02 mmol), PPh_3 (0.02 g, 0.55 mmol) and stirred for 5 minutes and utilised as required]. After stirring for 5 to 10 minutes the mixture was added to vinylzirconocene (**201**) using cannula. The mixture was allowed to stir at room temperature for 1.5 h. The hydrogen peroxide (0.09 ml, 30% v/v) was added and the mixture stirred for 10 minutes and filtered off. The filtrate was added 5% aqueous HCl and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with water (15 ml) and brine (15 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded yellowish oil with the absence of the desired compound **202**.

4.2.69 Preparation of 3-*O*-*tert*-butyldiphenylsilyloxy-2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentanal (203)[44]



203

To a solution of 3-*O*-*tert*-butyldiphenylsilyloxy-2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diethyl dithioacetal (**177**) (1.00 g, 2 mmol) in a mixture of acetone/water/acetonitrile 2:1:2 (v/v/v) was added mercury oxide (0.70 g, 3 mmol) and mercury chloride (0.80 g, 3 mmol) and the mixture was stirred at 60 ^{o}C for 18 h. Salts were removed by filtration and washed with acetone. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (20 ml). The organic solution was consecutively washed with potassium iodide solution (10 ml), saturated aqueous sodium thiosulfate, water (20 ml), brine (20 ml) and dried over magnesium sulfate and concentrated *in vacuo*. The chromatographic purification of the residue (elution with 90% hexane/ethyl acetate) afforded a yellowish oil of **3-*O*-*tert*-butyldiphenylsilyloxy-2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentanal (203)** (0.90 g, 90%).

$[\alpha]_D^{25}$ +12.9 (*c* 3.7, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:

0.96 [9H, s, $Si(Ph)_2C(CH_3)_3$], 1.13/1.23 [6H, 2xs, $OC(CH_3)_2$], 2.30-2.53 (2H, m, CH_2-2), 3.82 (1H, dd, *J*=2.5 Hz, CH-4), 4.02 (2H, 2xdd, *J*=6.1 Hz and 7.1 Hz, CH_2-5), 4.32 (1H, dd, *J*=5.4, CH-3), 7.24-7.62 (10H, m, *Ar*-H), 9.56 (1H, t, *J*=2.1 Hz, CHO).

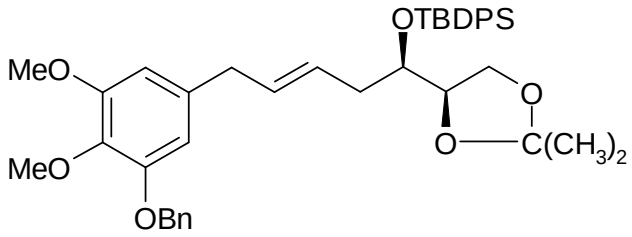
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:

19.3 [$Si(Ph)_2\underline{C}(CH_3)_3$], 26.9 [$Si(CH_3)_2C(\underline{C}H_3)_3$], 27.0 [$OC(\underline{C}H_3)_2$], 46.4 (CH-2), 48.0 ($CH_2$-5), 65.0 (CH-4), 68.8 (CH-3), 76.9 (CH-1), 109.8 [$OC(CH_3)_2$], 127.8 (2C, C-3' and C-5'), 129.6 (2C, C-3'' and C-5''), 134.9 (C-2' and C-6'), 131.0 (C-2'' and C-6''), 133.9 (C-4'), 134.8 (C-4''), 135.3 (C-1'), 135.9 (C-1''), 200.7 (CHO).

HRESIMS *m/z* $[M+H]^+$ 411.1990
(calc. for $C_{24}H_{31}O_4Si$-H, 411.1992)

IR ν_{max} (cm^{-1}): 2890, 1654.

4.2.70 Attempted preparation of [5-(3-benzyloxy-4,5-dimethoxyphenyl)-1-(2,2-dimethyl-[1,3]dioxolane-4-yl)-pent-3-enyloxy]-*tert*-butyldiphenylsilane (211)[24,45]



211

Method : 1[24]

Potassium bis(trimethylsilyl)amide (0.60 g, 3 mmol) was added at -78 ^oC to a solution of aldehyde (**203**) (1.00 g, 2.4 mmol) and the sulfone (**146**) (1.36 g, 2.9 mmol) in THF or 1,2-dimethoxyethane (20 ml) under an atmosphere of dry argon. The mixture was stirred for 16 h, maintaining the flask at -78 ^oC with warming slowly to room temperature. The reaction was added saturated solution of ammonium chloride and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with water (15 ml) and brine (15 ml), dried over magnesium sulfate and concentrated *in vacuo*.

The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded yellowish oil with the absence of the desired compound **211**.

Method : 2[24]

A suspension of cesium carbonate (2.40 g, 7.3 mmol), aldehyde (**203**) (1.00 g, 2.4 mmol) and sulfone (**146**) (1.47 g, 3 mmol) in DMF/THF (20 ml, 1:3) were heated at 70 ^{o}C for 16 h. After cooling to room temperature, the solution was added ice-cold water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (15 ml) and brine (15 ml), dried over magnesium sulfate and concentrated *in vacuo*.
The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded yellowish oil with the absence of the desired compound **211** but decomposed starting material.

Method : 3[45]

To a suspension of phosphonium iodide (**143**) (3.30 g, 5 mmol) in mixture of THF/hexamethyl phosphoroustriamide (HMPT) (15 ml, 2:1)was added butyllithium (3 ml, 5 mmol, 1.6 M in hexane) at -78 ^{o}C and the mixture was warmed to room temperature with stirring for 0.5 h. After cooling back to -78 ^{o}C, the aldehyde (**203**) (1.00 g, 2.4 mmol) in THF (5 ml) was added dropwise under nitrogen atmosphere. After 12 h of stirring the reaction was cooled back to -78 ^{o}C and added methanol (10 ml) and stirred for 20 minutes at room temperature. The reaction was added saturated solution of ammonium chloride and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (15 ml) and brine (15 ml), dried over magnesium sulfate and concentrated *in vacuo*. The chromatography of the residue (elution with 90% hexane/ethyl acetate) afforded yellowish oil with the absence of the desired compound **211**.

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