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**DIRECT SYNTHESIS OF PTEROCARPANS
VIA ALDOL CONDENSATION**

Thesis submitted in fulfilment of the requirements for the degree

PHILOSOPHIAE DOCTOR

in the

*Department of Chemistry
Faculty of Natural Sciences*

at the

*University of the Orange Free State
Bloemfontein*

by

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Co-supervisor: Prof. D. Ferreira

MAY 2000

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T.G. van Aardt

A part of this study resulted in the following publications:

1. *The First Direct Synthesis of Pterocarpanes via Aldol Condensation of Phenylacetates with Benzaldehydes.*

Theunis G. van Aardt, Pieter S. van Heerden, Daneel Ferreira,
Tetrahedron Lett., **1998**, 39, 3881-3884.

2. *Direct Synthesis of Pterocarpanes via Aldol Condensation of Phenylacetates with Benzaldehydes.*

Theunis G. van Aardt, Hendrik van Rensburg, Daneel Ferreira,
Tetrahedron, **1999**, 55, 11773-11786.

REAGENT ABBREVIATIONS

DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEA	=	diisopropylethylamine
DEAD	=	diethylazodicarboxylate
DHQ	=	dihydroquinine
DHQD	=	dihydroquinidine
DMTSF	=	dimethyl(methylthio)sulfonium tetrafluoroborate
LDA	=	lithium diisopropylamide
MOMCl	=	chloromethyl methyl ether
Ms ₂ O	=	methanesulfonic anhydride
NBS	=	N-bromosuccinimide
Py	=	pyridine
TBAF	=	tetrabutylammonium fluoride
TBDMSCl	=	<i>t</i> -butyldimethylchlorosilane
TMSCl	=	trimethylsilyl chloride
TPP	=	triphenylphosphine
TTN	=	thallium(III) nitrate

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Appendix A: Representative NMR spectra

References

Summary

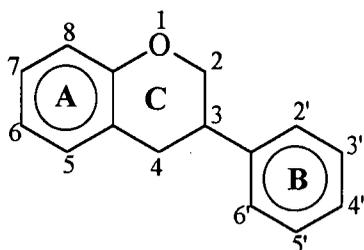
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LITERATURE SURVEY

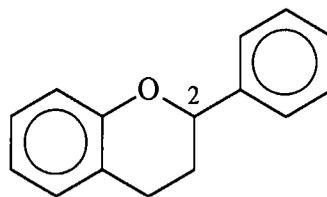
CHAPTER 1

INTRODUCTION

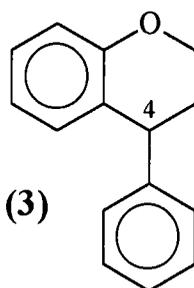
The study of flavonoid chemistry has emerged, like that of most natural products, from the search for new compounds with useful physiological properties. In many instances establishment of the structures as well as biological and physiological properties of these compounds have been severely hampered by their limited availability. The isoflavonoids **1**, unlike the flavonoids **2**, are restricted as far as their distribution in the plant kingdom is concerned. These metabolites, together with the neoflavonoids **3** are mainly found in the Leguminosae, notably the genus *Dalbergia*. Trace amounts of isoflavonoids are also found in a few other families such as Myristicaceae and Rosaceae.¹



(1)

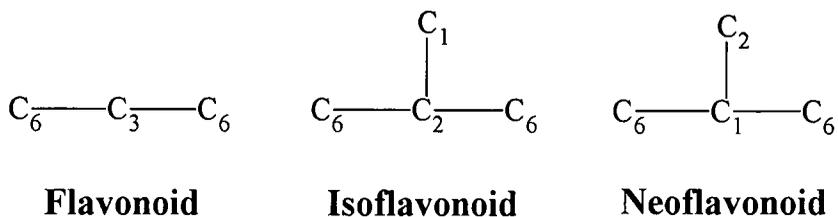


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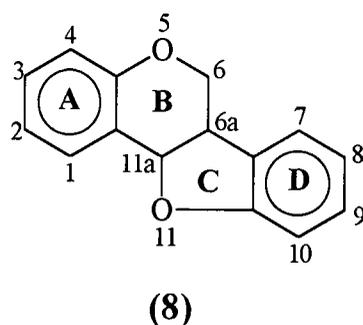
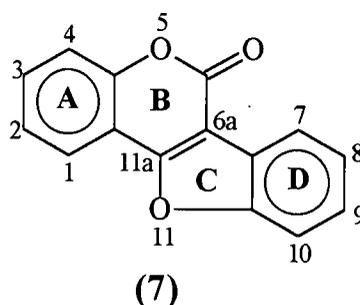
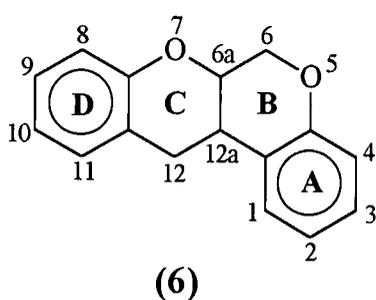
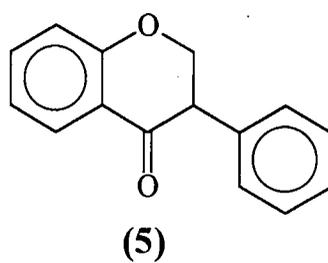
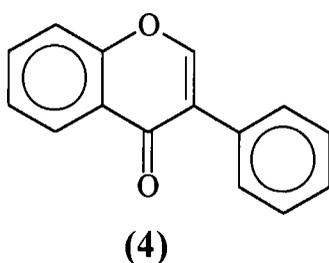


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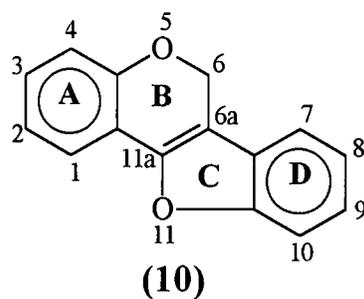
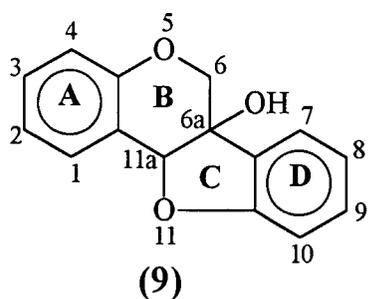
Isoflavonoids **1** share a common chalcone precursor with the flavonoids **2** and the neoflavonoids **3**, and are therefore biogenetically and structurally related to these groups. The key difference is the position of the phenyl group attached at position 2, 3 or 4 of the benzopyran skeleton which may be represented schematically as follows:



Despite their limited occurrence, isoflavonoids are remarkably diverse as far as structural variations are concerned, to such an extent that this class is subdivided into six groups namely, isoflavones **4**, isoflavanones **5**, isoflavanes **1**, rotenoids **6**, coumestanes **7** and pterocarpan **8**.²



Pterocarpan **8** represent the second largest group of natural isoflavonoids, second only to the isoflavones **4**, and are generated *via* the formation of an ether bond between the 2'- and 4-positions of the basic isoflavonoid skeleton producing a tetracyclic ring system. Pterocarpan are conveniently subdivided into three distinct groups namely, pterocarpan **8**, 6a-hydroxypterocarpan **9** and pterocarpenes **10**. These groups are numbered systematically in contrast to the other isoflavans.

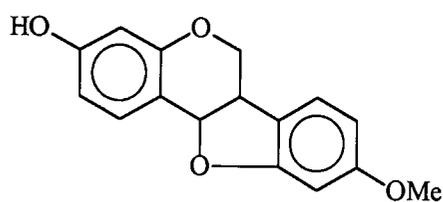


Almost all pterocarpan are phytoalexins and therefore biologically active, thus most are produced by plants only when required and are therefore rare and difficult to isolate.³ Synthetic routes to optically pure pterocarpan, exhibiting the aromatic oxygenation patterns of natural occurring isoflavonoids, are limited by the lack of readily accessible starting materials. A combination of these restrictions led to the development of synthetic approaches that not only allow easy access to these compounds but also incorporates stereocontrol. The results emanating from some of these studies are discussed in the next two chapters.

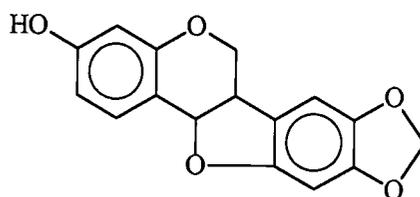
PTEROCARPANS

2.1 Introduction

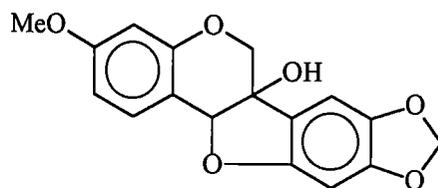
Over the last few years pterocarpanes have received considerable interest on account of their medicinal properties. These potent phytoalexins⁴ are not only employed as antitoxins⁵ but also display antifungal,^{6,7} antiviral⁴ and antibacterial³ properties. Pterocarpanes are mainly distributed in the leguminous plants and are not only found in heartwood and bark, but also in young tissues. Simple pterocarpanes like medicarpin **11** and maackiain **12**, are frequently reported either as constitutive materials or as phytoalexins.⁴ Medicarpin **11** is considered to be the most common of the class, although a wide variety, due to the number and complexity of substituents, are found in this group.⁸ Both 6a-hydroxypterocarpanes and pterocarpenes are far less frequently found in natural sources than pterocarpanes, resulting in a lack of research as to their synthesis, biosynthesis and biological properties. Indeed, pisatin **13**, an antifungal 6a-hydroxypterocarpan produced by *Pisum* spp., was considered to be the only member of this class for some years.⁸



(11)



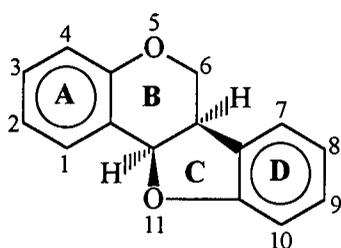
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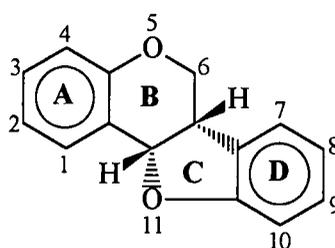
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2.2 Structure and NMR

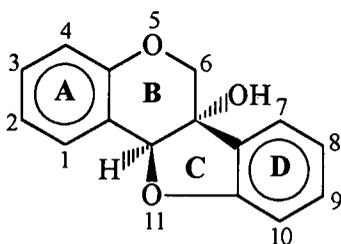
The ether bond between the 2'- and 4-positions of the basic isoflavonoid skeleton produces a tetracyclic ring system that is characteristic of pterocarpan. Despite the presence of two stereocenters at positions 6a and 11a, only two of the four possible diastereoisomers have been found in nature. These are the *cis*-(6a*R*, 11a*R*) and *cis*-(6a*S*, 11a*S*) analogues **14** and **15**. Computational studies confirmed that the *cis* configuration is more stable than the *trans*-fused ring system.⁹ 6a-Hydroxypterocarpan are derived from pterocarpan, therefore these compounds also possess a *cis*-B/C ring junction e.g. (6a*S*, 11a*S*) **16** and (6a*R*, 11a*R*) **17**.¹⁰



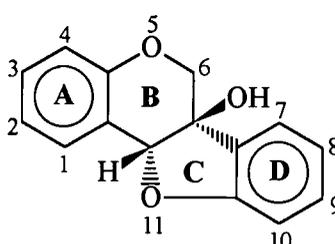
(-)-6a*R*, 11a*R* -(14)



(+)-6a*S*, 11a*S* -(15)

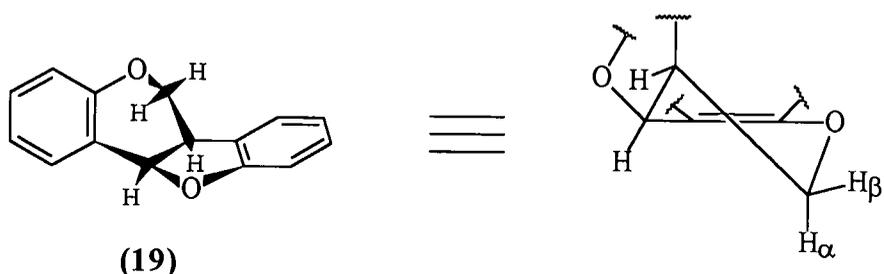
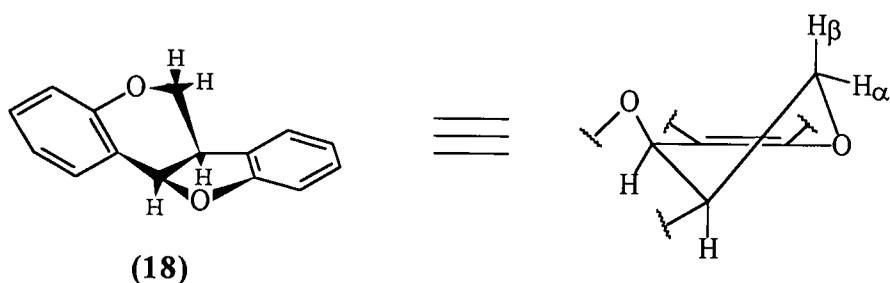


(-)-6a*S*, 11a*S* -(16)



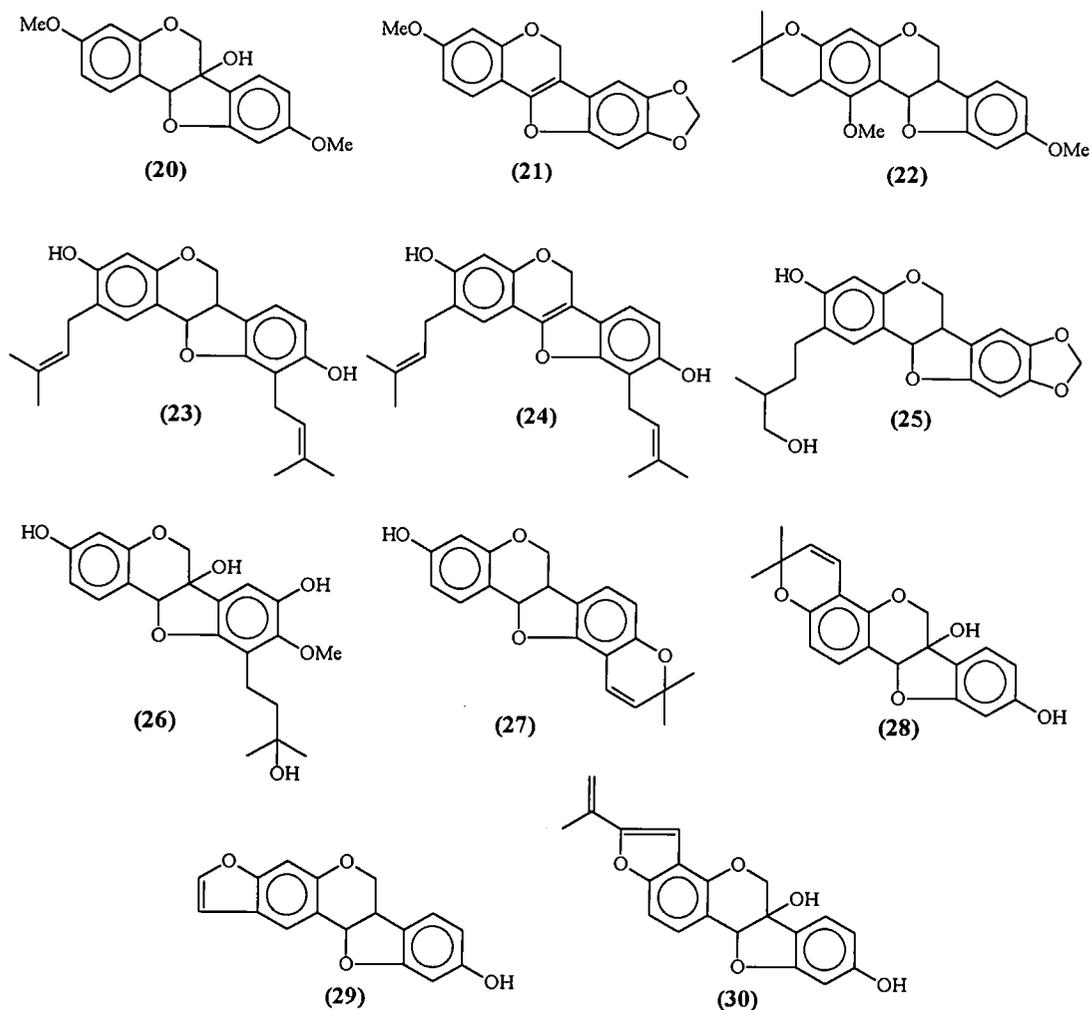
(+)-6a*R*, 11a*R* -(17)

It is generally accepted that (6a*R*, 11a*R*)-pterocarpan and (6a*S*, 11a*S*)-6a-hydroxypterocarpan exhibit large negative optical rotation $\{[\alpha]_D\}$ values while the (6a*S*, 11a*S*)-pterocarpan and (6a*R*, 11a*R*)-6a-hydroxypterocarpan display positive $[\alpha]_D$ values.^{2,4,10} This *cis*-fused ring system disposes two low energy conformations **18** and **19**, of which NMR studies indicated that conformation **18**, having the pyran ring approaching a half-chair conformation, is preferred.^{11,12} Consequently the aryl ring D and the 6 α -proton are quasi-equatorial and the 6 β -proton quasi-axial. These results were confirmed by X-ray structure determinations of gangetinin and edunol.^{13,14}



The ^1H NMR spectra of pterocarpanes display an isolated spin system for protons 6, 6a and 11a, as well as long range coupling between protons 6a and 11a and the aromatic protons 1 and 7, respectively.^{6,11} The 11a-proton, being next to an electronegative oxygen and aromatic ring, resonates at the lowest field, thus coupling constants allow identification of protons 6_{eq} , 6_{ax} and 6a.¹² The spin patterns of the B- and C-ring protons of both 6a-hydroxypterocarpanes and pterocarpanes are, as expected, less complicated than the corresponding pterocarpanes. 6a-Hydroxypterocarpanes display doublets for protons 6 and a singlet for H-11a, whereas pterocarpanes only display a two proton singlet for protons 6.^{10,15-17}

The diversity among pterocarpanes mainly results from the wide range of substitution patterns that are found among these compounds. The 3,9-di- (e.g. medicarpin **11**, variabilin **20**)¹⁸ and 3,8,9-trioxygenated (e.g. maackiain **12**, pisatin **13** and flemichapparin-B **21**)⁴ patterns are most common, while only a few analogues possessing oxygenation at the 1-position (e.g. edulane **22**)¹⁹ are known. A number of alkyl substituents are found of which the most common is geranyl (e.g. erythrabyssin II **23** and erycristagallin **24**), hydroxyisoamyl (e.g. cabenegrin A-II **25** and sphenostylin C **26**), chromene (e.g. phaseollin **27** and glyceollin I **28**), furane (e.g. neodunol **29** and clandestacarpin **30**) and chromane (e.g. edulane **22**) units.²

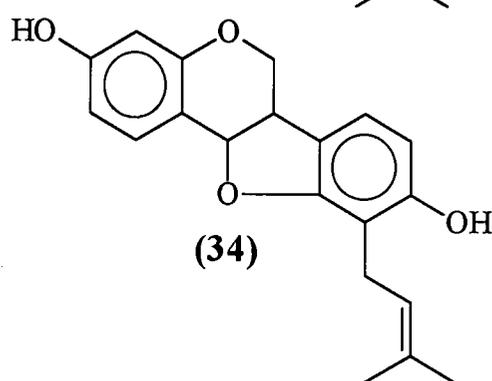
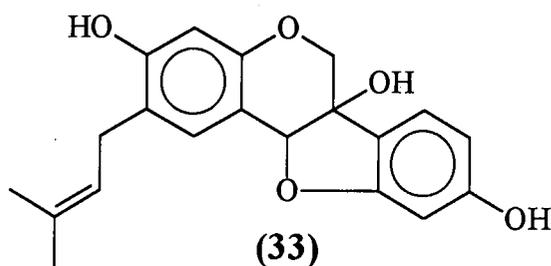
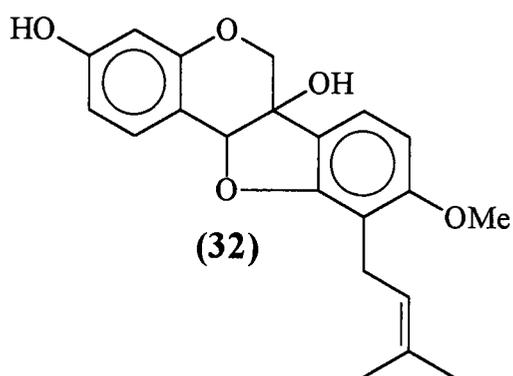
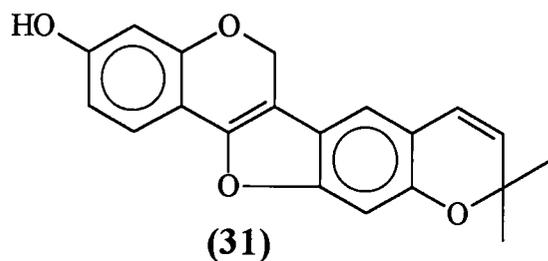


2.3 Biological Activity and Physiological effects of Pterocarpans

Phytoalexins are per definition compounds formed by plants that are exposed to external pathogens, albeit microbial or macrobial in nature.⁴ The production of phytoalexins by plants is therefore limited to conditions of “stress” and only takes place in small quantities.

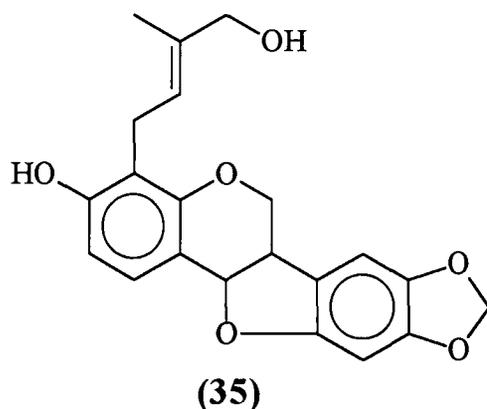
The first phytoalexins were isolated from infected peas (*Pisum sativum*) and were characterized as phaseollin 27⁶ and pisatin 13.^{4,20,21} This led to an increased interest in this class, which resulted in the isolation and confirmation of a large number of pterocarpans as phytoalexins with not only antifungal [e.g. phaseollin 27, (6a,11a)-

dehydrotuberosin **31** and cristacarpin **32**],^{10,22,23} but also antibacterial (e.g. maackiain **12** and glyceocarpin **33**)^{24,25} and antiviral (e.g. phaseollin **27** and phaseollidin **34**)^{5,26} activities. It has been shown that medicarpin **11** delays seed germination and seedling growth, while pisatin **13** not only inhibits the growth of pea cell cultures, but also retarded primary root growth in wheat.²⁷ Phaseollin **27**⁴, glyceollin I **28** and pisatin **13**^{20,28} are also phytotoxic to a number of plants.



Because of their activity as phytoalexins a number of pterocarpan have physiological activities in, not only animal species, but also humans. Apart from acting as feeding deterrents, some pterocarpan are highly toxic. Medicarpin **11**, phaseollin **27**, glyceollin I **28** and pisatin **13** lyse human red blood cells and can ultimately be fatal. Pisatin **13** also represses respiration in rat liver mitochondria.⁴

The only pterocarpan with medicinal value are cabenegrin A-I **35** and cabenegrin A-II **25**. These were isolated from the roots of a South American plant and proven as a potent antidote to both snake and spider venom.⁵ However, there are indications that certain pterocarpan may have estrogenic and enzyme inhibitory activities² as well as antitumor^{29,30} and antitubercular⁸ activities.

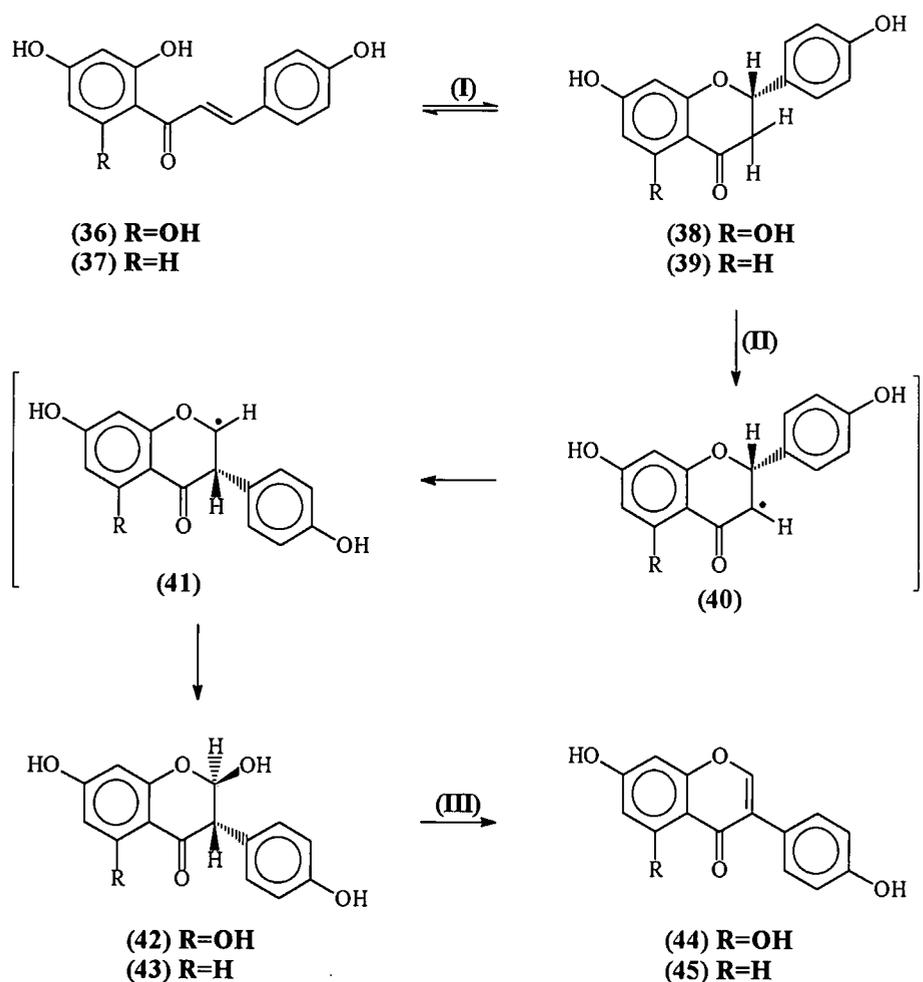


The exact mechanism by which pterocarpans function as phytoalexins is not yet known although the specific structure of pterocarpans was indicated as being directly linked to their activity.^{4,31} Stevenson and Veitch³² reported that 3-*O*-glucosyl pterocarpans are effective as antifungal compounds in *Cicer* species, while VanEtten²³ highlighted the importance of the 3,9-dihydroxylation as the prime requisite for biological activity.

Although a number of questions remain, the fact that many of our industrial crop species belong to the Leguminosae family makes research on the phytoalexin activity within these plants imperative, not only from an economic point of view but also as far as the possible influence on human health is concerned.⁴

2.4 Biosynthesis of Pterocarpans

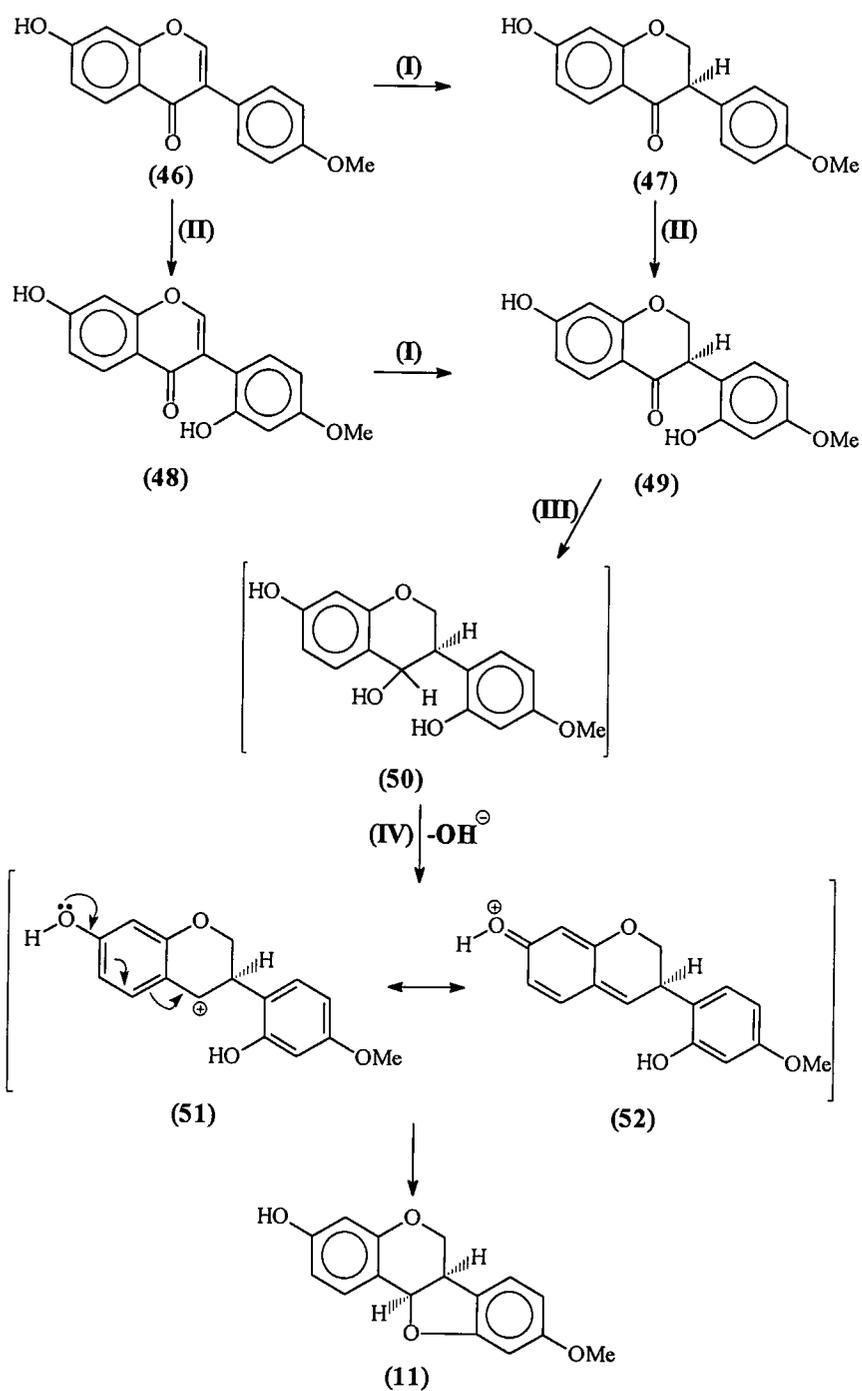
The link between isoflavonoids and flavonoids has been appreciated for many years, but only as late as 1984 had the isolation of isoflavone synthase led to the establishment of a biosynthetic route from chalcones *via* flavonoids to isoflavonoids. Hagmann and Grisebach³³ isolated isoflavone synthase from *Glycine max* (Soya bean) cell cultures and defined the characteristics as being that of a cytochrome P450-dependent monooxygenase that requires NADPH and molecular oxygen as cofactors. The flavanones 2*S*-naringenin **38** and 2*S*-liquiritigenin **39**, derived from chalcones **36** and **37**, respectively, are transformed by isoflavone synthase into the corresponding 2-hydroxyisoflavanones **42** and **43**, *via* radical intermediates **40** and **41**, which are dehydrated to the isoflavones genistein **44** and daidzein **45**, respectively (Scheme 1).^{33,34}



- (I) chalcone isomerase
(II) isoflavone synthase
(III) dehydrase

Scheme 1 : Possible biosynthetic pathway to isoflavones

The conversion of isoflavone **46** to pterocarpan **11** (Scheme 2) involves initial reduction (isoflavone reductase)³³ of the 2,3-double bond followed by oxidation (isoflavone hydroxylase)³⁵ of the 2'-position to isoflavanones **47** and **49**.³⁶ The 7,2'-dihydroxy-4-isoflavanone **49** may also be formed *via* isoflavone **48**. The exact mechanism of the conversion of vestitone **49** to pterocarpan **11** is still inconclusive.⁴ However, the enzyme isoflavanone reductase has been indicated in the reductive formation of isoflavan-4-ol **50**, while isoflavanol dehydratase leads to the formation of pterocarpan **11**, presumably *via* carbocation **51** / oxonium ion **52**.³⁷⁻³⁹



(I) isoflavone reductase

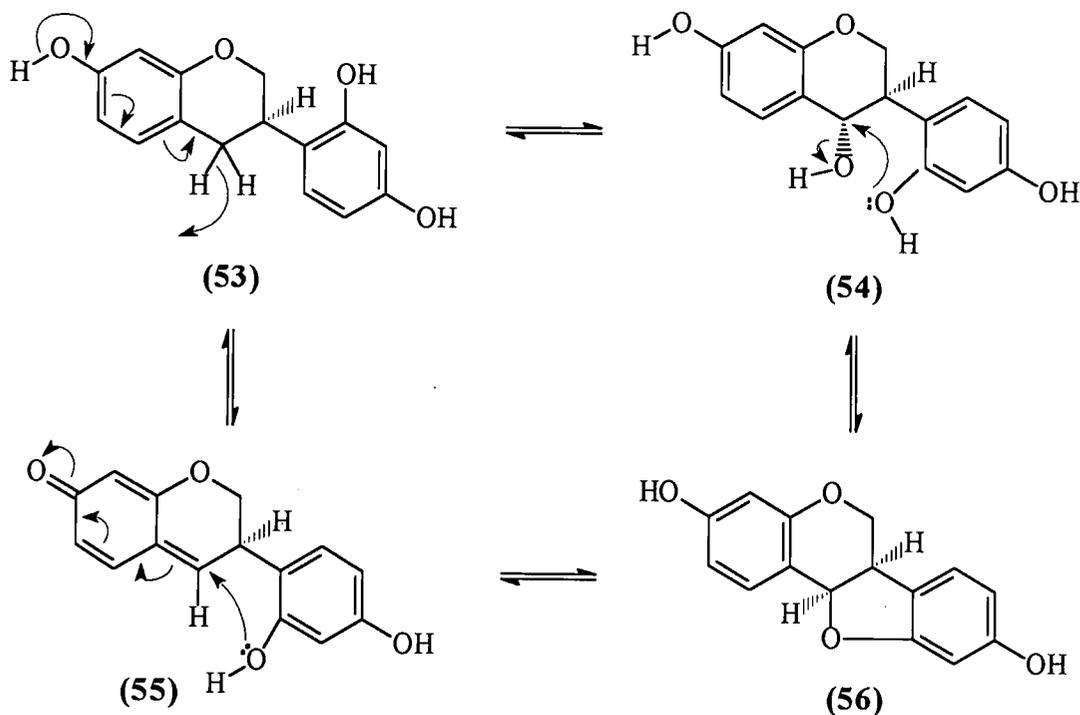
(II) isoflavone hydroxylase

(III) isoflavanone reductase

(IV) isoflavanol dehydratase

Scheme 2: Possible biosynthetic pathway to pterocarpans

Scheme 3 represents an alternative biosynthetic pathway to pterocarpan **56** based on the oxidation of 2'-hydroxyisoflavan **53** *via* intermediates **54** or **55**.⁴⁰

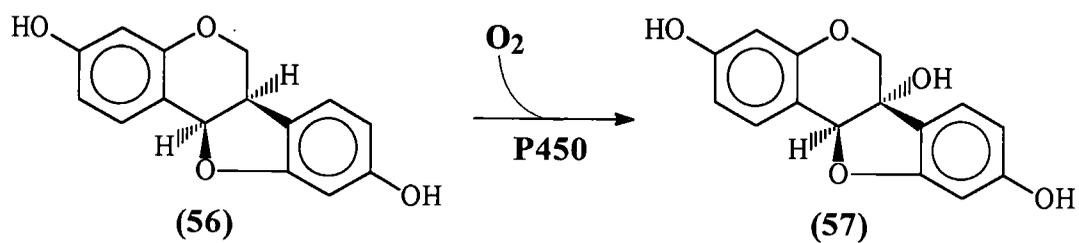


Scheme 3: Possible conversion of isoflavans to pterocarpan

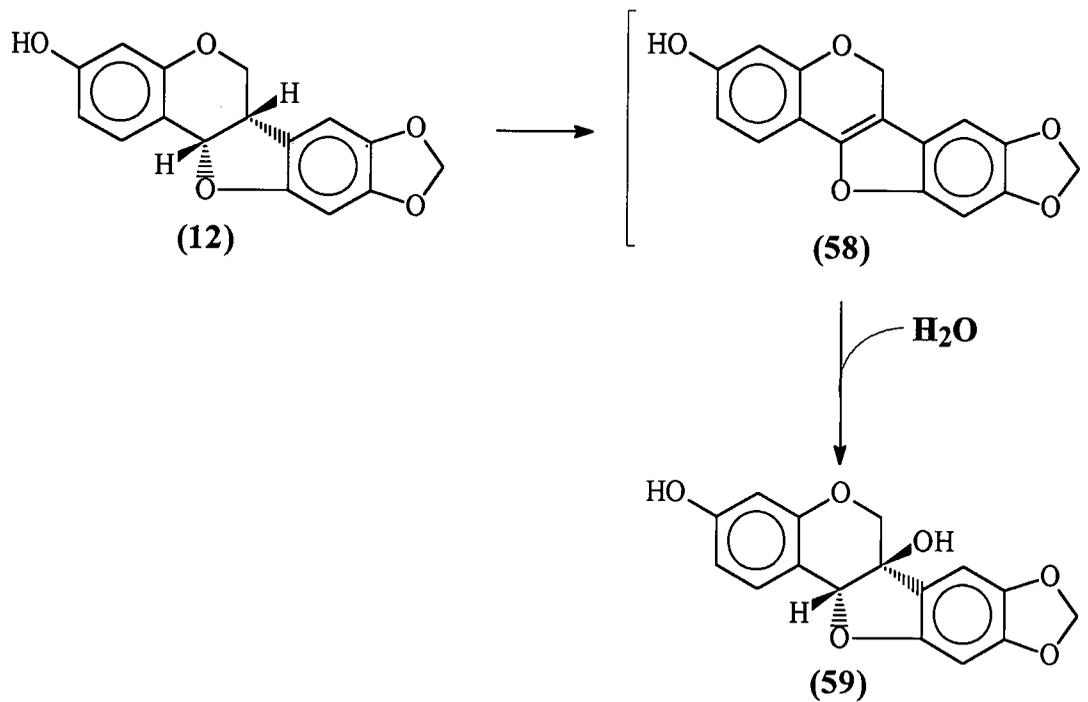
During the biosynthesis of 6a-hydroxypterocarpan it is believed that ring closure affording the pterocarpanoid nucleus, precedes 6a-hydroxylation which seemingly occurs with retention of configuration.⁴¹⁻⁴⁴

In the study of soybean cell cultures, 6a-hydroxylation of 3,9-dihydroxypterocarpan **56** to 3,6a,9-trihydroxypterocarpan **57** took place under the influence of a cytochrome P450 6a-hydroxylase, which was dependent on molecular oxygen (Scheme 4).^{45,46} However, during the formation of 6a-hydroxymaackiain **59** from maackiain **12** in pea seedlings, ¹⁸O-labeling experiments concluded that water, rather than molecular oxygen, was the source of the 6a-hydroxyl group, thereby indicating that pterocarpene **58** might be an intermediate within this system.²⁰

Soybean :



Pea :



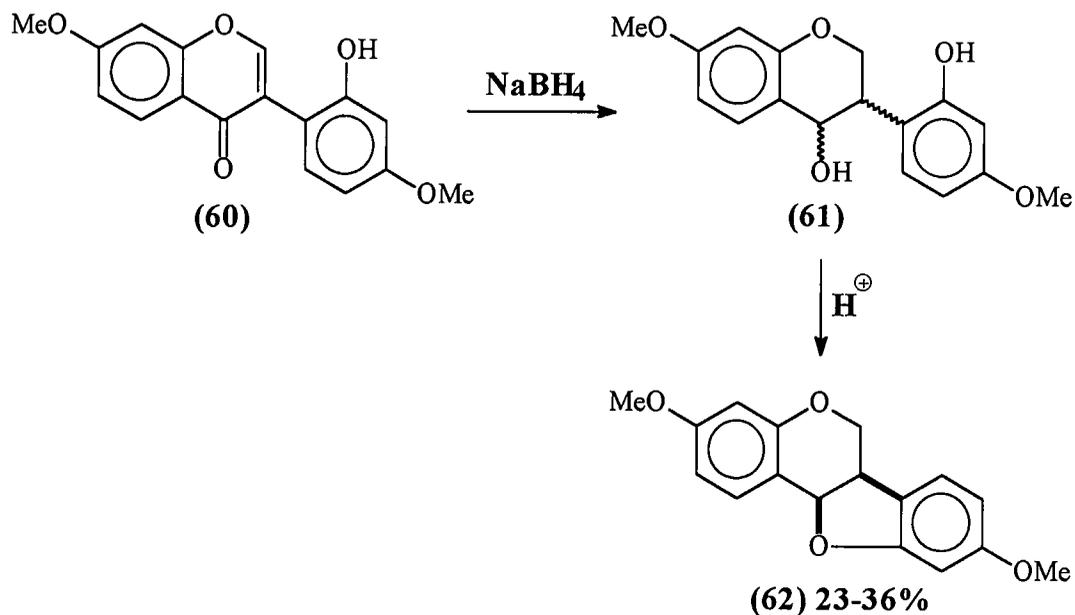
Scheme 4

Thus, despite intensive studies a number of problems still surround the biosynthesis of pterocarpan, 6a-hydroxypterocarpan and pterocarpenes.^{4,47,48}

2.5 Synthesis of pterocarpans.

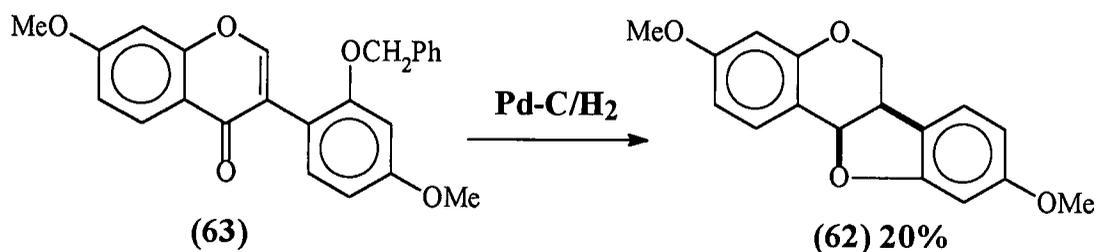
2.5.1 Pterocarpans

The most direct synthetic approach to pterocarpans involves isoflavones as starting material (Scheme 5). Reduction of **60** (LiAlH_4 or NaBH_4) yielded the isoflavan-4-ol **61**, which under acid catalysed cyclisation afforded the corresponding pterocarpan **62**.^{49,50}



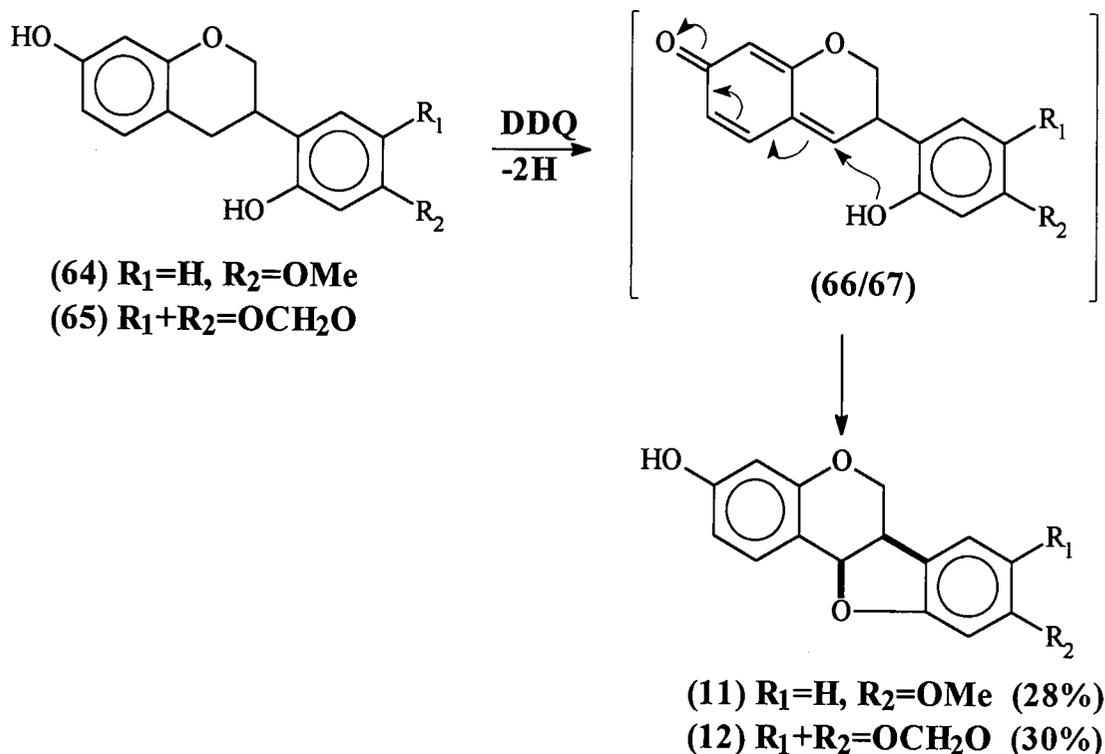
Scheme 5

Hydrogenative cyclisation of 2'-*O*-benzylisoflavone **63** gave pterocarpan **62** (Scheme 6).⁵¹ Although the reaction yield was only 20% this route envelops four consecutive steps, namely, debenzylation, reduction of the double bond and carbonyl functions as well as cyclisation to pterocarpan **62**.



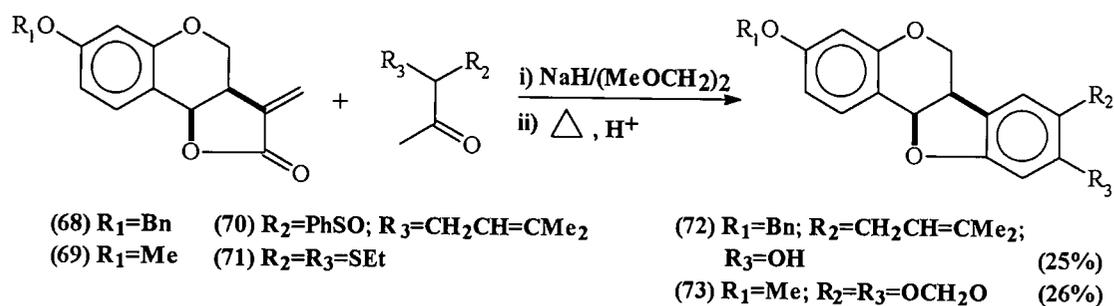
Scheme 6

2'-Hydroxyisoflavans also serve as precursors to pterocarpans (Scheme 7).⁴⁰ Oxidation of isoflavans **64** and **65** using DDQ, proceeds *via* the quinomethane intermediate **66** and **67** which undergo cyclisation to give pterocarpans **11** and **12** in low yields (28-30%).



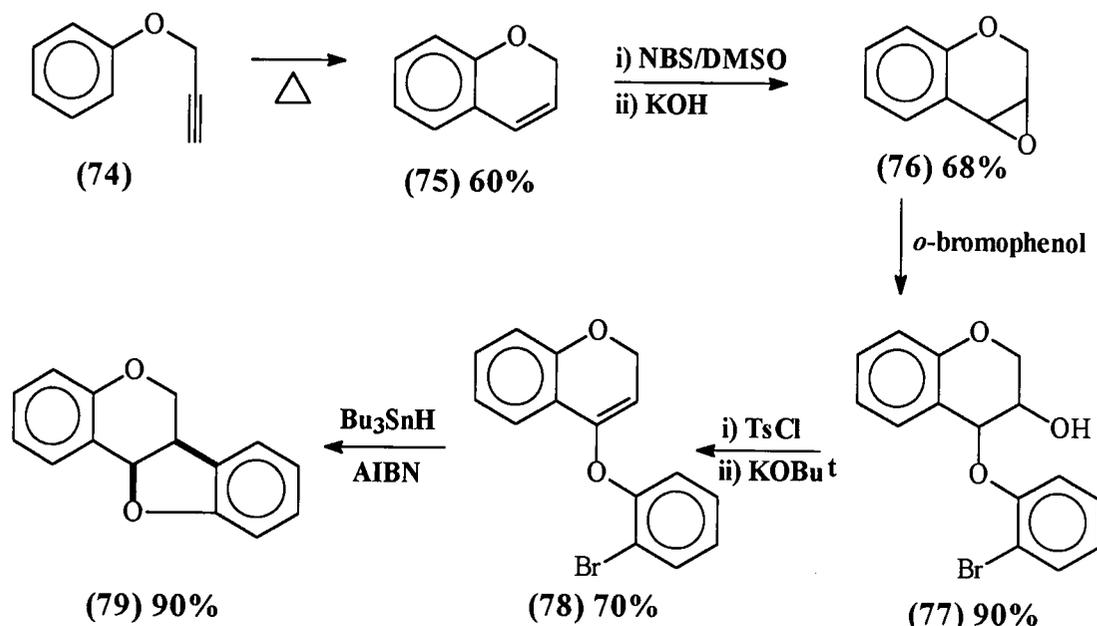
Scheme 7

3-Benzoyloxysophorapterocarpan A **72** and 3-benzoyloxymaackiain **73** were synthesised using a 1,3-Michael-Claisen annulation.^{52,53} Condensation of the methylenelactones **68** and **69** with ketones **70** and **71**, respectively, using NaH in 1,2-dimethoxyethane, followed by acid thermolysis gave the required pterocarpans **72** (25%) and **73** (26%) (Scheme 8).



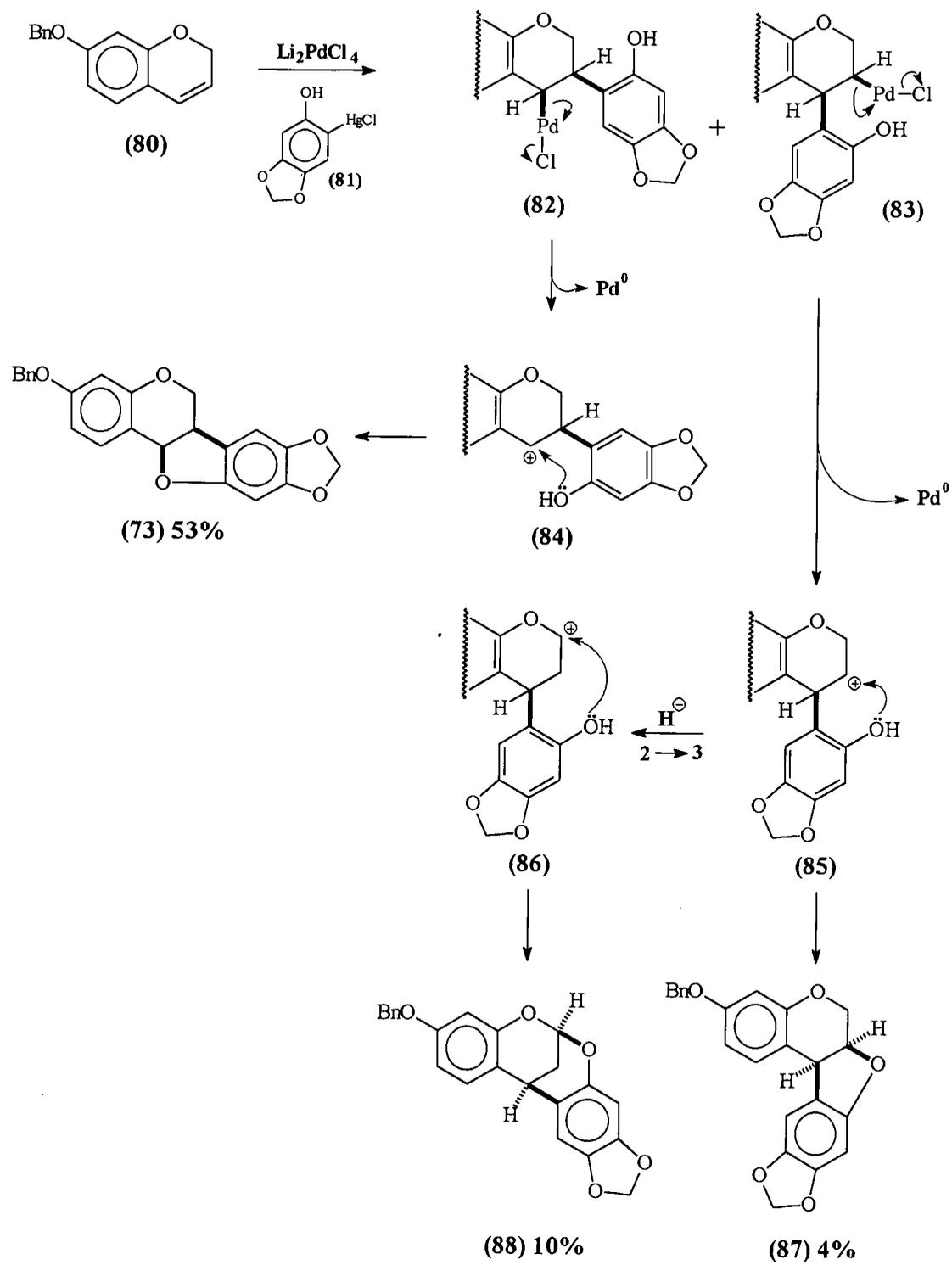
Scheme 8

The use of the 2*H*-1-benzopyran system found a number of applications which are outlined in Schemes 9. Firstly, the benzopyran **75**, produced from thermal rearrangement of the aryl propynyl ether **74**, was treated with *N*-bromosuccinimide (NBS) and aqueous dimethyl sulphoxide (DMSO) and directly converted to epoxide **76** using KOH (Scheme 9).⁵⁴ The epoxide ring was opened with *o*-bromophenol and the 4-(2'-bromophenoxy)chroman-3-ol **77** tosylated and treated with potassium *t*-butoxide to yield enol ether **78**. Radical cyclisation of **78** using tributyltin hydride and catalytic amounts of azoisobutyronitrile (AIBN) afforded the pterocarpanoid **79**. This route represents the first C-ring construction of pterocarpanoids *via* direct C-C bond formation.



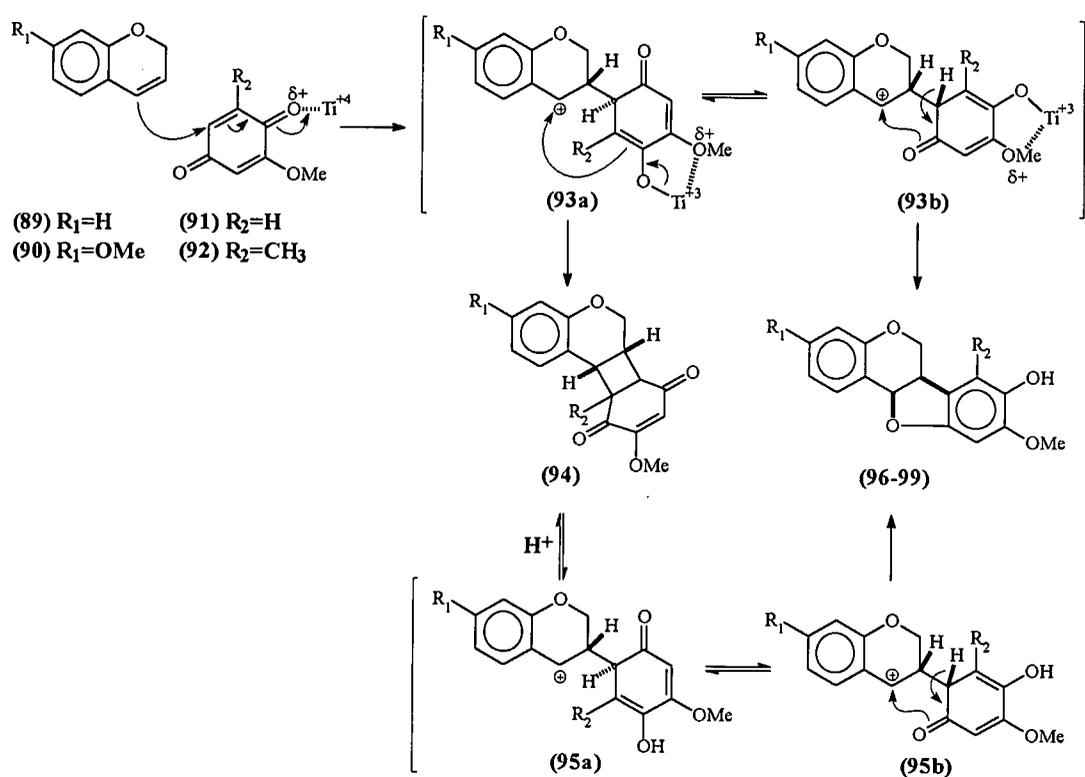
Scheme 9

The chromene / Heck arylation system^{55,56} was employed to synthesise several pterocarpan.⁵⁷⁻⁵⁹ It was suggested that these Heck arylations occurred with complete regioselectivity.⁵⁸ However, this view was challenged by Tókés *et. al.*⁶⁰ (Scheme 10). Heck arylation between chromene **80** and *o*-chloromercuriophenol **81** in the presence of lithium tetrachloropalladiate afforded the target **73** as well as 6a,12b-dihydro-6*H*-benzo[4,5]furo[2,3-*c*]chromene **87** and 6,12-methano-2,3-methylenedioxy-6*H*-dibenzo[*d,g*][1,3]dioxacin **88** as side products. This implied that coupling between **80** and **81** led to both arylated compounds **82** and **83**. The intermediate **82** converted to pterocarpan **73** *via* carbocation **84**, whereas **83** eliminated Pd⁰ to form carbocation **85** which could either undergo a 2,3-hydride migration to form the more stable carbocation **86** before cyclisation to **88**, or could directly cyclise to form **87**. Fortunately both these side products are formed in very low percentages. Therefore the Heck arylation provides access to pterocarpan where the appropriate isoflavones are unavailable.



Scheme 10

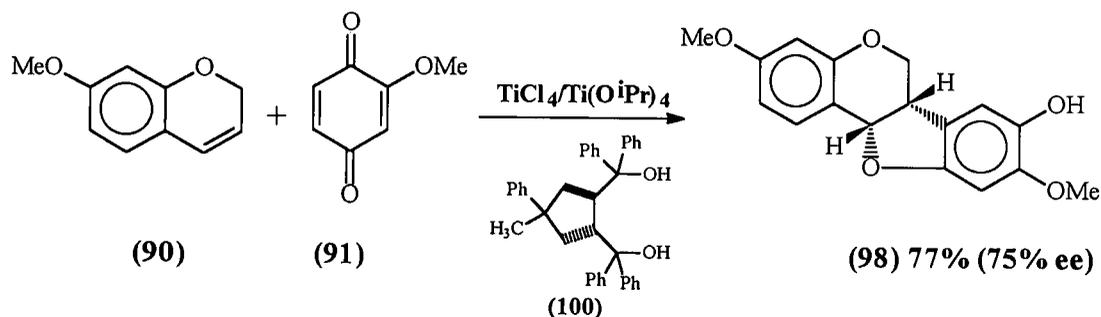
An interesting approach comprised the $\text{TiCl}_4/\text{Ti}(\text{O}^i\text{Pr})_4$ catalysed [3+2]-cycloaddition reaction of 2*H*-chromenes **89** and **90** with 2-alkoxy-1,4-benzoquinones **91** and **92** (Scheme 11).^{15,61} This reaction produced the [2+2]-adducts **94** via **93a** and the targeted [3+2]-products, namely pterocarpan **96-99**, via **93b**. This ratio could be altered by warming the reaction mixture and/or enriching it with TiCl_4 leading to almost exclusive formation of pterocarpan **96-99**. Also, the side product **94** could easily be converted to the corresponding pterocarpan via the intermediate carbocation **95a/b** by treatment with acid. A similar reaction was employed by Subburaj *et. al.*⁶² using ZnCl_2 in the synthesis of (\pm)-edulane **22**.



R_1	R_2	Pterocarpan	yield (%)
H	H	96	46
H	CH_3	97	67
OMe	H	98	58
OMe	CH_3	99	70

Scheme 11

Utilisation of chiral Ti(IV) complexes led to the first enantioselective syntheses of pterocarpan. ^{63,64} Reaction of 2*H*-chromene **90** with quinone **91** in the presence of chiral diol **100** yielded pterocarpan **98** in 77% yield and 75% ee (Scheme 12).

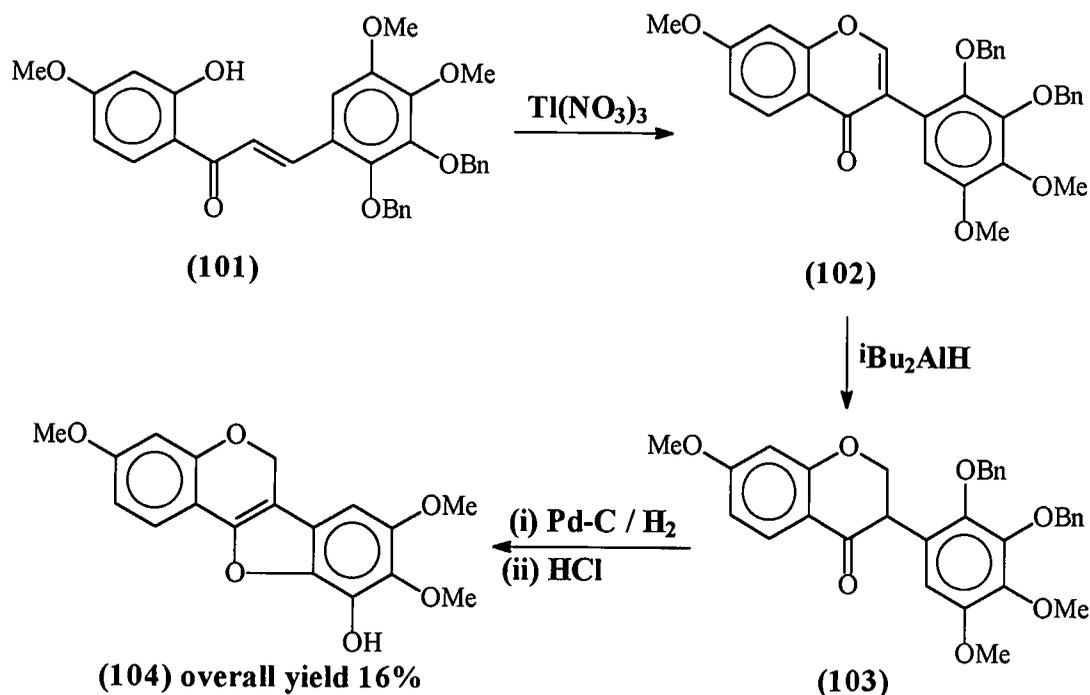


Scheme 12

Thus, although a number of synthetic alternatives to pterocarpan are available, most protocols are hampered by either low overall yields and/or restricted availability of starting materials, especially chromenes which are accessible in low yields and with limited substitution patterns. Also, only one synthetic approach incorporates stereocontrol.

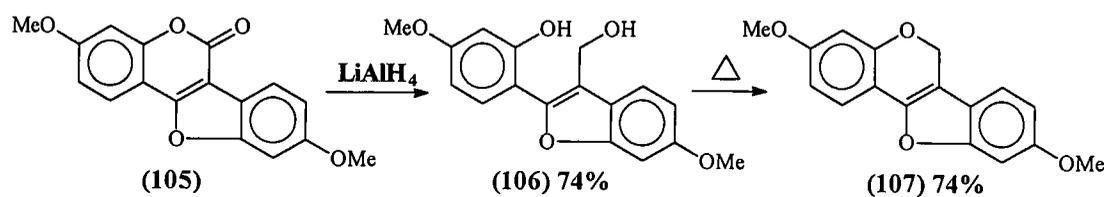
2.5.2 Pterocarpenes

A number of synthetic routes to pterocarpenes were developed, the simplest being a direct transformation *via* dehydration of the corresponding 6*a*-hydroxypterocarpan. ⁶⁵ Pterocarpenes are also readily synthesised by acid catalysed cyclisation of 2'-hydroxyisoflavanones (Scheme 13). ⁶⁶ Conversion of chalcone **101**, *via* thallium(III) nitrate rearrangement, gave the corresponding isoflavone **102** which was reduced to the isoflavanone **103**. Debenzylation and acid catalysed ring-closure afforded pterocarpene **104**.



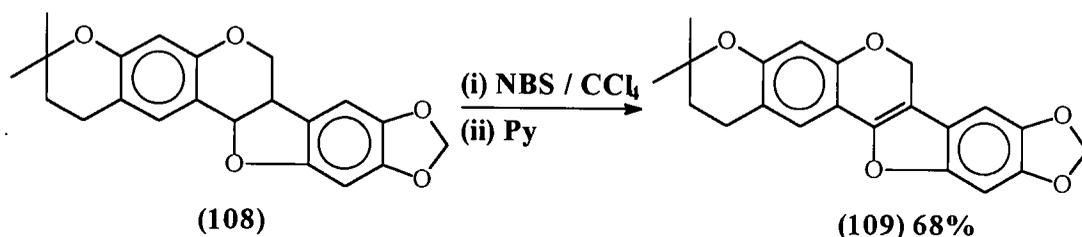
Scheme 13

Reduction of di-*O*-methylcoumestrol **105** by LiAlH_4 gave 2-(2'-hydroxy-4'-methoxyphenyl)-3-hydroxymethyl-6-methoxybenzofuran **106** that cyclised to give 3,4-dehydrohomoptercarpin **107** upon heating (Scheme 14).⁶⁷



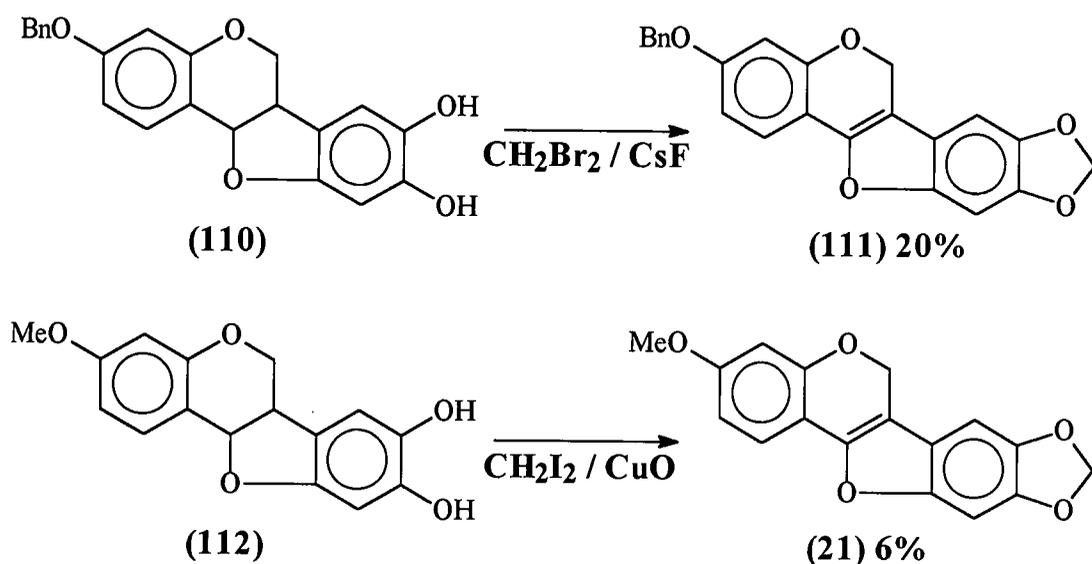
Scheme 14

Neorautane **108** was transformed to the corresponding pterocarpene **109** by halogenation, employing NBS, followed by dehydrohalogenation with pyridine (Scheme 15).^{2,52}



Scheme 15

3-Benzyloxy-8,9-dihydroxypterocarpan **110** in the presence of cesium fluoride (CsF) and dibromomethane (DBM), afforded the pterocarpene 3-benzyloxyanhydropisatin **111**.⁵³ Similarly, pterocarpan **112** could be converted to anhydropisatin **21** in low yield (6%) upon treatment with diiodomethane and cupric oxide (Scheme 16).^{15,68}



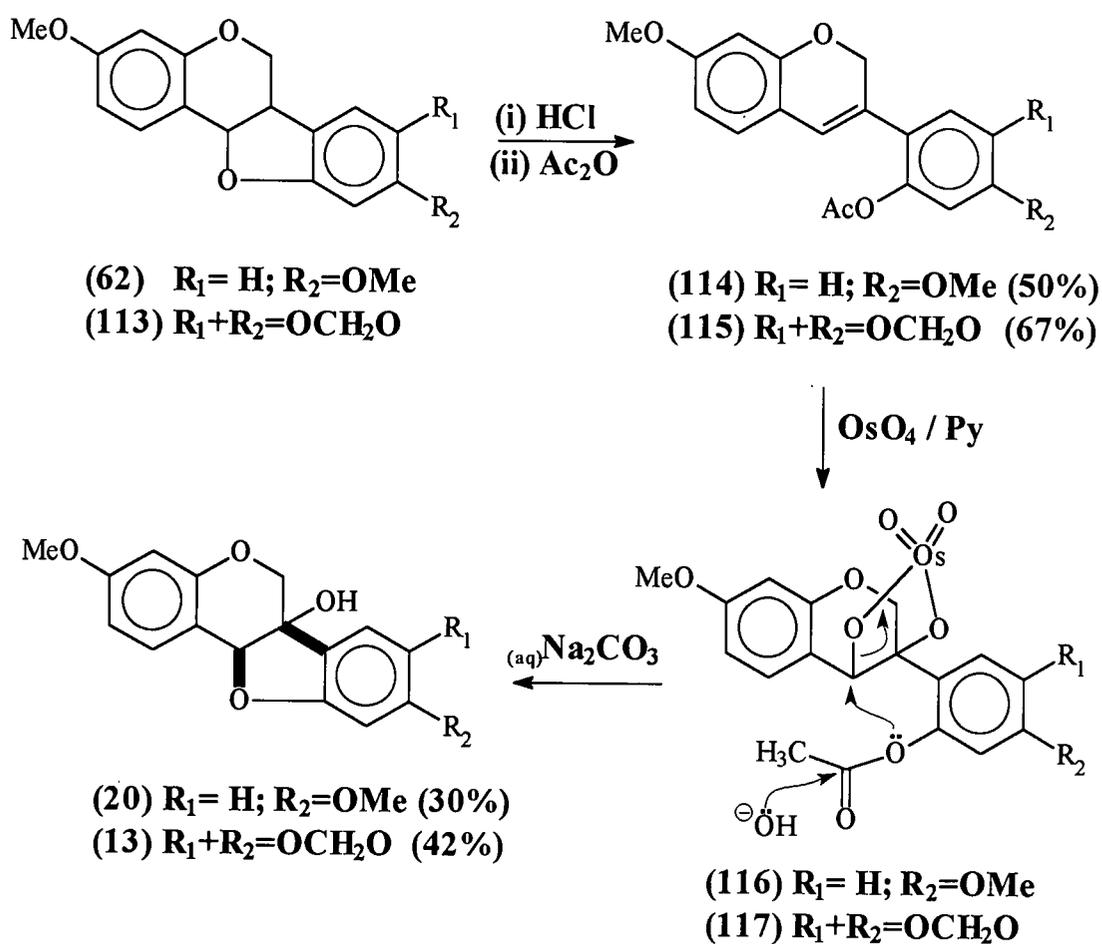
Scheme 16

2.5.3 6a-Hydroxypterocarpan

Hitherto, only two 6a-hydroxypterocarpan, namely pisatin **13** and variabilin **20**, had been synthesised.^{2,4} Apart from fungal modification of homopterocarpan **62** to variabilin

20,^{47,48} only one synthetic approach *i.e.* dihydroxylation of isoflav-3-enes, has met with success.

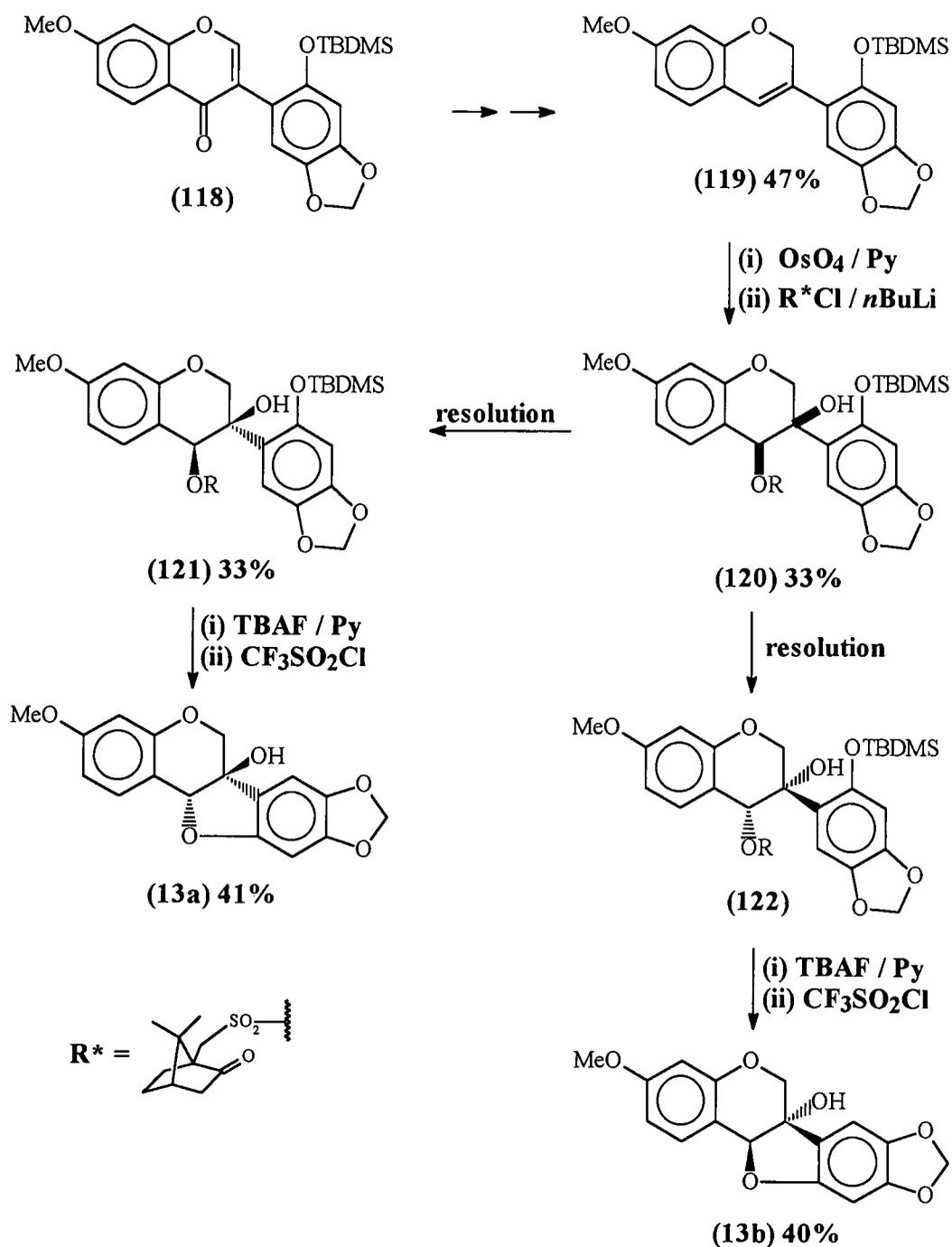
Isoflav-3-enes **114** and **115** could be obtained from homopterocarpin **62** and pterocarpin **113** upon treatment with hydrochloric acid (Scheme 17).^{69,70} Osmylation of the double bond, followed by hydrolysis of the osmate esters **116** and **117** with aqueous sodium carbonate, resulted in the first synthesis of (±)-pisatin **13** and (±)-variabilin **20**.



Scheme 17

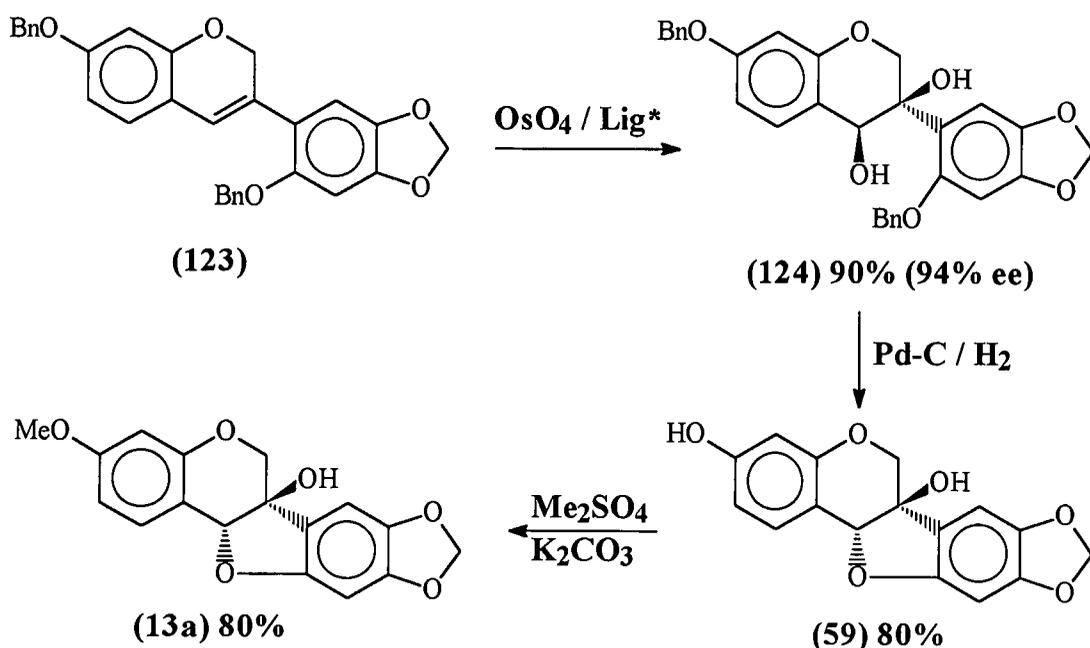
This protocol was adapted to produce both enantiomers of pisatin **13**. The 2'-*t*-butyldimethylsilyloxyisoflav-3-ene **119**, obtained from isoflavone **118** *via* reduction and

dehydration, was oxidised to diol **120** with osmium tetroxide. Resolution of the diastereomeric (+)-camphor-10-sulfonylethers **121** and **122**, followed by deprotection and cyclisation yielded (+)-pisatin **13a** and (-)-pisatin **13b** respectively (Scheme 18).⁷¹



Scheme 18

Employing dihydroquinine *p*-chlorobenzoate as a chiral ligand, dihydroxylation of **123** afforded diol **124** with an enantiomeric excess of 94% (Scheme 19).⁷² Cyclisation occurred spontaneously during hydrogenative debenzoylation to yield (+)-6a-hydroxymaackiain **59** that was methylated to (+)-pisatin **13a**. The cyclisation proved dependent on the presence of an unprotected hydroxyl at C-3 of the pterocarpanoid skeleton. The specific substitution pattern required and low overall yield of only 12%, limited the utility of this protocol.^{2,72}



Lig* = dihydroquinine *p*-chlorobenzoate

Scheme 19

CHAPTER 3

ALDOL CONDENSATION AND ASYMMETRIC DIHYDROXYLATION

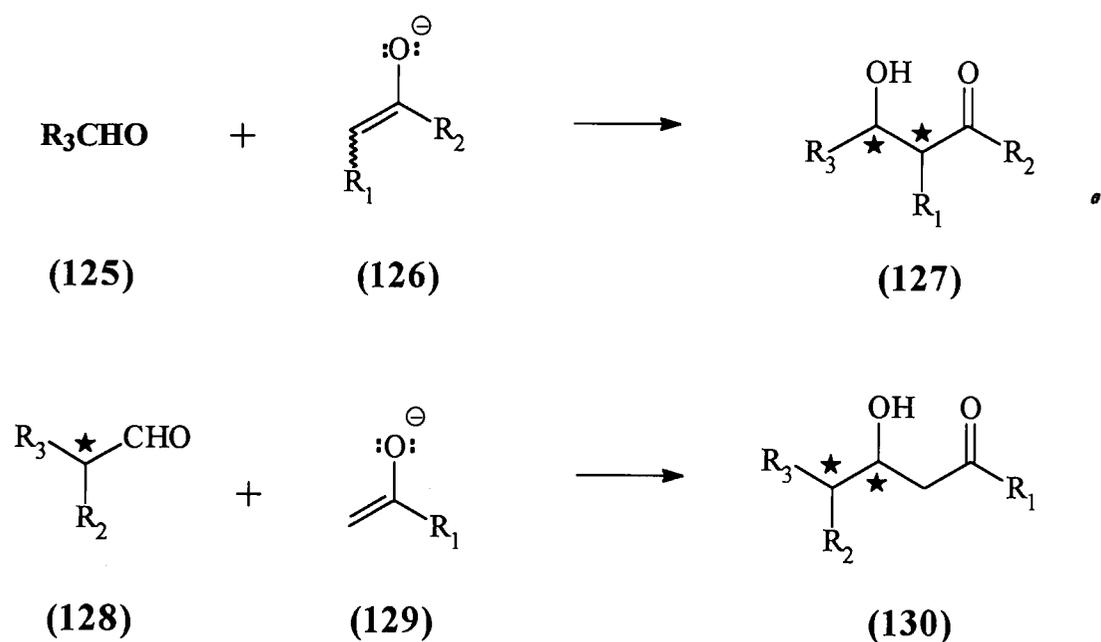
3.1 Aldol condensation

3.1.1 Introduction

Among the protocols applicable to control the stereochemistry of acyclic organic molecules, aldol reactions has enjoyed particular success, to such an extent that it has developed into one of the most important carbon-carbon bond-formation reactions in organic chemistry. This utility stems from the capability of generating two vicinal stereocenters with high levels of both diastereo- and enantioselection.⁷³

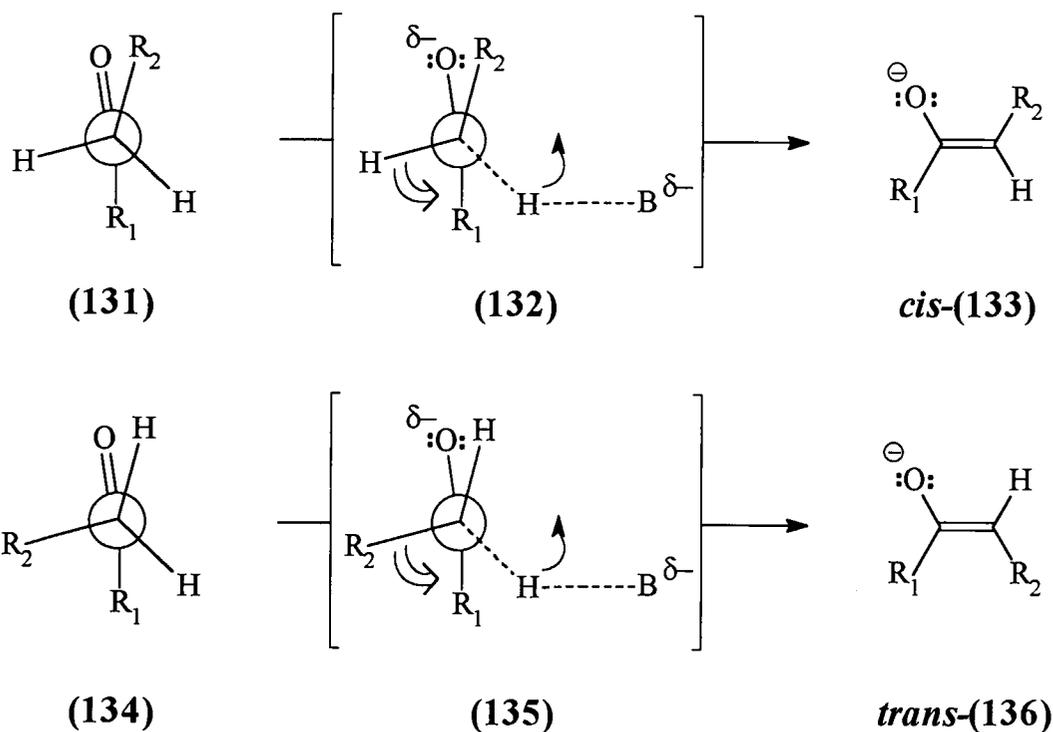
3.1.2 Diastereochemistry of the aldol condensation

Aldol condensation allows for two types of diastereoselectivities, namely simple diastereoselectivity and diastereofacial stereoselectivity. As depicted in Scheme 20, the former comprises the relative configurations of the two carbons being joined during the condensation of **125** and enolate **126** to yield **127**, while the latter involves the selective formation of diastereomers having relative configurations at the β and γ positions of the product **130** obtained from **128** and **129**.⁷⁴



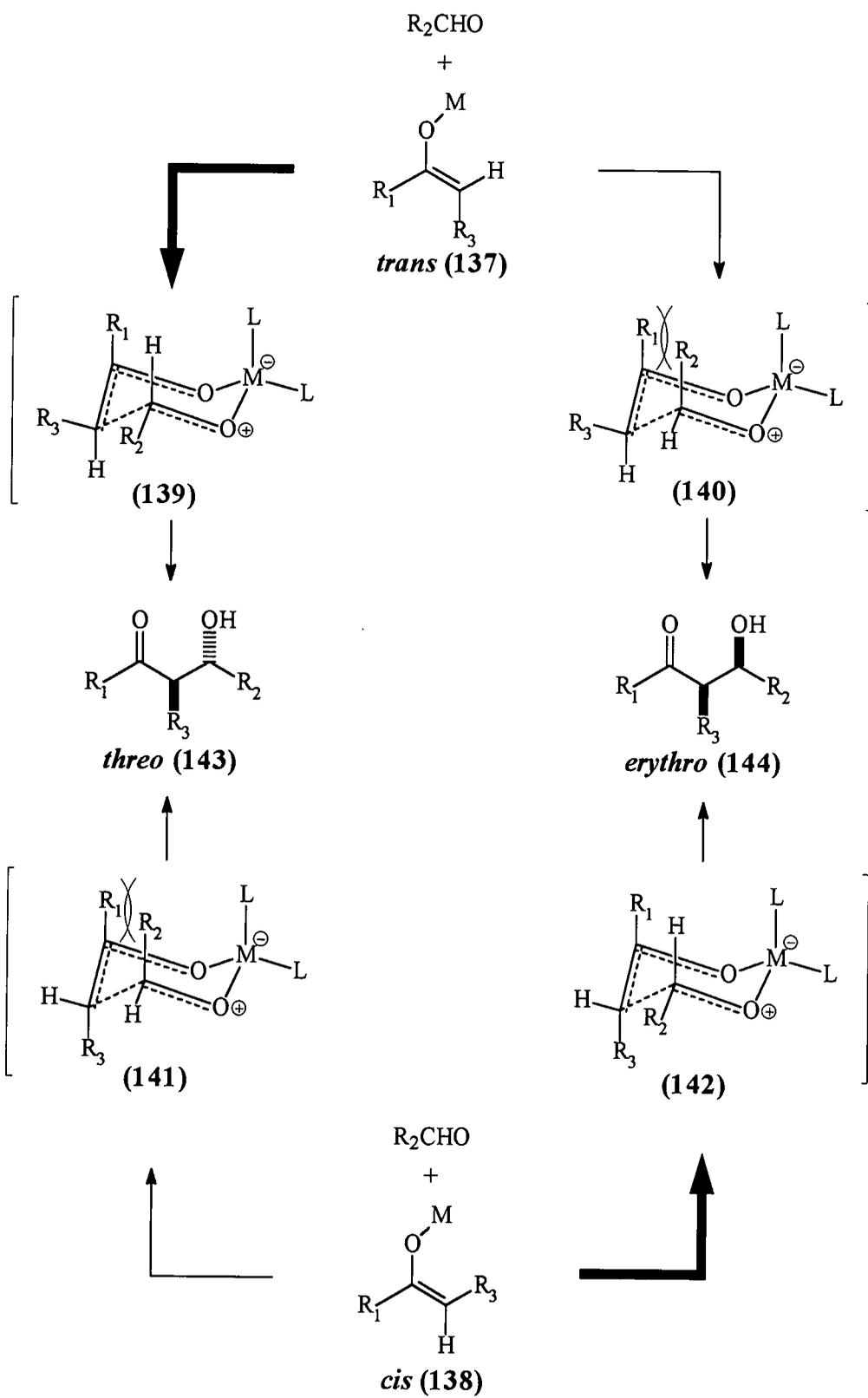
Scheme 20

The diastereoselectivity is firstly dependent on the enolate geometry.⁷⁵ Scheme 21 portrays the formation of both *cis*-133 and *trans*-136 enolates *via* their respective transition states 132 and 135. Both the nature of the base used and the relative bulk of R₁ and R₂ of the starting materials 131 and 134, substantially effect the *cis/trans* ratio during the reaction.⁷⁶ Formation of *cis*-enolate 133 is favored by sterically less demanding bases as well as bulkier R-groups.^{76,77}



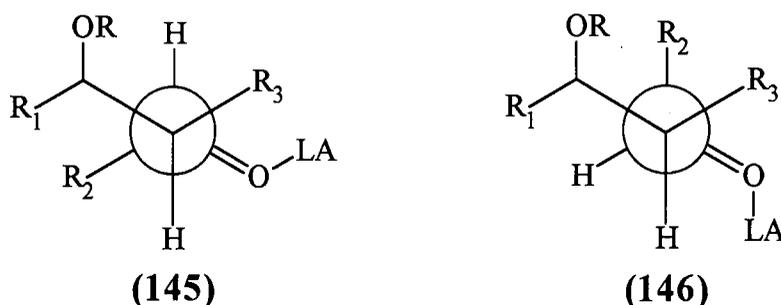
Scheme 21

It is generally accepted that with metal enolate formation, *cis*-enolates **138** leads to the formation of *syn*-(*erythro*)-aldols **144**, while *trans*-enolates **137** produce *anti*-(*threo*)-aldols **143** (Scheme 22).^{73,75,78} Zimmerman *et al.*⁷⁹ accounted for this diastereoselection by the hypothesis that the reaction proceeds *via* a preferred chairlike transition state. Both the enolate and carbonyl substrate are bonded to the cooperative metal ion in order to produce a six membered ring structure.⁷⁸ This coordination of *trans*-enolate **137** and *cis*-enolate **138** led to transition states **139** / **140** and **141** / **142** respectively.^{76,78} Diastereoselectivity from these transition states depends on the steric bulk of R₁ and R₂, which implies that transition states **140** and **141** are destabilised when R₁ and/or R₂ are sterically demanding. Thus, bulkier R groups favour the formation of **143** from **137** *via* the more stable **139**, while the same applies for the *cis*-enolate **138** where steric interaction promotes the formation of **144** *via* **142**.^{78,79} Furthermore, "transition state compression" by less polar solvents results in an enhancement of those steric factors which additionally regulates diastereoselection.⁷⁸



Scheme 22

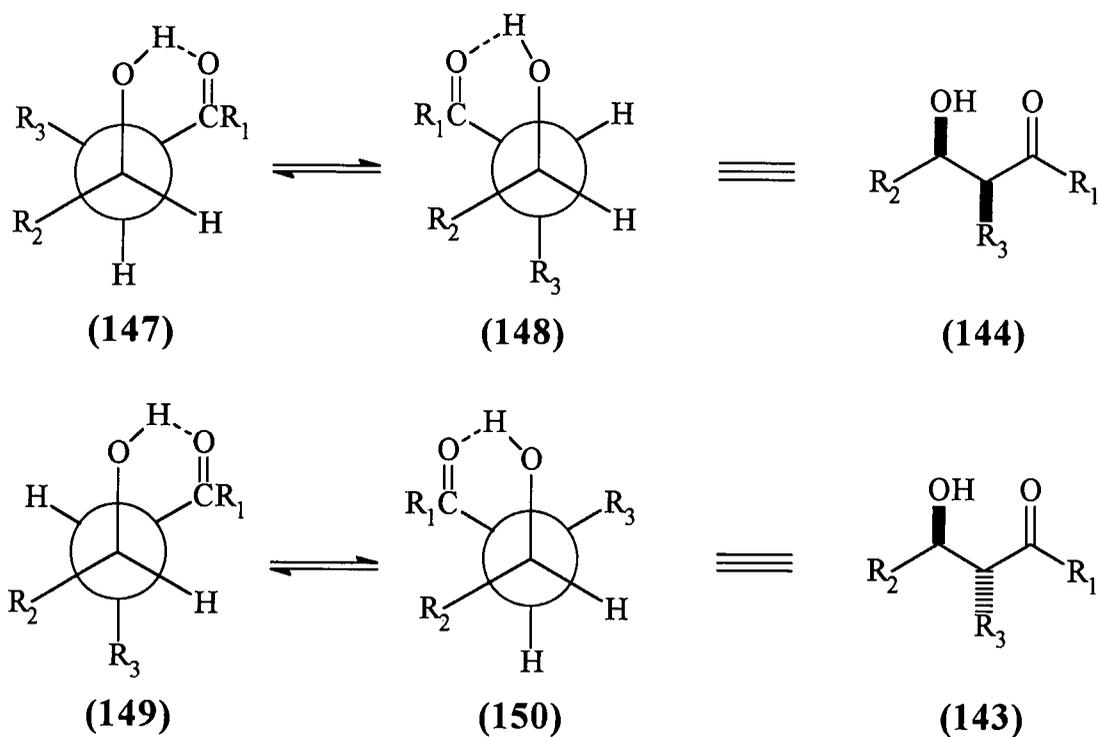
Condensation of silyl enol ethers with carbonyl compounds promoted by Lewis acids has emerged as an important access to cross aldol reactions.^{80,81} It was established that aldehyde-Lewis acid bonding precedes condensation, therefore an extended transition state model was developed to explain the independence of product configuration from enolate geometry (Scheme 23).⁸² Transition state **145** is preferred to **146** in cases where "small" Lewis acids are employed and *vice versa*, thus enabling the selective formation of *syn*- or *anti*-aldols, respectively.⁸³ This ability to manipulate the reaction conditions in order to produce specific aldol stereoisomers from the same carbonyl precursor,^{83,84} makes the use of Lewis acid-, instead of base-catalysed conditions, an attractive alternative.



R = R₃Si or M
LA = Lewis acid

Scheme 23

In general it is possible to assign the stereochemistry of aldol products from the ¹H NMR coupling constants observed for the vicinal α and β protons. This is made possible as a result of the hydrogen bonding between the β-OH and the carbonyl oxygen leading to a six membered "cyclic" conformation. Stiles *et. al.*⁸⁵ confirmed this by correlating infrared absorption frequencies for carbonyl functions of ketols and ketoacetates. Conformations **147** and **148** are preferred by the *syn*-(*erythro*) configuration **144**, thus displaying a smaller coupling constant than the *anti*-(*threo*) diastereoisomer **143** that preferentially adopts conformations **149** and **150** (Scheme 24).^{74,85}



Scheme 24

3.1.3 Enantioselectivity in the aldol condensation

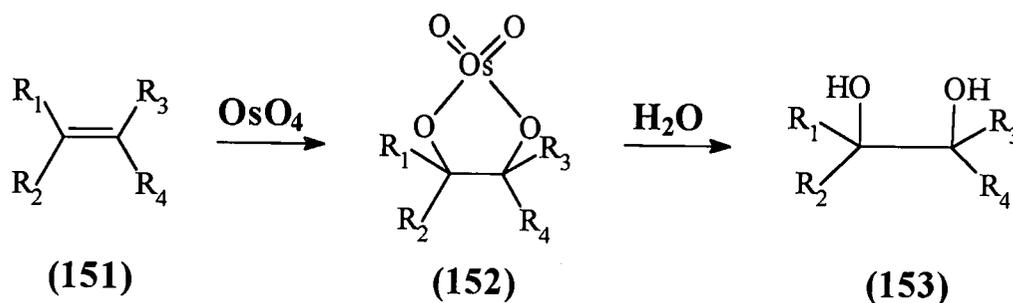
Enantioselective aldol condensation has emerged as an attractive synthetic tool in organic chemistry.^{73,86} Apart from chiral aldehydes,⁸⁷ the use of bornanesultam-,⁸⁸ oxazolidin-2-one-,⁸⁹ imidazolidin-2-one-⁹⁰ and thiazolidin-2-one⁹¹ derivatives of ester starting materials has led to enantiomerically pure aldols. In all instances steric interaction either within the transition states or in the enolates themselves is accepted as being responsible for the enantiomeric induction.^{87,89,91} Chiral metal complexes⁹²⁻⁹⁹ as well as chiral bases^{100,101} can be applied in systems where chiral starting materials are inaccessible. Within these systems transition state geometry is the main factor governing enantioselection.^{99,102,103} Reports of aberrant behavior,^{78,104} resulting in a lack of

stereocontrol, still limits the general application of adol condensations in synthesis where the starting materials possess bulky substituents.

3.2 Asymmetric dihydroxylation

3.2.1 Introduction

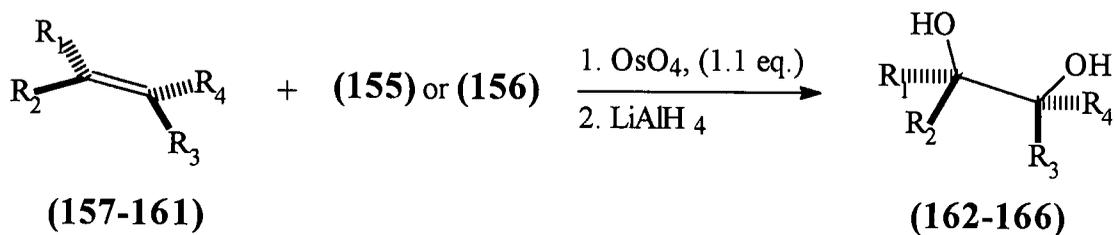
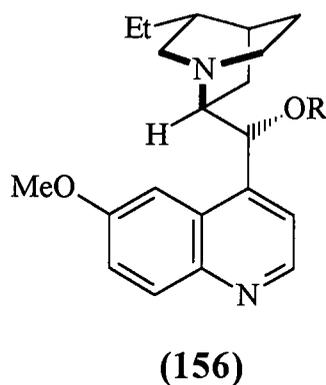
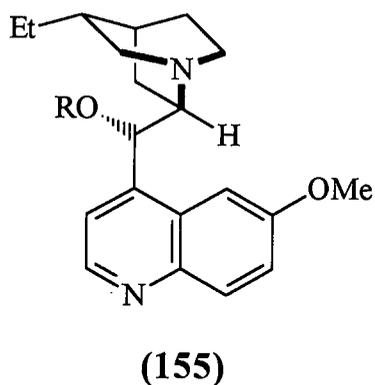
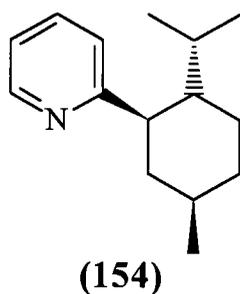
Dihydroxylation of alkenes **151** with osmium tetroxide to afford *syn*-diols **153** (Scheme 25), has developed as one of the most selective transformations in organic chemistry. The initial use of stoichiometric amounts of osmium tetroxide, resulted in the formation of osmate ester **152** that could be hydrolysed oxidatively to regenerate osmium tetroxide. Yet financial considerations led to the development of catalytic variants, employing inexpensive cooxidants, that greatly enhanced the synthetic utility of this reaction.¹⁰⁵⁻¹⁰⁷



Scheme 25

3.2.2 Asymmetric induction during dihydroxylations

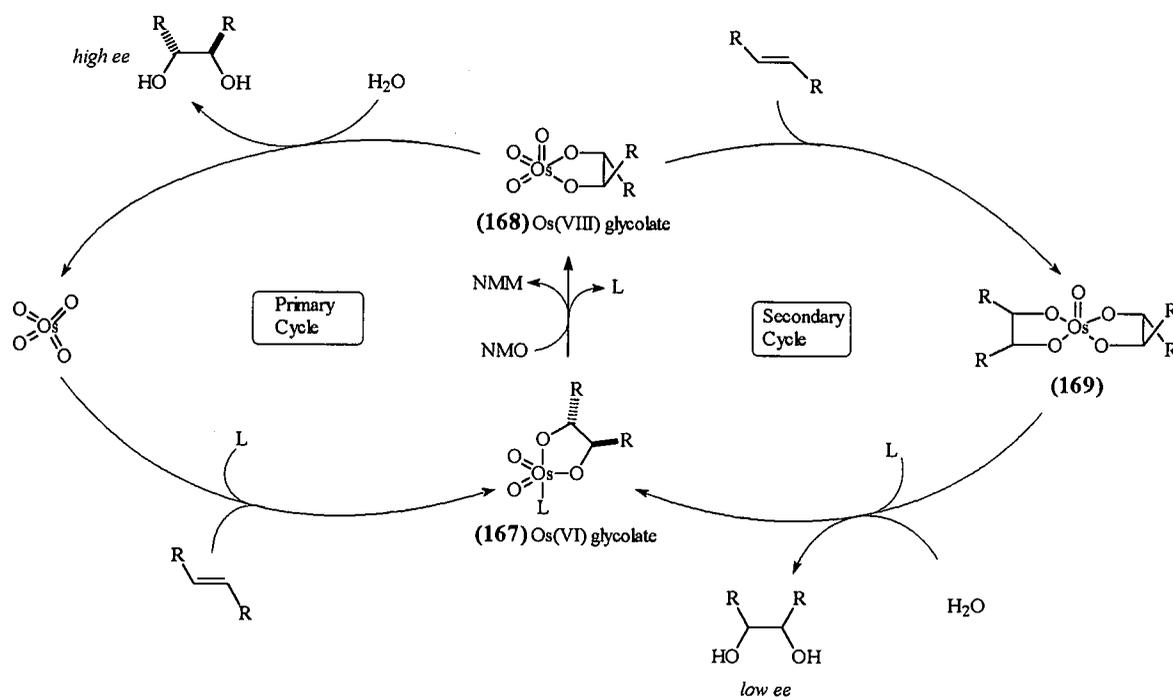
The utilisation of *L*-2-(2-menthyl)pyridine **154** as chiral ligand in osmylation reactions, albeit with poor enantioselectivities (3-18%), marked the initial attempts¹⁰⁸ towards performing asymmetric dihydroxylation (AD) of olefins. Hentges *et. al.*¹⁰⁸ utilised cinchona alkaloid acetates **155** and **156** as chiral ligands in AD reactions of olefins **157-161** (Table 1) and for the first time isolated diols **162-166** with moderate to good enantiomeric excesses.



Olefin	Ligand	Syn-diol	% yield	%ee	Confign.
(157) styrene	156	162	90	65	<i>S</i>
	155	162	62	61	<i>R</i>
(158) (<i>Z</i>)-1-phenylpropene	156	163	82	27	1 <i>S</i> ,2 <i>R</i>
	155	163	85	26	1 <i>R</i> ,2 <i>S</i>
(159) 1-phenylcyclohexene	156	164	88	68	1 <i>S</i> ,2 <i>S</i>
	155	164	87	67	1 <i>R</i> ,2 <i>R</i>
(160) (<i>E</i>)-stilbene	156	165	90	83	1 <i>S</i> ,2 <i>S</i>
	155	165	85	82	1 <i>R</i> ,2 <i>R</i>
(161) (<i>E</i>)-3-hexene	156	166	69	50	3 <i>S</i> ,4 <i>S</i>

Table 1: Cinchona alkaloid acetates **155** and **156** as chiral ligands in AD reactions.

Sharpless and co-workers¹⁰⁹ reported the first catalytic AD conditions employing *N*-methylmorpholine *N*-oxide (NMO) as cooxidant in a modified cinchona alkaloid protocol. Stereoselectivity is obtained *via* an osmium-ligand glycolate **167** which is oxidised to Os(VIII) glycolate **168** resulting in either diol formation (high ee) or an osmium glycolate species **169** in a secondary catalytic cycle exhibiting lower enantioselectivity (Scheme 26).¹¹⁰ In spite of the above, this method represented a major breakthrough in terms of economy and toxicity and became the basis for future development in catalytic AD reactions.

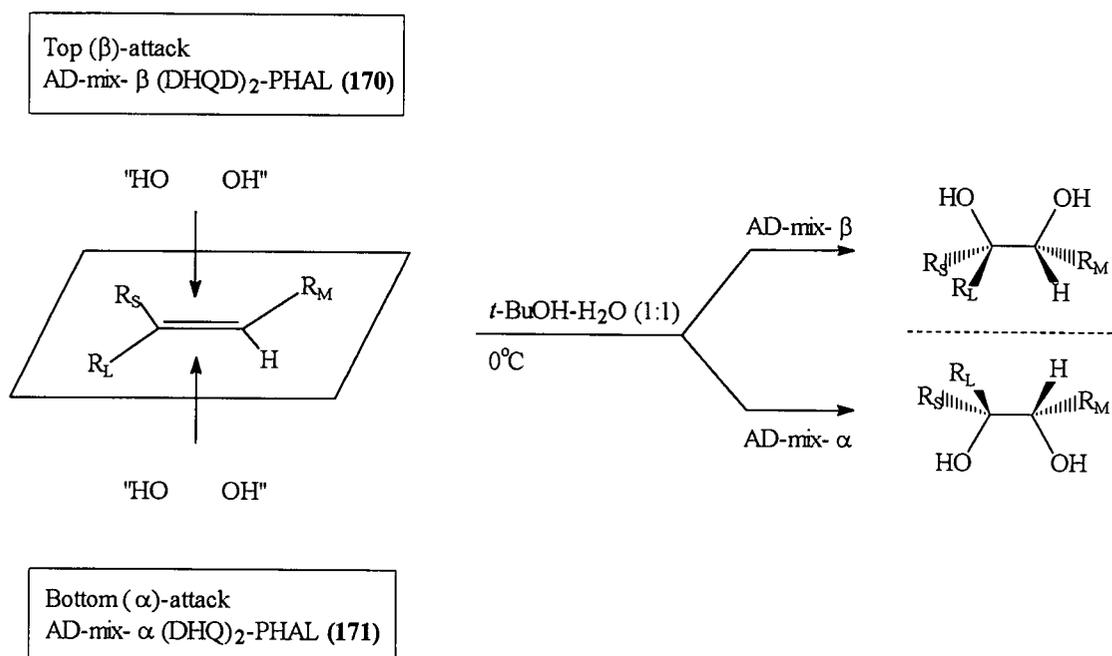


Scheme 26

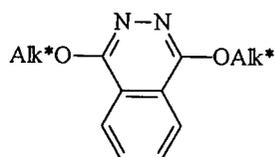
Key discoveries by Sharpless and co-workers virtually eliminated all problems surrounding the catalytic AD reaction: Firstly, they found that the second catalytic cycle is suppressed by two-phase reaction condition with $K_3Fe(CN)_6$ as reoxidant. Under these conditions OsO_4 is the only oxidant in the organic layer, resulting in a considerable increase in the enantiomeric excesses ($\pm 20\%$) of various diols.¹¹¹ Secondly, the hydrolysis of the osmium(VI) glycolate **167** can be accelerated substantially (up to 50

times) by addition of methanesulfonamide (MeSO_2NH_2).¹¹² Therefore most AD reactions can be carried out at 0°C rather than room temperature, which has a beneficial influence on the selectivity.¹¹³ Finally, the development of phthalazine (PHAL) alkaloid derivatives, $(\text{DHQD})_2\text{-PHAL}$ **170** and $(\text{DHQ})_2\text{-PHAL}$ **171**, as chiral ligands led to a substantial increase in both the enantioselectivity and scope of the reaction (Table 2).¹¹⁴

Extensive mechanistic investigations,^{115,107} ligand structure-activity studies¹¹⁶ and *ab initio* calculations^{117,118} led to a rationale for predicting the enantiofacial selectivity within AD reactions (Scheme 27). In this way Sharpless formulated a commercially available premix, AD-mix- α and AD-mix- β , consisting of $\text{K}_2\text{OsO}_2(\text{OH})_4$ as a non volatile source of osmium, $\text{K}_3\text{Fe}(\text{CN})_6$ as reoxidant and $(\text{DHQD})_2\text{-PHAL}$ **170** or $(\text{DHQ})_2\text{-PHAL}$ **171** as chiral ligand.



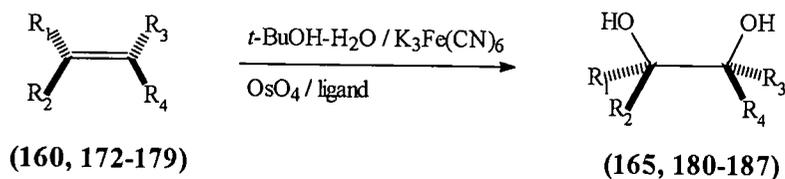
Scheme 27



Alk* = DHQD (155) or DHQ (156)

(170) (DHQD)₂-PHAL

(171) (DHQ)₂-PHAL



Olefin	Syn-diol	(DHQD) ₂ -PHAL (170)		(DHQ) ₂ -PHAL (171)	
		% ee	Confign.	% ee	Confign.
172	(180)	98	<i>R</i>	95	<i>S</i>
173	(181)	99	<i>R,R</i>	97	<i>S,S</i>
174	(182)	97	<i>R,R</i>	93	<i>S,S</i>
175	(183)	99	<i>2S,3R</i>	96	<i>2R,3S</i>
176	(184)	97	<i>2S,3R</i>	95	<i>2R,3S</i>
160	(165)	>99.5	<i>R,R</i>	>99.5	<i>S,S</i>
177	(185)	78	<i>R</i>	76	<i>S</i>
178	(186)	95	<i>R</i>	93	<i>S</i>
179	(187)	91	<i>S</i>	88	<i>R</i>

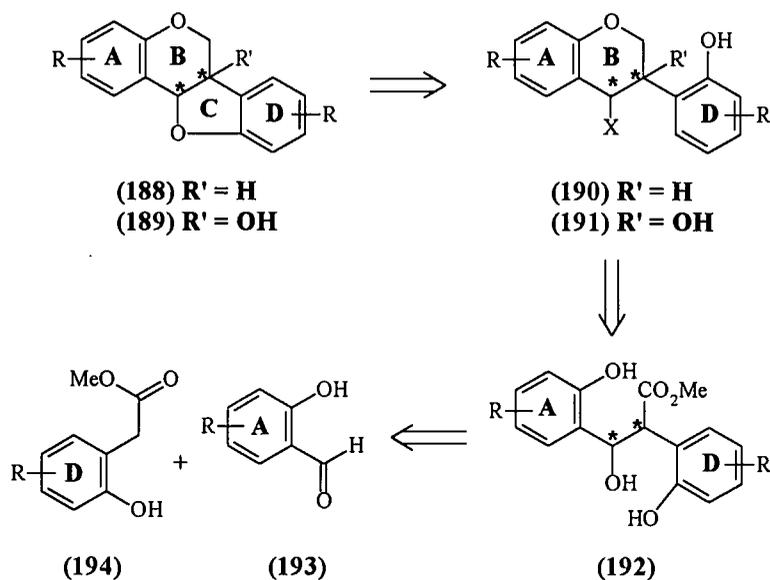
Table 2: Catalytic AD of olefins 160, 172-179 utilising (DHQD)₂-PHAL 170 and (DHQ)₂-PHAL 171 as chiral ligands.

DISCUSSION

CHAPTER 4

INTRODUCTION

Naturally occurring pterocarpan display a large variety of structures, linked to diverse biological and physiological activities from which mankind can benefit.^{3-7,20-32} Despite this, synthetic access to this group is limited to only a few protocols, which are in turn restricted to only a few substitution patterns. In order to alleviate these restrictions, a study was undertaken that would permit the production of a diverse series of oxygenated substrates with control of the stereochemistry at C-3 of the isoflavan skeleton, thereby ultimately providing access to optically enriched pterocarpan. The simple *retro*-synthetic sequence, **188**, **189** \Rightarrow **190**, **191** \Rightarrow **192** \Rightarrow **193** + **194**, indicates that our protocol for constructing the required C₆-C₃-C₆ framework involves oxygenated phenylacetates **194** (C₆-C₂ fragment) and benzaldehydes **193** (C₆-C₁ fragment) as starting materials, aldol products **192**, isoflavans **190** and **191** and final cyclisation to pterocarpan of type **188** and **189**, respectively (Scheme 28).

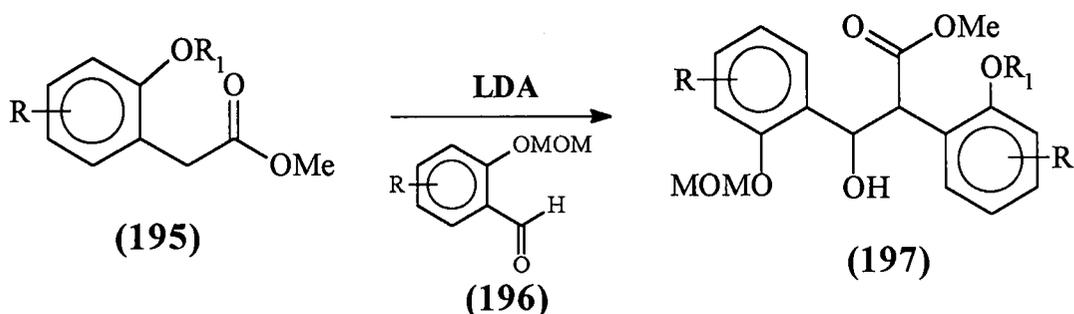


R = H; OMe, X = leaving group

Scheme 28: *Retro*-synthetic sequence to pterocarpan.

4.1 Aldol condensations

As depicted in Scheme 29, aldol condensations between the appropriate methyl phenylacetates **195** and benzaldehydes **196** were utilised to form the C₆-C₃-C₆ diaryl precursors **197**. The choice of protecting groups played an integral role in the development of effective synthetic sequences. Lithium diisopropylamide (LDA) proved to be the most effective base for the synthesis of the 2,3-diaryl propanoates **197**. These compounds were then transformed to the *cis*-, *trans*- and 6a-hydroxypterocarpan as indicated in Schemes 30, 31 and 33.



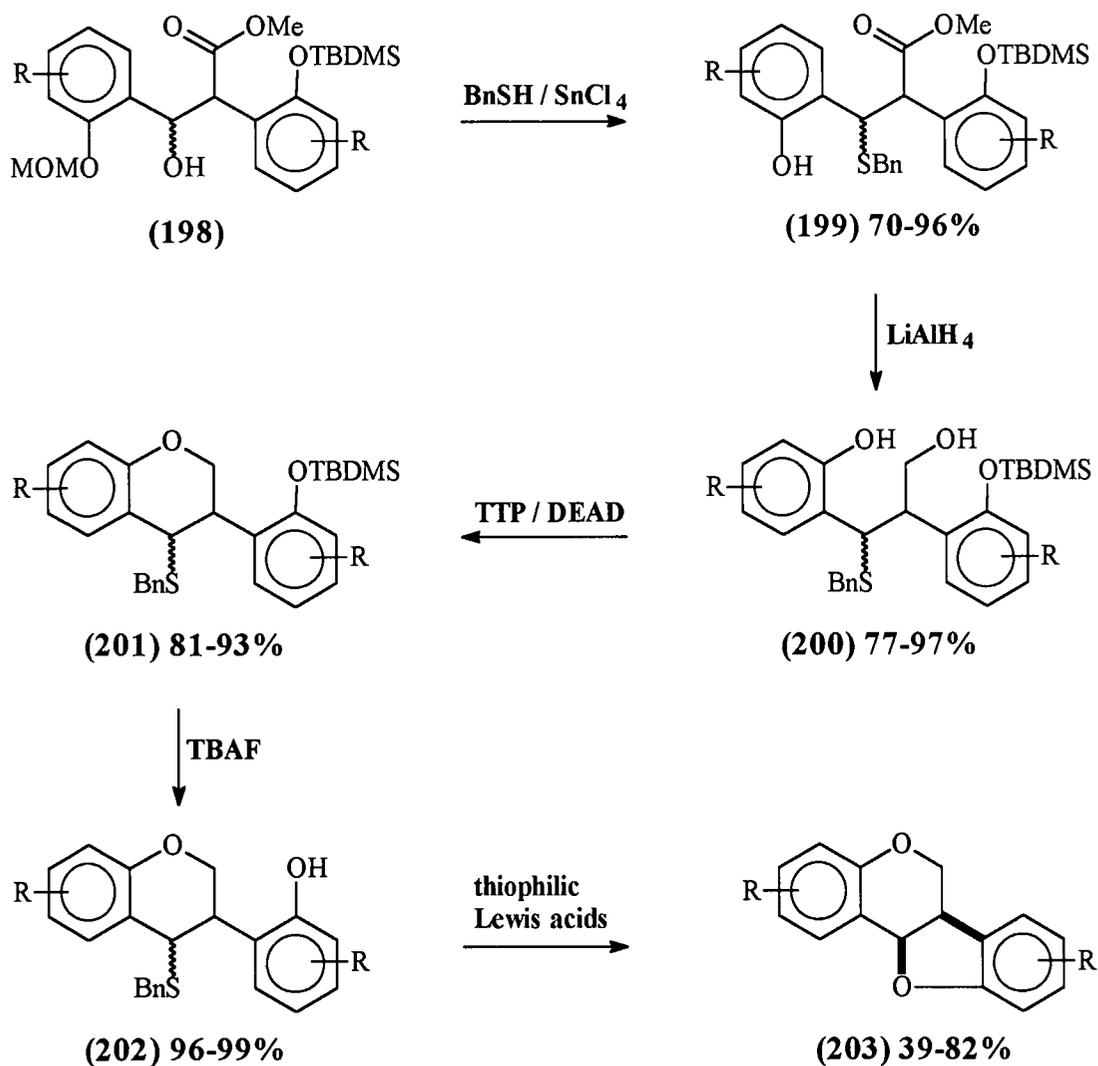
R = H, OMe

R₁ = MOM, iPr, TBDMS

Scheme 29: Aldol condensation between phenylacetates and benzaldehydes.

4.2 *Cis*-pterocarpan

Benzyl mercaptan (BnSH) / tin tetrachloride (SnCl₄) deprotection of the 2-*O*-MOM-ethers **198** with concomitant substitution of the benzylic hydroxy group afforded compounds **199** (70-96%), which were reduced (LiAlH₄) to the corresponding propanols **200** (77-97%). Mitsunobu cyclisation yielded isoflavans **201** which upon deprotection (tetrabutylammonium fluoride-TBAF) and thiophilic Lewis acid cyclisation furnished *cis*-pterocarpan **203** via **202** (Scheme 30).

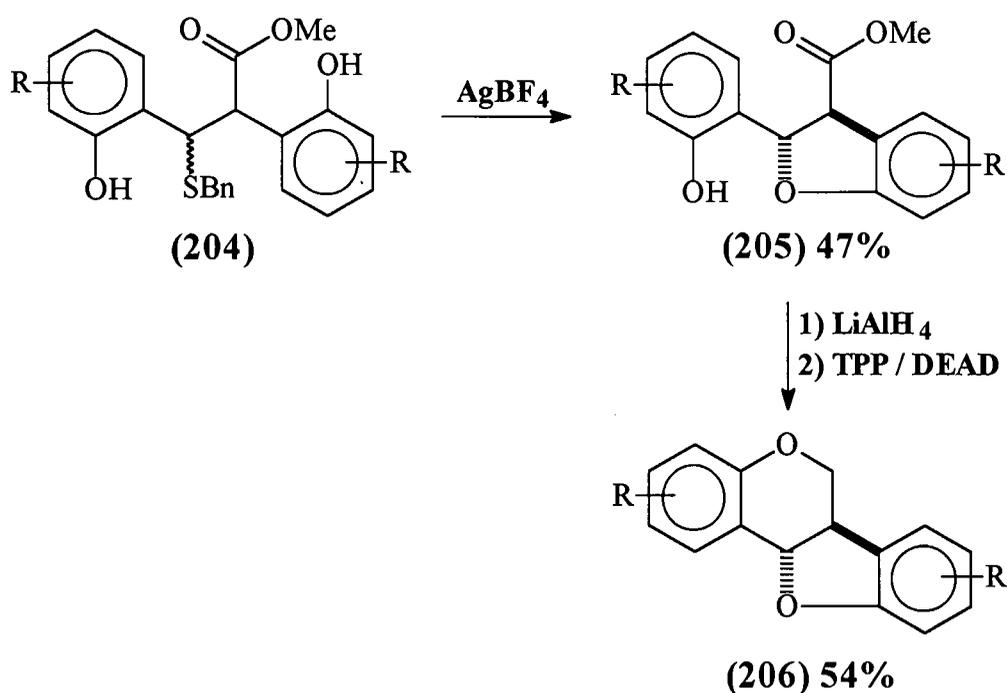


R = H, OMe

Scheme 30: Synthesis of *cis*-pterocarpan

4.3 *Trans*-pterocarpan

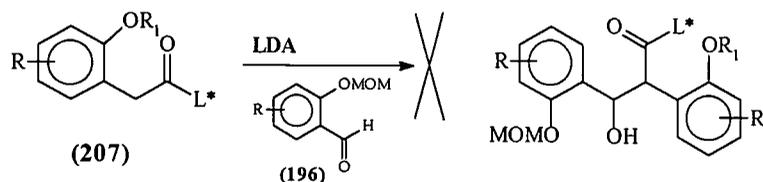
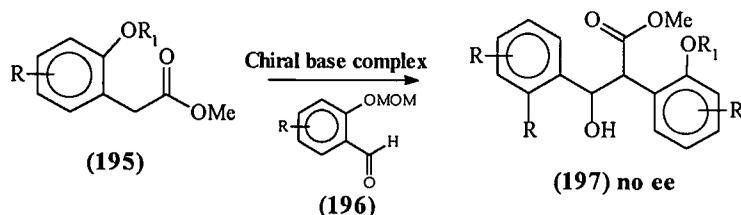
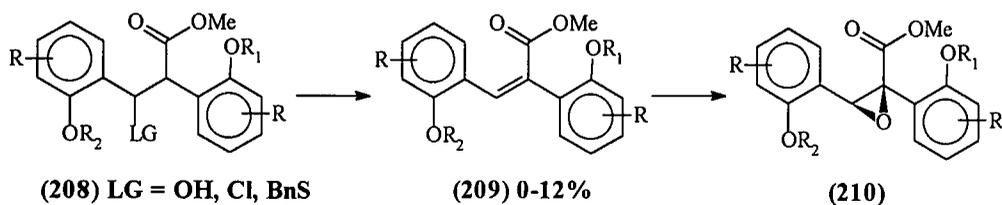
By changing the order of cyclisation, initial C-ring formation **204** \rightarrow **205** followed by reduction (LiAlH_4) and Mitsunobu cyclisation afforded *trans*-pterocarpan **206** (Scheme 31).



Scheme 31: Synthesis of *trans*-pterocarpan.

4.4 Asymmetric synthesis of *cis*-pterocarpan

Scheme 32 represents attempts to tailor the racemic protocol (Scheme 30) for the synthesis of optically enriched *cis*-pterocarpan. Firstly, introduction of enantioselectivity was attempted during the aldolisation step *via* chiral propanoate and propanamide derivatives **207** which only resulted in starting material recovery (Reaction 1). Secondly, using chiral bases yielded the required aldol products **197**, but with no enantiomeric enrichment (Reaction 2). Finally, in an effort to employ stereoselective epoxidation, attempts were made to synthesise 2-propenoates **209** which could be epoxidised to **210** using amongst other poly-amino acids as chiral catalysts. Elimination reactions of **208** yielded methyl 2-propenoates **209** in disappointingly low yields of 0-12% (Reaction 3).

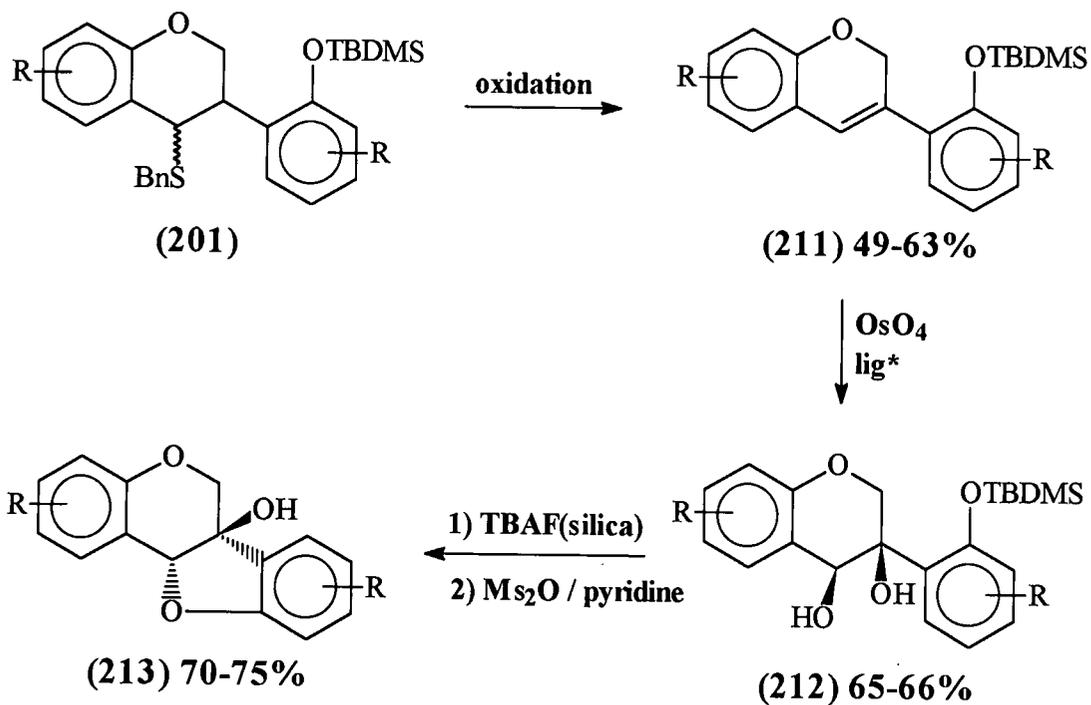
Reaction 1:**Reaction 2:****Reaction 3:**

R = H, OMe
 R₁ = Bn, TBDMS
 R₂ = H, MOM
 L* = chiral auxiliary

Scheme 32: Attempted asymmetric synthesis of *cis*-pterocarpan.

4.5 6a-Hydroxypterocarpan

The stereoselective synthesis of 6a-hydroxypterocarpan involved oxidative elimination of 4-benzylsulfanylisoflavans **201**, affording isoflav-3-enes **211** in moderate yields (49-63%). Asymmetric dihydroxylation led to optically enriched diols **212**, which upon deprotection and cyclisation furnished the 6a-hydroxypterocarpan **213** in good yields (46-50%) and essentially optically pure (>99% ee, Scheme 33).



lig* = dihydroquinine *p*-chlorobenzoate

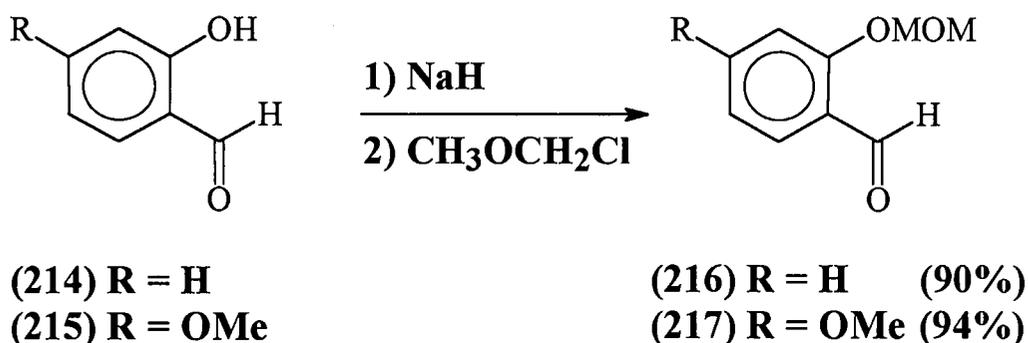
Scheme 33: Synthesis of enantiopure 6a-hydroxypterocarpan.

SYNTHESIS OF RACEMIC *CIS*-PTEROCARPANS

5.1 Preparation of benzaldehydes and phenylacetates

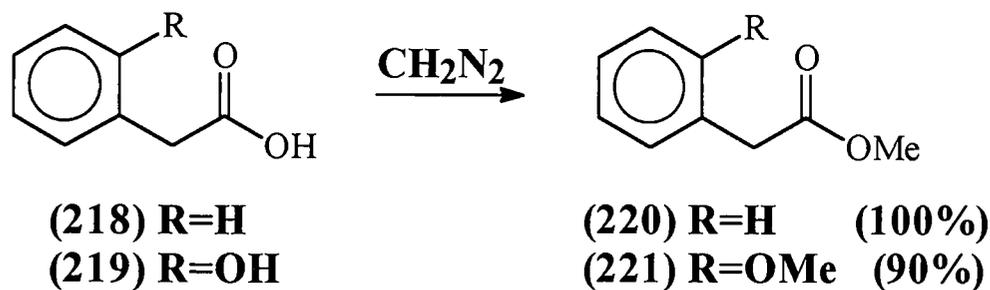
As indicated in the *retro*-synthetic sequence (Scheme 28) aldol products, namely 2,3-diaryl-3-hydroxypropanoates **192**, form the basis of this synthetic approach. Therefore a series of starting materials, *i.e.* 2-*O*-protected benzaldehydes **193** and propanoates **194**, were synthesised.

2-Hydroxybenzaldehydes **214** and **215** were protected as methoxymethylethers (chlorodimethylether, NaH)^{119,120} owing to their stability towards base catalysed aldol reaction conditions, and relative ease of selective deprotection,¹²¹ affording 2-*O*-methoxymethylbenzaldehydes **216** and **217** (Scheme 34).



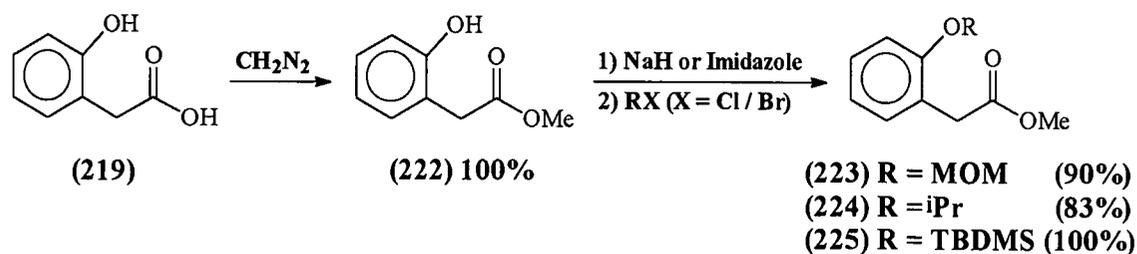
Scheme 34: Synthesis of 2-*O*-methoxymethylbenzaldehydes.

Commercially available phenylacetic acids **218** and **219** were methylated to give phenylacetates **220** and **221** respectively, *via* treatment with diazomethane for 2 hours at -10°C (Scheme 35).¹²²



Scheme 35: Methylation of phenylacetic acids **218** and **219**.

Selective methylation of **219** to methyl 2-hydroxyphenylacetate **222** was accomplished by reducing the reaction time to 30 minutes. Since the different synthetic sequences required deprotection of the 2-OH at different stages, diverse protective groups were employed, *i.e.*, methoxymethyl **223**,¹²¹ isopropyl (isopropylbromide / NaH)¹²³ **224** and *t*-butyldimethylsilyl (*t*-butyldimethylchlorosilane / imidazole)^{121,124,125} **225** (Scheme 36).

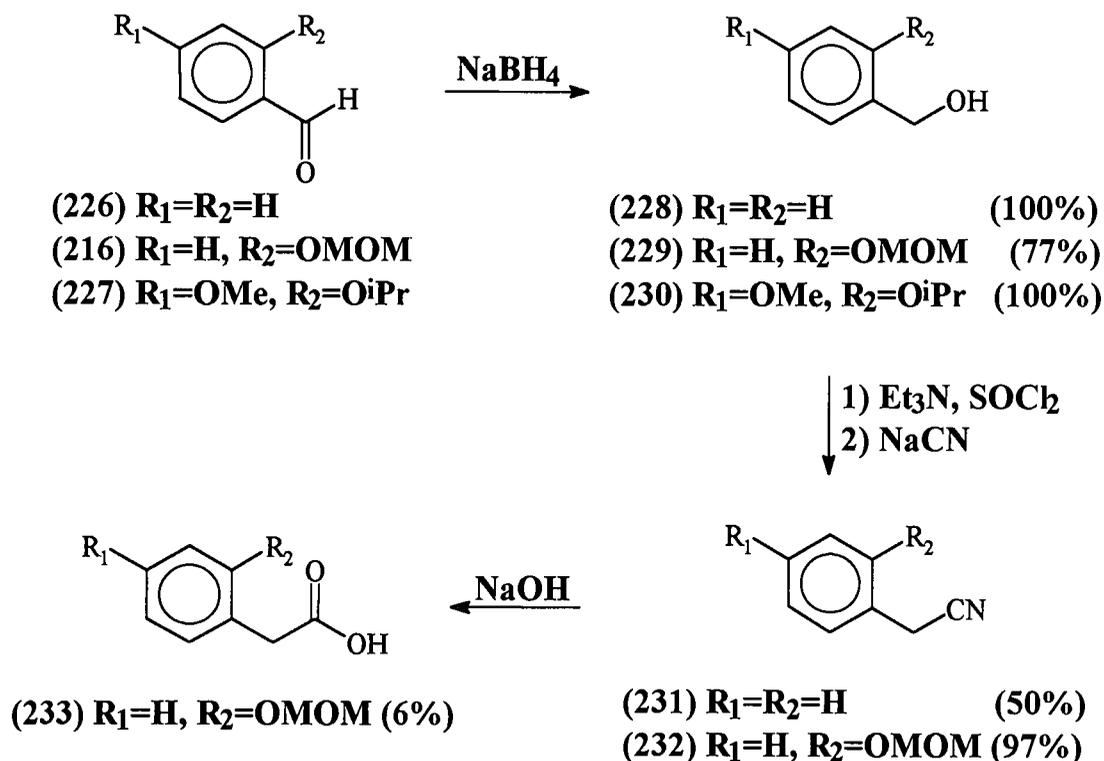


Scheme 36: Protection of 2-hydroxyphenylacetic acid.

Availability of 2-hydroxyphenylacetic acids is limited to only the 2-hydroxy- and 2,4,6-trihydroxy analogues, therefore development of a direct synthesis to alternatively oxygenated substrates greatly enhances the general application of the overall protocol.

Although the Wilgerodt-Kindler synthesis^{126,127} is used for the synthesis of substituted phenylacetic acids, high reaction temperatures and difficult isolation procedures

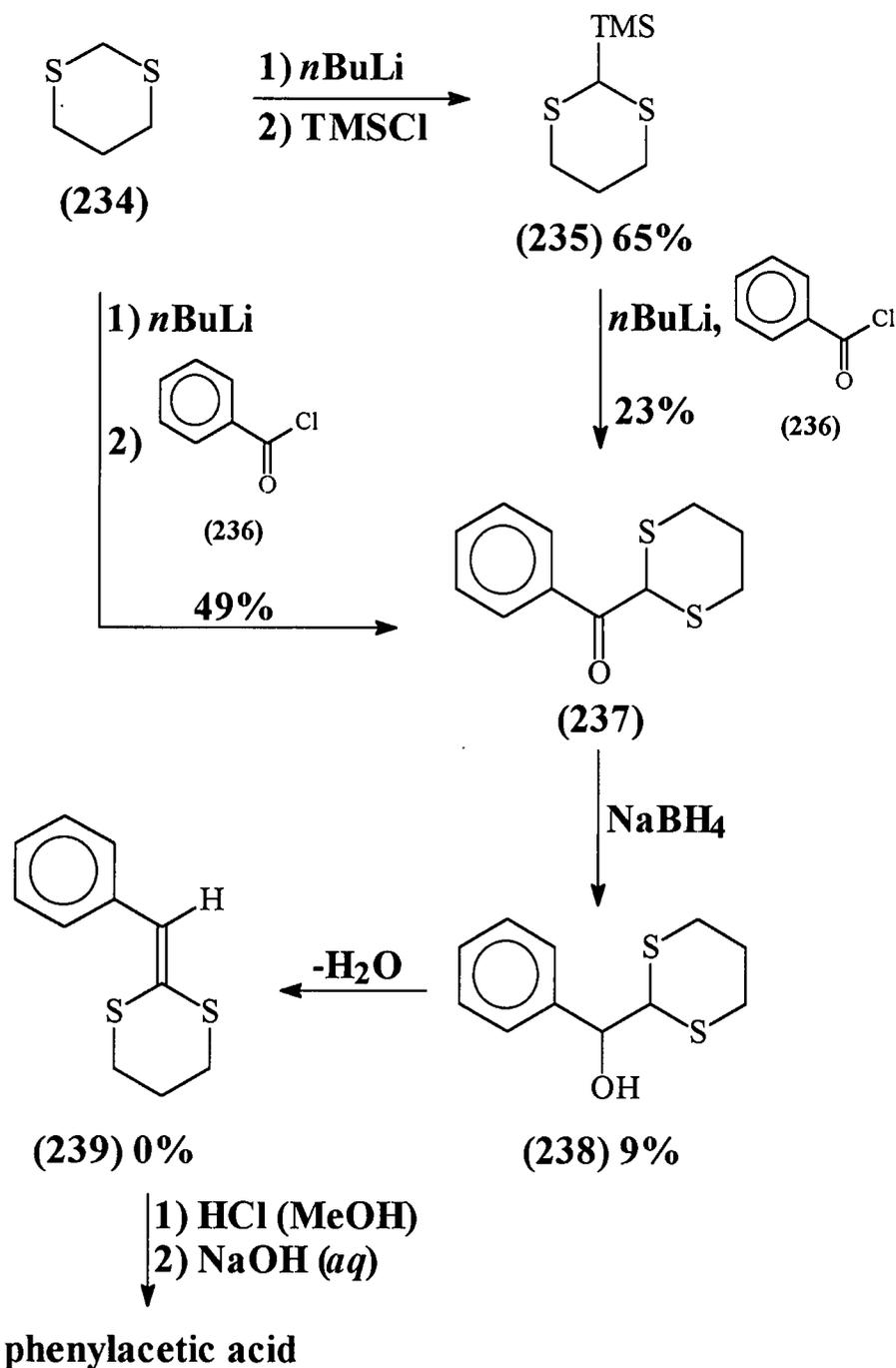
prompted us rather to obtain these compounds from their corresponding aldehydes *via* phenylacetonitriles, as indicated in Scheme 37.^{128,129} Protected benzaldehydes **216**, **226** and **227** were reduced to the respective alcohols **228-230** with NaBH₄. Chlorination (SOCl₂) and subsequent treatment with sodium cyanide afforded only phenylacetonitriles **231** and **232**. Hydrolysis of **232** gave phenylacetic acid **233** in low yield (6%), while **231** decomposed under the same reaction conditions.



Scheme 37: Synthesis of polyphenolic phenylacetic acids *via* phenylacetonitriles.

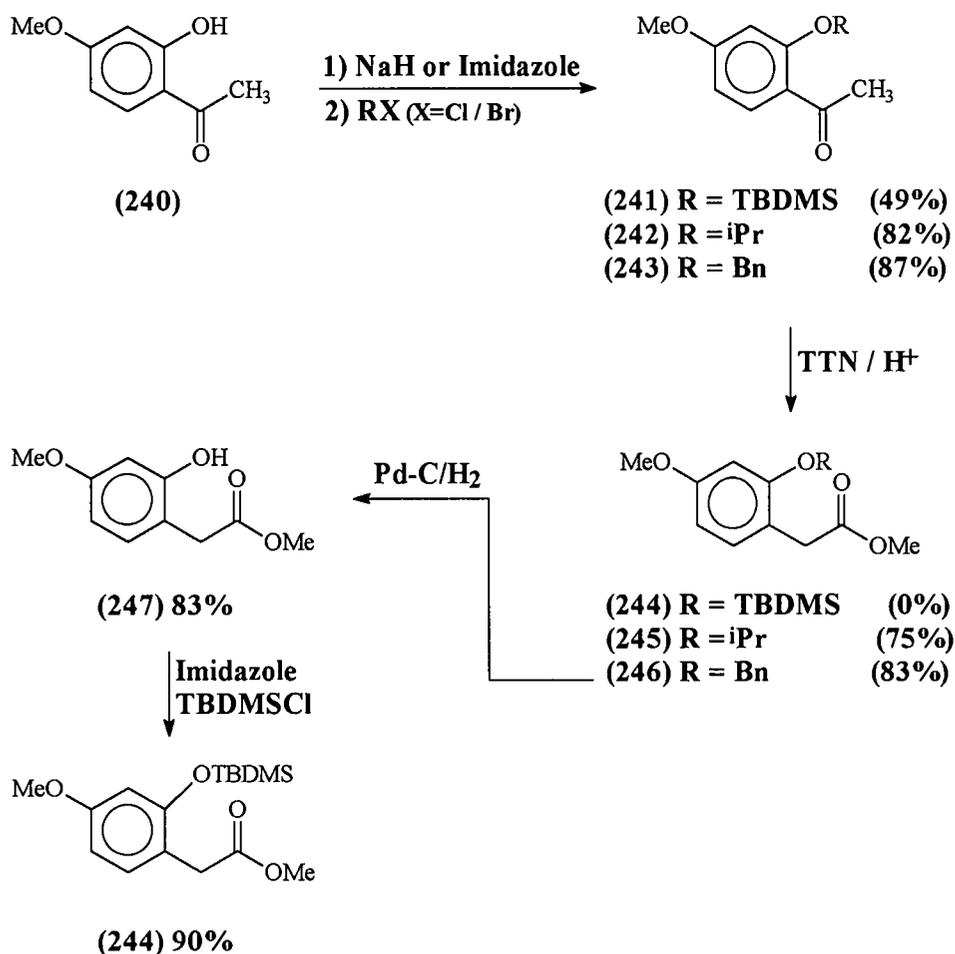
1,3-Dithiane **234** has found a number of synthetic applications,¹³⁰ among others in the synthesis of acetic acids *via* treatment of ketene dithioacetals similar to **239** with methanolic HCl followed by hydrolysis (*aq* NaOH).^{131,132} We therefore attempted the direct synthesis of **239** *via* condensation between the silylated (*n*BuLi / TMSCl) dithiane **235** and benzoyl chloride **236** (Scheme 38). This method only afforded benzophenone **237** instead of the expected dithiane **239**.¹³¹ An increased yield of **237** was later obtained

via direct condensation of **234** and **236**. Reduction (NaBH_4) of ketone **237** afforded alcohol **238** in low yield, however spontaneous dehydration to **239** did not occur.¹³³



Scheme 38: The use of 1,3-dithiane in the synthesis of phenylacetic acid.

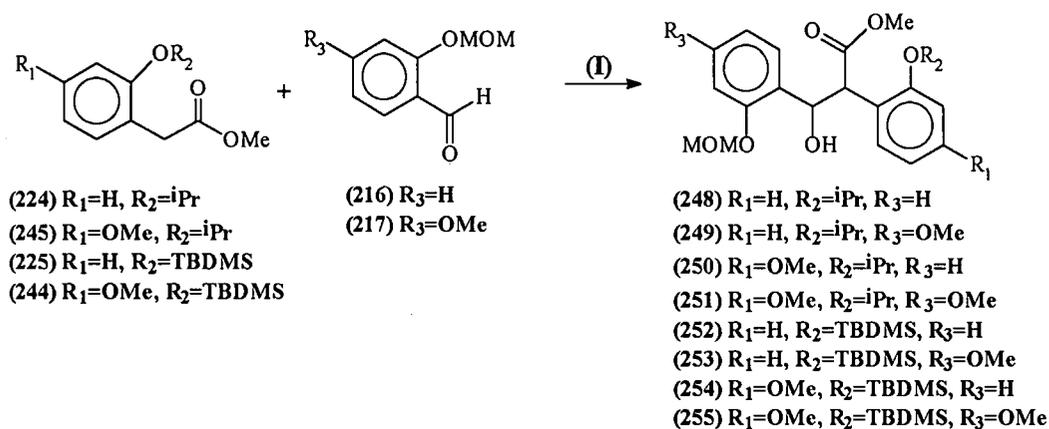
The thallium(III)nitrate (TTN) oxidative rearrangement of acetophenones was successfully utilised to synthesise phenylacetic acids.¹³⁴ 2-Hydroxy-4-methoxyacetophenone **240** was protected as TBDMS-, isopropyl- and benzylethers **241**, **242** and **243**, respectively (Scheme 39).^{135,136} Treatment of the silylated substrate **241** with TTN / H⁺ only yielded the desilylated acetophenone **240**, while ethers **242** and **243** smoothly converted to their corresponding methyl phenylacetates **245** and **246**. In order to obtain the silylated product **244**, 2-*O*-benzylphenylacetate **246** was debenzylated (H₂ / Pd-C) to the phenol **247** and silylated to afford **244** in good yield.



Scheme 39: Synthesis of phenylacetates **244-246** via TTN oxidative rearrangement of acetophenones.

5.2 Aldol condensation

Good results reported for aldolisation between esters and aldehydes^{137,138} employing the hindered base lithium diisopropylamide (LDA) encouraged us to utilise this reagent for the condensation of methyl phenylacetates with benzaldehydes. The efficiency of this system to produce *trans*-enolates within 30 minutes at -78°C was confirmed by quenching with D_2O . Subsequent condensation between the ester enolates of **224**, **225**, **244** and **245** and benzaldehydes **216** and **217** afforded 2,3-diaryl-3-hydroxypropanoates **248-255** in moderate to good yields (Table 3). The low degree of diastereoselectivity for certain entries is in accordance with literature precedents.^{75,78}



(I) LDA (1.1 eq.), Et_2O , -78°C , then benzaldehydes **216**, **217**, -78 to 0°C

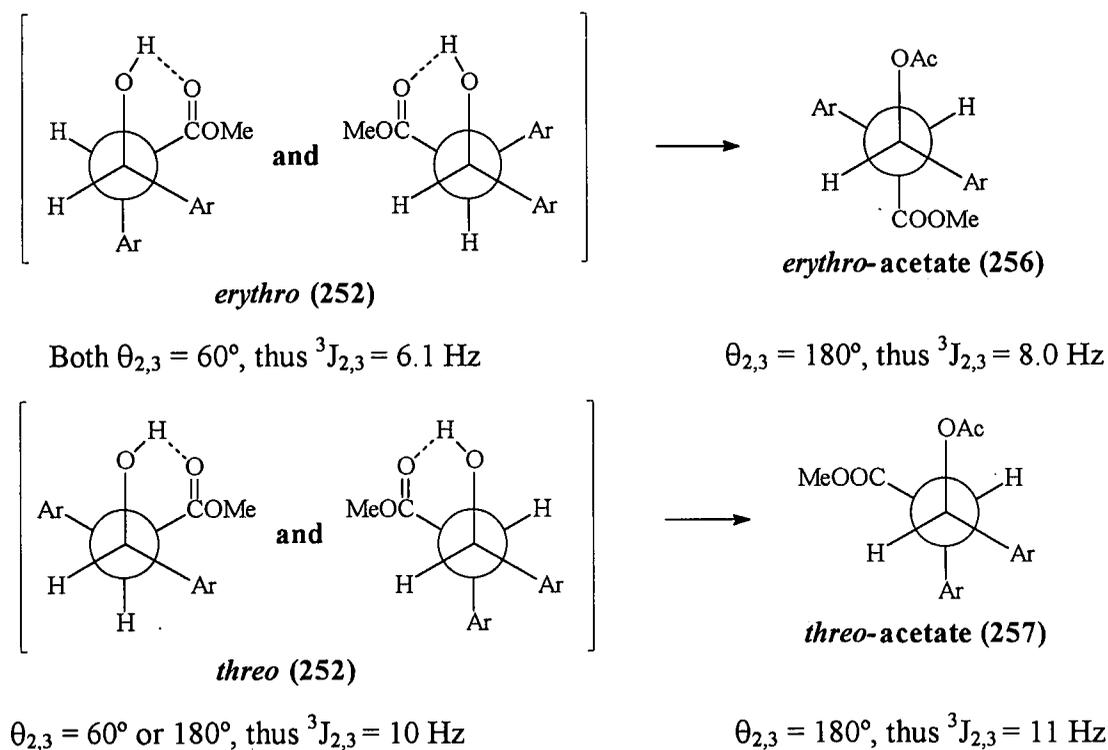
2,3-diarylpropanoates	<i>threo</i> (%)	<i>erythro</i> (%)	de (%) ^a	yield (%)
248	71	29	42	66
249	88	12	76	50
250	72	28	44	67
251	100	0	100	40
252	64	36	28	78
253	77	23	55	67
254	61	39	22	76
255	66	34	32	69

^a Determined by $^1\text{H NMR}$ ⁸⁵

Table 3: Aldol condensation of phenylacetates **224**, **225**, **244** and **245** with aldehydes **216** and **217**.

Stereochemical assignment of the aldol products was effected by comparing the observed ^1H NMR coupling constants ($^3J_{2,3}$, Tables 4 and 5) with the H-C₂-C₃-H dihedral angles of the predicted hydrogen bonded conformations displayed in Scheme 40 (Scheme 24, Chapter 3).⁸⁵ In all instances the *erythro* products displayed "small" coupling values (4-7 Hz) compared to the "large" values (9-10 Hz) of the corresponding *threo* products.

In order to confirm hydrogen bonding, the 3-OH function of both the *erythro* and *threo* isomers of methyl 2-(2"-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate **252** were acetylated, thereby preventing intramolecular hydrogen bonding. This not only led to the anticipated shifting of the IR carbonyl band toward higher frequency ($1730\text{ cm}^{-1} \rightarrow 1740\text{ cm}^{-1}$), but also the *erythro*-acetate of **252** displayed an increase in the $^3J_{2,3}$ -value from 6.1 to 8.0 Hz, while the *threo*-acetate showed an increase from 10.0 to 11.0 Hz, thus correlating with the predicted conformations **256** and **257** (Scheme 40).⁸⁵



Scheme 40: Newman projections for acetylated *erythro*- and *threo*-propanoates **256** and **257**.

Table 4: ^1H NMR data of the *erythro*- and *threo*-2,3-diaryl-3-hydroxypropanoates **248-251** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	248		249		250		251
	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>threo</i>
2-H	4.55 (d; 4.9)	4.36 (d; 9.0)	4.53 (d; 5.0)	4.34 (d; 9.5)	4.46 (d; 4.5)	4.29 (d; 9.0)	4.27 (d; 9.1)
3-H	5.72 (dd; 4.9, 4.9)	5.66 (dd; 5.0, 9.0)	5.62 (dd; 5.0, 5.0)	5.60 (dd; 4.9, 9.5)	5.69 (dd; 4.5, 4.8)	5.61 (dd; 5.0, 9.0)	5.54 (dd; 5.0, 9.1)
$\text{C}_3\text{-OH}$	3.61 (d; 4.9)	4.03 (d; 5.0)	3.49 (d; 5.0)	3.94 (d; 4.9)	3.59 (d; 4.8)	4.01 (d; 5.0)	3.89 (d; 5.0)
OCH_2OCH_3	5.25, 5.31 (2xd; 6.5)	4.85, 4.95 (2xd; 6.9)	5.22, 5.27 (2xd; 6.9)	4.82, 4.93 (2xd; 6.9)	5.25, 5.31 (2xd; 6.5)	4.90, 4.99 (2xd; 6.9)	4.88, 4.97 (2xd; 6.9)
OCH_2OCH_3	3.55 (s)	3.39 (s)	3.54 (s)	3.37 (s)	3.55 (s)	3.40 (s)	3.39 (s)
$\text{CH}(\text{CH}_3)_2$	1.11, 1.31 (2xd; 6.0)	1.19, 1.36 (2xd; 6.0)	1.16, 1.31 (2xd; 6.0)	1.22, 1.36 (2xd; 6.0)	1.08, 1.30 (2xd; 6.0)	1.19, 1.35 (2xd; 6.0)	1.21, 1.35 (2xd; 6.0)
$\text{CH}(\text{CH}_3)_2$	4.49 (m; 6.0)	4.50 (m; 6.0)	4.51 (m; 6.0)	4.50 (m; 6.0)	4.42 (m; 6.0)	4.44 (m; 6.0)	4.45 (m; 6.0)
OCH_3	4.66 (s)	3.70 (s)	3.64, 3.76 (2xs)	3.70, 3.74 (2xs)	3.66, 3.78 (2xs)	3.69, 3.72 (2xs)	3.69, 3.73, 3.74 (3xs)
3'-H	6.98 (dd; 1.9, 8.2)	6.94 (dd; 1.1, 8.0)	6.69 (d; 2.2)	6.54 (d; 2.2)	7.07 (dd; 1.1, 8.1)	6.90-6.97 (m)	6.55 (d; 2.5)
4'-H	7.20 (ddd; 1.1, 7.5, 8.2)	7.12 (ddd; 2.0, 7.5, 7.5)	—	—	7.16 (ddd; 1.1, 7.1, 8.1)	7.13 (ddd; 1.9, 7.0, 8.2)	—
5'-H	6.81 (ddd; 1.1, 7.1, 7.5)	6.72 (ddd; 1.1, 7.5, 7.5)	6.37 (dd; 2.2, 8.5)	6.48 (dd; 2.2, 8.5)	6.83 (ddd; 1.1, 7.1, 7.9)	6.90-6.97 (m)	6.47 (dd; 2.5, 8.5)
6'-H	7.08 (dd; 1.1, 7.1)	7.38 (dd; 2.0, 8.0)	6.89 (d; 8.5)	7.28 (d; 8.5)	6.98 (dd; 1.9, 7.9)	7.36 (dd; 1.9, 7.5)	7.25 (d; 8.5)
3''-H	6.79 (dd; 1.0, 8.2)	6.70 (dd; 0.9, 8.0)	6.80 (dd; 1.1, 8.1)	6.71 (dd; 1.1, 7.9)	6.35 (d; 2.5)	6.27 (d; 2.2)	6.27 (d; 2.8)
4''-H	7.16 (ddd; 1.9, 7.5, 8.2)	7.09 (ddd; 1.9, 7.5, 7.5)	7.20 (ddd; 1.9, 7.1, 8.1)	7.09 (ddd; 1.9, 7.5, 7.9)	—	—	—
5''-H	6.83 (ddd; 1.0, 7.5, 8.2)	6.94 (ddd; 0.9, 7.0, 7.0)	6.85 (ddd; 1.1, 7.1, 7.5)	6.73 (ddd; 1.1, 7.5, 7.5)	6.39 (dd; 2.5, 8.1)	6.26 (dd; 2.2, 9.0)	6.26 (dd; 2.8, 9.0)
6''-H	7.12 (dd; 1.9, 8.2)	7.11 (dd; 1.9, 7.5)	7.16 (dd; 1.9, 7.5)	7.11 (dd; 1.9, 7.5)	7.04 (d; 8.1)	7.03 (d; 9.0)	7.02 (d; 9.0)

Table 5: ^1H NMR data of the *erythro*- and *threo*-2,3-diaryl-3-hydroxypropanoates **252-255** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

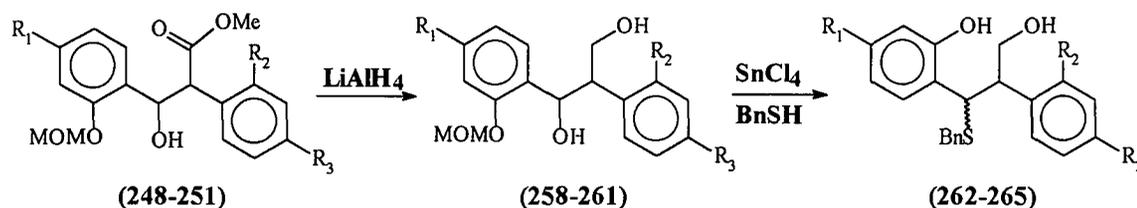
	252		253		254		255	
	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>
2-H	4.67 (d; 6.1)	4.54 (d; 10.0)	4.66 (d; 7.0)	4.51 (d; 10.0)	4.56 (d; 6.5)	4.46 (d; 10.0)	4.55 (d; 7.0)	4.45 (d; 10.0)
3-H	5.69 (dd; 5.5, 6.1)	5.74 (dd; 4.9, 10.0)	5.59 (dd; 5.1, 7.0)	5.66 (dd; 4.5, 10.0)	5.65 (dd; 5.1, 6.5)	5.69 (dd; 5.0, 10.0)	5.55 (dd; 5.1, 7.0)	5.64 (dd; 4.5, 10.0)
C ₃ -OH	3.30 (d; 5.5)	3.64 (d; 4.9)	3.11 (d; 5.1)	3.50 (d; 4.5)	3.27 (d; 5.1)	3.59 (d; 5.0)	3.11 (d; 5.1)	3.47 (d; 4.5)
OCH ₂ OCH ₃	5.20, 5.26 (2xd; 6.5)	4.86, 4.98 (2xd; 6.9)	5.18, 5.21 (2xd; 6.9)	4.85, 4.96 (2xd; 6.9)	5.20, 5.26 (2xd; 6.5)	4.93, 5.03 (2xd; 6.9)	5.18, 5.22 (2xd; 6.5)	4.91, 5.02 (2xd; 6.9)
OCH ₂ OCH ₃	3.51 (s)	3.40 (s)	3.51 (s)	3.39 (s)	3.51 (s)	3.41 (s)	3.50 (s)	3.40 (s)
SiCH ₃	0.19, 0.22 (2xs)	0.20, 0.25 (2xs)	0.20, 0.24 (2xs)	0.21, 0.26 (2xs)	0.18, 0.22 (2xs)	0.20, 0.26 (2xs)	0.20, 0.24 (2xs)	0.23, 0.27 (2xs)
Bu ^t	0.99 (s)	1.05 (s)	1.00 (s)	1.05 (s)	0.98 (s)	1.05 (s)	1.00 (s)	1.06 (s)
OCH ₃	3.57 (s)	3.71 (s)	3.56, 3.77 (2xs)	3.71, 3.73 (2xs)	3.57, 3.78 (2xs)	3.70, 3.71 (2xs)	3.55, 3.77, 3.78 (3xs)	3.69, 3.70, 3.74 (3xs)
3'-H	7.07 (dd; 1.1, 8.1)	6.94 (dd; 1.1, 8.5)	6.69 (d; 2.2)	6.54 (d; 2.3)	7.07 (dd; 1.1, 8.5)	6.95 (dd; 1.1, 8.1)	6.68 (d; 2.2)	6.55 (d; 2.5)
4'-H	7.19 (ddd; 1.9, 7.1, 8.1)	7.12 (ddd; 1.9, 7.1, 8.5)	—	—	7.19 (ddd; 1.9, 7.3, 8.5)	7.12 (ddd; 1.9, 7.0, 8.1)	—	—
5'-H	6.87 (ddd; 1.1, 7.1, 7.4)	6.91 (ddd; 1.1, 7.1, 7.5)	6.44 (dd; 2.2, 8.9)	6.45 (dd; 2.3, 8.5)	6.88 (ddd; 1.1, 7.3, 7.5)	6.91 (ddd; 1.1, 7.0, 7.6)	6.44 (dd; 2.2, 8.9)	6.45 (dd; 2.5, 8.5)
6'-H	7.06 (dd; 1.9, 7.4)	7.39 (dd; 1.9, 7.5)	6.98 (d; 8.9)	7.30 (d; 8.5)	7.05 (dd; 1.9, 7.5)	7.37 (dd; 1.9, 7.6)	6.99 (d; 8.9)	7.28 (d; 8.5)
3''-H	6.77 (dd; 1.1, 8.1)	6.65 (dd; 1.1, 8.1)	6.80 (dd; 1.1, 8.1)	6.66 (dd; 1.1, 8.0)	6.35 (d; 2.5)	6.22 (d; 2.2)	6.36 (d; 2.5)	6.24 (d; 2.5)
4''-H	7.16 (ddd; 1.9, 7.1, 8.1)	7.01 (ddd; 1.9, 7.5, 8.1)	7.16 (ddd; 1.9, 7.5, 8.1)	7.01 (ddd; 1.9, 7.5, 8.0)	—	—	—	—
5''-H	6.96 (ddd; 1.1, 7.1, 7.5)	6.79 (ddd; 1.1, 7.5, 7.9)	6.97 (ddd; 1.1, 7.5, 7.5)	6.79 (ddd; 1.1, 7.5, 8.1)	6.55 (dd; 2.5, 8.5)	6.36 (dd; 2.2, 8.9)	6.55 (dd; 2.5, 8.5)	6.37 (dd; 2.5, 8.6)
6''-H	7.52 (dd; 1.9, 7.5)	7.30 (dd; 1.9, 7.9)	7.55 (dd; 1.9, 7.5)	7.29 (dd; 1.9, 8.1)	7.44 (d; 8.5)	7.23 (d; 8.9)	7.45 (d; 8.5)	7.24 (d; 8.6)

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5.3 Cleavage of the 2'-MOM derivatives and reduction of propanoates

In order to produce 2'-hydroxypropanols, the corresponding esters **248-251** were reduced using lithium aluminum hydride (LiAlH_4), which afforded the 2'-MOM-propanols **258-261** (Table 7: ^1H NMR data) in acceptable yields of 63-78% (Table 6). Deprotection of the 2'-MOM-ethers under acidic conditions (3N HCl , MeOH)¹³⁹ resulted in decomposition of the propanols, therefore the milder tin tetrachloride (SnCl_4) / benzenemethanethiol (BnSH) system (DCM , -15 to 5°C) was utilised as selective deprotecting agent,^{140,141} affording the 2,3-diaryl-3-benzylsulfanylpropanols **262-265** (Table 8: ^1H NMR data) in 45-72% yield.



esters	R_1	R_2	R_3	2'-MOM-propanol	yield (%)	2'-OH-propanol	yield (%)	ratio <i>erythro</i> : <i>threo</i>	de (%)
248	H	O'Pr	H	258	78	262	72	17 : 83	66
249	OMe	O'Pr	H	259	63	263	66	14 : 86	72
250	H	O'Pr	OMe	260	75	264	68	24 : 76	52
251	OMe	O'Pr	OMe	261	65	265	45	33 : 67	34

Table 6: Reaction yields for reduction and deprotection of propanoates **248-251**.

Erythro- and *threo*-2,3-diaryl-3-hydroxypropanols **258-261** were assigned from the stereochemistry of the preceding esters. Furthermore, the individual *erythro*- and *threo*-propanols **258-261** yielded, within experimental deviation, the same ratio of *erythro*- and *threo*-3-benzylsulfanylpropanols **262-265**.

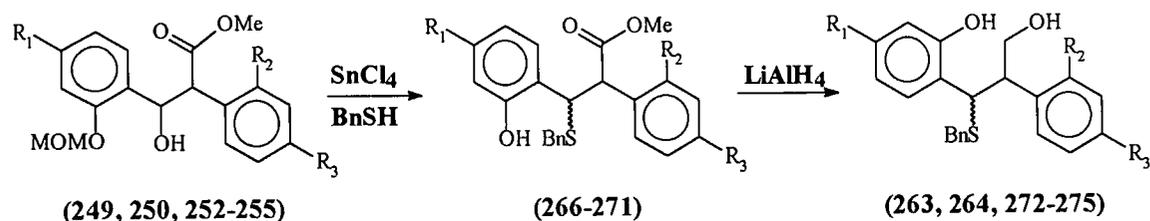
Table 7: ^1H NMR data of the *erythro*- and *threo*-2,3-diaryl-3-hydroxypropanols **258-261** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	258		259		260		261
	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>threo</i>
2-H	3.72-3.80 (m)	3.86 (ddd; 4.1, 7.0, 8.0)	3.74-3.76 (m)	3.84 (ddd; 3.0, 7.0, 8.1)	3.65 (ddd; 6.0, 6.5, 7.1)	3.77 (ddd; 4.5, 7.2, 8.1)	3.79 (ddd; 4.2, 7.8, 8.2)
3-H	5.47 (dd; 7.0, 7.0)	5.47-5.53 (m)	5.40 (dd; 6.0, 7.8)	5.46 (dd; 4.5, 8.1)	4.44 (dd; 6.0, 7.1)	5.46 (dd; 5.5, 8.1)	5.41 (dd; 5.0, 8.2)
1- CH_2	3.84-3.89 (m)	3.90-3.40, 4.16-4.25 (m)	3.79-3.84 (m)	3.85-3.94 (m), 4.16 (dd; 7.0, 10.1)	3.79-3.85 (m)	3.90 (ddd; 4.5, 7.9, 11.0), 4.16 (ddd; 4.1, 7.2, 11.0)	3.86 (ddd; 4.2, 8.0, 11.1), 4.14 (ddd; 3.8, 7.8, 11.1)
$\text{C}_1\text{-OH}$	1.78-1.84 (m)	2.93-3.01 (m)	1.79-1.85 (m)	3.20-3.27 (m)	1.73-1.78 (m)	2.91 (dd; 4.1, 7.9)	3.05-3.12 (m)
$\text{C}_3\text{-OH}$	2.95-2.99 (m)	3.49-3.51 (m)	2.83 (d; 6.0)	3.53 (d; 4.5)	2.89 (d; 6.0)	3.54 (d; 5.5)	3.35-3.40 (m)
OCH_2OCH_3	3.52 (s)	3.49 (s)	3.50 (s)	3.46 (s)	3.52 (s)	3.50 (s)	3.48 (s)
OCH_2OCH_3	5.16, 5.20 (2xd; 6.0)	5.11, 5.18 (2xd; 6.5)	5.13, 5.16 (2xd; 6.8)	5.04, 5.12 (2xd; 6.8)	5.19, 5.22 (2xd; 6.9)	5.14, 5.19 (2xd; 6.9)	5.09, 5.15 (2xd; 6.8)
$\text{CH}(\text{CH}_3)_2$	1.29, 1.37 (2xd; 6.0)	1.26, 1.37 (2xd; 6.0)	1.32, 1.37 (2xd; 6.0)	1.27, 1.36 (2xd; 6.0)	1.27, 1.36 (2xd; 6.0)	1.26, 1.36 (2xd; 6.0)	1.28, 1.36 (2xd; 6.0)
$\text{CH}(\text{CH}_3)_2$	4.59 (m; 6.0)	4.54 (m; 6.0)	4.60 (m; 6.0)	4.53 (m; 6.0)	4.54 (m; 6.0)	4.49 (m; 6.0)	4.49 (m; 6.0)
OCH_3	—	—	3.80 (s)	3.73 (s)	3.80 (s)	3.74 (s)	3.74, 3.74 (s)
3'-H	7.10 (dd; 1.0, 8.0)	7.02-7.22 (m)	6.71 (d; 2.2)	6.60 (d; 2.2)	7.10 (dd; 1.0, 8.1)	7.04 (dd; 1.1, 8.1)	6.61 (d; 2.5)
4'-H	7.20-7.23 (m)	7.02-7.22 (m)	—	—	7.21 (ddd; 1.9, 7.1, 8.1)	7.14 (ddd; 1.9, 7.5, 8.1)	—
5'-H	6.99 (ddd; 1.0, 7.0, 7.0)	6.84-6.90 (m)	6.55 (dd; 2.2, 8.5)	6.41 (dd; 2.2, 8.5)	6.99 (ddd; 1.0, 7.1, 7.1)	6.89 (ddd; 1.1, 7.5, 7.5)	6.41 (dd; 2.5, 8.5)
6'-H	7.20-7.23 (m)	7.02-7.22 (m)	7.23 (d; 8.5)	7.14 (d; 8.5)	7.23 (dd; 1.9, 7.1)	7.20 (dd; 1.9, 7.5)	7.11 (d; 8.5)
3''-H	6.86-6.90 (m)	6.75-6.80 (m)	6.89 (dd; 1.0, 8.1)	6.73-6.79 (m)	6.45 (d; 2.5)	6.34 (d; 2.5)	6.34 (d; 2.5)
4''-H	7.28-7.31 (m)	7.02-7.22 (m)	7.21 (ddd; 1.9, 7.2, 8.1)	7.05-7.12 (m)	—	—	—
5''-H	6.93 (ddd; 1.0, 7.0, 7.0)	6.75-6.80 (m)	6.93 (ddd; 1.0, 7.2, 7.2)	6.73-6.79 (m)	6.47 (dd; 2.5, 8.1)	6.41 (dd; 2.5, 8.0)	6.30 (dd; 2.5, 8.1)
6''-H	7.28-7.31 (m)	7.22 (m)	7.31 (dd; 1.9, 7.2)	7.05-7.12 (m)	7.29 (d; 8.1)	6.99 (d; 8.0)	6.96 (d; 8.1)

Table 8: ^1H NMR data of the *erythro*- and *threo*-2,3-diaryl-3-benzylsulfanylpropanols **262-265** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	262		263		264		265	
	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>
2-H	3.60-3.65 (m)	3.75 (ddd; 6.0, 6.0, 9.0)	3.60-3.66 (m)	3.68-3.75 (m)	3.55-3.61 (m)	3.67 (ddd; 6.0, 6.0, 9.1)	3.59-3.64 (m)	3.64 (ddd; 6.1, 6.1, 9.0)
3-H	4.64-4.71 (m)	4.39 (d; 9.0)	4.59-4.66 (m)	4.33 (d; 9.1)	4.61-4.69 (m)	4.36 (d; 9.1)	4.50-4.58 (m)	4.31 (d; 9.0)
1- CH_2	3.60-3.65 (m)	4.06 (dd; 6.0, 6.0)	3.60-3.66 (m)	4.01-4.06 (m)	3.55-3.61 (m)	4.01 (dd; 6.0, 6.0)	3.59-3.64 (m)	3.96-4.01 (m)
$\text{C}_1\text{-OH}$	1.81-1.83 (m)	1.75-1.85 (m)	1.95-2.03 (m)	1.71-1.80 (m)	1.76-1.83 (m)	1.85 (t; 6.0)	1.70-1.75 (m)	1.74-1.82 (m)
ArCH_2S	3.30, 3.43 (2xd; 13.1)	3.45, 3.60 (2xd; 13.0)	3.31, 3.43 (2xd; 13.0)	3.44, 3.59 (2xd; 13.8)	3.29, 3.42 (2xd; 13.8)	3.44, 3.59 (2xd; 13.2)	3.30, 3.43 (2xd; 13.8)	3.43, 3.59 (2xd; 13.5)
$\text{CH}(\text{CH}_3)_2$	1.19, 1.35 (2xd; 6.0)	1.24, 1.27 (2xd; 6.0)	1.17, 1.35 (2xd; 6.0)	1.25, 1.27 (2xd; 6.0)	1.16, 1.34 (2xd; 6.0)	1.24, 1.26 (2xd; 6.0)	1.15, 1.34 (2xd; 6.0)	1.24, 1.26 (2xd; 6.0)
$\text{CH}(\text{CH}_3)_2$	4.60 (m; 6.0)	4.50 (m; 6.0)	4.59 (m; 6.0)	4.51 (m; 6.0)	4.54 (m; 6.0)	4.45 (m; 6.0)	4.53 (m; 6.0)	4.45 (m; 6.0)
OCH_3	—	—	3.85 (s)	3.74 (s)	3.81	3.72 (s)	3.81, 3.85 (2xs)	3.74, 3.75 (2xs)
3'-H	6.89 (dd; 1.0, 8.0)	6.79-6.85 (m)	6.58 (d; 2.5)	6.39 (d; 2.8)	6.99-7.10 (m)	6.81 (dd; 2.2, 7.5)	6.57 (d; 2.5)	6.45 (d; 1.0)
4'-H	7.00-7.13 (m)	6.79-6.85 (m)	—	—	6.99-7.10 (m)	6.99-7.10 (m)	—	—
5'-H	6.91 (ddd; 1.0, 7.2, 7.2)	6.64-6.75 (m)	6.56 (dd; 2.5, 7.0)	6.24 (dd; 2.8, 8.5)	6.82 (ddd; 1.5, 7.5, 7.5)	6.69 (ddd; 1.1, 7.2, 7.2)	6.55 (dd; 2.5, 8.1)	6.40 (dd; 1.0, 8.0)
6'-H	7.00-7.13 (m)	7.03-7.11 (m)	7.09 (d; 8.1)	7.10 (d; 8.5)	6.99-7.10 (m)	6.99-7.10 (m)	7.00 (d; 8.1)	7.06 (d; 8.0)
3''-H	7.00-7.13 (m)	6.64-6.75 (m)	6.88 (dd; 1.0, 8.1)	6.68-6.77 (m)	6.44 (d; 2.2)	6.29 (d; 2.2)	6.45 (d; 2.5)	6.24-6.31 (m)
4''-H	7.00-7.13 (m)	6.64-6.75 (m)	7.08 (ddd; 1.9, 7.2, 8.1)	6.68-6.77 (m)	—	—	—	—
5''-H	7.00-7.13 (m)	7.03-7.11 (m)	6.91 (ddd; 1.0, 7.2, 7.2)	6.68-6.77 (m)	6.43 (dd; 2.2, 8.0)	6.25 (dd; 2.2, 8.0)	6.43 (dd; 2.5, 8.5)	6.24-6.31 (m)
6''-H	7.00-7.13 (m)	6.96 (dd; 1.9, 7.9)	7.18 (dd; 1.9, 7.2)	6.94-6.97 (m)	7.06 (d; 8.0)	6.85 (d; 8.0)	6.70 (d; 8.5)	6.84 (d; 8.1)
ArOH	7.75-7.84 (m)	7.23-7.32 (m)	7.99-7.83 (m)	7.21-7.28 (m)	7.82-7.86 (m)	7.12-7.29 (m)	7.89-7.98 (m)	7.15-7.32 (m)
ArCH_2S	7.21-7.30 (m)	7.23-7.32 (m)	7.22-7.30 (m)	7.21-7.28 (m)	7.12-7.29 (m)	7.12-7.29 (m)	7.20-7.33 (m)	7.15-7.32 (m)

Although propanols **262-265** were obtained in moderate overall yields (29-56%), a change in the order of reactions, namely, first deprotecting propanoates **249**, **250** and **252-255** (SnCl_4 / BnSH), to afford 2'-hydroxypropanoates **266-271** (Table 10: ^1H NMR data), followed by reduction to yield the 2,3-diaryl-3-benzylsulfanylpropanols **263**, **264** and **272-275** (Table 11: ^1H NMR data) resulted in an increased overall yield of 54-81% (Table 9).



esters	R ₁	R ₂	R ₃	propanoates	yield (%)	ratio erythro : threo	de (%)	propanols	yield (%)
249	OMe	O ⁱ Pr	H	266	75	21 : 79	58	263	93
250	H	O ⁱ Pr	OMe	267	74	27 : 73	46	264	90
252	H	OTBDMS	H	268	96	13 : 87	74	272	80
253	OMe	OTBDMS	H	269	70	47 : 53	6	273	77
254	H	OTBDMS	OMe	270	83	0 : 100	100	274	97
255	OMe	OTBDMS	OMe	271	81	47 : 53	6	275	80

Table 9: Reaction yields for deprotection and reduction of propanoates **249**, **250**, **252-255**.

Similar to propanols **258-261**, the individual *erythro*- and *threo*-propanoates **249**, **250**, **252-255** afforded mixtures of *erythro*- and *threo*-3-benzylsulfanylpropanoates **266-271** with almost the same yield and diastereoselectivity, while both isomers of **254** gave only the *threo*-isomers **270**. This implied an $\text{S}_{\text{N}}1$ mechanism *via* a stabilised incipient carbocation **277**, which is susceptible to thiolysis to give **278** (Scheme 41).

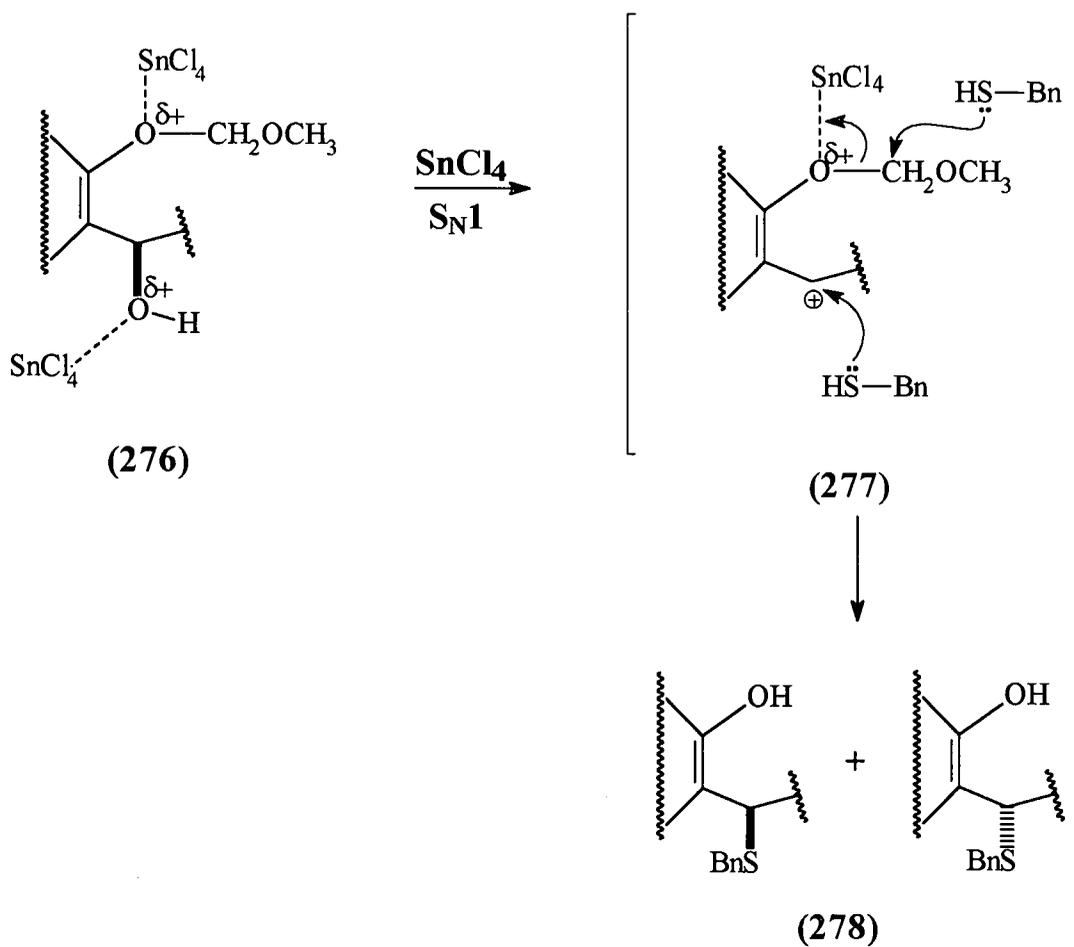
Table 10: ^1H NMR data of the *erythro*- and *threo*-3-benzylsulfanyl-2,3-diaryl-3-hydroxypropanoates **266-271** in CDCl_3 at 300 MHz.

Splitting patterns and J-values (in Hz) are given in parentheses.

	266		267		268		269		270	271	
	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>
2-H	4.47 (d; 7.0)	4.46 (d; 7.0)	4.46 (d; 8.0)	4.44 (d; 7.1)	4.46-4.63 (m)	4.70 (d; 11.0)	4.38-4.55 (m)	4.61 (d; 10.9)	4.70 (d; 11.0)	4.40-4.51 (m)	4.58 (d; 10.5)
3-H	4.64 (d; 7.0)	4.61 (d; 7.0)	4.75 (d; 8.0)	4.70 (d; 7.1)	4.70-4.89 (m)	4.86 (d; 11.0)	4.66-4.87 (m)	4.81 (d; 10.9)	4.77 (d; 11.0)	4.59-4.74 (m)	4.70 (d; 10.5)
ArCH_2S	3.26, 3.38 (2xd; 13.1)	3.44, 3.55 (2xd; 13.5)	3.24, 3.36 (2xd; 13.0)	3.46, 3.56 (2xd; 13.0)	3.27, 3.39 (2xd; 13.0)	3.55, 3.66 (2xd; 13.0)	3.29, 3.42 (2xd; 14.5)	3.53, 3.62 (2xd; 13.0)	3.55, 3.65 (2xd; 12.9)	3.29, 3.41 (2xd; 13.1)	3.51, 3.61 (2xd; 13.0)
SiCH_3	—	—	—	—	0.26, 0.34 (2xs)	0.22 (2xs)	0.26, 0.34 (2xs)	0.22 (2xs)	0.24 (2xs)	0.26, 0.34 (2xs)	0.23 (2xs)
Bu^1	—	—	—	—	1.07 (s)	1.06 (s)	1.08 (s)	1.06 (s)	1.06 (s)	1.06 (s)	1.05 (s)
$\text{CH}(\text{CH}_3)_2$	1.30, 1.38 (2xd; 6.0)	1.09, 1.15 (2xd; 6.0)	1.29, 1.36 (2xd; 6.0)	1.06, 1.14 (2xd; 6.0)	—	—	—	—	—	—	—
$\text{CH}(\text{CH}_3)_2$	4.61 (m; 6.0)	4.30 (m; 6.0)	4.54 (m; 6.0)	4.23 (m; 6.0)	—	—	—	—	—	—	—
OCH_3	3.46, 3.83 (2xs)	3.67, 3.72 (2xs)	3.45, 3.82 (2xs)	3.68, 3.75 (2xs)	3.40 (s)	3.70 (s)	3.43, 3.82 (2xs)	3.69, 3.71 (2xs)	3.67, 3.70 (2xs)	3.42, 3.80, 3.82 (3xs)	3.68, 3.69, 3.72 (3xs)
3'-H	6.56 (d; 2.5)	6.39 (d; 2.5)	6.95-7.06 (m)	6.82 (dd; 1.1, 7.9)	6.84-7.05 (m)	6.73-6.82 (m)	6.55 (d; 2.9)	6.34 (d; 2.9)	6.75 (dd; 1.1, 8.0)	6.54 (d; 2.9)	6.34 (d; 2.9)
4'-H	—	—	6.95-7.06 (m)	7.05 (ddd; 1.9, 7.0, 7.9)	6.84-7.05 (m)	6.99 (ddd; 1.9, 7.2, 8.0)	—	—	7.04 (ddd; 1.9, 7.1, 8.0)	—	—
5'-H	6.51 (dd; 2.5, 8.5)	6.15 (dd; 2.5, 8.9)	6.77 (ddd; 1.5, 7.5, 7.5)	6.61 (ddd; 1.1, 7.0, 7.5)	6.84-7.05 (m)	6.61 (ddd; 1.1, 7.2, 7.5)	6.51 (dd; 2.9, 8.1)	6.16 (dd; 2.9, 8.5)	6.65 (ddd; 1.1, 7.1, 7.2)	6.51 (dd; 2.9, 8.9)	6.37 (dd; 2.9, 8.9)
6'-H	6.89 (d; 8.5)	6.53 (d; 8.9)	6.95-7.06 (m)	6.72 (dd; 1.9, 7.5)	7.16-7.32 (m)	6.73-6.82 (m)	7.16-7.31 (m)	6.65 (d; 8.5)	6.79-6.86 (m)	7.19 (d; 8.9)	6.67 (d; 8.9)
3''-H	7.05 (dd; 1.9, 8.1)	6.60 (dd; 1.5, 8.0)	6.45 (d; 2.5)	6.16 (d; 2.5)	6.84-7.05 (m)	6.62 (dd; 1.1, 8.0)	6.86 (dd; 1.1, 8.0)	6.64 (dd; 1.1, 8.0)	6.19 (d; 2.9)	6.42 (d; 2.2)	6.20 (d; 2.9)
4''-H	6.16-7.31 (m)	7.10-7.19 (m)	—	—	6.84-7.05 (m)	7.02 (ddd; 1.9, 7.2, 8.0)	6.94 (ddd; 1.1, 7.1, 7.3)	7.00 (ddd; 1.9, 7.2, 8.0)	—	—	—
5''-H	6.92 (ddd; 1.0, 7.2, 7.2)	6.82 (ddd; 1.5, 7.5, 7.9)	6.46 (dd; 2.5, 8.9)	6.36 (dd; 2.5, 8.2)	6.84-7.05 (m)	6.73-6.82 (m)	7.02-7.06 (m)	6.80 (ddd; 1.1, 7.1, 7.2)	6.35 (dd; 2.9, 8.5)	6.49 (dd; 2.2, 8.5)	6.19 (dd; 2.9, 8.5)
6''-H	6.16-7.31 (m)	7.10-7.19 (m)	6.95-7.06 (m)	7.23 (d; 8.2)	7.16-7.32 (m)	7.17-7.36 (m)	7.02-7.06 (m)	7.16-7.32 (m)	7.16-7.31 (m)	7.03-7.07 (m)	7.16-7.31 (m)
ArOH	7.61-7.64 (m)	7.80-7.89 (m)	7.51-7.54 (m)	7.65-7.70 (m)	7.16-7.32 (m)	6.73-6.82 (m)	7.44 (m)	7.06 (m)	6.79-6.86 (m)	7.40-7.47 (m)	7.05-7.10 (m)
ArCH_2S	6.16-7.31 (m)	7.22-7.33 (m)	7.20-7.36 (m)	7.16-7.32 (m)	7.16-7.32 (m)	7.17-7.36 (m)	7.16-7.31 (m)	7.16-7.32 (m)	7.16-7.31 (m)	7.20-7.27 (m)	7.16-7.31 (m)

Table 11: ^1H NMR data of the *erythro*- and *threo*-2,3-diaryl-3-benzylsulfanylpropanols **272-275** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	272	273		274	275	
	<i>threo</i>	<i>erythro</i>	<i>threo</i>	<i>threo</i>	<i>erythro</i>	<i>threo</i>
2-H	3.91-4.06 (m)	3.70-3.82 (m)	3.89-4.02 (m)	3.82-4.01 (m)	3.61-3.71 (m)	3.77-3.96 (m)
3-H	4.50 (d; 9.1)	4.31 (d; 12.0)	4.40 (d; 8.9)	4.47 (d; 9.1)	4.29 (d; 11.1)	4.37 (d; 9.0)
1- CH_2	3.91-4.06 (m)	3.47-3.60 (m)	3.89-4.02 (m)	3.82-4.01 (m)	3.47-3.54 (m)	3.77-3.96 (m)
$\text{C}_1\text{-OH}$	1.79-1.86 (m)	1.61 (m)	1.68-1.74 (m)	1.80-1.91 (m)	1.41-1.54 (m)	1.70-1.79 (m)
ArCH_2S	3.47, 3.60 (2xd; 13.0)	3.35, 3.47 (2xd; 13.5)	3.46, 3.59 (2xd; 13.1)	3.46, 3.57 (2xd; 10.9)	3.35, 3.47 (2xd; 13.5)	3.44, 3.57 (2xd; 13.1)
SiCH_3	0.22, 0.24 (2xs)	0.25, 0.30 (2xs)	0.21, 0.24 (2xs)	0.23, 0.25 (2xs)	0.25, 0.30 (2xs)	0.22, 0.25 (2xs)
Bu^t	1.04 (s)	1.01 (s)	1.02 (s)	1.03 (s)	1.01 (s)	1.02 (s)
OCH_3	—	3.84 (s)	3.74 (s)	3.70 (s)	3.80, 3.84 (2xs)	3.71, 3.75 (2xs)
3'-H	6.77 (dd; 1.1, 8.0)	6.56 (d; 2.9)	6.36 (d; 2.9)	6.79 (dd; 1.1, 8.1)	6.56 (d; 2.5)	6.38 (d; 2.9)
4'-H	7.06 (ddd; 1.9, 7.1, 8.0)	—	—	7.08 (ddd; 1.9, 7.1, 8.1)	—	—
5'-H	6.69 (ddd; 1.1, 7.1, 7.9)	6.54 (dd; 2.9, 8.1)	6.25 (dd; 2.9, 8.5)	6.71 (ddd; 1.1, 7.1, 7.9)	6.49 (dd; 2.5, 8.5)	6.27 (dd; 2.9, 8.1)
6'-H	6.86 (dd; 1.9, 7.9)	7.09 (d; 8.1)	6.72 (d; 8.5)	6.89 (dd; 1.9, 7.9)	6.92 (d; 8.5)	6.74 (d; 8.1)
3''-H	6.70 (dd; 1.1, 7.9)	6.85 (dd; 1.1, 8.0)	6.71 (dd; 1.1, 8.1)	6.28 (d; 2.5)	6.43 (d; 2.9)	6.29 (d; 2.5)
4''-H	7.01 (ddd; 1.9, 7.1, 7.9)	7.16 (ddd; 1.9, 7.2, 8.0)	7.03 (ddd; 1.9, 7.1, 8.1)	—	—	—
5''-H	6.75 (ddd; 1.1, 7.1, 7.5)	6.91 (ddd; 1.1, 7.2, 7.5)	6.77 (ddd; 1.1, 7.1, 7.1)	6.32 (dd; 2.5, 8.1)	6.53 (dd; 2.9, 8.0)	6.34 (dd; 2.5, 8.2)
6''-H	6.96 (dd; 1.9, 7.5)	7.02 (dd; 1.9, 7.5)	6.94 (dd; 1.9, 7.1)	6.82 (d; 8.1)	7.10 (d; 8.0)	6.81 (d; 8.2)
ArOH	6.92-6.94 (m)	7.59-7.61 (m)	7.12-7.15 (m)	6.98-7.05 (m)	7.55-7.65 (m)	7.15-7.32 (m)
ArCH_2S	7.16-7.33 (m)	7.07-7.12 (2H, m) 7.24-7.31 (3H, m)	7.15-7.33 (m)	7.15-7.32 (m)	7.07-7.12 (2H, m) 7.20-7.31 (3H, m)	7.15-7.32 (m)

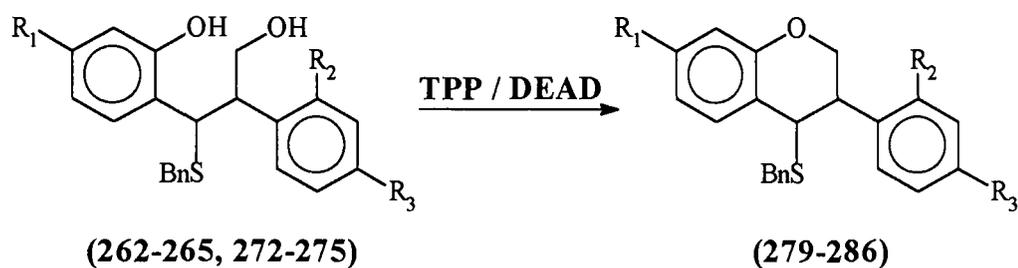


Scheme 41: SnCl₄/BnSH deprotection and substitution of 2'-MOM-ethers.

5.4 Synthesis of 4-benzylsulfanylisoflavans 279-286

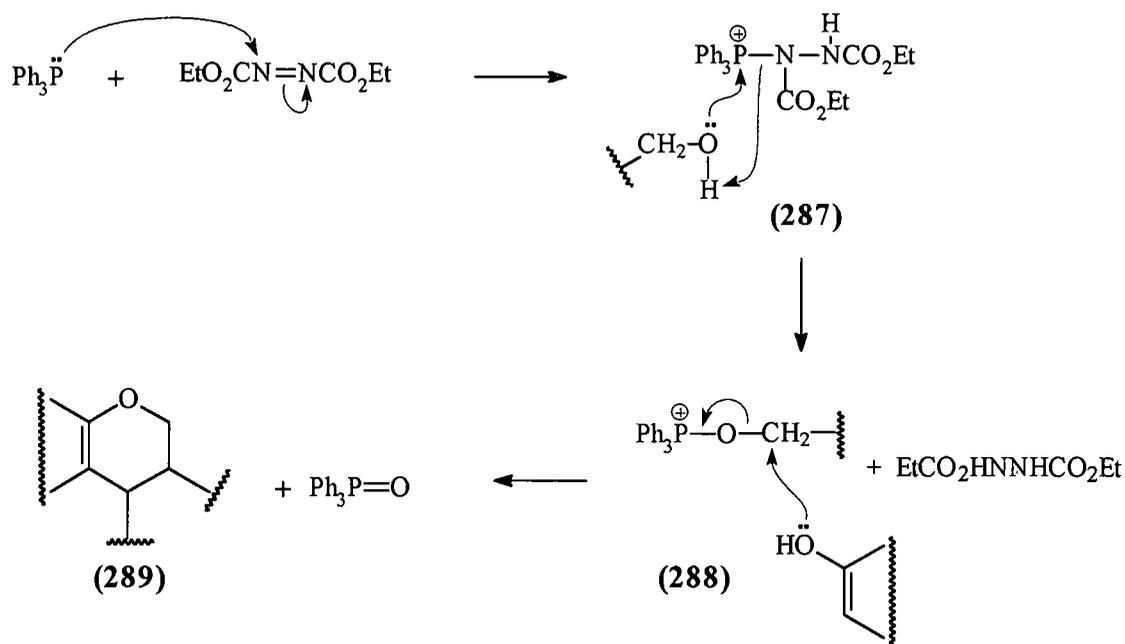
The effective utilisation of Mitsunobu cyclisation^{142,143} [PPh₃-diethylazodicarboxylate (DEAD)] in the synthesis of isoflavans,^{144,145} encouraged us to employ this procedure to convert *erythro*- and *threo*-propanols **262-265** and **272-275** to the respective *trans*- and *cis*-4-benzylsulfanylisoflavans **279-286** in excellent yields (Table 12).

It is generally accepted that this reaction proceeds in three steps (Scheme 42). Firstly, reaction between PPh_3 and DEAD to form a colourless zwitterionic adduct **287**. Secondly, activation of the alcohol substrate as the oxyphosphonium salt **288** which then undergoes $\text{S}_{\text{N}}2$ substitution affording product **289**.¹⁴³



propanol	3-benzylsulfanylisoflavan	R ₁	R ₂	R ₃	yield (%)
<i>threo</i> -262	<i>cis</i> -279	H	O ⁱ Pr	H	92
<i>threo</i> -263	<i>cis</i> -280	OMe	O ⁱ Pr	H	92
<i>threo</i> -264	<i>cis</i> -281	H	O ⁱ Pr	OMe	83
<i>threo</i> -265	<i>cis</i> -282	OMe	O ⁱ Pr	OMe	97
<i>threo</i> -272	<i>cis</i> -283	H	OTBDMS	H	81
<i>threo</i> -273	<i>cis</i> -284	OMe	OTBDMS	H	82
<i>erythro</i> -273	<i>trans</i> -284	OMe	OTBDMS	H	80
<i>threo</i> -274	<i>cis</i> -285	H	OTBDMS	OMe	93
<i>threo</i> -275	<i>cis</i> -286	OMe	OTBDMS	OMe	86
<i>erythro</i> -275	<i>trans</i> -286	OMe	OTBDMS	OMe	85

Table 12: Reaction yields for Mitsunobu cyclisation of propanols.



Scheme 42: Mechanism of the Mitsunobu reaction

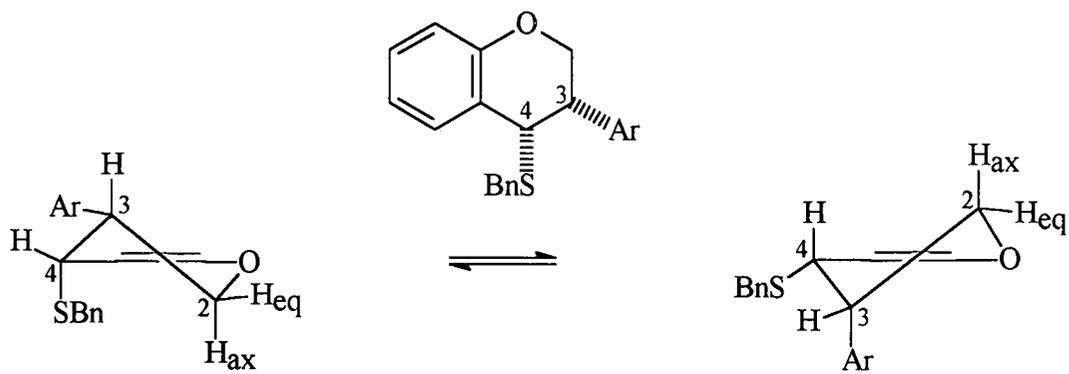
Scheme 43 represents the possible conformations of both *cis*- and *trans*-4-benzylsulfanylisoflavans **279-286**. ^1H NMR spectra (Tables 13 and 14) of the isomeric pairs display small coupling constants between H-3 and H-4 ($^3J_{3,4} = 3.5\text{-}4.0$ Hz), as well as between H-3 and H-2_{eq} ($^3J_{2\text{eq},3} = 3.0\text{-}4.8$ Hz). One of the isomers, however, exhibits a large coupling between H-3 and H-2_{ax} ($^3J_{2\text{ax},3} = 11.5\text{-}11.8$ Hz) and the other a small coupling ($^3J_{2\text{ax},3} = 3.0\text{-}3.1$ Hz). The small coupling between H-3 and H-4 eliminates **293** leaving **292** with its *trans*-diaxial benzylsulfanyl and aryl groups as the preferred conformation with a dihedral angle of *ca.* 60° between H-3 and both H-2_{eq} and H-2_{ax}. Thus, the large $^3J_{2\text{ax},3}$ coupling eliminates **291**, hence **290**, with the benzylsulfanyl group axial and the aryl equatorial, is the favoured conformation for the 3,4-*cis*-isomer. Both pairs of spectra also display W-coupling between H-4 and H-2_{eq} ($^4J_{2\text{eq},4} = 1\text{-}2$ Hz) which is only permitted for conformations **290** and **292**. This data is in accordance with NMR data for isoflavan-4-ols^{146,147} and facilitated identification of both isomers and this could be extrapolated to determine the configuration of structures **262-265** (Table 8) and **272-275** (Table 11).

Table 13: ^1H NMR data of the 2'-O-isopropyl-4-benzylsulfanylisoflavans **279-282** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	279	280	281	282
	<i>cis</i>	<i>cis</i>	<i>cis</i>	<i>cis</i>
2- H_{eq}	4.40 (ddd; 2.0, 3.0, 10.1)	4.40 (ddd; 2.0, 3.1, 10.0)	4.36 (ddd; 2.0, 3.0, 10.0)	4.34 (ddd; 2.0, 3.0, 10.2)
2- H_{ax}	4.74 (dd; 10.1, 11.9)	4.75 (dd; 10.0, 11.9)	4.71 (dd; 10.0, 11.9)	4.68 (dd; 10.1, 12.0)
3-H	4.01 (ddd; 3.0, 3.0, 11.9)	4.00 (ddd; 3.1, 3.1, 11.9)	3.94 (ddd; 3.0, 3.5, 11.9)	3.90 (ddd; 3.0, 4.0, 12.0)
4-H	4.21 (dd; 2.0, 3.0)	4.19 (dd; 2.0, 3.1)	4.17 (dd; 2.0, 3.5)	4.12 (dd; 2.0, 4.0)
$\text{CH}(\text{CH}_3)_2$	1.31, 1.32 (2xd; 6.0)	1.33, 1.33 (2xd; 6.0)	1.33, 1.34 (2xd; 6.0)	1.31, 1.31 (2xd; 6.0)
$\text{CH}(\text{CH}_3)_2$	4.64 (m; 6.0)	4.64 (m; 6.0)	4.60 (m; 6.0)	4.58 (m; 6.0)
OCH_3	—	3.79 (s)	3.88 (s)	3.77, 3.86 (2xs)
ArCH_2S	2.70, 3.00 (2xd; 13.1)	2.67, 2.98 (2xd; 13.0)	2.80, 3.10 (2xd; 13.0)	2.76, 3.05 (2xd; 13.0)
5-H	6.95 (dd; 1.9, 8.9)	6.94 (d; 8.1)	7.11-7.19 (m)	6.91 (d; 8.5)
6-H	6.85 (ddd; 1.1, 7.2, 7.2)	6.50 (dd; 2.5, 8.1)	6.83-6.90 (m)	6.47 (dd; 2.5, 8.5)
7-H	7.17-7.37 (m)	—	7.11-7.19 (m)	—
8-H	6.83 (dd; 1.1, 8.0)	6.39 (d; 2.5)	6.83-6.90 (m)	6.37 (d; 2.5)
3'-H	6.99-7.07 (m)	6.91-6.98 (m)	6.56 (d; 2.2)	6.54 (d; 2.2)
4'-H	6.99-7.07 (m)	6.91-6.98 (m)	—	—
5'-H	6.99-7.07 (m)	6.81 (ddd; 1.1, 7.5, 7.5)	6.59 (dd; 2.2, 8.1)	6.56 (dd; 2.2; 8.5)
6'-H	7.17-7.37 (m)	6.91-6.98 (m)	7.11-7.19 (m)	7.14 (d; 8.5)
ArCH_2S	7.17-7.37 (m)	7.20-7.38 (m)	7.25-7.38 (m)	7.20-7.31 (m)

Table 14: ^1H NMR data of the *cis*- and *trans*-2'-*O*-TBDMS-4-benzylsulfanylisoflavans **283-286** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	283	284		285	286	
	<i>cis</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>cis</i>	<i>trans</i>
2- H_{eq}	4.41 (ddd; 2.0, 3.0, 10.5)	4.39 (ddd; 2.0, 3.0, 10.1)	4.26 (ddd; 1.1, 4.5, 10.9)	4.38 (ddd; 2.1, 3.1, 10.1)	4.34 (ddd; 2.0, 3.0, 10.1)	4.24 (ddd; 1.1, 4.8, 10.9)
2- H_{ax}	4.77 (dd; 10.1, 11.5)	4.75 (dd; 10.1, 11.8)	4.57 (dd; 3.0, 10.9)	4.74 (dd; 10.1, 11.8)	4.71 (dd; 10.1, 11.9)	4.56 (dd; 3.1, 10.9)
3-H	3.93 (ddd; 3.0, 3.5, 11.5)	3.90 (ddd; 3.0, 3.8, 11.8)	3.87 (ddd; 3.0, 4.0, 4.5)	3.86 (ddd; 3.1, 3.9, 11.8)	3.82 (ddd; 3.0, 3.9, 11.9)	3.77 (ddd; 3.1, 3.9, 4.8)
4-H	4.24 (dd; 2.0, 3.5)	4.20 (dd; 2.0, 3.8)	4.08 (d; 4.0)	4.19 (dd; 2.1, 3.9)	4.14 (dd; 2.0, 3.9)	4.05 (d; 3.9)
SiCH_3	0.21, 0.34 (2xs)	0.21, 0.34 (2xs)	0.34, 0.35 (2xs)	0.23, 0.36 (2xs)	0.22, 0.34 (2xs)	0.35, 0.36 (2xs)
Bu^t	0.89 (s)	0.88 (s)	1.07 (s)	0.88 (s)	0.88 (s)	1.07 (s)
OCH_3	—	3.76 (s)	3.78 (s)	3.85 (s)	3.76, 3.84 (2xs)	3.76, 3.78 (2xs)
ArCH_2S	2.71, 3.01 (2xd; 13.1)	2.67, 2.96 (2xd; 13.1)	3.69, 3.80 (2xd; 12.9)	2.79, 3.10 (2xd; 13.1)	2.75, 3.05 (2xd; 13.1)	3.70, 3.80 (2xd; 13.0)
5-H	7.05-7.16 (m)	6.80 (d; 8.2)	7.20-7.28 (m)	7.08-7.35 (m)	6.78 (d; 9.0)	7.20-7.30 (m)
6-H	7.05-7.16 (m)	6.43 (dd; 2.9, 8.2)	6.53 (dd; 2.8, 8.8)	6.79-6.91 (m)	6.42 (dd; 2.5, 9.0)	6.53 (dd; 2.8, 8.5)
7-H	7.05-7.16 (m)	—	—	6.79-6.91 (m)	—	—
8-H	6.79-6.85 (m)	6.35 (d; 2.9)	6.37 (d; 2.8)	6.79-6.91 (m)	6.34 (d; 2.5)	6.38 (d; 2.8)
3'-H	6.88-6.95 (m)	6.91 (dd; 1.1, 8.0)	6.76-6.90 (m)	6.52 (d; 2.9)	6.50 (d; 2.8)	6.46 (d; 2.5)
4'-H	7.05-7.16 (m)	7.11-7.18 (m)	7.13 (ddd; 2.2, 6.2, 8.0)	—	—	—
5'-H	6.79-6.85 (m)	7.06 (ddd; 1.1, 7.2, 7.5)	6.76-6.90 (m)	6.65 (dd; 2.9, 8.5)	6.62 (dd; 2.8, 8.5)	6.36 (dd; 2.5, 8.5)
6'-H	6.88-6.95 (m)	7.11-7.18 (m)	6.76-6.90 (m)	7.14 (d; 8.5)	7.11 (d; 8.5)	6.74 (d; 8.5)
ArCH_2S	7.20-7.32 (m)	7.18-7.32 (m)	7.20-7.28 (m)	7.08-7.35 (m)	7.14-7.32 (m)	7.20-7.30 (m)



(290)

$$\theta_{3,4} = 60^\circ$$

$$\theta_{3,2ax} = 180^\circ$$

$$\theta_{3,2eq} = 60^\circ$$

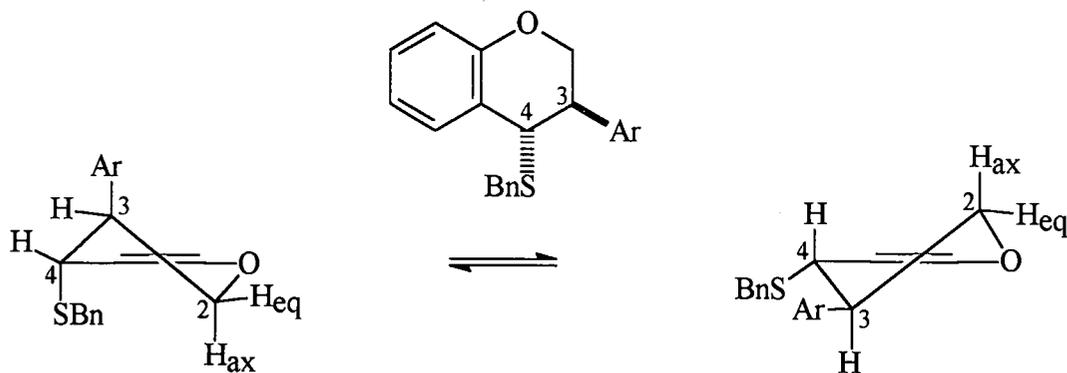
W-coupling between H-2_{eq} and H-4

(291)

$$\theta_{3,4} = 60^\circ$$

$$\theta_{3,2ax} = 60^\circ$$

$$\theta_{3,2eq} = 60^\circ$$



(292)

$$\theta_{3,4} = 60^\circ$$

$$\theta_{3,2ax} = 60^\circ$$

$$\theta_{3,2eq} = 60^\circ$$

W-coupling between H-2_{eq} and H-4

(293)

$$\theta_{3,4} = 180^\circ$$

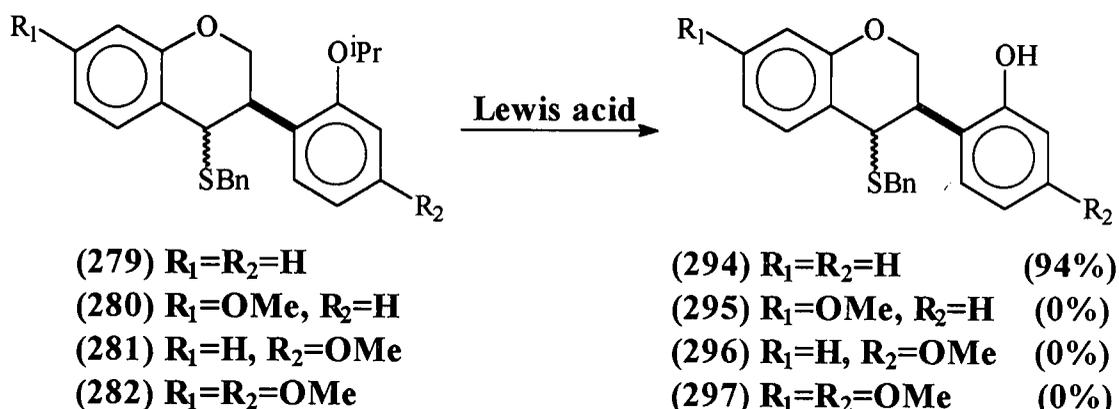
$$\theta_{3,2ax} = 180^\circ$$

$$\theta_{3,2eq} = 60^\circ$$

Scheme 43: Possible conformations for 3,4-*cis*- and *trans*-isoflavans

5.5 Cleavage of the 2'-ⁱPr-(279-282) and 2'-TBDMS ethers (283-286)

The final cyclisation step required deprotection at 2'-OH. Cleavage of 2'-OⁱPr ethers **279-282** employing standard conditions (BBR₃ / DCM / 25°C)^{148,149} gave disappointing results. The only product that could be obtained was 2'-hydroxy-4-benzylsulfanylisoflavan **294** (94%), while ethers **280-282** decomposed, mainly *via* cleavage of the C-ring ether bond.¹⁵⁰ Boron(III)-,¹⁵⁰ titanium(IV)-¹⁵¹ and aluminum chloride¹⁵² also resulted in decomposition of the starting materials.

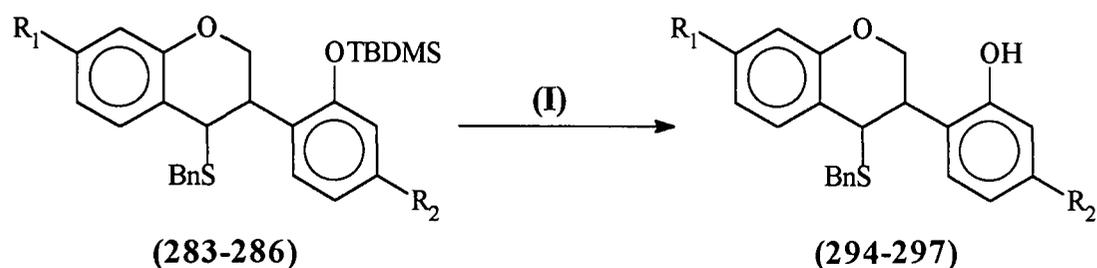


Scheme 44: Deprotection of isopropylethers employing Lewis acids.

These disappointing results obtained with the 2'-OⁱPr-isoflavans shifted our efforts to 2'-O-TBDMS derivatives owing to their stability to all the preceding reaction conditions but relative ease of deprotection employing either potassium-¹⁵³ sodium-¹⁵⁴ or tetrabutylammonium fluoride (TBAF).^{139,155} Clark¹⁵⁶ reported that TBAF suspended on silica gel acts as a stable non-hygroscopic source of naked fluoride ions, therefore we opted for this reagent in order to cleave the TBDMS-ethers **283-286**. The corresponding 2'-hydroxyisoflavans **294-297** (Table 15: ¹H NMR data) were thus obtained in excellent yields of 96-99 % (Table 16).

Table 15: ^1H NMR data of the *cis*- and *trans*-2'-hydroxy-4-benzylsulfanylisoflavans **294-297** in CDCl_3 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	294	295		296	297	
	<i>cis</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>cis</i>	<i>trans</i>
2- H_{eq}	4.44 (ddd; 2.0, 3.0, 10.5)	4.41 (ddd; 2.0, 3.0, 10.1)	4.40 (dd; 5.1, 11.0)	4.39 (ddd; 2.1, 2.9, 10.5)	4.37 (ddd; 2.0, 3.0, 10.5)	4.35 (dd; 5.5, 10.9)
2- H_{ax}	4.76 (dd; 10.5, 11.8)	4.75 (dd; 10.1, 11.5)	4.61 (dd; 3.1, 11.0)	4.72 (dd; 10.5, 11.5)	4.72 (dd; 10.5, 11.5)	4.57 (dd; 3.0, 10.9)
3-H	3.96 (ddd; 3.0, 4.0, 11.8)	3.92 (ddd; 3.0, 4.0, 11.5)	3.74 (ddd; 3.1, 5.1, 5.1)	3.85 (ddd; 2.9, 4.9, 11.5)	3.82 (ddd; 3.0, 4.0, 11.5)	3.65 (ddd; 3.0, 5.0, 5.5)
4-H	4.27 (dd; 2.0, 4.0)	4.22 (dd; 2.0, 4.0)	4.14 (d; 5.1)	4.19 (dd; 2.1, 4.9)	4.16 (dd; 2.0, 4.0)	4.08 (d; 5.0)
OCH_3	—	3.76 (s)	3.78 (s)	3.84 (s)	3.76, 3.84 (2xs)	3.76, 3.78 (2xs)
ArOH	5.37-5.51 (m)	5.16 (bs)	5.16 (bs)	5.38-5.44 (m)	5.48-5.60 (m)	5.35-5.41 (m)
Ar CH_2S	2.85, 3.08 (2xd; 13.0)	2.81, 3.05 (2xd; 13.1)	3.73, 3.84 (2xd; 13.0)	2.92, 3.17 (2xd; 13.0)	2.90, 3.14 (2xd; 13.0)	3.73, 3.82 (2xd; 13.1)
5-H	7.11-7.16 (m)	6.88 (d; 8.5)	7.21 (d; 8.5)	7.08-7.19 (m)	6.86 (d; 8.5)	7.21 (d; 8.5)
6-H	6.80-6.89 (m)	6.46 (dd; 2.8, 8.5)	6.50 (dd; 2.5, 8.5)	6.79-6.86 (m)	6.46 (dd; 2.5, 8.5)	6.50 (dd; 2.5, 8.5)
7-H	6.80-6.89 (m)	—	—	6.79-6.86 (m)	—	—
8-H	6.96-7.00 (m)	6.36 (d; 2.8)	6.39 (d; 2.5)	6.92-6.97 (m)	6.35 (d; 2.5)	6.40 (d; 2.5)
3'-H	6.80-6.89 (m)	6.86 (dd; 1.0, 7.9)	6.81 (dd; 1.1, 7.8)	6.46 (d; 2.5)	6.46 (d; 2.5)	6.40 (d; 2.5)
4'-H	7.11-7.16 (m)	7.10-7.14 (m)	7.14 (ddd; 1.9, 7.2, 7.8)	—	—	—
5'-H	7.03-7.10 (m)	7.05 (ddd; 1.0, 7.2, 7.5)	6.86 (ddd; 1.1, 7.2, 7.8)	6.61 (dd; 2.5, 8.5)	6.60 (dd; 2.5, 8.5)	6.41 (dd; 2.5, 9.0)
6'-H	7.11-7.16 (m)	7.10-7.14 (m)	7.07 (dd; 1.9, 7.8)	7.08-7.19 (m)	7.13 (d; 8.5)	6.96 (d; 9.0)
Ar CH_2S	7.20-7.33 (m)	7.19-7.32 (m)	7.21-7.31 (m)	7.08-7.34 (m)	7.14-7.33 (m)	7.20-7.31 (m)



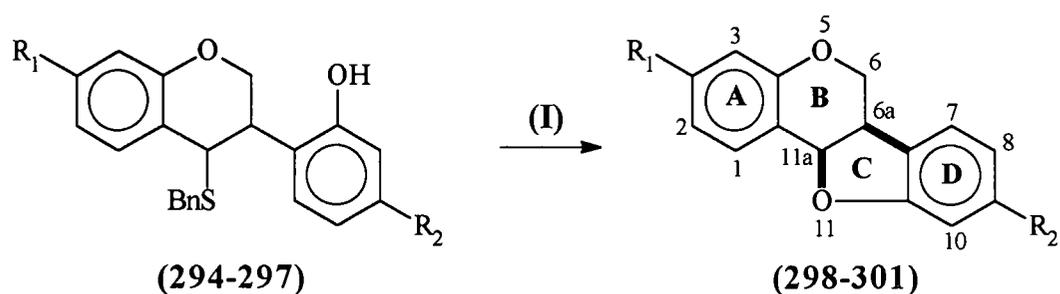
(I) TBAF (silica), THF, rt., 15 minutes

2'-hydroxyisoflavan	R ₁	R ₂	yield (%)
<i>cis</i> -294	H	H	96
<i>cis</i> -295	Ome	H	99
<i>trans</i> -295	Ome	H	99
<i>cis</i> -296	H	OMe	99
<i>cis</i> -297	Ome	OMe	99
<i>trans</i> -297	Ome	OMe	99

Table 16: Reaction yields for the cleavage of TBDMS-ethers **283-286**.

5.6 Synthesis of pterocarpan 298-301

The 2'-hydroxy-4-benzylsulfanylisoflavans **294-297** are perfectly set up for cyclisation and were converted to (6a,11a)-*cis*-pterocarpan **298-301** in yields of 39-82%, using thiophilic Lewis acids to activate the 4-benzylsulfanyl as leaving group (Table 17). Although silver tetrafluoroborate (AgBF₄)^{140,157} was employed to synthesise pterocarpan **298** in a good yield of 82% (entry 1), this reagent afforded pterocarpan **299-301** in low yields of 0-23% (entries 3, 5 and 8). Alternative Lewis acids *i.e.* dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)¹⁵⁸⁻¹⁶⁰ (entry 7) and silver trifluoromethanesulfonate (CF₃SO₃Ag)^{161,162} were employed and produced pterocarpan **298-301** in moderate to good yields (entries 2, 4, 6 and 9). This not only indicated that the Lewis acid selection is dependent on specific substrates, with AgSO₃CF₃ being the most general within this protocol, but that increased oxygenation, especially of the pterocarpan D-ring, may negatively influence cyclisation.

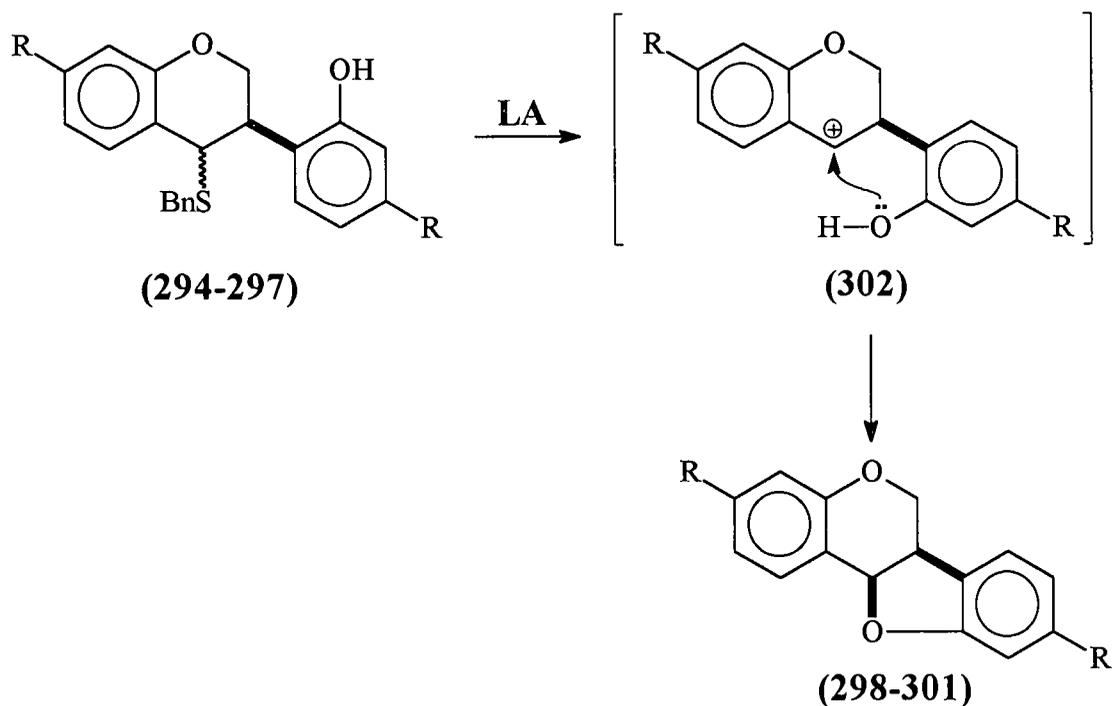


(I) AgBF₄ / DMTSF / AgOTf, DCM, rt. or -10°C

entry	2'-OH-isoflavan	R ₁	R ₂	pterocarpan	Lewis acid	yield (%)
1	294	H	H	298	AgBF ₄	82
2	294	H	H	298	AgOTf	82
3	295	OMe	H	299	AgBF ₄	23
4	295	OMe	H	299	AgOTf	57
5	296	H	OMe	300	AgBF ₄	0
6	296	H	OMe	300	AgOTf	0
7	296	H	OMe	300	DMTSF	39
8	297	OMe	OMe	301	AgBF ₄	14
9	297	OMe	OMe	301	AgOTf	50

Table 17: Thiophilic Lewis acid mediated synthesis of pterocarpan **298-301**.

The reactivity of the 3,4-*cis*- and 3,4-*trans*-benzylsulfanylisoflavans **294-297** was the same and both afforded *cis*-pterocarpan **298-301** in comparable yields. This presumably reflects a thermodynamically controlled S_N1 cyclisation mechanism, where carbocation **302** acts as intermediate, prior to the occurrence of the conformationally favoured *cis*-cyclisation of the C-ring (Scheme 45).



R = H or OMe

LA = Thiophilic Lewis acid

Scheme 45: Mechanism of pterocarpin C-ring formation.

^1H - and ^{13}C NMR data (Table 18: ^1H NMR data), mass spectra and melting point correlation of synthetic pterocarpin **301** with natural occurring homoptercarpin¹⁶³ served as final confirmation of its structure and could be extrapolated to confirm structures **298-300**.

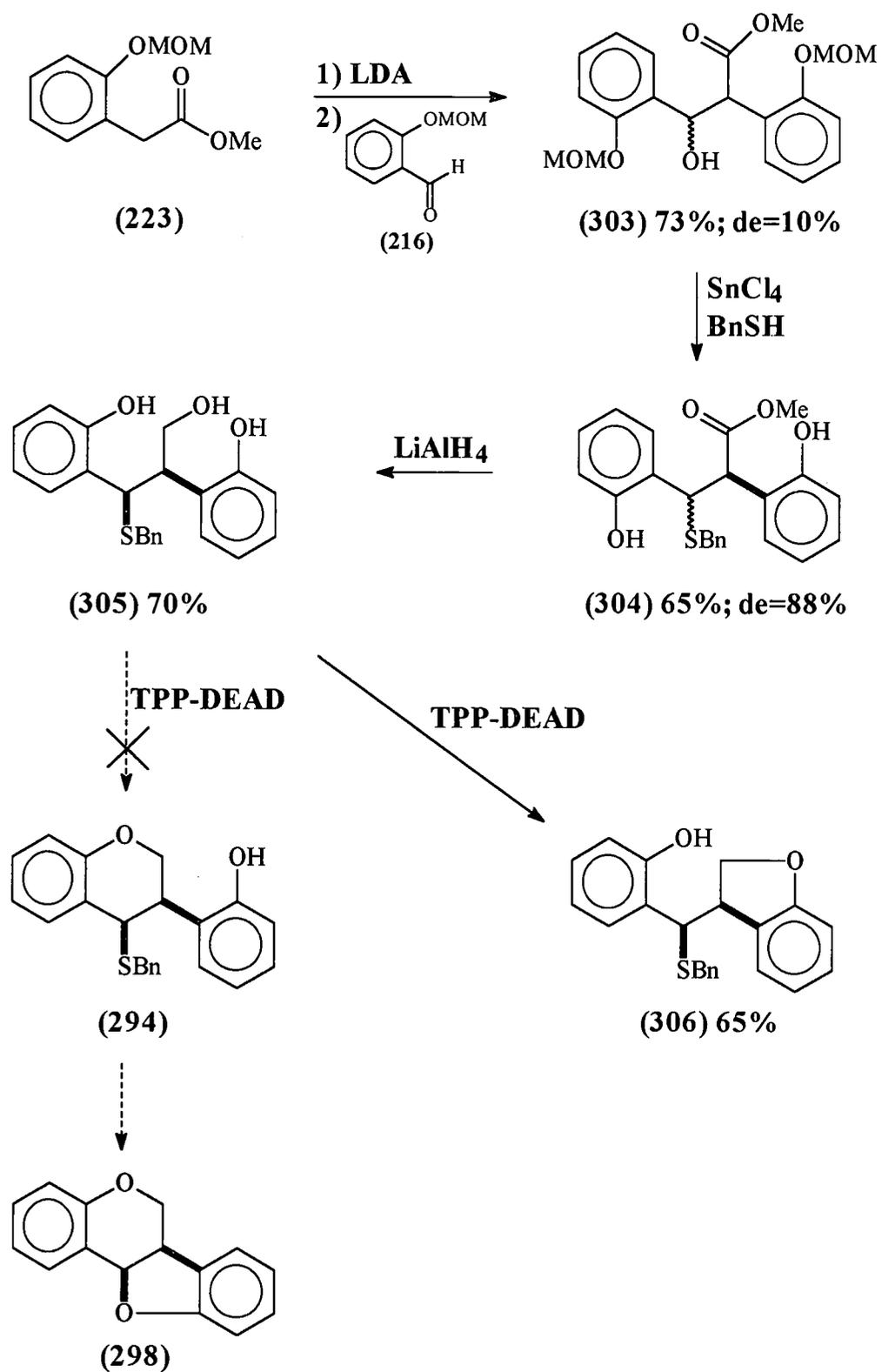
5.7 A shortened approach to *cis*-pterocarpanes

Although the preceding synthetic approach represents an effective multi-step synthesis towards *cis*-pterocarpanes, we attempted to shorten the protocol. It was recognised that if a single protective functionality was used, deprotection of both hydroxy functions could be accomplished in one step. Therefore, methyl 2-(2''-O-methoxymethylphenyl)-3-hydroxy-3-(2'-O-methoxymethylphenyl)propanoate **303** was synthesised from the

Table 18: ^1H NMR data of the *cis*-pterocarpanes **298-301** in C_6D_6 at 300 MHz. Splitting patterns and J-values (in Hz) are given in parentheses.

	298	299	300	301
6a-H	3.13 (ddd; 5.0, 7.1, 11.0)	3.14 (ddd; 5.0, 7.0, 11.0)	3.15 (ddd; 5.1, 7.1, 11.0)	3.15 (ddd; 5.0, 7.0, 10.9)
6-H _{ax}	3.50 (dd; 11.0, 11.0)	3.58 (dd; 11.0, 11.0)	3.55 (dd; 11.0, 11.0)	3.63 (dd; 10.9, 10.9)
6-H _{eq}	3.96 (ddd; 0.8, 5.0, 11.0)	3.99 (dd; 5.0, 11.0)	4.00 (dd; 5.1, 11.0)	4.03 (dd; 5.0, 10.9)
11a-H	5.23 (d; 7.1)	5.28 (d; 7.0)	5.30 (d; 7.1)	5.35 (d; 7.0)
OCH ₃	—	3.31 (s)	3.35 (s)	3.33, 3.35 (2xs)
1-H	7.57-7.62 (m)	7.49-7.52 (m)	7.60-7.64 (m)	7.52 (d; 9.0)
2-H	6.82 (ddd; 1.0, 7.0, 7.0)	6.68-6.72 (m)	6.95 (ddd; 2.5, 6.0, 7.5)	6.71 (dd; 2.2, 9.0)
3-H	7.04-7.14 (m)	—	7.07-7.15 (m)	—
4-H	7.04-7.14 (m)	6.68-6.72 (m)	7.07-7.15 (m)	6.71 (d; 2.2)
7-H	6.90-6.97 (m)	6.92-6.98 (m)	6.83 (d; 8.1)	6.86 (d; 8.0)
8-H	6.90-6.97 (m)	6.81-6.87 (m)	6.51 (dd; 2.1, 8.1)	6.54 (dd; 2.1, 8.0)
9-H	7.04-7.14 (m)	7.05-7.12 (m)	—	—
10-H	6.90-6.97 (m)	6.92-6.98 (m)	6.65 (d; 2.1)	6.68 (d; 2.1)

corresponding methoxymethylated benzaldehyde **216** and phenylacetate **223**, employing LDA as base, in 73% yield and 10% de. Complete deprotection (SnCl_4 , BnSH) of the respective diastereoisomers afforded mainly the *threo* isomer **304** in 65% yield (de = 88%), while ensuing reduction (LiAlH_4) yielded the benzylsulfanylpropanol **305** (70%). Identification of the *erythro* and *threo* diastereoisomers of **303**, **304** and **305** was achieved by comparison with the isomers of **252**, **268** and **283**, respectively. However, the anticipated Mitsunobu B-ring formation and subsequent thiophilic C-ring closure were encumbered by exclusive formation of the 2,3-dihydroxybenzofurane **306** (Scheme 46). The formation of the 5-membered instead of 6-membered ring, most likely occurs under the influence of steric interaction within the Mitsunobu intermediate. We therefore persisted with the previous protocol.



Scheme 46: Attempted shortened protocol to pterocarpan.

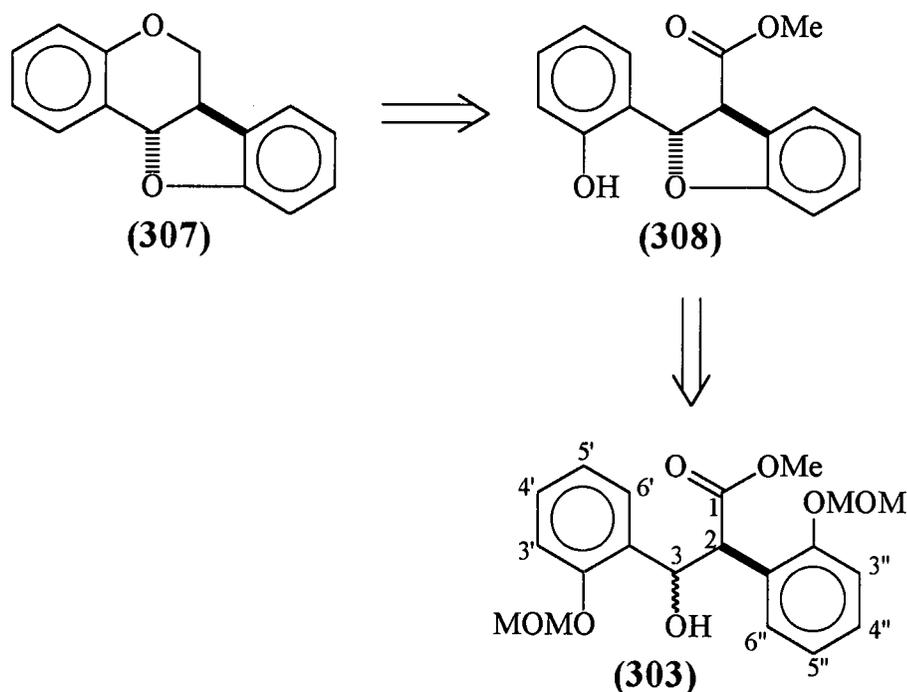
5.8 Conclusion

An effective, novel synthetic route to racemic *cis*-pterocarpan, exhibiting aromatic oxygenation patterns usually encountered in naturally occurring pterocarpan, has thus been established using readily available phenylacetates and benzaldehydes as aldol starting materials. This protocol should contribute substantially towards the chemistry of the pterocarpan class of isoflavonoids.

SYNTHESIS OF RACEMIC *TRANS*-PTEROCARPANS

6.1 Introduction

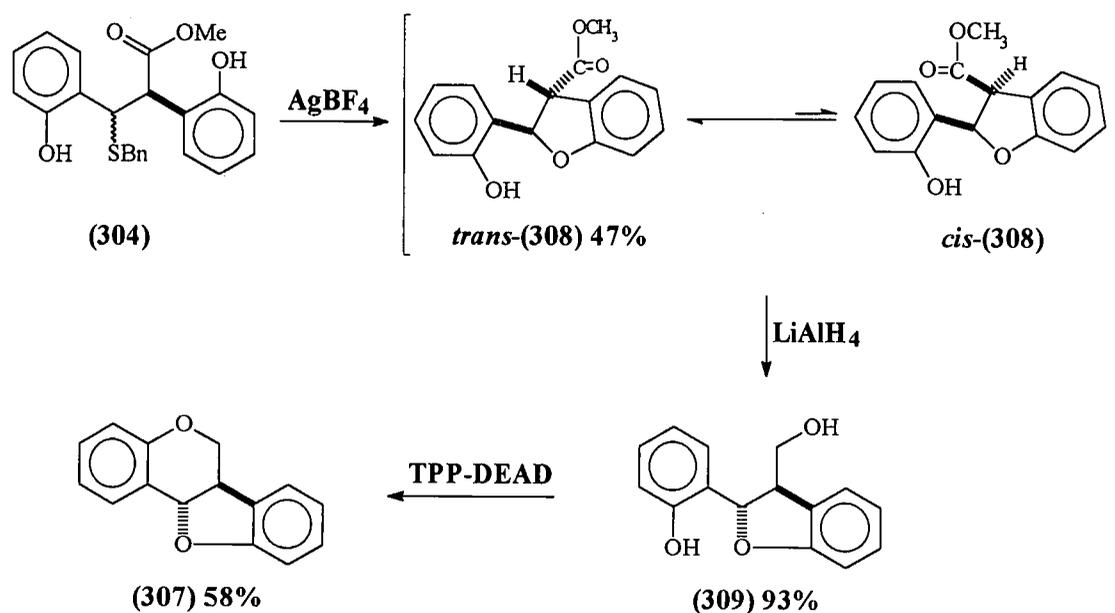
Computational studies concur that a *trans*-fused B/C-ring system in pterocarpan is less favourable than the *cis*-fused system,⁹ thus corresponding with all known natural occurring pterocarpan possessing *cis*-(6a,11a)-stereochemistry. Nevertheless, we anticipated that our protocol, developed for the synthesis of *cis*-isomers, could be modified to synthesise *trans*-pterocarpan. The prime requisite for this synthesis was the reversed order of ring formation, namely initial C-ring construction followed by B-ring closure (Scheme 47).



Scheme 47: *Retro*-synthesis of *trans*-pterocarpan.

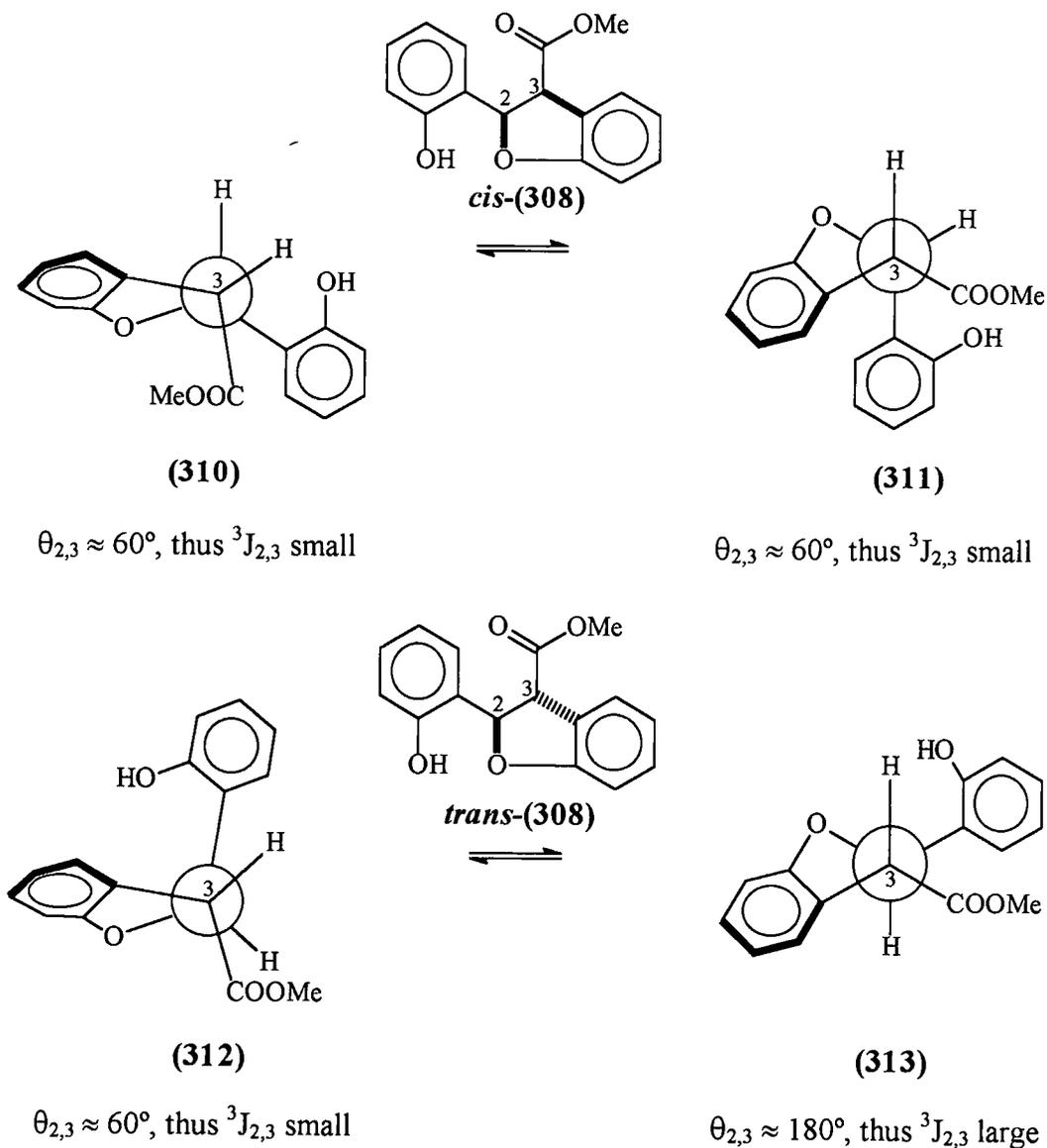
6.2 Synthesis of *trans*-pterocarpan

Since no selective deprotection was required (Scheme 46), both the 2'- and 2''-OH groups were protected as methoxymethylethers and 3-benzylsulfanyl-2-(2''-hydroxyphenyl)-3-(2'-hydroxyphenyl)propanoate **304** could be obtained from **303** as described in Scheme 45. Cyclisation (AgBF_4) of both *erythro* and *threo* **304**, to produce the pterocarpan C-ring, afforded the thermodynamically more stable *trans*-fused benzofuran **308**. Subsequent reduction with LiAlH_4 to **309**, followed by Mitsunobu cyclisation, gave the *trans*-pterocarpan **307** in a moderate yield of 54% (Scheme 48).



Scheme 48: Synthesis of *trans*-pterocarpan **307**.

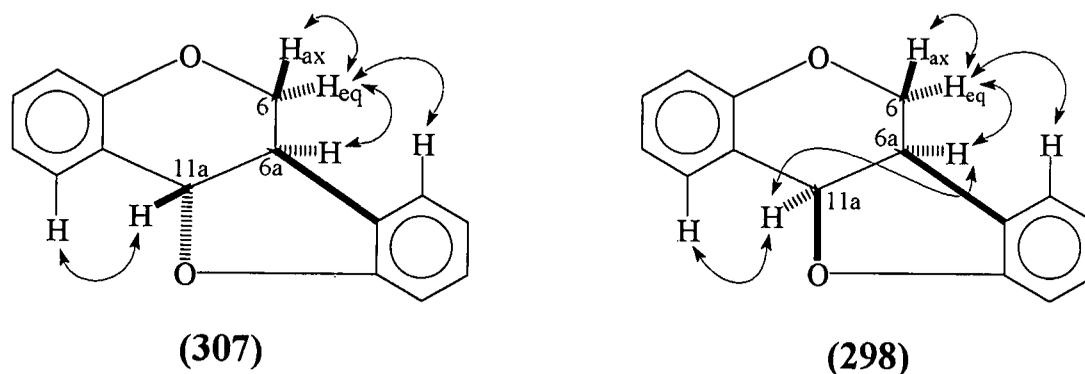
In order to confirm the stereochemistry of dihydrobenzofuran **308**, structures **310-313** were considered as the possible conformations of both *cis*- and *trans*-dihydrobenzofurans **308** (Scheme 49). The ^1H NMR spectrum of **308** exhibited a $^3J_{2,3}$ -value of 8.5 Hz, indicating a large dihedral angle between the vicinal protons, thereby eliminating *cis*-conformers **310** and **311**.



Scheme 49: Possible conformations for *trans*- and *cis*-benzofurans **308**.

The ${}^1\text{H}$ NMR spectrum of *trans*-pterocarpan **307** displayed two large couplings for 6a-H with 6- H_{ax} and 11a-H (${}^3J_{6\text{a},6\text{ax}} = 12.1$ and ${}^3J_{6\text{a},11\text{a}} = 13.5$ Hz), and a small coupling with 6- H_{eq} (${}^3J_{6\text{a},6\text{eq}} = 4.9$ Hz). The corresponding *cis*-pterocarpan **298** displayed a smaller coupling between 6a-H and 11a-H (${}^3J_{6\text{a},11\text{a}} = 7.1$ Hz) and a W-coupling of 0.8 Hz between 6- H_{eq} and 11a-H. This permitted distinction between structures **298** and **307** that could be confirmed *via* NOESY experiments that clearly indicated the absence of NOESY

interaction between 6a- and 11a-H for the *trans*-isomer **307** in contrast to the observed interaction in the *cis*-isomer **298** (Scheme 50).



Scheme 50: NOESY interactions in *trans*-(**307**)- and *cis*-(**298**)-pterocarpan.

6.3 Conclusion

Although some of the yields in this protocol are still low, optimisation of reaction conditions have not been done. This protocol nevertheless represents the first synthetic access to *trans*-pterocarpan which may then be revisited should future needs arise.

STEREOSELECTIVE SYNTHESIS OF *CIS*- PTEROCARPANS

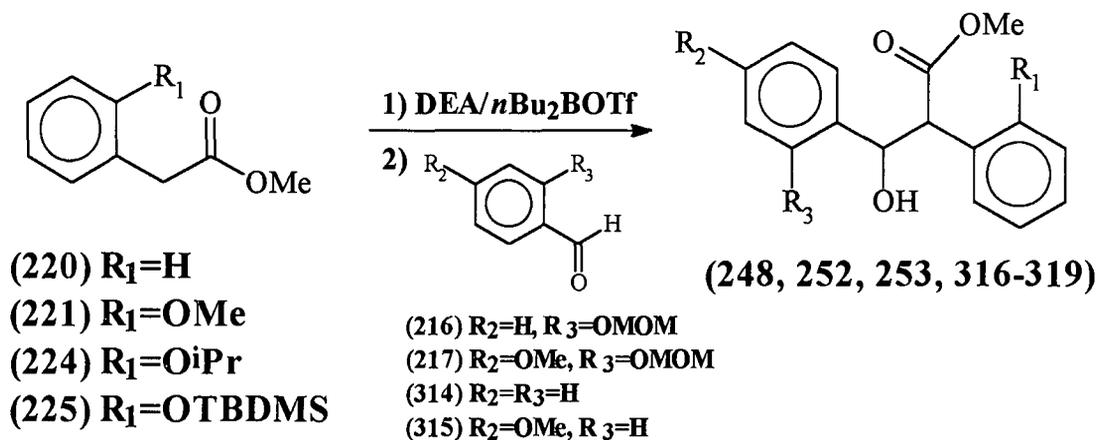
7.1 Introduction

The asymmetric aldol reaction is not only a powerful tool for construction of new carbon-carbon bonds, but also for control of the absolute configurations of these newly created centers.¹⁶⁴ This utility has been demonstrated in the synthesis of natural products such as macrolide, polyether antibiotics and carbohydrates, among others.¹⁶⁵⁻¹⁶⁷ Base catalysed aldol reactions allow asymmetric induction *via* three distinct methods, during which the stereochemical outcome is determined by formation of six-membered cyclic transition states. These methods involve, firstly, the use of chiral metal complexes, for example those of boron,^{102,103} titanium,^{95,96} nickel⁹⁹ and tin,⁹²⁻⁹⁴ secondly, employing either or both chiral aldehydes and chiral enolates,⁸⁷⁻⁹¹ and finally, stereoselectivity has been obtained *via* deprotonation with chiral bases.^{100,101,168} While these reactions normally proceed with good yields and diastereoselectivities, the general application of enantioselective aldol reactions is still troublesome.

7.2 Aldol condensation employing boron triflate

Owing to the good results reported for stereoselective aldol condensation between methyl ketones and aldehydes employing diisopropylethylamine (DEA) in the presence of chiral boron triflates,^{169,170} this system was evaluated *via* initial utilisation of achiral dibutylborontriflate (*n*Bu₂BOTf)¹⁷¹ as metal ligand and condensation of simple starting materials, *i.e.*, methyl propanoates **220**, **221**, **224** and **225** and benzaldehydes **216**, **217**, **314** and **315** (Table 19). The ability of DEA to successfully catalyse deprotonation of the

propanoates was confirmed by D₂O trapping of the formed *n*Bu₂B-enolates which indicated complete deprotonation after one hour at -78°C. Entries 2-5 indicated that DCM as solvent afforded better yields than Et₂O, although a slight decrease in diastereoselectivity was observed, while entries 6-9 indicated that sterically more demanding groups led to a decrease in yields.



Entry	R ₁	R ₂	R ₃	Solvent	product	yield (%)	de (%)
1	H	H	H	Et ₂ O	316	70	100
2	H	OMe	H	Et ₂ O	317	23	100
3	H	OMe	H	DCM	317	78	98
4	H	H	OMOM	Et ₂ O	318	26	100
5	H	H	OMOM	DCM	318	68	88
6	OMe	H	OMOM	DCM	319	46	44
7	O ⁱ Pr	H	OMOM	DCM	248	17	6
8	OTBDMS	H	OMOM	DCM	252	14	100
9	OTBDMS	OMe	OMOM	DCM	253	9	100

Table 19: Product formation of aldol condensation employing DEA and *n*Bu₂BOTf.

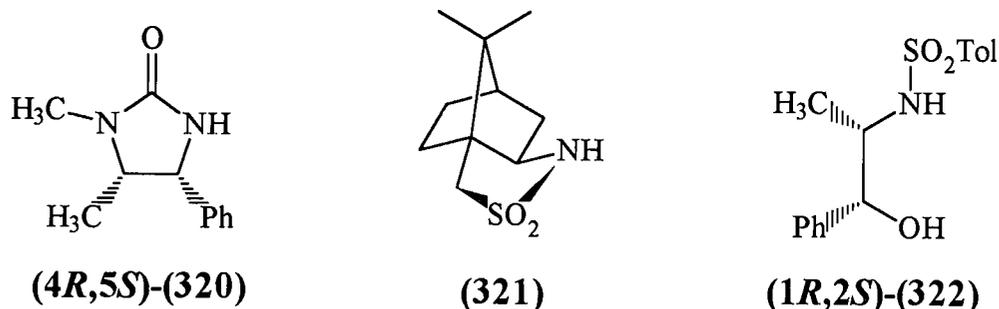
These results clearly indicated that the DEA / *n*Bu₂BOTf system does not tolerate the use of a broad range of protective groups and highly oxygenated starting materials, which were essential for this synthesis.

7.3 Aldol condensation employing chiral enolates

The use of chiral enolates to induce stereoselectivity during aldol condensations is well documented.¹⁶⁴ Even so, this technique is limited when bulky starting materials are used. Notwithstanding, we opted to employ chiral derivatives of propanoates in an attempt to control the stereochemical outcome of the aldolisation step, thereby controlling the chirality at C-3 of the propanoates and ultimately that of the pterocarpan.

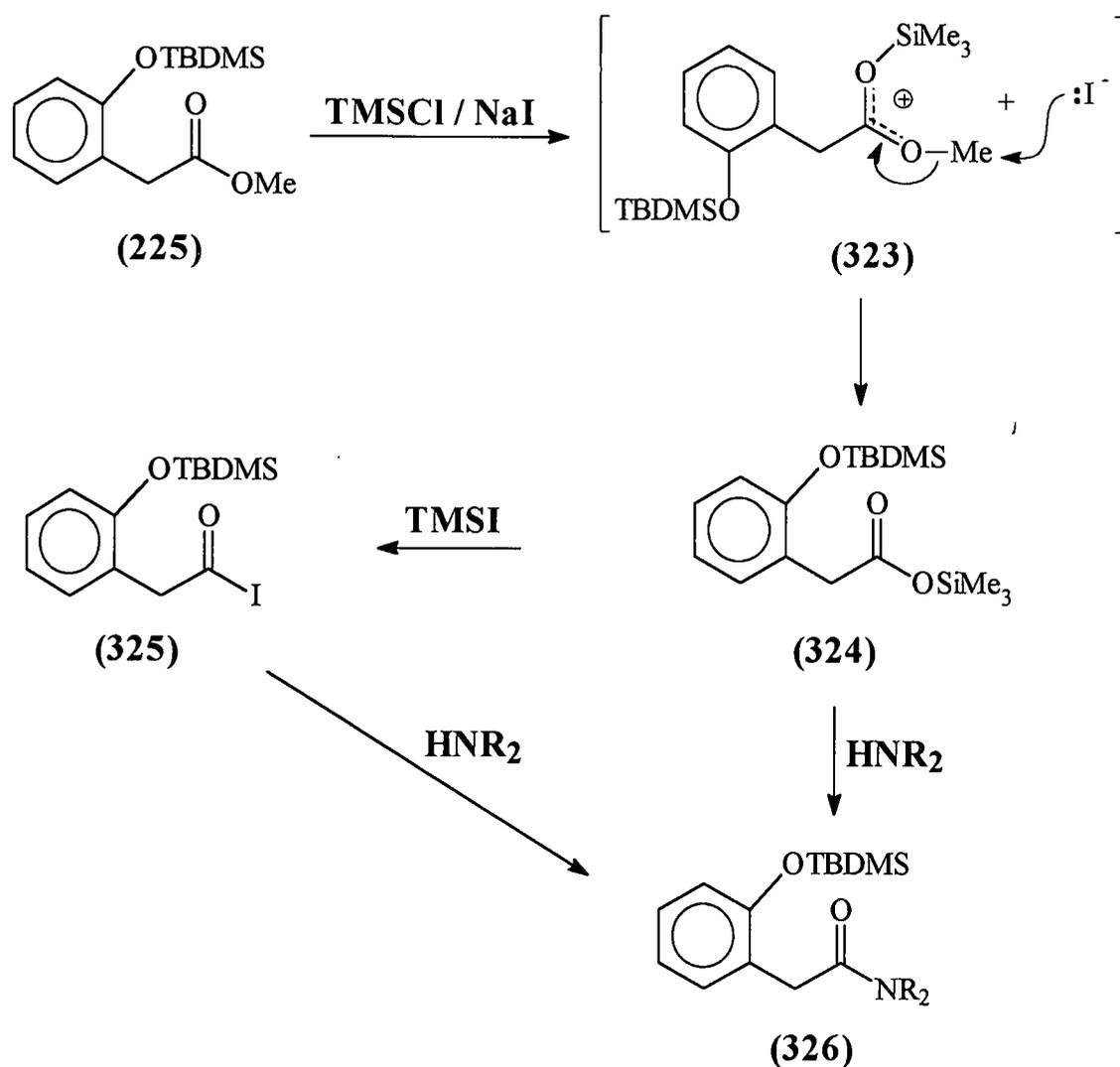
7.3.1 Synthesis of chiral propanoate derivatives

The successful asymmetric induction obtained during aldol condensations employing imidazolidin-2-one **320**,^{90,172} bornane-10,2-sultam **321**^{173,174} and (1*R*,2*S*)-*p*-tol-*N*-norephedrine **322**¹⁷⁵ as chiral ligands (Scheme 51) encouraged us to convert a series of methyl propanoates into these derivatives.



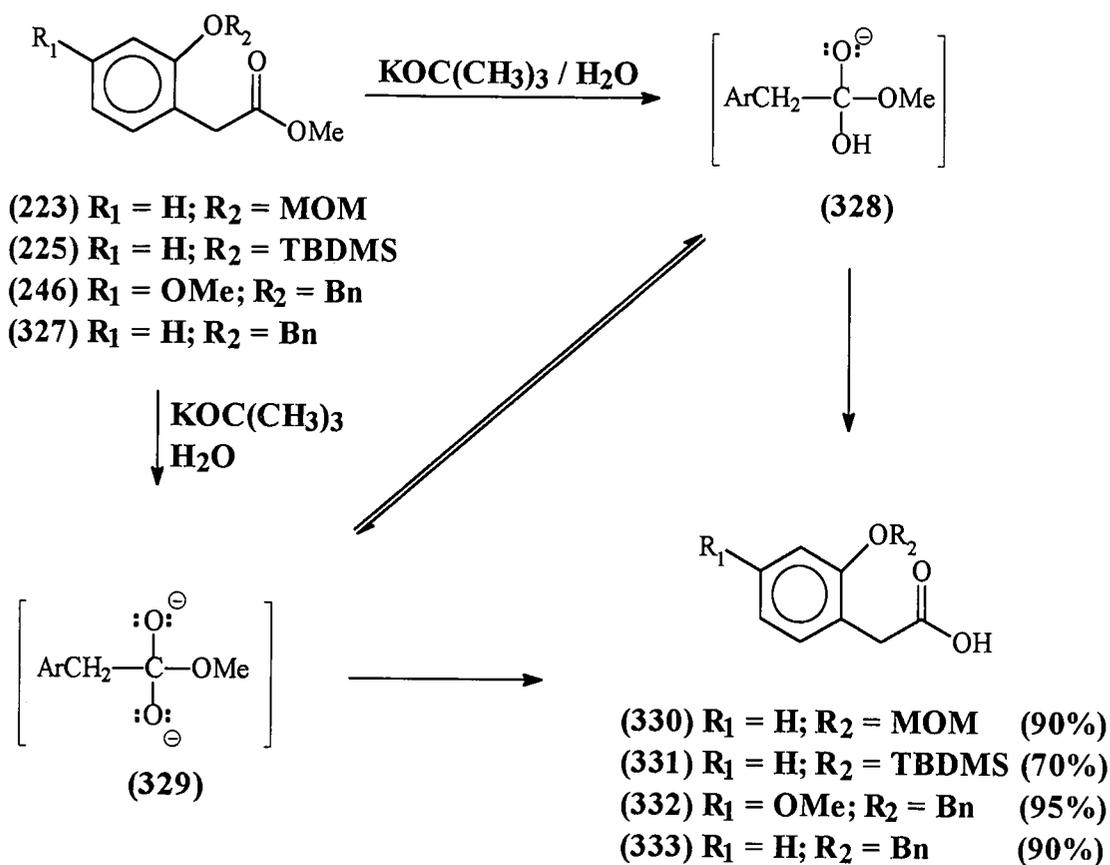
Scheme 51: Chiral ligands employed during enantioselective aldol condensations.

Trimethylsilyl activation of methyl propanoate **225** using trimethylsilyl iodide (TMSI), prepared *in situ* from trimethylsilyl chloride (TMSCl) and sodium iodide was attempted.¹⁷⁶⁻¹⁷⁸ As indicated in Scheme 52 it was anticipated that treatment of **225** with TMSI should produce silyl ester **324** *via* intermediate **323** which could then directly undergo nucleophilic substitution, or first be converted to acyl iodide **325**,¹⁷⁶ before amine substitution, affording product **326**. However, treatment of **225** with TMSCl / NaI only resulted in recovery of the starting material.



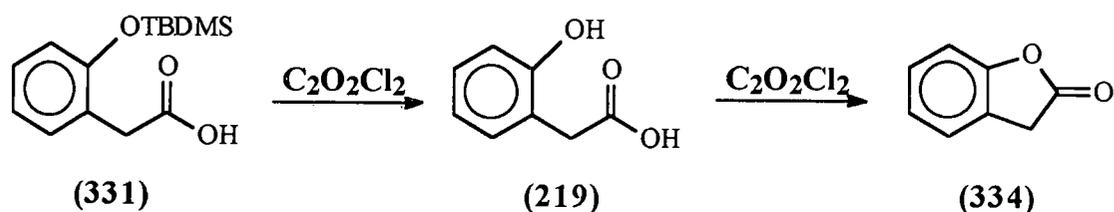
Scheme 52: Direct conversion of propanoate **225** to amide **326**.

Hydrolysis of propanoates **223**, **225**, **246** and **327** to their corresponding acids **330-333** was accomplished employing “anhydrous hydroxide”, generated *via* reaction between 2 equiv. of potassium *tert*-butoxide and 1 equiv. of water (Scheme 53).¹⁷⁹ Although the exact mechanism is uncertain, either monoanion **328** or dianion **329** acts as intermediate, affording the corresponding acids in good yields (70-95%).



Scheme 53: Hydrolysis of methyl propanoates employing “anhydrous hydroxide”.

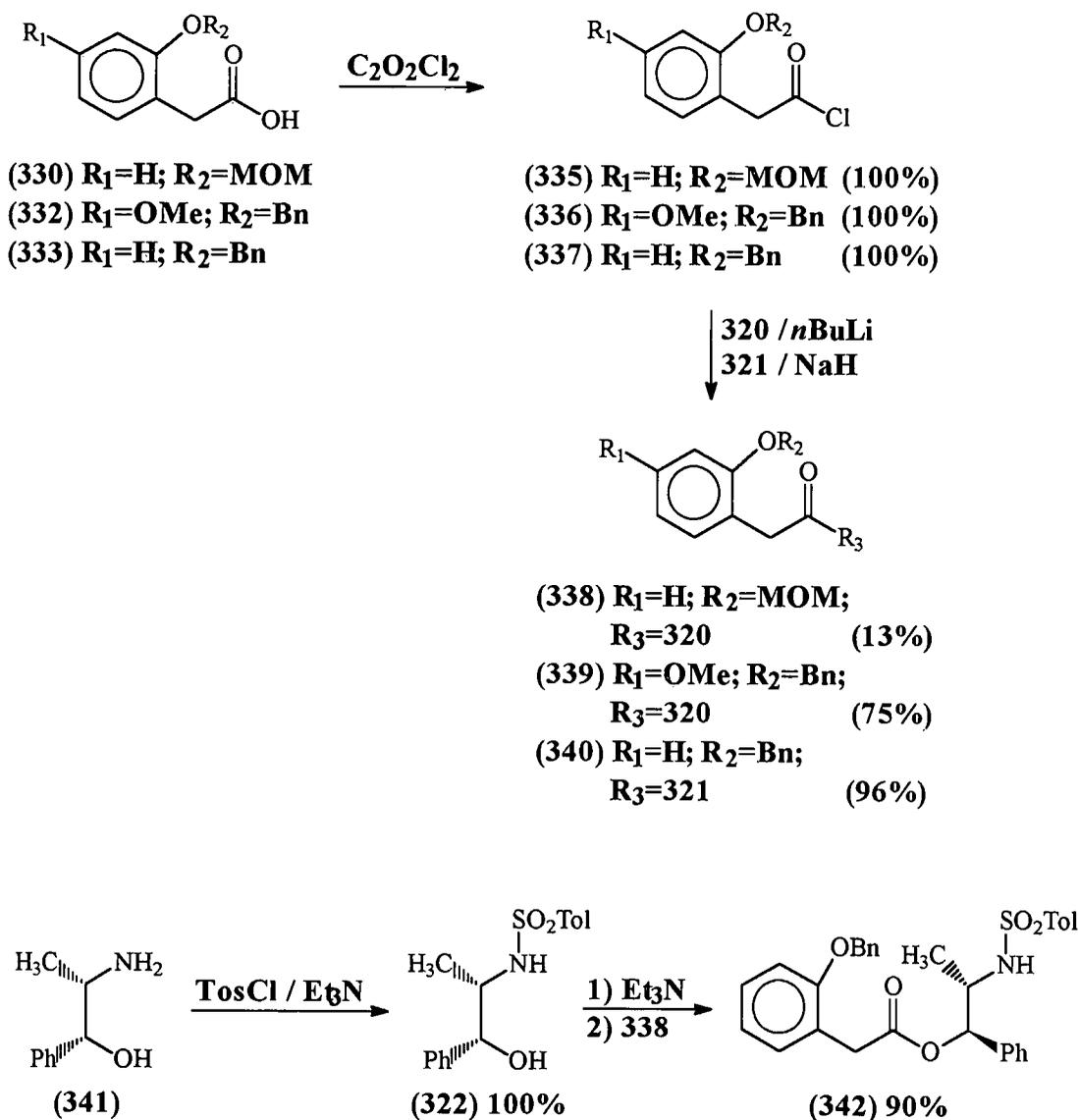
In order to synthesise the chiral derivatives, chlorination (oxalyl chloride) of acids **330-333** resulted in deprotection of the 2-*O*-TBDMS ether **331** to give 2-hydroxyphenylacetic acid **219** which cyclised to the lactone **334** (Scheme 54).



Scheme 54: Chlorination of TBDMS-ether **331** and phenol **219**.

The benzyl- and MOM-ethers **330**, **332** and **333** were converted into their respective acid chlorides **335-337** in quantitative yields. Thus, imidazolidinone and bornane-10,2-sultam

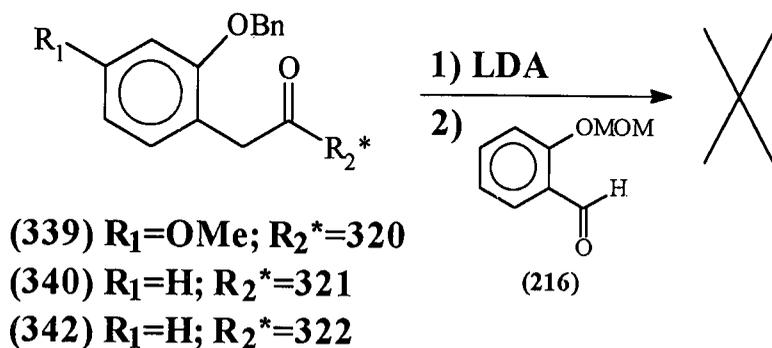
derivatives **338**, **339** and **340** were obtained *via* treatment of the deprotonated auxiliaries **320** and **321** with the respective acids chlorides **335-337**. (1*R*,2*S*)-Norephedrine **341** was converted to its *p*-toluenesulfonyl derivative **322** before deprotonation and treatment with phenylacetyl chloride **336** yielding product **342** as indicated in Scheme 55.



Scheme 55: Synthesis of chiral derivatives **338-340** and **342**.

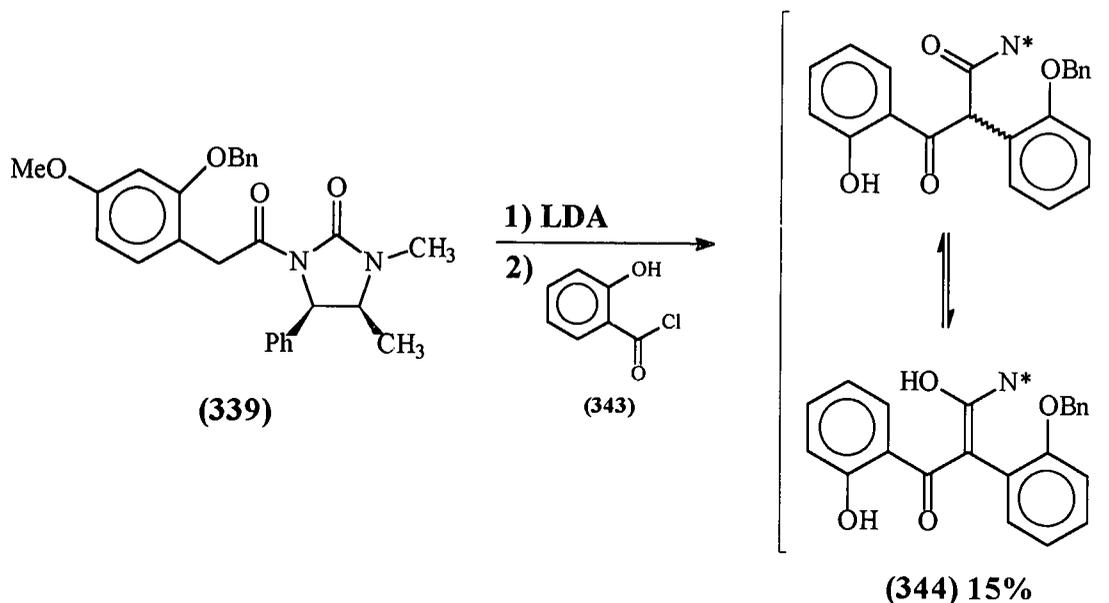
7.3.2 Asymmetric aldol condensation of chiral amides

Aldol condensation between the respective chiral derivatives **339**, **340** and **342** and benzaldehyde **216**, employing LDA as base, in all instances only led to recovery of the starting materials (Scheme 56).



Scheme 56: Attempted enantioselective aldol condensation.

In an attempt to enhance electrophilic activity, the Li-enolate of **339** was condensed with 2-hydroxybenzoyl chloride **343**. This resulted in the formation of **344** (15%), which displayed a dynamic keto-enol equilibrium, thereby destroying any stereoselectivity (Scheme 57).



Scheme 57: Condensation between **339** and benzoyl chloride **343**.

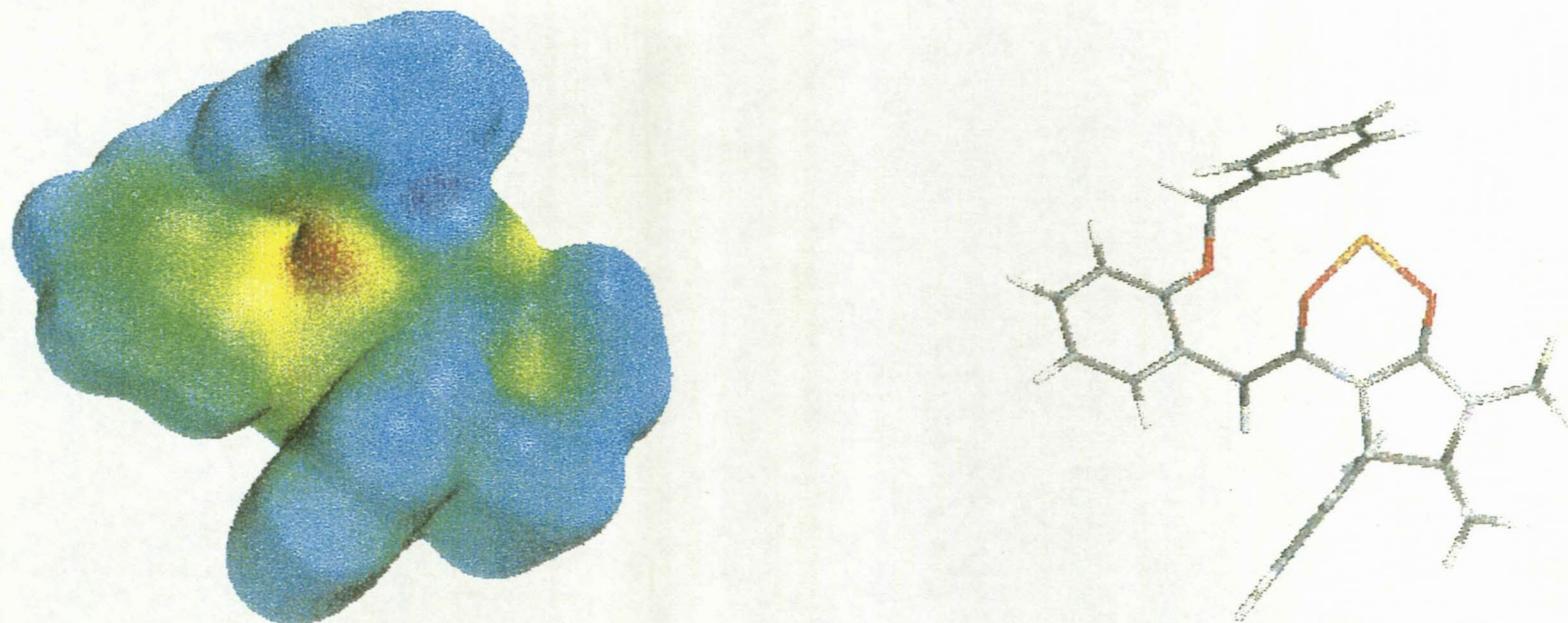


Figure 1: Potential electron density surface as calculated for **345**; *Re*-face indicated.

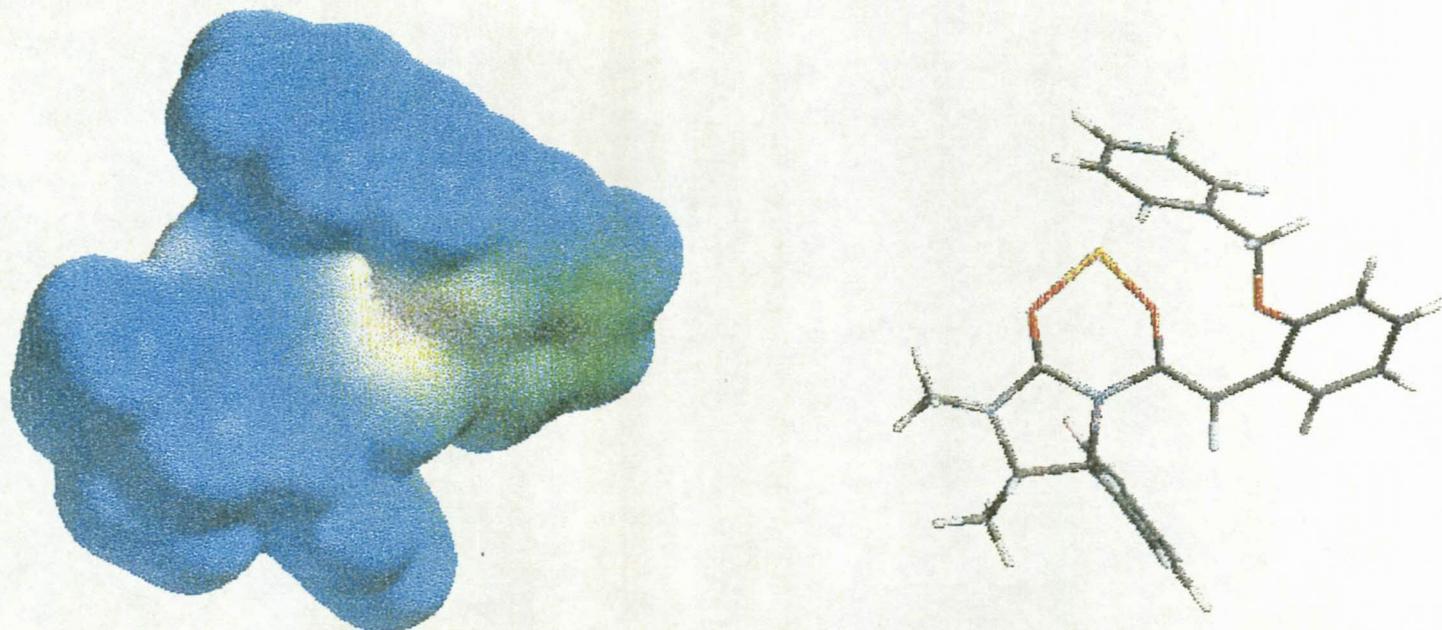
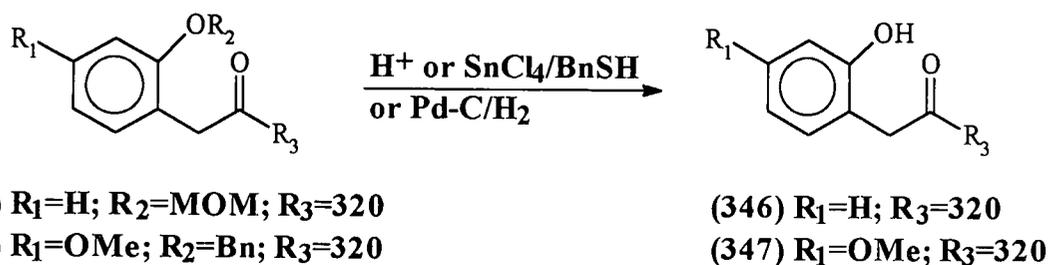


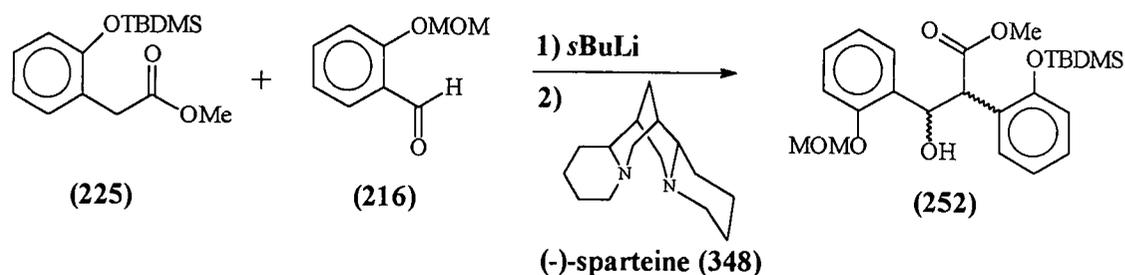
Figure 2: Potential electron density surface as calculated for **345**; *Si*-face indicated.



Scheme 59: Attempted synthesis of phenolic chiral derivatives **346** and **347**.

7.4 Asymmetric aldol condensation employing chiral base complexes

Aldol condensation between phenylacetate **225** and benzaldehyde **216**, promoted by *s*BuLi / sparteine **348** as chiral base complex,¹⁸⁰⁻¹⁸² afforded 2,3-diaryl-3-hydroxypropanoate **252** in good yield (78%). The diastereomeric and enantiomeric excesses were however a disappointing 28% and 0%, respectively (Scheme 60). This indicated that the aldol transition state may be sterically too demanding for effective coordination with the chiral complex.

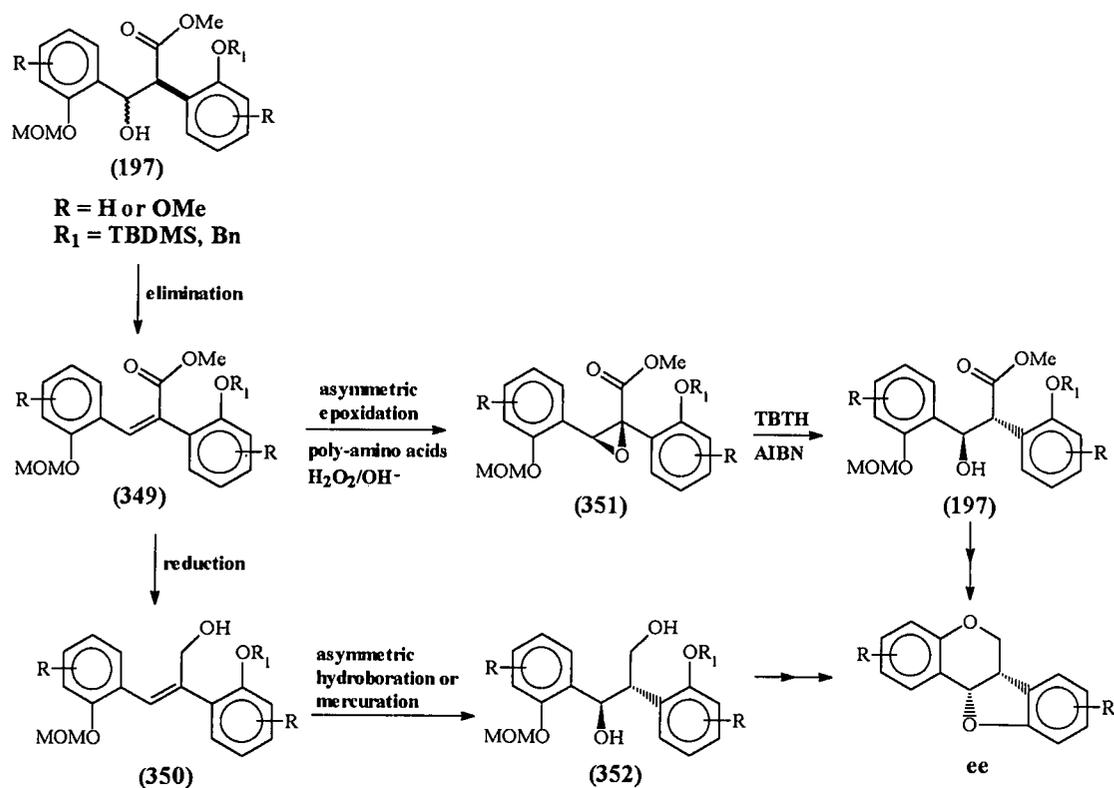


Scheme 60: Aldol condensation employing *s*BuLi / sparteine as chiral base.

Having attempted three possibilities of enantiomeric induction using base catalysed aldol reactions, attention was turned to an alternative for obtaining stereoselectivity.

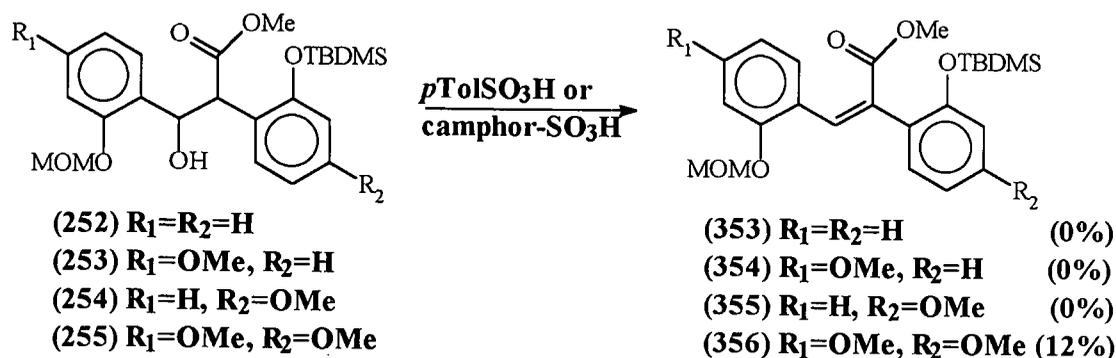
7.5 Asymmetric induction via 2-propenoates

A number of synthetic alternatives, *i.e.* asymmetric epoxidation,¹⁸³ hydroboration¹⁸⁴ and oxymercuration-demercuration reactions,^{185,186} are available for the introduction of an asymmetric hydroxyl group into molecules possessing ethylenic functionalities. Therefore, the synthesis of propenoates **349** *via* elimination of the 3-hydroxy of 2,3-diaryl-3-propanoates **197** was undertaken. The propenoates could then undergo asymmetric epoxidation (poly-amino acids/H₂O₂/OH⁻)^{183,187} followed by reduction (tributyltin hydride/ AIBN)^{188,189} to afford **197** with enantiomeric excess. Alternatively, reduction of **349** would give the allylic alcohols **350** which could then be stereoselectively converted into 1,3-diols **352** *via* asymmetric hydroboration or oxymercuration (Scheme 61).



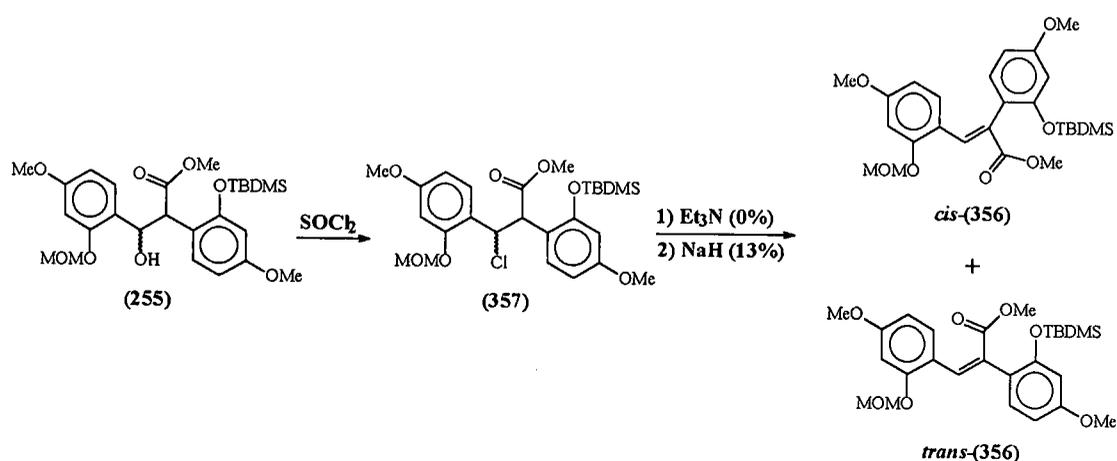
Scheme 61: Synthetic sequences for the stereoselective introduction of 3-OH.

Dehydration of propanoates **252-255** using *p*-toluenesulfonic acid¹⁹⁰ caused extensive starting material decomposition, while the somewhat milder camphorsulfonic acid¹⁹¹ afforded only propenoate **356** in low yield (12%)(Scheme 62).



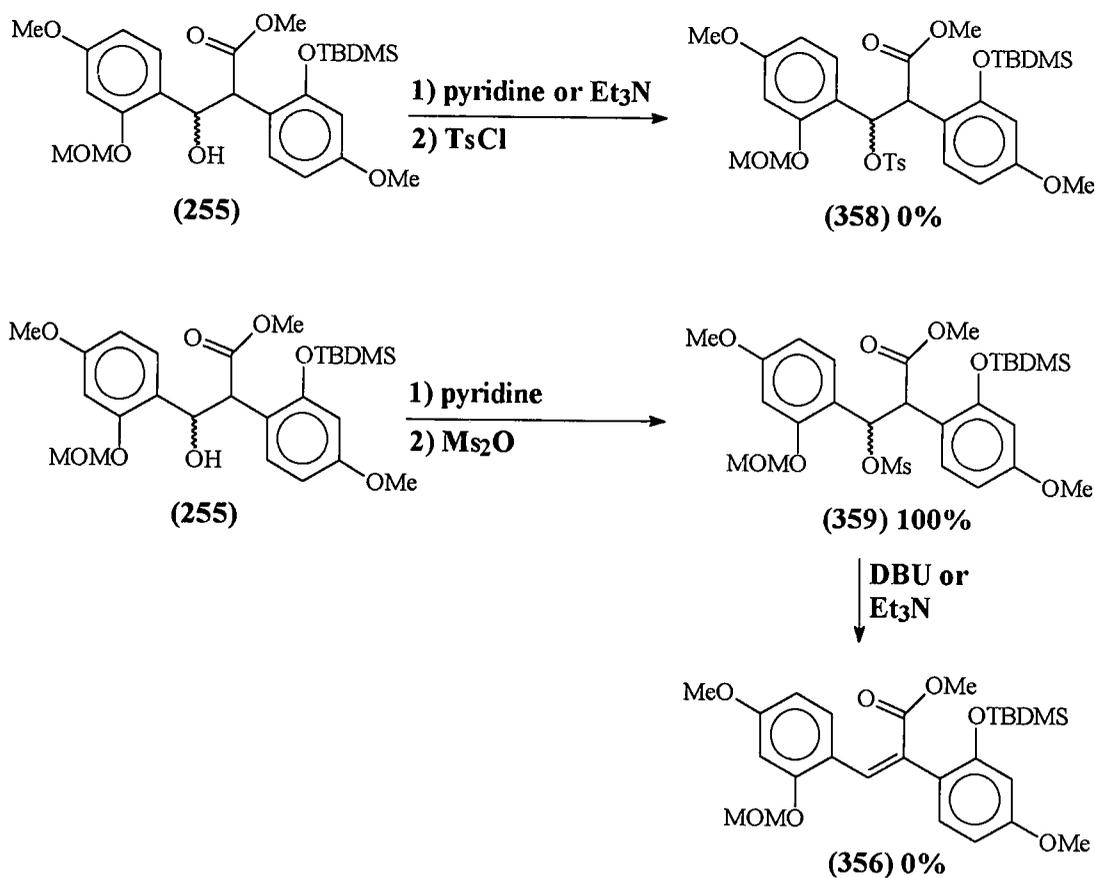
Scheme 62: Acid dehydration of propanoates **252-255**.

These disappointing acid dehydrations prompted us to activate the 3-position either *via* chlorination or as the sulfonate derivatives. Chlorination ($SOCl_2$) of **255** (confirmed by 1H NMR) afforded 3-chloride **357** which was subjected to basic conditions. Elimination using Et_3N proved unsuccessful, while NaH yielded an inseparable mixture of *cis*- and *trans*-**356** in only 13% yield (Scheme 63). Furthermore, this product was unstable and decomposed within 24 hours.



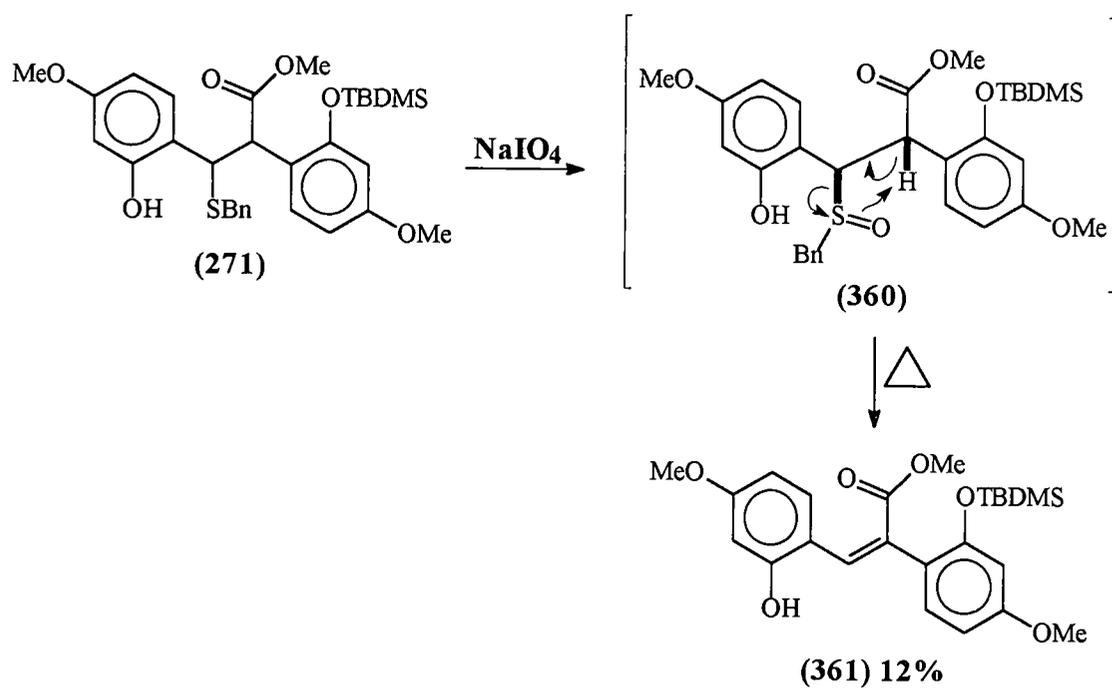
Scheme 63: Formation of propenoate **356** *via* chlorination of **255**.

Activation of the 3-OH of **255** via tosylation (TsCl / pyridine, Et₃N or NaH)¹⁹² to **358** was unsuccessful, as is often found with secondary hydroxy groups. In comparison, mesylation of **255** (Ms₂O, pyridine)¹⁹³ afforded **359** in quantitative yield, but elimination employing either DBU or Et₃N did not yield the required product **356** (Scheme 64).



Scheme 64: Formation of propenoate **356** via tosylation and mesylation of **255**.

The scope of the protocol involving transformation of ketones to enones by sulfenylation followed by sulfoxide elimination is well documented.¹⁹⁴⁻¹⁹⁸ Thus, oxidation of 3-benzylsulfanylpropanoate **271** (NaIO₄),¹⁹⁸ followed by thermal elimination of **360** (CHCl₃, 60°C) yielded propenoate **361** (Scheme 65). Although oxidation proceeded in quantitative yield, thermal elimination afforded **361** in low yield (12%), thereby hampering the applicability of this protocol.



Scheme 65: Oxidative elimination of 271.

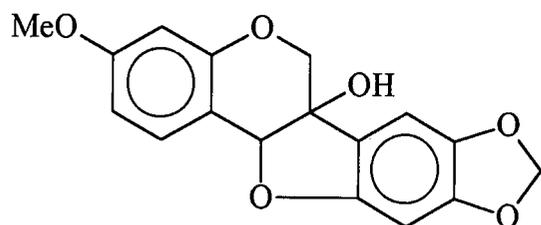
7.6 Conclusion

It is clear that the methods exploited here are unsuitable for the targeted enantioselective aldolisations. Although our attempts to introduce chirality *via*, amongst others, asymmetric epoxidation, hydroboration and oxymercuration failed, numerous alternatives still needs to be investigated. Our envisaged synthetic protocol may thus eventually still be converted into a viable asymmetric synthesis of pterocarpan.

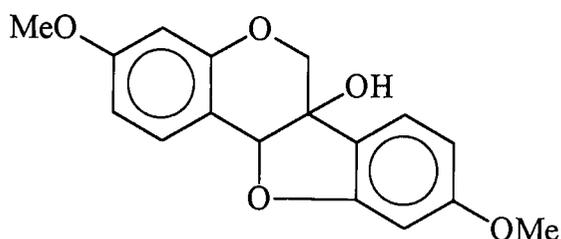
STEREOSELECTIVE SYNTHESIS OF 6a-HYDROXY-PTEROCARPANS

8.1 Introduction

Despite identification of the first 6a-hydroxypterocarpan in 1960,²¹ synthetic protocols to these potent phytoalexins are limited by lengthy multi-step synthetic routes and a lack of diversity as far as substitution patterns is concerned.^{4,8} These confinements are so restrictive that only two 6a-hydroxypterocarpan, *i.e.* pisatin **12** and variabilin **19**, have been synthesised.^{4,70,72}

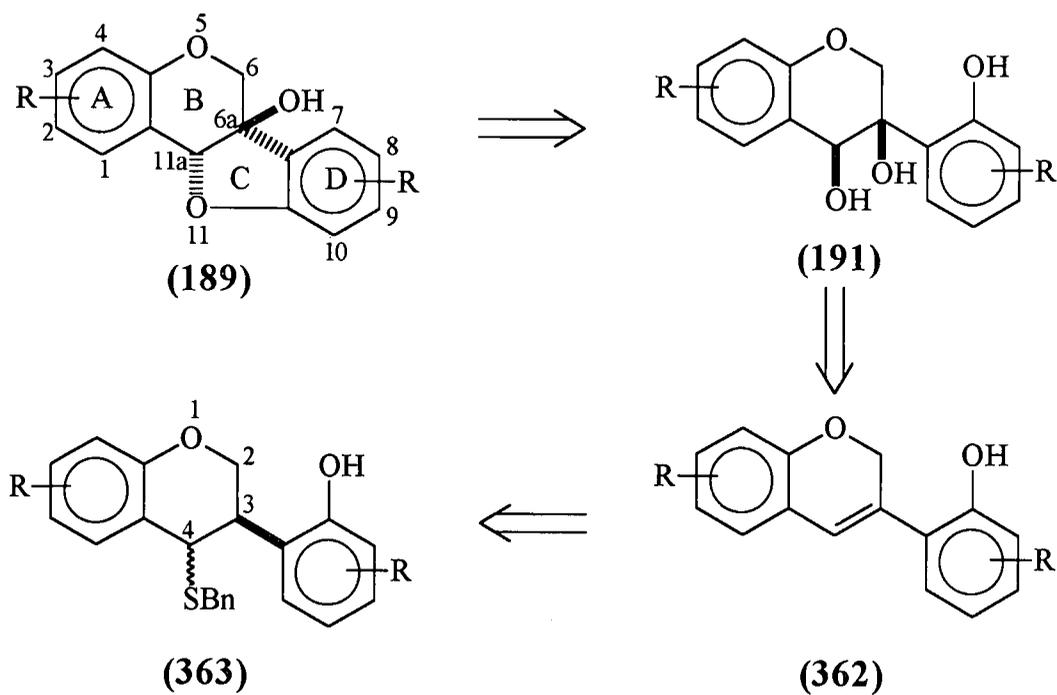


pisatin (12)



variabilin (19)

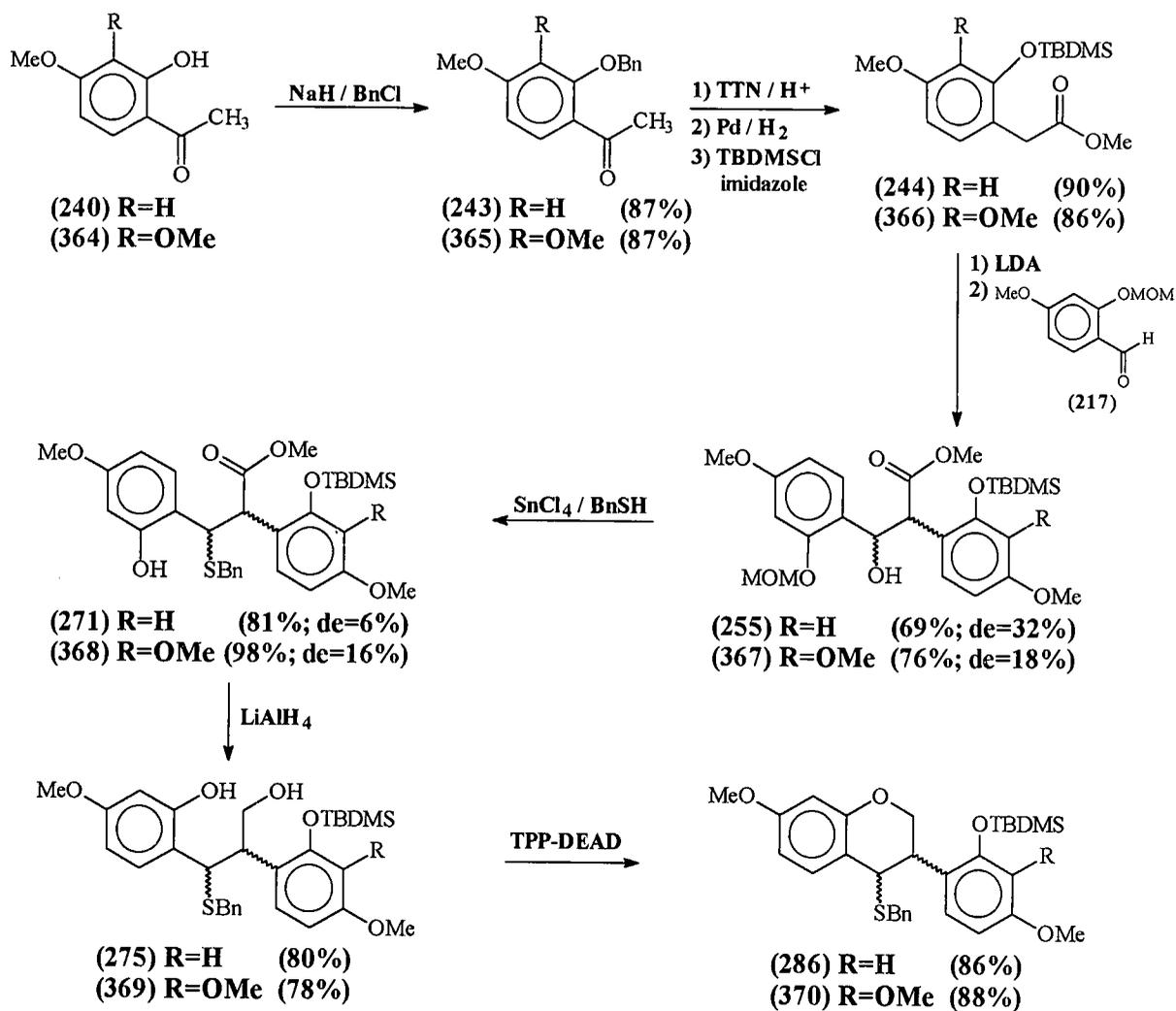
We thus adapted the synthesis of *cis*-pterocarpan (Chapter 5), to permit access to diastereoisomeric pure 6a-hydroxypterocarpan exhibiting a variety of oxygenation patterns. Scheme 66 represents the *retro*-synthetic sequence involving initial elimination of 3-benzylsulfanylisoflavans **363** yielding isoflav-3-enes **362** followed by asymmetric dihydroxylation to diol **191** and subsequent deprotection and cyclisation to afford 6a-hydroxypterocarpan **189**.



Scheme 66: *Retro*-synthesis of 6a-hydroxypterocarpan **189**.

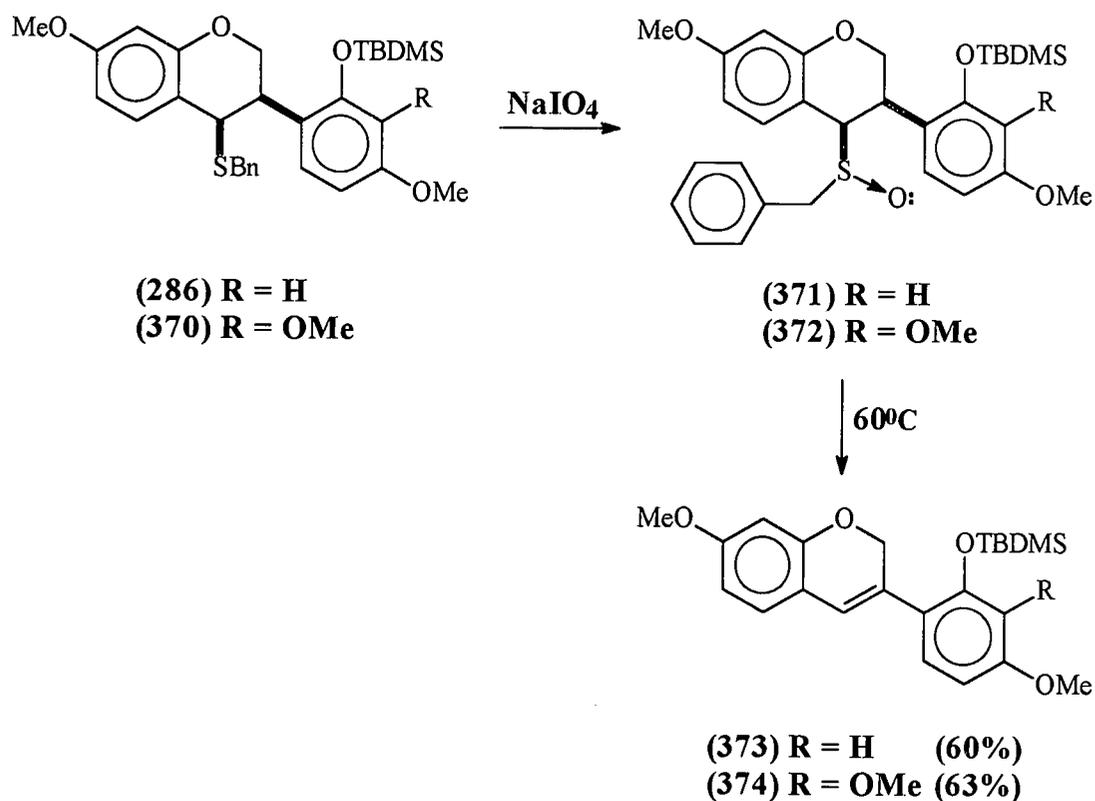
8.2 Synthesis of isoflav-3-enes

3-Benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan **286** and its 3',4',7-trimethoxy analogous **370** were synthesised as discussed in Chapter 5. Aldol condensation (LDA) between phenylacetates **244** and **366**, and benzaldehyde **217**, afforded propanoates **255** and **367** which were deprotected ($\text{SnCl}_4/\text{BnSH}$) to yield **271** and **368**. Subsequent reduction (LiAlH_4) to propanols **275** and **369** and ensuing cyclisation (TPP-DEAD) afforded 4-benzylsulfanylisoflavans **286** and **370** in good overall yields (Scheme 67).



Scheme 67: Synthesis of isoflavans **275** and **370**

Isoflav-3-enes **373** and **374** were obtained *via* oxidation (0.4M NaIO₄) of the *cis*- and *trans*-4-benzylsulfanylisoflavans **286** and **370** followed by thermal elimination of the sulfoxides **371** and **372** (Scheme 68).¹⁹⁴⁻¹⁹⁸

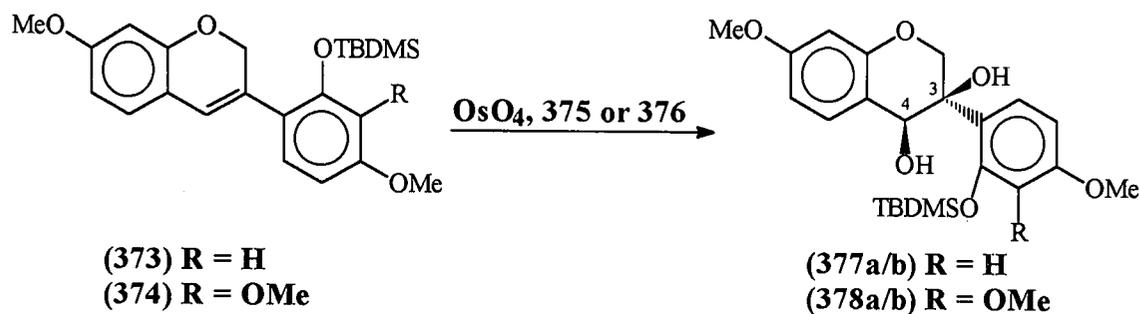
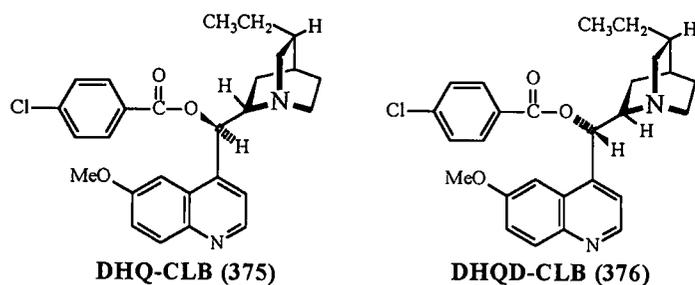


Scheme 68: Oxidative elimination of 4-benzylsulfanylisoflavans **275** and **370**.

8.3 Asymmetric dihydroxylation of isoflav-3-enes **373** and **374**

Owing to the instability of isoflav-3-enes **373** and **374**, swift transformation to the corresponding isoflavan-3,4-diols was essential. The commercially available AD-mix- α or - β ¹¹² was not reactive enough to affect asymmetric dihydroxylation. Therefore, treatment of isoflav-3-enes **373** and **374** with stoichiometric amounts of OsO₄ in the presence of the chiral catalyst dihydroquinine *p*-chlorobenzoate (DHQ-CLB) **375** afforded (-)-(3*R*,4*S*)-*syn*-diols **377a** and **378a** in acceptable yields and excellent enantiomeric excesses. The (+)-(3*S*,4*R*)-*syn*-diols **377b** and **378b** were similarly obtained by using dihydroquinidine *p*-chlorobenzoate (DHQD-CLB) **376** as chiral ligand (Table 20).^{72,199} The optical purity was assessed by ¹H NMR employing Eu(hfc)₃ as chiral shift reagent which consistently indicated the presence of only one enantiomer (plate 33).

The absolute configuration was tentatively assigned according to the Sharpless model^{199,200} for asymmetric dihydroxylation reactions utilising cinchona alkaloids as chiral ligands (Figure 3; Scheme 69).



isoflav-3-ene	ligand	diol	configuration	yield (%)	ee (%)*	$[\alpha]_D$
373	375	377a	3 <i>R</i> ,4 <i>S</i> (configuration shown)	65	>99	-28.7
373	376	377b	3 <i>S</i> ,4 <i>R</i> (enantiomer)	68	>99	+28.6
374	375	378a	3 <i>R</i> ,4 <i>S</i> (configuration shown)	66	>99	-25.8
374	376	378b	3 <i>S</i> ,4 <i>R</i> (enantiomer)	63	>99	+26.0

* determined by ¹H NMR employing Eu(hfc)₃ as chiral shift reagent

Table 20: Yields and ee's for the asymmetric dihydroxylation of **373** and **374**.

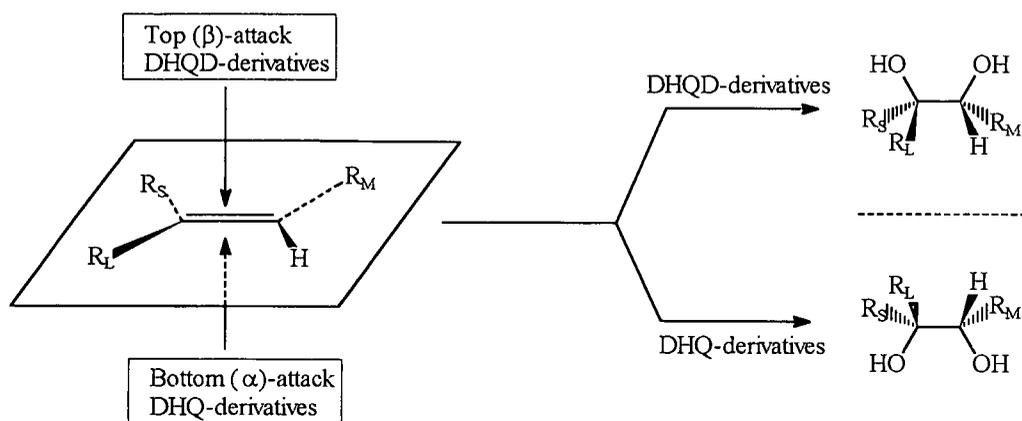
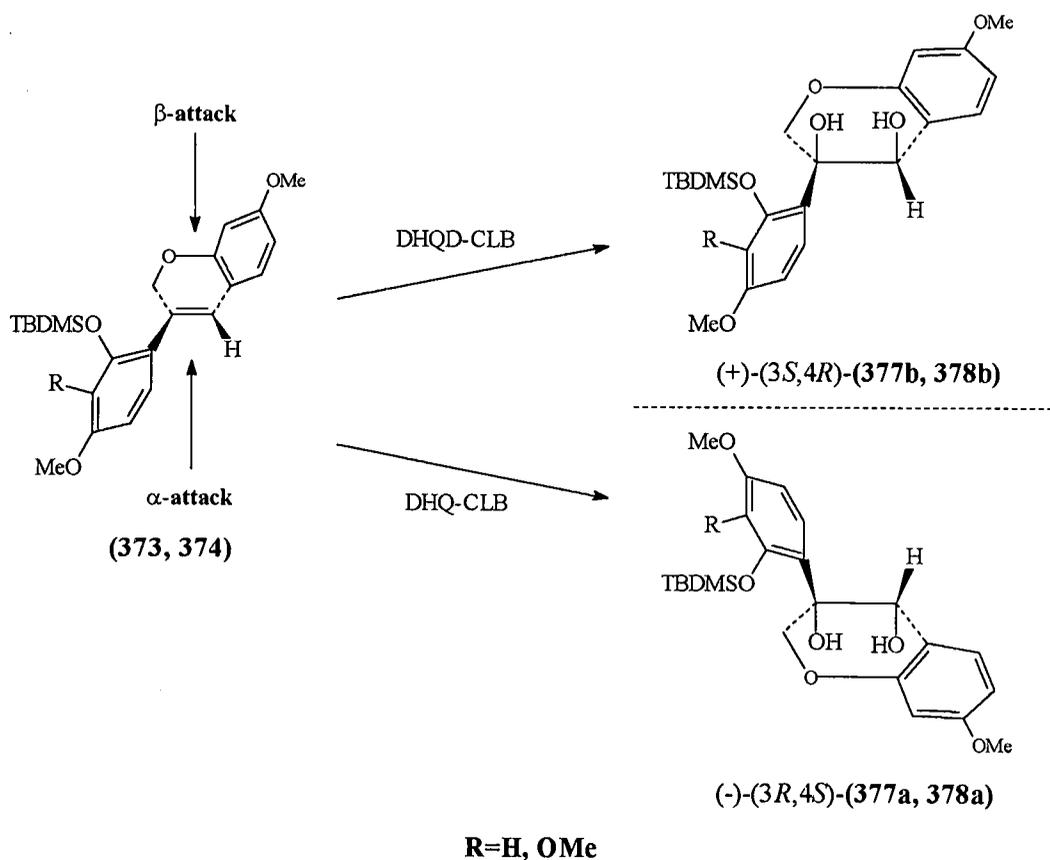


Figure 3: Sharpless model.^{199,200}



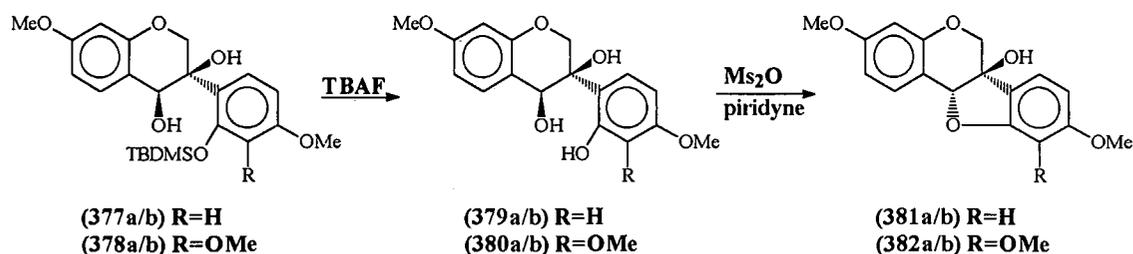
Scheme 69: Asymmetric dihydroxylation of isoflav-3-enes **373** and **374**.

The CD curves of the (-)-(3*R*,4*S*)-diols **377a** and **378a** display positive Cotton effects in the 200-240 nm and negative Cotton effects in the 240-295 nm regions, the signs of these

Cotton effects being reversed for the (+)-(3*S*,4*R*)-diols **377b** and **378b**. Comparison of this data with those of similar derivatives^{71,72} corroborate the absolute stereochemistry as assigned.

8.4 Synthesis of enantiopure 6a-hydroxypterocarpan

Deprotection (TBAF) of diols **377a/b** and **378a/b** afforded 2'-hydroxyisoflavan-3,4-diols **379a/b** and **380a/b** in quantitative yields which could then be converted to the respective 6a-hydroxypterocarpan. Attempted cyclisation employing Mitsunobu reaction conditions was unsuccessful. However, selective mesylation (Ms₂O, pyridine) activated the 4-hydroxy sufficiently to afford the requisite (6a,11a)-*cis*-6a-hydroxypterocarpan **381a/b** and **382a/b** in good yields and essentially optically pure form (Table 21). The (-)-(3*R*,4*S*)-diols **377a** and **378a** afforded the (+)-(6a*R*,11a*R*)-*cis*-products **381a** and **382a** while the (+)-(3*S*,4*R*)-diols **377b** and **378b** gave the (-)-(6a*S*,11a*S*)-*cis*-6a-hydroxypterocarpan **381b** and **382b**, respectively.

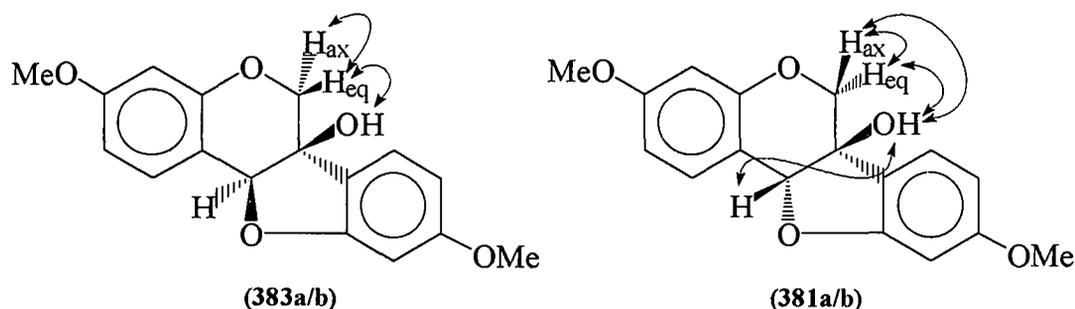


2'-hydroxy	yield (%)	pterocarpan	yield (%)	configuration	ee (%)	[α] _D
379a	100	381a	70	6a <i>R</i> ,11a <i>R</i> (as indicated)	>99	+223.6
379b	100	381b	75	6a <i>S</i> ,11a <i>S</i> (enantiomer)	>99	-220.8
380a	100	382a	75	6a <i>R</i> ,11a <i>R</i> (as indicated)	>99	+185.6
380b	100	382b	73	6a <i>S</i> ,11a <i>S</i> (enantiomer)	>99	-186.2

Table 21: Deprotection and cyclisation of diols **377** and **378**.

It is interesting to note that diols **379a** (3*R*,4*S*) and **379b** (3*S*,4*R*) also afforded (6a*R*,11a*S*)- and (6a*S*,11a*R*)-*trans*-6a-hydroxypterocarpan **383a** and **383b**, respectively, as minor product (9-10%). Apart from MS data, comparison of the NOESY interactions observed for **383** with those of the corresponding *cis*-**381**, clearly indicated the absence of

6a-OH / 11a-H interaction for **383**, thereby confirming a *trans* B/C-ring structure (Scheme 70).



a = configuration shown
b = enantiomer

Scheme 70: Comparison of NOESY interactions for **381a/b** and **383a/b**.

The (6a*R*,11a*R*)-isomers **381a** and **382a** exhibited positive and negative Cotton effects, respectively, in the 235-255 nm (n,π^* transition) and 275-300 nm (π,π^* transition) regions of their CD spectra, these Cotton effects being reversed in the same regions for the (6a*S*,11a*S*)-isomers **381b** and **382b** (Figures 4 and 5).

Owing to limited sample quantities and the unavailability of racemic mixtures, we could not establish the ee's of the synthetic 6a-hydroxypterocarpan *via* ^1H NMR using chiral shift reagents. The absolute stereochemistry of the (+)-(6a*R*,11a*R*)- and (-)-(6a*S*,11a*S*)-*cis*-6a-hydroxypterocarpan **381a** and **b** and **382a** and **b** was derived from the corresponding diols **377a** and **b** and **378a** and **b**, respectively, as determined according to the Sharpless model (Scheme 69), *assuming* that optical integrity was preserved at C-6a during cyclisation. The absolute configuration of (6a*R*,11a*S*)-*trans*-**383a** and (6a*S*,11a*R*)-*trans*-6a-hydroxypterocarpan **383b** was derived in a similar manner. However, final confirmation of the absolute stereochemistry and enantiomeric excess of (6a*R*,11a*R*)-**381a** was obtained by comparison of the CD and optical rotation data with those of authentic (+)-variabilin ($[\alpha]_{\text{D}} + 211^\circ$ [c 0.90, MeOH] vs $[\alpha]_{\text{D}} + 224^\circ$ [c 0.72, CHCl₃] for **381a**).^{10,18,65} The mirror-image relationship of the two sets of isomers (Figures 4 and

5), confirmed their enantiomeric connection and hence served as proof of the (6a*S*,11a*S*) absolute configurations of analogous **381b** and **382b**. This data should contribute towards the establishment of correlation between optical rotation and CD data with absolute stereochemistry of 6a-hydroxypterocarpan.

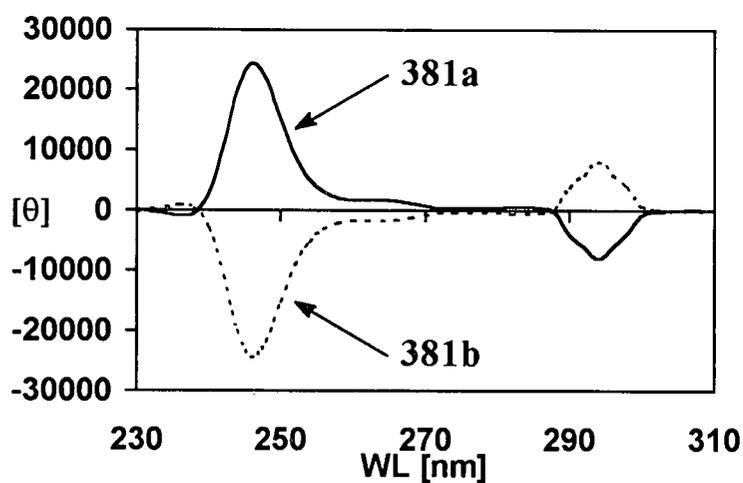


Figure 4: CD curves of (6a*R*,11a*R*)-*cis* **381a** and (6a*S*,11a*S*)-*cis*-6a-hydroxypterocarpan **381b**.

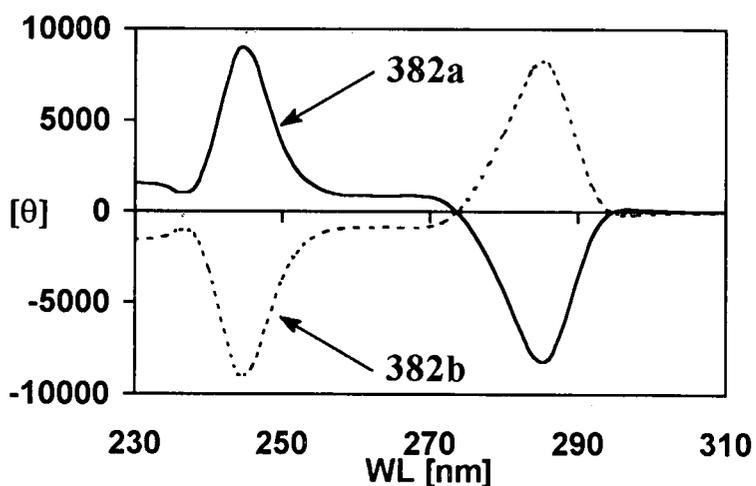


Figure 5: CD curves of (6a*R*,11a*R*)-*cis* **382a** and (6a*S*,11a*S*)-*cis*-6a-hydroxypterocarpan **382b**.

8.5 Conclusion

We have thus succeeded in modifying the protocol developed for the synthesis of racemic *cis*-pterocarpan to permit the stereoselective synthesis of 6a-hydroxypterocarpan in moderate yields and essentially enantiopure form. Our methodology, although broadly similar to that reported by Pinard *et al.*⁷² for the synthesis of (+)-pisatin, extends access to 6a-hydroxypterocarpan exhibiting diverse oxygenation patterns and improved overall yields. It should hence contribute significantly to advancing the chemistry of this important group of phytoalexins.

EXPERIMENTAL

CHAPTER 9

STANDARD EXPERIMENTAL PROCEDURES

Unless mentioned otherwise the following experimental procedures were applied throughout the course of this study.

9.1 CHROMATOGRAPHY

9.1.1 Thin layer chromatography

Qualitative thin layer chromatography (TLC) was performed on "Merck TLC-plastic sheets : silica Gel F₂₅₄" (0.25 mm layer) divided into strips of *ca.* 3x5 cm. All R_F-values were obtained from these plates.

Prepared thin layer chromatography (PLC) was performed on glass plates (20 x 20 cm) coated with a layer (1.25 or 0.5 mm) of unactivated kieselgel (Merck PF₂₅₄) and dried overnight at room temperature. After development in a suitable eluent the plates were dried in an air current at room temperature. The different bands were distinguished using UV-light (254 nm), scraped from the glass and the silica washed with acetone. After evaporation of the acetone under reduced pressure the products were obtained. The plates were loaded with 10-30 mg/plate of crude product, depending on the nature of each separation, while small scale separations were performed on Merck TLC plates : Silica gel F₂₅₄ pre-coated (0.25 mm) with loading of 3-5 mg crude mixture per plate.

9.1.2 Flash column chromatography (FCC)

Using 100g of unactivated Merck Kieselgel 60 (230-400 mesh) for every 1g of crude product, a glass column (10-50 mm diameter) was charged with a slurry of Kieselgel in the minimum volume of the appropriate eluent. The column was compacted under N₂-pressure (*ca.* 50 kPa) using 500-1000 ml of eluent. The crude product was dissolved in a minimum volume of eluent and applied to the column. Using N₂-pressure, the pure product could be obtained with the chosen eluent and collected by hand in fractions of 10-20 ml.

9.2 SPRAY REAGENTS

9.2.1 Sulfuric acid-formaldehyde

Thin layer chromatograms were lightly sprayed with a 2% (v/v) solution of formaldehyde (40% solution in H₂O) in concentrated H₂SO₄ and then gently heated to *ca.* 120°C for optimum colour development.

9.2.2 Palladium chloride-hydrochloric acid (for divalent sulfur)

A 0.02M PdCl₂ solution in 6% HCl was used to spray the TLC plates. Heating to 120°C resulted in a unique bright yellow spot for compounds containing divalent sulfur.

9.3 ABBREVIATIONS

The following abbreviations for solvents were used throughout the experimental section :

A	=	acetone
B	=	benzene
H	=	hexane
Et ₂ O	=	diethylether
EtOAc	=	ethyl acetate

THF	=	tetrahydrofurane
DCM	=	dichloromethane
DMF	=	<i>N,N</i> -dimethylformamide
MeOH	=	methanol

9.4 ANHYDROUS SOLVENTS AND REAGENTS

Acetone was left to stand over dry K_2CO_3 (oven-dried, 24 hours, 200°C) for 24 hours. After filtration, the solvent was refluxed over 3Å molecular sieves, distilled, collected and stored under nitrogen.

Benzene, diethylether, hexane and THF were refluxed over sodium wire under a nitrogen atmosphere. Benzophenone as indicator produces a purple to dark blue colour when the solvents were free of water. All solvents were freshly distilled before use.

Acetonitrile, dichloromethane and DMF were separately refluxed over CaH_2 (12-24 hours) under a nitrogen atmosphere and freshly collected before use.

Diisopropylethylamine and diisopropylamine were separately refluxed over sodium for 24 hours under a nitrogen atmosphere and collected before use.

TMSCl was distilled over CaH_2 and tributylamine under a nitrogen atmosphere before use.

9.5 SPECTROMETRIC AND SPECTROSCOPIC METHODS

9.5.1 Nuclear magnetic resonance spectrometry (NMR)

NMR-spectrometry was performed on a Bruker AM-300 FT-spectrometer. Chemical shifts are presented in parts per million (ppm) on the δ -scale, while coupling constants (J) are reported in Hz. Unless otherwise mentioned, all spectra were taken in $CDCl_3$ at 297K

using the solvent as an internal standard. Where applicable, NOESY and COSY experiments were performed to confirm assignment of peaks or relative stereochemistry.

The following abbreviations were used throughout:

s = singlet	b = broadened
d = doublet	<i>eq</i> = equatorial
t = triplet	<i>ax</i> = axial
m = multiplet	i = impurities
q = quartet	

Combinations of the abbreviations display a combination of the appropriate multiplicities.

9.5.2 Fast atom bombardment (FAB) mass spectrometry (MS)

All FAB mass spectra were recorded on a VG70-70E double-focusing mass spectrometer using a VG11-250J data system and iontech saddlefield FAB gun.

9.5.3 Infrared spectrometry (IR)

Infrared spectra were obtained using a Hitachi infrared model 270-50 spectrophotometer with chloroform as solvent.

9.5.4 Circular dichroism (CD) and optical rotation

CD spectra were obtained using a Jasco J-710 spectropolarimeter for solutions in spectrophotometric grade methanol (~ 1mg/10ml). Optical rotations were measured with a Jasco Dip-370 digital polarimeter for solutions in CHCl₃ and recorded as 10⁻¹ deg.cm².g⁻¹.

9.5.5 Enantiomeric excess (ee)

The ee's of stereogenically enriched isoflavan-3,4-diols were determined in CDCl₃, utilising tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III) [Eu(hfc)₃] as chiral shift reagent.

9.6 MELTING POINTS

Melting points were obtained using a Reichert Thermopan microscope with a Koffler hot-stage, and are reported as the uncorrected values in °C.

9.7 COMPUTATIONAL METHODS

Calculations were performed employing PC Spartan Pro 1.0.3²⁰¹ on a Pentium II 333 MHz processor. Conformer distribution calculations were performed *via* Molecular Mechanics incorporating the Molecular Mechanics Force Field (MMFF94).²⁰² The most stable conformer was further subjected to semi empirical geometry optimisation using the PM3 model.²⁰³

9.8 CHEMICAL METHODS

9.8.1 Standardization of *n*-butyllithium

A solution of *n*BuLi in hexane was added *via* a syringe under N₂ to a stirred solution of 2,2'-bipyridine (*ca.* 1mg) in anhydrous Et₂O (*ca.* 1ml) until persistence of a dark red colour. *s*BuOH was added drop wise from a microsyringe until the first permanent colour change (dark red → yellow) was observed. *n*BuLi (exactly 100 μl) was then added and the mixture subsequently titrated with *s*BuOH. This was repeated until consistent titration values were obtained (reaction stoichiometry: 1 mol *s*BuOH for 1 mol *n*BuLi).

9.8.2 Protection of R-OH and carboxylic acids

9.8.2.1 Acetylation²⁰⁴

The alcohol was dissolved in a minimum volume of pyridine, *ca.* twice the volume of acetic anhydride added, the reaction vessel sealed and the mixture left standing at *ca.* 30-40°C for 24 to 48 hours. The reaction was quenched by addition of ice and the excess of pyridine was washed out with cold water. The products were azeotropically dried with benzene/MeOH and separated by PLC.

9.8.2.2 Methoxymethylation

To a suspension of NaH (1.5→2 equiv.) in anhydrous THF at 0°C, the phenolic substrate (1 equiv.) was slowly added. After 5 minutes, freshly distilled chloromethyl methyl ether (1.1 equiv.) was added. The reaction was followed on TLC until all starting material was consumed. Crushed ice was added slowly to the mixture and the aqueous phase extracted with EtOAc (3x50ml), the combined organic layers were washed with brine (2x100ml) and dried over Na₂SO₄. Filtration and evaporation of the EtOAc followed by separation (FCC or PLC) yielded the products.

9.8.2.3 Methylation

Methylations were performed with an excess of diazomethane prepared by the reaction of *N*-methyl-*N*-nitroso-*p*-toluene sulphonamide (15g) with potassium hydroxide [(5 g) in a 95% (v/v) ethanol solution] in Et₂O and distilled directly into a previously prepared flask cooled to -10°C. The dry phenolic or phenylacetic acid substrates (*ca.* 200 mg per 15 g sulphonamide) was dissolved in the minimum volume of methanol, cooled to 0°C and treated with diazomethane. After about 0.5 to 48 hours at -15°C the excess diazomethane and solvent were evaporated at room temperature in a rapid air current. Purification *via* PLC followed by crystallisation from ethanol afforded the products.

9.8.2.4 Isopropylation

To a suspension of NaH (1.2 equiv.) in anhydrous DMF at 0°C, the phenolic material (1 equiv.) was added in small portions over 20 minutes. After 5 minutes isopropylbromide (2 equiv.) was added dropwise, the reaction allowed to warm to room temperature and stirred overnight. The excess NaH was destroyed with ice and the mixture extracted with EtOAc (3x50ml), the combined EtOAc extracts were washed with water (3x50ml), dried (Na₂SO₄), evaporated and separated by PLC.

9.8.2.5 Benzylation

To a suspension of NaH (2 equiv.) in anhydrous DMF at 0°C, the phenolic material (1 equiv.) was added in small portions over 20 minutes. After 5 minutes benzylchloride (4 equiv.) was added drop wise. The reaction was stirred at 25°C for 3 hours and the excess NaH destroyed with ice. The mixture was extracted with EtOAc (3 x 50ml), the combined EtOAc extracts washed with water (3x50ml), dried (Na₂SO₄), evaporated and separated by FCC.

9.8.2.6 TBDMS-ethers

Solutions of the 2-hydroxyphenylacetates (1 equiv.) in anhydrous DMF were treated with imidazole (2.5 equiv.) and TBDMSCl (1.2 equiv.) and stirred at 25°C for 16 h. Et₂O was added and the mixture washed with water, brine and again with water, dried (Na₂SO₄), evaporated and separated by PLC.

9.8.3 **Hydrogenation of benzylethers**

A solution of 2-*O*-benzylphenylacetate (1 equiv.) in acetone was treated with 10% Pd/C (20% m/m) / H₂ at ambient temperature until all the starting material had been consumed (TLC). The catalyst was filtered off and the acetone evaporated at reduced pressure and the product purified by PLC.

9.8.4 Oxidative rearrangement (TTN)

Acetophenone (1 equiv.) was dissolved in MeOH and added dropwise to a solution of TTN (1 equiv.) and 60% perchloric acid in MeOH. After stirring at rt. for 5 to 16 hours the MeOH was decanted, water added and the mixture extracted with CHCl_3 . The combined chloroform extract was washed with water, dried (Na_2SO_4), evaporated and separated by PLC.

9.8.5 Aldol condensation between phenylacetates and benzaldehydes

Diisopropylamine (1.1 equiv.) in anhydrous Et_2O at 0°C was treated with *n*BuLi (1.1 equiv.). The propanoate (1.0 mmol) was dissolved in the minimum volume of Et_2O and transferred to the lithium diisopropylamine (LDA) mixture at -78°C . After stirring for 30 min the aldehyde (1.0 equiv.), dissolved in the minimum volume of Et_2O , was added. The mixture was stirred at -78°C for 1 h and then heated to 0°C . After a further 2 h, a phosphate buffer (pH = 7) was added and the mixture extracted with EtOAc. The combined EtOAc layer was washed with water, dried (Na_2SO_4), evaporated, separated by PLC and crystallised from ethanol.

9.8.6 BnSH/ SnCl_4 cleavage of the 2'-MOM derivatives

The 2'-*O*-methoxymethyl substrate (1 equiv.), in anhydrous DCM at -15°C , was treated with BnSH (4 equiv.) followed by SnCl_4 (1.2 equiv.). The reaction was stirred under N_2 at -15°C for 15 min and then at 5°C for a further 15 min. Water was added and the mixture extracted with EtOAc. The combined EtOAc layer was washed with water, dried (Na_2SO_4), evaporated and separated (PLC) and crystallised from ethanol.

9.8.7 LiAlH_4 reduction of propanoates

Propanoate (1 equiv.), dissolved in anhydrous Et_2O at 10°C , was treated with LiAlH_4 (10-15 equiv.) for 10 min. The excess LiAlH_4 was destroyed by the addition of moist Et_2O

followed by *aq.* NH_4Cl . The mixture was extracted with EtOAc and the combined organic layer washed with saturated NaHCO_3 and water, dried (Na_2SO_4), evaporated and separated by PLC.

9.8.8 Mitsunobu cyclisation

The alcohol substrate (1 equiv.) was dissolved in anhydrous THF and treated with a solution of TPP-DEAD complex [TPP (10 equiv.) and DEAD (5 equiv.) in dry THF] at 25°C for 4 hours. After evaporation of the THF the crude product was separated by PLC and crystallised from ethanol.

CHAPTER 10

SYNTHESIS OF RACEMIC *CIS*-PTEROCARPANS

10.1 SYNTHESIS OF 2-*O*-METHOXYMETHYLBENZALDEHYDES (216 and 217)

10.1.1 2-*O*-Methoxymethylbenzaldehyde (216)

Method : see paragraph 9.8.2.2

Reagents : 2-hydroxybenzaldehyde **214** (2.494g, 20.41 mmol.), 80% NaH (1.225 g, 40.84 mmol, 2 equiv.), THF (50 ml), chlorodimethylether (1.64 g, 20.41 mmol, 1 equiv.)

Reaction time: 30 minutes

Yield : 3.059 g, 90% (orange oil)

R_f : 0.66 (B:A 9:1)

IR : ν_{\max} 1675 (CO), 1220, 1210, 1020 and 900 cm⁻¹

¹H NMR (CDCl₃): δ 3.55 (OCH₂OCH₃, s, 3H), 5.33 (OCH₂OCH₃, s, 2H), 7.11 (5-H, ddd, J = 1.0, 7.0, 8.5 Hz, 1H), 7.24 (3-H, dd, J = 1.0, 8.5 Hz, 1H), 7.56 (4-H, ddd, J = 1.9, 7.0, 8.5 Hz, 1H), 7.87 (6-H, dd, J = 1.9, 7.5 Hz, 1H), 10.53 (CHO, s, 1H).

10.1.2 2-*O*-Methoxymethyl-4-methoxybenzaldehyde (217)

Method : see paragraph 9.8.2.2

Reagents : 2-hydroxy-4-methoxybenzaldehyde **215** (1 g, 6.57 mmol.), 80% NaH (295 mg, 9.85 mmol, 1.5 equiv.), THF (20 ml), chlorodimethylether (582 mg, 7.23 mmol, 1.1 equiv.)

Reaction time: 15 minutes

Yield : 1.217 g, 94% (yellow oil)

R_f : 0.60 (B:A 9:1)

IR : ν_{\max} 1675 (CO), 1225, 1215, 1005 and 935 cm⁻¹

MS : m/z 197 (M+H⁺, 6%), 152 (61); Found : (M+H⁺), 197.0814 C₁₀H₁₃O₄ requires (M+H⁺), 197.0814

¹H NMR (CDCl₃, plate 1): δ 3.55 (OCH₂OCH₃, s, 3H), 3.89 (OCH₃, s, 3H), 5.30 (OCH₂OCH₃, s, 2H), 6.63 (5-H, dd, J = 2.2, 8.9 Hz, 1H), 6.73 (3-H, d, J = 2.2 Hz, 1H), 7.84 (6-H, d, J = 8.9 Hz, 1H), 10.35 (CHO, s, 1H).

10.1.3 2-*O*-Isopropyl-4-methoxybenzaldehyde (227)

Method : see paragraph 9.8.2.4

Reagents : 2-hydroxy-4-methoxybenzaldehyde **215** (4.099 g, 26.94 mmol.), 80% NaH (970 mg, 32.33 mmol, 1.2 equiv.), DMF (50 ml), isopropylbromide (6.627 g, 53.88 mmol, 2 equiv.)

Reaction time: 16 hours

Yield : 1.068 g, 20% (orange oil)

R_f : 0.70 (B:A 9:1)

IR : ν_{\max} 1670 (CO), 1215, 1025 and 920 cm⁻¹

¹H NMR (CDCl₃): δ 1.41 (CH(CH₃)₂, d, J = 6.0 Hz, 6H), 3.87 (OCH₃, s, 3H), 4.65 (CH(CH₃)₂, m, J = 6.0 Hz, 1H), 6.46 (3-H, d, J = 2.1 Hz, 1H), 6.54 (5-H, dd, J = 2.1, 8.9 Hz, 1H), 7.84 (6-H, d, J = 8.9 Hz, 1H), 10.34 (CHO, s, 1H).

10.2 SYNTHESIS OF METHYL PHENYLACETATES (220-225)

10.2.1 Methylation

10.2.1.1 Methyl phenylacetate (220)

Method : see paragraph 9.8.2.3

Reagents : phenylacetic acid **218** (2.00g, 15.00 mmol)

Reaction time: 30 min. at 0°C

Yield : 2.206 g, 100% (light yellow oil)

R_f : 0.72 (B:A 9:1)

IR : ν_{\max} 1730 (CO), 1498, 1462, 1342 and 1254 cm⁻¹

¹H NMR (CDCl₃): δ 3.51 (ArCH₂, s, 2H), 3.57 (OCH₃, s, 3H), 7.11-7.25 (ArH, m, 5H).

10.2.1.2 Methyl 2-methoxyphenylacetate (221)

Method : see paragraph 9.8.2.3

Reagents : 2-hydroxyphenylacetic acid **219** (966 mg, 6.35 mmol.).

Reaction time: 48 hours at 0°C

Yield : 1.030 g, 90% (yellow oil), (lit.,²⁰⁵ oil)

R_f : 0.69 (B:A 9:1)

IR : ν_{\max} 1738 (CO), 1254, 1236, 1194 and 934 cm⁻¹

¹H NMR (CDCl₃): δ 3.66 (ArCH₂, s, 2H), 3.71, 3.84 (2xOCH₃, 2xs, 2x3H), 6.90 (3-H, dd, J = 1.0, 8.0 Hz, 1H), 6.95 (5-H, ddd, J = 1.0, 7.5, 7.5 Hz, 1H), 7.20 (6-H, dd, J = 2.0, 8.0 Hz, 1H), 7.28 (4-H, ddd, J = 2.0, 7.5, 8.0 Hz, 1H).

10.2.1.3 Methyl 2-hydroxyphenylacetate (222)

Method : see paragraph 9.8.2.3

Reagents : 2-hydroxyphenylacetic acid **219** (1 g, 6.57 mmol.).

Reaction time: 20 minutes

Yield : 1.093 g, 100% (white needles), mp. 70°C (lit.,²⁰⁶ m.p. 70-72°)

R_f : 0.45 (B:A 9:1)

IR : ν_{\max} 1730 (CO), 1490, 1258, 1036 and 906 cm⁻¹

¹H NMR (CDCl₃): δ 3.71 (ArCH₂, s, 2H), 3.77 (OCH₃, s, 3H), 6.90 (4-H, ddd, J = 1.1, 7.5, 7.5 Hz, 1H), 6.97 (6-H, dd, J = 1.1, 8.0 Hz, 1H), 7.12 (3-H, dd, J = 1.9, 7.5 Hz, 1H), 7.23 (5-H, ddd, J = 1.9, 7.5, 8.0 Hz, 1H), 7.39 (ArOH, bs, 1H).

10.2.2 **Protection of methyl 2-hydroxyphenylacetates**

10.2.2.1 Methyl 2-O-methoxymethylphenylacetate (223)

Method : see paragraph 9.8.2.2

Reagents : methyl 2-hydroxyphenylacetate **222** (1 g, 6.02 mmol.), 80% NaH (271 mg, 9.03 mmol, 1.5 equiv.), THF (20 ml), chlorodimethylether (533 mg, 6.62 mmol, 1.1 equiv.)

Reaction time: 30 minutes

Yield : 1.139 g, 90% (yellow oil)

R_f : 0.67 (B:A 9:1)

IR : ν_{\max} 1225 (CO), 1215, 1005 and 935 cm⁻¹

¹H NMR (CDCl₃): δ 3.47 (OCH₂OCH₃, s, 3H), 3.68 (ArCH₂, s, 2H), 3.70 (OCH₃, s, 3H), 5.20 (OCH₂OCH₃, s, 2H), 6.99 (5-H, ddd, J = 1.0, 7.2, 7.2 Hz, 1H), 7.12 (3-H, dd, J = 1.0, 8.1 Hz, 1H), 7.20-7.27 (ArH, m, 2H).

10.2.2.2 Methyl 2-*O*-isopropylphenylacetate (224)

Method : see paragraph 9.8.2.4

Reagents : methyl 2-hydroxyphenylacetate **222** (200 mg, 1.20 mmol), 80% NaH (43 mg, 1.44 mmol, 1.2 equiv.), DMF (10ml), isopropylbromide (296 mg, 2.41 mmol, 2 equiv.)

Reaction time: 16 hours

Yield : 209 mg, 83% (yellow oil)

R_f : 0.71 (B:A 9:1)

IR : ν_{\max} 1738 (CO), 1496, 1458, 1290 and 1252 cm⁻¹

¹H NMR (CDCl₃): δ 1.33 (CH(CH₃)₂, d, J = 6.0 Hz, 6H), 3.62 (ArCH₂, s, 2H), 3.70 (OCH₃, s, 3H), 4.57 (CH(CH₃)₂, m, J = 6.0 Hz, 1H), 6.87 (3-H, dd, J = 1.1, 8.0 Hz, 1H), 6.90 (5-H, ddd, J = 1.1, 7.1, 7.1 Hz, 1H), 7.17-7.27 (6-;4-H, m, 2H).

10.2.2.3 Methyl 2-*O*-*t*-butyldimethylsilylphenylacetate (225)

Method : see paragraph 9.8.2.6

Reagents : methyl 2-hydroxyphenylacetate **222** (1.093 g, 6.58 mmol.), imidazole (1.120 g, 16.44 mmol, 2.5 equiv.), TBDMSCl (1.189 g, 7.89 mmol, 1.2 equiv.), DMF (5ml)

Reaction time: 16 hours

Yield : 1.844 g, 100% (light yellow oil)

R_f : 0.74 (B:A 9:1)

IR : ν_{\max} 1756 (CO), 1476, 1348, 1300 and 1180 cm⁻¹

¹H NMR (CDCl₃): δ 0.25 (Si(CH₃)₂, s, 6H), 1.01 (^tBu, s, 9H), 3.64 (ArCH₂, s, 2H), 3.69 (OCH₃, s, 3H), 6.84 (3-H, dd, J = 1.1, 8.0 Hz, 1H), 6.94 (5-H, ddd, J = 1.1, 7.5, 7.5 Hz, 1H), 7.17 (4-H, ddd, J = 2.0, 7.5, 8.0 Hz, 1H), 7.20 (6-H, dd, J = 2.0, 7.5 Hz, 1H).

10.3 SYNTHESIS OF POLYOXYGENATED METHYL PHENYL-ACETATES (244-246)

10.3.1 *Via benzonitriles*

10.3.1.1 Reduction of benzaldehydes

The benzaldehydes (1.32→1.95 mmol) were dissolved in MeOH (20→30ml) and treated with NaBH₄ (1.2 equiv.) for 30 minutes at room temperature. After the addition of ice, the aqueous layer was extracted with EtOAc (3x25ml) and the combined organic layer washed with water (2x100ml). The EtOAc was dried (Na₂SO₄) and evaporated to give the benzyl alcohols in sufficiently pure form.

10.3.1.1.1 *Benzyl alcohol (228)*

Method : see paragraph 10.3.1.1

Reagents : benzaldehyde **226** (208 mg, 1.95 mmol.), NaBH₄ (89 mg, 2.34 mmol, 1.2 equiv.), MeOH (30ml).

Reaction time: 30 minutes

Yield : 212 mg, 100% (light yellow oil)

R_f : 0.32 (B:A 9:1)

¹H NMR (CDCl₃): δ 2.19 (BnOH, t, J = 5.5 Hz, 1H), 4.69 (ArCH₂, d, J = 5.5 Hz, 2H), 7.32-7.42 (Ar-H, m, 5H).

10.3.1.1.2 *2-O-Methoxymethylbenzyl alcohol (229)*

Method : see paragraph 10.3.1.1

Reagents : 2-O-methoxymethylbenzaldehyde **216** (219 mg, 1.32 mmol.), NaBH₄ (60 mg, 1.58 mmol, 1.2 equiv.), MeOH (20 ml).

Reaction time: 30 minutes

Yield : 171 mg, 77% (yellow oil)

R_f : 0.36 (B:A 9:1)

¹H NMR (CDCl₃): δ 2.22 (BnOH, t, J = 6.5 Hz, 1H), 3.52 (OCH₂OCH₃, s, 3H), 4.74 (ArCH₂, d, J = 6.5 Hz, 2H), 5.27 (OCH₂OCH₃, s, 2H), 7.04 (5-H, ddd, J = 1.1, 7.0, 7.1 Hz, 1H), 7.13 (3-H, dd, J = 1.9, 7.1 Hz, 1H), 7.25- 7.37 (4-,6-H, m, 2H).

10.3.1.1.3 *2-O-Isopropyl-4-methoxybenzyl alcohol (230)*

Method : see paragraph 10.3.1.1

Reagents : *2-O-isopropyl-4-methoxybenzaldehyde* **227** (337 mg, 1.74 mmol.), NaBH₄ (79 mg, 2.09 mmol, 1.2 equiv.), MeOH (20 ml).

Reaction time: 1 hour

Yield : 341 mg, 100% (yellow oil)

R_f : 0.38 (B:A 9:1)

¹H NMR (CDCl₃): δ 1.39 (CH(CH₃)₂, d, J = 6.0 Hz, 6H), 2.37 (BnOH, t, J = 6.5 Hz, 1H), 3.81 (OCH₃, s, 3H), 4.60 (CH(CH₃)₂, m, J = 6.0 Hz, 1H), 4.61 (ArCH₂, d, J = 6.5 Hz, 2H), 6.44 (5-H, dd, J = 2.2, 8.1 Hz, 1H), 6.48 (3-H, d, J = 2.2 Hz, 1H), 7.16 (6-H, d, J = 8.1 Hz, 1H).

10.3.1.2 Synthesis of benzonitriles

Benzyl alcohols (1.01→1.96mmol) and triethylamine (1.3 equiv.) were dissolved in dry benzene (20 ml) and treated with thionyl chloride (1.2 equiv.) for 20 minutes at 30°C. The benzene and excess SOCl₂ were evaporated and the residue redissolved in dry THF (20ml). Sodium cyanide (2 equiv.) was added and the mixture was stirred under N₂ for a further 1½ hours at room temperature. After addition of water (40ml), the mixture was extracted with EtOAc (3x25ml) and the combined organic layers washed with water (2x100ml), dried (Na₂SO₄), evaporated and the product purified by FCC.

10.3.1.2.1 *Benzonitrile (231)*

Method : see paragraph 10.3.1.2

Reagents : benzyl alcohol **228** (212 mg, 1.96 mmol.), triethylamine (258 mg, 2.55 mmol, 1.3 equiv.), SOCl₂ (279 mg, 2.35 mmol, 1.2 equiv.), benzene (20 ml), THF(20ml), NaCN (192 mg, 3.92 mmol, 2 equiv.).

Reaction time: 20 minutes, followed by 1½ hours

Yield : 113 mg, 50% (yellow oil)

R_f : 0.60 (B:A 9:1)

¹H NMR (CDCl₃): δ 4.61 (ArCH₂, s, 2H), 7.34-7.41 (Ar-H, m, 5H).

10.3.1.2.2 *2-O-Methoxymethylbenzonitrile (232)*

Method : see paragraph 10.3.1.2

Reagents : 2-O-methoxymethylbenzyl alcohol **229** (170 mg, 1.01 mmol.), triethylamine (133 mg, 1.31 mmol, 1.3 equiv.), SOCl₂ (144 mg, 1.21 mmol, 1.2 equiv.), benzene (20 ml), THF(20ml), NaCN (99 mg, 2.02 mmol, 2 equiv.).

Reaction time: 20 minutes, followed by 1½ hours

Yield : 175 mg, 97% (yellow oil)

R_f : 0.60 (B:A 9:1)

¹H NMR (CDCl₃): δ 3.54 (OCH₂OCH₃, s, 3H), 4.70 (ArCH₂, s, 2H), 5.29 (OCH₂OCH₃, s, 2H), 7.01 (5-H, ddd, J = 1.1, 7.5, 7.5 Hz, 1H), 7.13 (3-H, dd, J = 1.1, 8.1 Hz, 1H), 7.31 (4-H, ddd, J = 2.0, 7.5, 8.1 Hz, 1H), 7.39 (6-H, dd, J = 2.0, 7.5 Hz, 1H).

10.3.1.2.3 *2-O-Isopropyl-4-methoxybenzonitrile*

Method : see paragraph 10.3.1.2

Reagents : 2-*O*-isopropyl-4-methoxybenzyl alcohol **230** (271 mg, 1.38 mmol.), triethylamine (182 mg, 1.79 mmol, 1.3 equiv.), SOCl₂ (197 mg, 1.66 mmol, 1.2 equiv.), benzene (40 ml), THF(40ml), NaCN (135 mg, 2.76 mmol, 2 equiv.).

Reaction time: 20 minutes, followed by 1½ hours

Yield : 0 mg, 0%

10.3.1.3 Hydrolysis of benzonitriles to phenylacetic acids

The respective nitriles (*ca.* 0.9 mmol) were refluxed in EtOH (20ml) and 1M NaOH (8ml) for 24 hour. When no starting material could be detected (TLC), the reaction mixture was poured unto ice and acidified with 2% HCl to a pH of 3. Extraction with Et₂O (3x25ml), followed by washing of the combined ether layers with brine (100ml) and water (100ml), drying (Na₂SO₄), evaporation and separation by PLC, yielded the products.

10.3.1.3.1 *Phenylacetic acid (218)*

Method : see paragraph 10.3.1.3

Reagents : benzonitrile **231** (113mg, 0.96 mmol.), EtOH (20ml), 1M NaOH (8ml).

Reaction time: 24 hours

Yield : 0 mg, 0%

10.3.1.3.2 *2-O-Methoxymethylphenylacetic acid (233)*

Method : see paragraph 10.3.1.3

Reagents : 2-*O*-methoxymethylbenzonitrile **232** (174 mg, 0.98 mmol.), EtOH (20ml), 1M NaOH (8ml).

Reaction time: 24 hours

Yield : 12 mg, 6% (colourless oil)

R_f : 0.60 (B:A 9:1)

^1H NMR (CDCl_3): δ 3.49 (OCH_2OCH_3 , s, 3H), 3.75 (ArCH_2 , s, 2H), 5.20 (OCH_2OCH_3 , s, 2H), 6.97 (4-H, ddd, $J = 1.5, 7.5, 7.5$ Hz, 1H), 7.10 (6-H, dd, $J = 1.5, 8.1$ Hz, 1H), 7.22 (5-H, ddd, $J = 2.0, 7.5, 8.1$ Hz, 1H), 7.30 (3-H, dd, $J = 2.0, 7.5$ Hz, 1H), 10.32 (COOH , m, 1H).

10.3.2 Via 1,3-dithiane

10.3.2.1 2-Trimethylsilyl-1,3-dithiane (235)

1,3-Dithiane **234** (273 mg, 2.27 mmol), dissolved in dry THF (15ml) and cooled to -20°C was treated with *n*BuLi (2.37 mmol, 1.05 equiv.) for one hour. Freshly distilled TMSCl (2.265 mmol, 1 equiv.) was added and the mixture stirred for another 3 hours at 0°C . The reaction mixture was carefully acidified with 2% HCl until precipitation occurred. Following filtration, the aqueous layer was extracted with EtOAc (3x25ml) and the combined organic layers washed with brine (2x50ml), dried (Na_2SO_4), evaporated and separated by FCC.

Yield : 283 mg, 65 % (clear oil)

R_f : 0.76 (B)

^1H NMR (CDCl_3): δ 0.14 ($\text{Si}(\text{CH}_3)_3$, s, 9H), 1.95-2.16 (5-H, m, 2H), 2.70 (4-;6- H_{eq} , ddd, $J = 3.2, 4.1, 14.0$ Hz, 2H), 2.85 (4-;6- H_{ax} , ddd, $J = 3.0, 12.0, 14.0$ Hz, 2H), 3.67 (2-H, s, 1H).

10.3.2.2 2-Phenylpropylenedithioethene (239)

2-Trimethylsilyl-1,3-dithiane **235** (828 mg, 4.59 mmol) in dry THF (20ml) was cooled to -30°C and treated with *n*BuLi (5.05 mmol, 1.1 equiv.) for one hour. Benzoyl chloride **236** (775 mg, 5.51 mmol, 1.2 equiv.) was added and the mixture stirred at -30°C (20 hours) and then at 0°C (2 hours). Following acidification with 2% HCl and extraction with

EtOAc (3x20ml), the combined EtOAc was washed with water (3x50ml), dried (Na₂SO₄) and evaporated. The mixture was separated by FCC.

Yield : 0 mg, 0%

Propylenedithiomethyl phenyl ketone **237** (234 mg, 23%, light yellow oil) was obtained.

¹H NMR : see paragraph 10.3.2.3

10.3.2.3 Propylenedithiomethyl phenyl ketone (237)

1,3-Dithiane **234** (154 mg, 1.28 mmol) dissolved in anhydrous THF (10ml) was treated with *n*BuLi (1.28 mmol, 1 equiv.) at -30°C for 2 hours. Benzoyl chloride **236** (216 mg, 1.54 mmol, 1.2 equiv.) was added and the mixture stirred at -30°C for 7 hours followed by stirring at 0°C for 12 hours. After acidification with 2% HCl the aqueous layer was extracted with EtOAc (3x25ml) and the combined organic layers washed with water (2x100ml), dried (Na₂SO₄), evaporated and the product separated by FCC.

Yield : 141 mg, 49% (light yellow oil)

R_f : 0.59 (B)

¹H NMR (CDCl₃): δ 1.97-2.21 (4'-H, m, 2H), 2.66 (3'-;5'-H_{eq}, ddd, J = 3.0, 6.0, 14.0 Hz, 2H), 3.37 (3'-;5'-H_{ax}, ddd, J = 3.0, 11.0, 14.0 Hz, 2H), 5.14 (1'-H, s, 1H), 7.42-7.48 (3-;5-H, m, 2H), 7.52-7.59 (4-H, m, 1H), 7.91-7.95 (2-;6-H, m, 2H).

10.3.2.4 α-Propylenedithiobenzyl alcohol (238)

Propylenedithiomethyl phenyl ketone **237** (33 mg, 0.147 mmol) was dissolved in methanol (5ml) and treated with NaBH₄ (22 mg, 0.59 mmol, 4 equiv.) for 12 hours at room temperature. Following the addition of ice and extraction with EtOAc (3x20ml), the organic layer was washed with water (2x50ml), dried and evaporated. The product was purified by FCC (B).

Yield : 3 mg, 9% (colourless oil)

R_f : 0.20 (B)

¹H NMR (CDCl₃): δ 1.91-2.12 (4'-H, m, 2H), 2.68-2.78 (3'-;5'-Heq, m, 2H), 2.86-3.03 (3'-;5'-Hax, m, 2H), 4.06 (1'-H, d, J = 8.0 Hz, 1H), 4.91 (ArCH, dd, J = 2.0, 8.0 Hz, 1H), 7.27 (ArCOH, d, J = 2.0 Hz, 1H), 7.32-7.49 (ArH, m, 5H).

10.3.3 *Via* TTN-rearrangement of acetophenones

10.3.3.1 Protection of 2-hydroxyacetophenones

10.3.3.1.1 *2-O-t-Butyldimethylsilyl-4-methoxyacetophenone (241)*

Method : see paragraph 9.8.2.6

Reagents : 2-hydroxy-4-methoxyacetophenone **240** (200 mg, 1.20 mmol), imidazole (205 mg, 3.01 mmol, 2.5 equiv.), TBDMSCl (200 mg, 1.32 mmol, 1.1 equiv.), DCM (1ml).

Reaction time: 16 hours

Yield : 164 mg, 49% (colourless oil)

R_f : 0.86 (B:A 9:1)

IR : ν_{max} 1740 (CO), 1328, 1260, 1223 and 1010 cm⁻¹

¹H NMR (CDCl₃): δ 0.31 (Si(CH₃)₂, s, 6H), 1.03 (^tBu, s, 9H), 2.59 (COCH₃, s, 3H), 3.83 (OCH₃, s, 3H), 6.39 (3-H, d, J = 2.1 Hz, 1H), 6.56 (5-H, dd, J = 2.1, 8.9 Hz, 1H), 7.74 (6-H, d, J = 8.9 Hz, 1H).

10.3.3.1.2 *2-O-Isopropyl-4-methoxyacetophenone (242)*

Method : see paragraph 9.8.2.4

Reagents : 2-hydroxy-4-methoxyacetophenone **240** (1.082 g, 6.51 mmol.), 80% NaH (234 mg, 7.81 mmol, 1.2 equiv.), DMF (10 ml), isopropylbromide (1.601 g, 13.01 mmol, 2 equiv.).

Reaction time: 16 hours

Yield : 1.117 g, 82% (dark yellow oil)

R_f : 0.86 (B:A 9:1)

IR : ν_{\max} 1680 (CO), 1318, 1220, 1173 and 978 cm⁻¹

¹H NMR (CDCl₃): δ 1.43 (CH(CH₃)₂, d, J = 6.0 Hz, 6H), 2.60 (COCH₃, s, 3H), 3.86 (OCH₃, s, 3H), 4.67 (CH(CH₃)₂, m, J = 6.0 Hz, 1H), 6.45 (3-H, d, J = 2.5 Hz, 1H), 6.51 (5-H, dd, J = 2.5, 9.0 Hz, 1H), 7.04 (3-H, d, J = 9.0 Hz, 1H).

10.3.3.1.3 2-O-Benzyl-4-methoxyacetophenone (**243**)

Method : see paragraph 9.8.2.5

Reagents : 2-hydroxy-4-methoxyacetophenone **240** (2 g, 12.04 mmol.), 80% NaH (720 mg, 24.07 mmol, 2 equiv.), DMF (50ml), benzoyl chloride (6.076 g, 48.14 mmol, 4 equiv.).

Reaction time: 3 hours

Yield : 2.683 g, 87% (dark orange oil)

R_f : 0.24 (B)

IR : ν_{\max} 1675 (CO), 1320, 1210, 1089 and 1004 cm⁻¹

¹H NMR (CDCl₃): δ 2.57 (COCH₃, s, 3H), 3.86 (OCH₃, s, 3H), 5.16 (ArCH₂, s, 2H), 6.54 (3-H, d, J = 2.5 Hz, 1H), 6.56 (5-H, dd, J = 2.5, 8.1 Hz, 1H), 7.35-7.49 (Ar-H, m, 5H), 7.87 (6-H, d, J = 8.1 Hz, 1H).

10.3.3.2 Oxidative rearrangement (TTN)

10.3.3.2.1 *Methyl 2-O-t-butyldimethylsilyl-4-methoxyphenylacetate (244)*

Method : see paragraph 9.8.4

Reagents : 2-O-t-butyldimethylsilyl-4-methoxyacetophenone **241** (164 mg, 0.528 mmol.), TTN (206 mg, 0.528 mmol, 1 equiv.), 60% perchloric acid (0.5ml), MeOH (5ml).

Reaction time: 4 hours

Yield : 0 mg, 0%

The reaction lead to the deprotection of the 2-hydroxyl functionality.

10.3.3.2.2 *Methyl 2-O-isopropyl-4-methoxyphenylacetate (245)*

Method : see paragraph 9.8.4

Reagents : 2-O-isopropyl-4-methoxyacetophenone **242** (1.124 g, 5.40 mmol.), TTN (2.107 g, 5.40 mmol, 1 equiv.), 60% perchloric acid (3ml), MeOH (40ml).

Reaction time: 2½ hours

Yield : 959 mg, 75% (yellow oil)

R_f : 0.74 (B:A 9:1)

IR : ν_{\max} 1738 (CO), 1490, 1463, 1290 and 1250 cm⁻¹

¹H NMR (CDCl₃): δ 1.32 (CH(CH₃)₂, d, J = 6.0 Hz, 6H), 3.55 (ArCH₂, s, 2H), 3.69, 3.80 (2xOCH₃, 2xs, 2x3H), 4.53 (CH(CH₃)₂, m, J = 6.0 Hz, 1H), 6.44 (5-H, dd, J = 2.2, 8.5 Hz, 1H), 6.46 (3-H, d, J = 2.2 Hz, 1H), 7.09 (6-H, d, J = 8.5 Hz, 1H).

10.3.3.2.3 *Methyl 2-O-benzyl-4-methoxyphenylacetate (246)*

Method : see paragraph 9.8.4

Reagents : 2-*O*-benzyl-4-methoxyacetophenone **243** (1.663 g, 6.49 mmol.), TTN (2.533 g, 6.49 mmol, 1 equiv.), 60% perchloric acid (6ml), MeOH (40ml).

Reaction time: 4 hours

Yield : 1.542 g, 83% (yellow oil)

R_f : 0.72 (B:A 9:1)

IR : ν_{\max} 1740 (CO), 1498, 1236, 1176 and 1132 cm⁻¹

¹H NMR (CDCl₃): δ 3.64 (ArCH₂, s, 2H), 3.65, 3.80 (2xOCH₃, 2xs, 2x3H), 5.08 (ArCH₂O, s, 2H), 6.50 (5-H, dd, J = 2.2, 8.1 Hz, 1H), 6.54 (3-H, d, J = 2.2 Hz, 1H), 7.14 (6-H, d, J = 8.1 Hz, 1H), 7.33-7.45 (Ar-H, m, 5H).

10.3.3.3 Hydrogenation and silylation of methyl 2-*O*-benzyl-4-methoxyphenylacetate

10.3.3.3.1 *Methyl 2-hydroxy-4-methoxyphenylacetate (247)*

Method : see paragraph 9.8.3

Reagents : methyl 2-*O*-benzyl-4-methoxyphenylacetate **246** (1.542 g, 5.39 mmol), 10% Pd-C (150 mg), A (20ml).

Reaction time: 5 hours

Yield : 877 mg, 83% (colourless oil)

R_f : 0.42 (B:A 9:1)

IR : ν_{\max} 1730 (CO), 1256, 1030 and 906 cm⁻¹

¹H NMR (CDCl₃): δ 3.64 (ArCH₂, s, 2H), 3.76, 3.79 (2xOCH₃, 2xs, 2x3H), 6.46 (5-H, dd, J = 2.5, 8.1 Hz, 1H), 6.55 (3-H, d, J = 2.5 Hz, 1H), 6.99 (6-H, d, J = 8.1 Hz, 1H), 7.63 (ArOH, bs, 1H).

10.3.3.3.2 *Methyl 2-O-t-butyldimethylsilyl-4-methoxyphenylacetate (244)*

Method : see paragraph 9.8.2.6

Reagents : methyl 2-hydroxy-4-methoxyphenylacetate **247** (870 mg, 4.43 mmol.), imidazole (755 mg, 11.08 mmol, 2.5 equiv.), TBDMSCl (1.003 g, 6.65 mmol, 1.5 equiv.), DMF (5ml).

Reaction time: 16 hours

Yield : 1.239 g, 90% (yellow oil)

R_f : 0.71 (B:A 9:1)

IR : ν_{\max} 1756 (CO), 1480, 1341, 1315 and 1193 cm⁻¹

MS : *m/z* 311 (M+H⁺, 17%), 196 (55); Found : (M+H⁺), 311.1681 C₁₆H₂₇O₄Si requires (M+H⁺), 311.1679

¹H NMR (CDCl₃, plate 2): δ 0.26 (Si(CH₃)₂, s, 6H), 1.01 (^tBu, s, 9H), 3.57 (ArCH₂, s, 2H), 3.69, 3.79 (2xOCH₃, 2xs, 2x3H), 6.42 (3-H, d, J = 2.2 Hz, 1H), 6.50 (5-H, dd, J = 2.2, 8.1 Hz, 1H), 7.11 (6-H, d, J = 8.1 Hz, 1H).

10.4 ALDOL CONDENSATION OF PHENYLACETATES WITH BENZALDEHYDES EMPLOYING LDA AS BASE

10.4.1 *Erythro- and threo-methyl 3-hydroxy-2-(2''-O-isopropylphenyl)-3-(2'-O-methoxymethylphenyl)propanoate (248)*

Method : see paragraph 9.8.5

Reagents : methyl 2-O-isopropylphenylacetate **224** (207 mg, 0.99 mmol), diisopropylamine (111 mg, 1.09 mmol, 1.1 equiv.), *n*BuLi (1.1 equiv.), Et₂O (2ml), 2-O-methoxymethylbenzaldehyde **216** (165 mg, 0.99 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *erythro* : 72 mg (light yellow oil)

threo : 175 mg (white flakes), mp. 44°C

total yield : 66 %

de : 42 %

R_f : *erythro* : 0.63 (B:A 9:1)

threo : 0.53 (B:A 9:1)

IR : *erythro* : ν_{\max} 1734 (CO), 1496, 1458, 1440 and 1290 cm⁻¹

threo : ν_{\max} 1730 (CO), 1504, 1476, 1434 and 1279 cm⁻¹

MS : *erythro* : *m/z* 375 (M+H⁺, 26%), 357 (78); Found : (M+H⁺), 375.1804

C₂₁H₂₇O₆ requires (M+H⁺), 375.1808

threo : *m/z* 375 (M+H⁺, 20%), 357 (51); Found : (M+H⁺), 375.1800

C₂₁H₂₇O₆ requires (M+H⁺), 375.1808

¹H NMR (CDCl₃):

[*erythro*]: see Table 4,

[*threo*] : see Table 4.

10.4.2 *Erythro*- and *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate (249)

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-isopropylphenylacetate **224** (355 mg, 1.70 mmol), diisopropylamine (190 mg, 1.88 mmol, 1.1 equiv.), *n*BuLi (1.1 equiv.), Et₂O (4ml), 2-*O*-methoxymethyl-4-methoxybenzaldehyde **217** (335 mg, 1.70 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *erythro* : 43 mg (light yellow oil)

threo : 305 mg (white flakes), mp. 81°C

total yield : 50 %

de : 76 %

R_f : *erythro* : 0.56 (B:A 9:1)
 threo : 0.47 (B:A 9:1)
IR : *erythro* : ν_{\max} 1720 (CO), 1614, 1600, 1590 and 1512 cm⁻¹
 threo : ν_{\max} 1726 (CO), 1603, 1623, 1623 and 1496 cm⁻¹

¹H NMR (CDCl₃):
[*erythro*]: see Table 4,
[*threo*] : see Table 4.

10.4.3 *Erythro*- and *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate (250)

Method : see paragraph 9.8.5
Reagents : methyl 2-*O*-isopropyl-4-methoxyphenylacetate **245** (158 mg, 0.66 mmol), diisopropylamine (74 mg, 0.73 mmol, 1.1 equiv.), *n*BuLi (0.73 mmol, 1.1 equiv.), Et₂O (2ml), 2-*O*-methoxymethylbenzaldehyde **216** (110 mg, 0.66 mmol, 1 equiv.).
Reaction time: 1 hour at -78°C followed by 2 hours at 0°C
Yield : *erythro* : 50 mg (light yellow oil)
 threo : 130 mg (white flakes), mp. 102°C
 total yield : 67 %
 de : 44 %

R_f : *erythro* : 0.89 (B:A 9:1)
 threo : 0.80 (B:A 9:1)
IR : *erythro* : ν_{\max} 1718 (CO), 1608, 1588, 1506 and 1496 cm⁻¹
 threo : ν_{\max} 1722 (CO), 1600, 1595, 1608 and 1434 cm⁻¹

¹H NMR (CDCl₃):
[*erythro*]: see Table 4,
[*threo*] : see Table 4.

10.4.4 ***Threo*-methyl 3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate (251)**

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-isopropyl-4-methoxyphenylacetate **245** (410 mg, 1.72 mmol), diisopropylamine (192 mg, 1.89 mmol, 1.1 equiv.), *n*BuLi (1.89 mmol, 1.1 equiv.), Et₂O (4ml), 2-*O*-methoxymethyl-4-methoxybenzaldehyde **217** (338 mg, 1.72 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *threo* : 299 mg, 40% (light yellow oil)

R_f : *threo* : 0.38 (B:A 9:1)

IR : ν_{\max} 1720 (CO), 1620, 1592, 1500 and 1464 cm⁻¹

¹H NMR (CDCl₃):

[*threo*] : see Table 4.

10.4.5 ***Erythro*- and *threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoates (252)**

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-*t*-butyldimethylsilylphenylacetate **225** (231 mg, 0.82 mmol), diisopropylamine (92 mg, 0.91 mmol, 1.1 equiv.), *n*BuLi (0.91 mmol, 1.1 equiv.), Et₂O (3ml), 2-*O*-methoxymethylbenzaldehyde **216** (136 mg, 0.82 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *erythro* : 103 mg, (light yellow oil)

threo : 184 mg, (yellow needles), m.p. 113°C

total yield : 78 %

de : 28 %

R_f : *erythro* : 0.69 (B:A 9:1)
 threo : 0.53 (B:A 9:1)

IR : *erythro* : ν_{\max} 2934, 1730 (CO), 1501 and 1268 cm⁻¹
 threo : ν_{\max} 2902, 1732 (CO), 1504 and 1279 cm⁻¹

MS : *erythro* : *m/z* 447 (M+H⁺, 15%), 429 (42); Found : (M+H⁺), 447.2201
 C₂₄H₃₅O₆Si requires (M+H⁺), 447.2203
 threo : *m/z* 447 (M+H⁺, 20%), 429 (58); Found : (M+H⁺), 447.2197
 C₂₄H₃₅O₆Si requires (M+H⁺), 447.2203

¹H NMR (CDCl₃):

[*erythro*, plate 3] : see Table 5,

[*threo*, plate 4] : see Table 5.

10.4.6 *Erythro*- and *threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoates (253)

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-*t*-butyldimethylsilylphenylacetate **225** (223 mg, 0.80 mmol), diisopropylamine (89 mg, 0.88 mmol, 1.1 equiv.), *n*BuLi (0.88 mmol, 1.1 equiv.), Et₂O (3ml), 2-*O*-methoxymethyl-4-methoxybenzaldehyde **217** (156 mg, 0.80 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *erythro* : 58 mg, (yellow oil)
 threo : 197 mg, (white needles), m.p. 85°C
 total yield : 67 %
 de : 55 %

R_f : *erythro* : 0.63 (B:A 9:1)
 threo : 0.50 (B:A 9:1)

IR : *erythro* : ν_{\max} 2936, 1734 (CO), 1494 and 1260 cm⁻¹

threo : ν_{\max} 2930, 1738 (CO), 1504 and 1272 cm^{-1}

MS : *erythro* : m/z 477 ($\text{M}+\text{H}^+$, 23%), 459 (64); Found : ($\text{M}+\text{H}^+$), 477.2258
 $\text{C}_{25}\text{H}_{37}\text{O}_7\text{Si}$ requires ($\text{M}+\text{H}^+$), 477.2260
threo : m/z 477 ($\text{M}+\text{H}^+$, 18%), 459 (43); Found : ($\text{M}+\text{H}^+$), 477.2267
 $\text{C}_{25}\text{H}_{37}\text{O}_7\text{Si}$ requires ($\text{M}+\text{H}^+$), 477.2260

^1H NMR (CDCl_3):

[*erythro*] : see Table 5,

[*threo*] : see Table 5.

g)

10.4.7 *Erythro*- and *threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoates (254)

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-*t*-butyldimethylsilyl-4-methoxyphenylacetate **244** (405 mg, 1.30 mmol), diisopropylamine (145 mg, 1.43 mmol, 1.1 equiv.), *n*BuLi (1.43 mmol, 1.1 equiv.), Et_2O (3ml), 2-*O*-methoxymethylbenzaldehyde **216** (216 mg, 1.30 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *erythro* : 202 mg, (light yellow oil)
threo : 268 mg, (yellow needles), m.p. 91°C
total yield : 76 %
de : 22 %

R_f : *erythro* : 0.42 (B:A 95:5)

threo : 0.30 (B:A 95:5)

IR : *erythro* : ν_{\max} 3008, 1738 (CO), 1496 and 1270 cm^{-1}

threo : ν_{\max} 2995, 1731 (CO), 1500 and 1271 cm^{-1}

MS : *erythro* : m/z 477 ($M+H^+$, 18%), 459 (49); Found : ($M+H^+$), 477.2261
 $C_{25}H_{37}O_7Si$ requires ($M+H^+$), 477.2260
threo : m/z 477 ($M+H^+$, 26%), 459 (35); Found : ($M+H^+$), 477.2260
 $C_{25}H_{37}O_7Si$ requires ($M+H^+$), 477.2260

1H NMR ($CDCl_3$):

[*erythro*] : see Table 5,

[*threo*] : see Table 5.

10.4.8 ***Erythro*- and *threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)-propanoates (255)**

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-*t*-butyldimethylsilyl-4-methoxyphenylacetate **244** (404 mg, 1.30 mmol), diisopropylamine (145 mg, 1.43 mmol, 1.1 equiv.), *n*BuLi (1.43 mmol, 1.1 equiv.), Et_2O (3ml), 2-*O*-methoxymethyl-4-methoxybenzaldehyde **217** (255 mg, 1.30 mmol, 1 equiv.).

Reaction time: 1 hour at $-78^\circ C$ followed by 2 hours at $0^\circ C$

Yield : *erythro* : 156 mg, (yellow oil)
threo : 299 mg, (yellow needles), m.p. $64^\circ C$
total yield : 69 %
de : 32 %

R_f : *erythro* : 0.33 (B:A 95:5)

threo : 0.24 (B:A 95:5)

IR : *erythro* : ν_{max} 2940, 1734 (CO), 1494 and 1265 cm^{-1}

threo : ν_{max} 2932, 1730 (CO), 1492 and 1287 cm^{-1}

MS : *erythro* : m/z 507 ($M+H^+$, 12%), 489 (50); Found : ($M+H^+$), 507.2366
 $C_{26}H_{39}O_8Si$ requires ($M+H^+$), 507.2366

threo : m/z 507 ($M+H^+$, 9%), 489 (68); Found : ($M+H^+$), 507.2360
 $C_{26}H_{39}O_8Si$ requires ($M+H^+$), 507.2366

1H NMR ($CDCl_3$):

[*erythro*, plate 5] : see Table 5,

[*threo*, plate 6] : see Table 5.

10.5 ACETYLATION OF METHYL 2,3-DIARYL-3-HYDROXY-PROPANOATES

10.5.1 *Erythro*-methyl 3-acetoxy-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate (256)

Method : see paragraph 9.8.2.1

Reagents : *erythro*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate **252** (20mg, 0.04 mmol.), acetic anhydride (20 drops), pyridine (10 drops)

Reaction time: 48 hours, 40°C

Yield : 21.8 mg, 100% (light yellow oil)

R_f : 0.79 (B:A 9:1)

IR : ν_{max} 1740 (CO), 1497, 1377 and 1257 cm^{-1}

1H NMR ($CDCl_3$, plate 7): δ 0.20, 0.24 (2xSiCH₃, 2xs, 2x3H), 1.01 (^tBu, s, 9H), 1.89 (OAc, s, 3H), 3.54 (OCH₂OCH₃, s, 3H), 3.56 (OCH₃, s, 3H), 4.86 (2-H, d, J = 8.0 Hz, 1H), 5.20, 5.31 (OCH₂OCH₃, 2xd, J = 6.9 Hz, 2x1H), 6.75 (3''-H, dd, J = 1.1, 8.0 Hz, 1H), 6.89 (3-H, d, J = 8.0 Hz, 1H), 6.90 (5'-H, ddd, J = 1.1, 7.1, 7.9 Hz, 1H), 6.97 (5''-H, ddd, J = 1.1, 7.1, 7.8 Hz, 1H), 7.08 (3'-H, dd, J = 1.1, 8.1 Hz, 1H), 7.11 (6'-H, dd, J = 1.9, 7.9 Hz, 1H), 7.16 (4''-H, ddd, J = 1.9, 7.1, 8.0 Hz, 1H), 7.21 (4'-H, ddd, J = 1.9, 7.1, 8.1 Hz, 1H), 7.61 (6''-H, dd, J = 1.9, 7.8 Hz, 1H).

10.5.2 ***Threo*-methyl 3-acetoxy-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate (257)**

Method : see paragraph 9.8.2.1

Reagents : *threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate **252** (10 mg, 0.02 mmol.), acetic anhydride (10 drops), pyridine (5 drops)

Reaction time: 48 hours

Yield : 11 mg, 100% (yellow oil)

R_f : 0.74 (B:A 9:1)

IR : ν_{\max} 1745 (CO), 1502, 1372 and 1264 cm⁻¹

¹H NMR (CDCl₃, plate 8): δ 0.13, 0.22 (2xSiCH₃, 2xs, 2x3H), 1.05 (^tBu, s, 9H), 2.04 (OAc, s, 3H), 3.42 (OCH₂OCH₃, s, 3H), 3.70 (OCH₃, s, 3H), 4.82 (2-H, d, J = 11.0 Hz, 1H), 4.89, 4.97 (OCH₂OCH₃, 2xd, J = 7.0 Hz, 2x1H), 6.58 (3''-H, dd, J = 1.2, 8.0 Hz, 1H), 6.82 (5''-H, ddd, J = 1.2, 7.1, 8.0 Hz, 1H), 6.83 (3-H, d, J = 11.0 Hz, 1H), 6.89 (3'-H, dd, J = 1.2, 8.1 Hz, 1H), 6.89 (5'-H, ddd, J = 1.2, 7.8, 8.1 Hz, 1H), 6.99 (4''-H, ddd, J = 2.0, 7.1, 8.0 Hz, 1H), 7.09 (4'-H, ddd, J = 1.9, 7.1, 8.2 Hz, 1H), 7.36 (6''-H, dd, J = 2.0, 8.0 Hz, 1H), 7.56 (6'-H, dd, J = 1.9, 7.8 Hz, 1H).

10.6 **LiAlH₄ REDUCTION OF METHYL 2,3-DIPHENYL-PROPANOATES (248-251)**

10.6.1 ***Erythro*-3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propan-1-ol (258)**

Method : see paragraph 9.8.7

Reagents : *erythro*-methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate **248** (114 mg, 0.30 mmol), Et₂O (5ml), LiAlH₄ (171 mg, 4.50 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield : 80 mg, 76 %, (light yellow oil)

R_f: 0.40 (B:A 8:2)

MS : *m/z* 347 (M+H⁺, 23%), 329 (45), Found : (M+H⁺), 347.1859; C₂₀H₂₇O₅
(M+H⁺) requires 347.1858

¹H NMR (CDCl₃, plate 9): see Table 7.

10.6.2 ***Threo*-3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propan-1-ol (258)**

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate **248** (240 mg, 0.64 mmol), Et₂O (10ml), LiAlH₄ (364 mg, 9.60 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield : 179 mg, 78 %, (light yellow oil)

R_f: 0.42 (B:A 8:2)

MS : *m/z* 347 (M+H⁺, 20%), 329 (38), Found : (M+H⁺), 347.1854; C₂₀H₂₇O₅
(M+H⁺) requires 347.1858

¹H NMR (CDCl₃, plate 10): see Table 7.

10.6.3 ***Erythro*-3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propan-1-ol (259)**

Method : see paragraph 9.8.7

Reagents : *erythro*-methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **249** (71 mg, 0.18 mmol), Et₂O (5ml), LiAlH₄ (102 mg, 2.70 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield : 29 mg, 43 %, (light yellow oil)

R_f : 0.17 (B:A 8:2)

¹H NMR (CDCl₃): see Table 7.

10.6.4 ***Threo*-3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propan-1-ol (259)**

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **249** (376 mg, 0.93 mmol), Et₂O (15ml), LiAlH₄ (529 mg, 13.95 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield : 229 mg, 63 %, (light yellow oil)

R_f : 0.20 (B:A 9:1)

¹H NMR (CDCl₃): see Table 7.

10.6.5 ***Erythro*-3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethylphenyl)propan-1-ol (260)**

Method : see paragraph 9.8.7

Reagents : *erythro*-methyl 3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate **250** (129 mg, 0.32 mmol), Et₂O (5ml), LiAlH₄ (182 mg, 4.80 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield : 84 mg, 70 % (light yellow oil)

R_f: 0.17 (B:A 9:1)

¹H NMR (CDCl₃): see Table 7.

10.6.6 ***Threo*-3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethylphenyl)propan-1-ol (260)**

Method: see paragraph 9.8.7

Reagents: *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate **250** (287 mg, 0.71 mmol), Et₂O (10ml), LiAlH₄ (404 mg, 10.65 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield: 201 mg, 75 % (colourless oil)

R_f: 0.20 (B:A 9:1)

¹H NMR (CDCl₃): see Table 7.

10.6.7 ***Threo*-3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propan-1-ol (261)**

Method: see paragraph 9.8.7

Reagents: *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **251** (298 mg, 0.69 mmol), Et₂O (10ml), LiAlH₄ (393 mg, 10.35 mmol, 15 equiv.).

Reaction time: 1 hour at room temperature

Yield: 182 mg, 65 % (colourless oil)

R_f: 0.26 (B:A 9:1)

¹H NMR (CDCl₃): see Table 7.

10.7 SnCl₄/BnSH CLEAVAGE OF THE 2'-O-METHOXYMETHYL-PROPANOL DERIVATIVES (258-261)

10.7.1 *Erythro*- and *threo*-3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-O-isopropylphenyl)propan-1-ols (262)

Method : see paragraph 9.8.6

Reagents : 3-hydroxy-2-(2''-O-isopropylphenyl)-3-(2'-O-methoxymethylphenyl)-propan-1-ol **258** (53 mg, 0.15 mmol), BnSH (76 mg, 0.61 mmol, 4 equiv.), SnCl₄ (60 mg, 0.23 mmol, 1.5 equiv.), DCM (1ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 8 mg, (light yellow oil)
threo : 37 mg, (light yellow oil)
total yield : 72%
de : 66 %

R_f : *erythro* : 0.46 (B:A 9:1)
threo : 0.44 (B:A 9:1)

MS : *erythro* : *m/z* 409 (M+H⁺, 24%), 365 (45); Found : (M+H⁺), 409.1837
C₂₅H₂₉O₃S requires (M+H⁺), 409.1837
threo : *m/z* 409 (M+H⁺, 39%), 365 (28); Found : (M+H⁺), 409.1834
C₂₅H₂₉O₃S requires (M+H⁺), 409.1837

¹H NMR (CDCl₃):

[*erythro*] : see Table 8,

[*threo*] : see Table 8.

10.7.2 *Erythro*- and *threo*-3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-O-isopropylphenyl)propan-1-ols (263)

Method : see paragraph 9.8.6

Reagents : 3-hydroxy-2-(2''-O-isopropylphenyl)-3-(2'-O-methoxymethyl-4'-methoxyphenyl)propan-1-ol **259** (224 mg, 0.60 mmol), BnSH (370 mg, 2.98 mmol, 4 equiv.), SnCl₄ (233 mg, 0.89 mmol, 1.5 equiv.), DCM (5ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 25 mg, (yellow oil)
threo : 148 mg, (light yellow oil)
total yield : 66%
de : 72 %

R_f : *erythro* : 0.44 (B:A 9:1)
threo : 0.41 (B:A 9:1)

¹H NMR (CDCl₃):

[*erythro*]: see Table 8,

[*threo*] : see Table 8.

10.7.3 *Erythro-* and *threo*-3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-O-isopropyl-4''-methoxyphenyl)propan-1-ols (**264**)

Method : see paragraph 9.8.6

Reagents : 3-hydroxy-2-(2''-O-isopropyl-4''-methoxyphenyl)-3-(2'-O-methoxymethylphenyl)propan-1-ol **260** (268 mg, 0.71 mmol), BnSH (354 mg, 2.85 mmol, 4 equiv.), SnCl₄ (286 mg, 1.10 mmol, 1.5 equiv.), DCM (5ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 51 mg, (light yellow oil)
threo : 162 mg, (light yellow oil)
total yield : 68 %
de : 52 %

R_f : *erythro* : 0.45 (B:A 9:1)
threo : 0.40 (B:A 9:1)

¹H NMR (CDCl₃):

[*erythro*]: see Table 8,

[*threo*] : see Table 8.

10.7.4 ***Erythro-* and *threo*-3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-O-isopropyl-4''-methoxyphenyl)propan-1-ols (265)**

Method : see paragraph 9.8.6

Reagents : 3-hydroxy-2-(2''-O-isopropyl-4''-methoxyphenyl)-3-(2'-O-methoxymethyl-4'-methoxyphenyl)propan-1-ol **261** (182 mg, 0.45 mmol), BnSH (222 mg, 1.79 mmol, 4 equiv.), SnCl₄ (175 mg, 0.67 mmol, 1.5 equiv.), DCM (5ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 31 mg, (yellow oil)
threo : 64 mg, (light yellow oil)
total yield : 45 %
de : 34 %

R_f : *erythro* : 0.40 (B:A 9:1)

threo : 0.38 (B:A 9:1)

¹H NMR (CDCl₃):

[*erythro*]: see Table 8,

[*threo*] : see Table 8.

10.8 **SnCl₄/BnSH CLEAVAGE OF THE 2'-O-METHOXYMETHYL-PROPANOATE DERIVATIVES (249, 250, 252-255)**

10.8.1 ***Erythro-* and *threo*-methyl 3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-O-isopropylphenyl)propanoates (266)**

Method : see paragraph 9.8.6

Reagents : methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **249** (300 mg, 0.74 mmol), BnSH (369 mg, 2.97 mmol, 4 equiv.), SnCl₄ (290 mg, 1.11 mmol, 1.5 equiv.), DCM (5ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 54 mg, (light yellow oil)
threo : 199 mg, (light yellow oil)
total yield : 75 %
de : 58 %

R_f : *erythro* : 0.70 (B:A 9:1)
threo : 0.68 (B:A 9:1)

IR : *erythro* : ν_{\max} 1732 (CO), 1622, 1504, 1456 and 1256 cm⁻¹
threo : ν_{\max} 1736 (CO), 1632, 1521 and 1253 cm⁻¹

¹H NMR (CDCl₃):

[*erythro*]: see Table 10,

[*threo*] : see Table 10.

10.8.2 *Erythro*- and *threo*-methyl 3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-*O*-isopropyl-4''-methoxyphenyl)propanoates (267)

Method : see paragraph 9.8.6

Reagents : methyl 3-hydroxy-2-(2''-*O*-isopropyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate **250** (148 mg, 0.37 mmol), BnSH (182 mg, 1.46 mmol, 4 equiv.), SnCl₄ (143 mg, 0.55 mmol, 1.5 equiv.), DCM (5ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 34 mg, (yellow oil)
threo : 92 mg, (light yellow oil)
total yield : 74 %
de : 46 %

R_f : *erythro* : 0.71 (B:A 9:1)
 threo : 0.69 (B:A 9:1)
IR : *erythro* : ν_{\max} 1732 (CO), 1526, 1492, 1294 and 1250 cm⁻¹
 threo : ν_{\max} 1735 (CO), 1520, 1486, 1301 and 1242 cm⁻¹

¹H NMR (CDCl₃):

[*erythro*]: see Table 10,

[*threo*] : see Table 10.

10.8.3 ***Erythro*- and *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxyphenyl)propanoates (268)**

Method : see paragraph 9.8.6

Reagents : methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate **252** (178 mg, 0.40 mmol), BnSH (198 mg, 1.59 mmol, 4 equiv.), SnCl₄ (125 mg, 0.48 mmol, 1.2 equiv.), DCM (5ml)

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 25 mg, (dark orange oil)
 threo : 170 mg, (light yellow plates), m.p. 108°C
 total yield : 96 %
 de : 74 %

R_f : *erythro* : 0.64 (B:A 9:1)

threo : 0.77 (B:A 9:1)

IR : *erythro* : ν_{\max} 1736 (CO), 1620, 1496 and 1250 cm⁻¹

threo : ν_{\max} 1730 (CO), 1592, 1501 and 1287 cm⁻¹

MS : *erythro* : *m/z* 509 (M+H⁺, 26%), 450 (38); Found : (M+H⁺), 509.2183
 C₂₉H₃₇O₄SiS requires (M+H⁺), 509.2182

threo : m/z 509 ($M+H^+$, 39%), 450 (68); Found : ($M+H^+$), 509.2180
 $C_{29}H_{37}O_4SiS$ requires ($M+H^+$), 509.2182

1H NMR ($CDCl_3$):

[*erythro*]: see Table 10,

[*threo*] : see Table 10.

10.8.4 *Erythro*- and *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoates (269)

Method : see paragraph 9.8.6

Reagents : methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **253** (197 mg, 0.41 mmol), BnSH (205 mg, 1.65 mmol, 4 equiv.), $SnCl_4$ (129 mg, 0.50 mmol, 1.2 equiv.), DCM (5ml)

Reaction time: 15 minutes at $-15^\circ C$ followed by 15 minutes at $5^\circ C$

Yield : *erythro* : 74 mg, (light yellow oil)

threo : 82 mg, (white needles), m.p. $140^\circ C$

total yield : 70 %

de : 6 %

R_f : *erythro* : 0.30 (B)

threo : 0.35 (B)

IR : *erythro* : ν_{max} 1736 (CO), 1530, 1490 and 1249 cm^{-1}

threo : ν_{max} 1732 (CO), 1590, 1514 and 1284 cm^{-1}

MS : *erythro* : m/z 539 ($M+H^+$, 24%), 480 (40); Found : ($M+H^+$), 539.2288
 $C_{30}H_{39}O_5SiS$ requires ($M+H^+$), 539.2287

threo : m/z 539 ($M+H^+$, 29%), 480 (28); Found : ($M+H^+$), 539.2287
 $C_{30}H_{39}O_5SiS$ requires ($M+H^+$), 539.2287

¹H NMR (CDCl₃):

[*erythro*]: see Table 10,

[*threo*] : see Table 10.

10.8.5 ***Threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxyphenyl)propanoates (270)**

Method : see paragraph 9.8.6

Reagents : methyl 2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate **254** (190 mg, 0.40 mmol), BnSH (198 mg, 1.59 mmol, 4 equiv.), SnCl₄ (125 mg, 0.48 mmol, 1.2 equiv.), DCM (5ml)

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *threo* : 178 mg, (white needles), m.p. 129°C

total yield : 83 %

de : 100 %

R_f : *threo* : 0.23 (B)

IR : ν_{\max} 1734 (CO), 1620, 1535 and 1254 cm⁻¹

MS : *m/z* 539 (M+H⁺, 26%), 480(42), Found : (M+H⁺), 539.2287 C₃₀H₃₉O₅SiS requires (M+H⁺), 539.2287

¹H NMR (CDCl₃):

[*threo*]: see Table 10.

10.8.6 ***Erythro*- and *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoates (271)**

Method : see paragraph 9.8.6

Reagents : methyl 2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **255** (262 mg, 0.52

mmol), BnSH (257 mg, 2.07 mmol, 4 equiv.), SnCl₄ (162 mg, 0.62 mmol, 1.2 equiv.), DCM (5ml)

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 113 mg, (yellow oil)
threo : 126 mg, (white needles), m.p. 160°C
total yield : 81 %
de : 6 %

R_f : *erythro* : 0.25 (B)
threo : 0.27 (B)

IR : *erythro* : ν_{\max} 1738 (CO), 1632, 1510 and 1464 cm⁻¹
threo : ν_{\max} 1734 (CO), 1596, 1518 and 1484 cm⁻¹

MS : *erythro* : *m/z* 569 (M+H⁺, 20%), 510 (38); Found : (M+H⁺), 569.2393
C₃₁H₄₁O₆SiS requires (M+H⁺), 569.2393
threo : *m/z* 569 (M+H⁺, 39%), 510 (31); Found : (M+H⁺), 569.2390
C₃₁H₄₁O₆SiS requires (M+H⁺), 569.2393

¹H NMR (CDCl₃):

[*erythro*, plate 11]: see Table 10,

[*threo*, plate 12] : see Table 10.

10.9 LiAlH₄ REDUCTION OF BENZYL SULFANYLPROPANOATES (266-271)

10.9.1 *Threo*-3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-*O*-isopropylphenyl)propan-1-ol (263)

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-*O*-isopropylphenyl)propanoate **266** (237 mg, 0.51 mmol), Et₂O (10ml), LiAlH₄ (194 mg, 5.10 mmol, 10 equiv.).

Reaction time: 10 minutes at 10°C

Yield : 212 mg, 93 % (yellow oil)

R_f : 0.41 (B:A 9:1)

¹H NMR (CDCl₃): see Table 8.

10.9.2 *Threo*-3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-*O*-isopropyl-4''-methoxyphenyl)propan-1-ol (**264**)

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-*O*-isopropyl-4''-methoxyphenyl)propanoate **267** (110 mg, 0.24 mmol), Et₂O (5ml), LiAlH₄ (91 mg, 2.40 mmol, 10 equiv.).

Reaction time: 10 minutes at 10°C

Yield : 92 mg, 90 % (light yellow oil)

R_f : 0.40 (B:A 9:1)

¹H NMR (CDCl₃): see Table 8.

10.9.3 *Threo*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxyphenyl)-propan-1-ol (**272**)

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyloxyphenyl)-3-(2'-hydroxyphenyl)propanoate **268** (202 mg, 0.40 mmol), LiAlH₄ (152 mg, 4.00 mmol, 10 equiv.), Et₂O (5ml)

Reaction time: 10 minutes at 10°C

Yield : 153 mg, 80% (yellow oil)

R_f : 0.44 (B:A 9:1)
MS : *m/z* 481 (M+H⁺, 41%), 463(36), Found : (M+H⁺), 481.2230 C₂₈H₃₇O₃SiS
requires (M+H⁺), 481.2233

¹H NMR (CDCl₃): see Table 11.

10.9.4 ***Erythro*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (273)**

Method : see paragraph 9.8.7
Reagents : *erythro*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate **269** (197 mg, 0.37 mmol), LiAlH₄ (140 mg, 3.70 mmol, 10 equiv.), Et₂O (5ml)

Reaction time: 10 minutes at 10°C

Yield : 140 mg, 75% (yellow oil)

R_f : 0.54 (B:A 9:1)
MS : *m/z* 511 (M+H⁺, 30%), 493(48), Found : (M+H⁺), 511.2336 C₂₉H₃₉O₄SiS
requires (M+H⁺), 511.2338

¹H NMR (CDCl₃): see Table 11.

10.9.5 ***Threo*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (273)**

Method : see paragraph 9.8.7
Reagents : *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate **269** (215 mg, 0.40 mmol), LiAlH₄ (152 mg, 4.00 mmol, 10 equiv.), Et₂O (5ml)

Reaction time: 10 minutes at 10°C

Yield : 157 mg, 77% (yellow oil)

R_f : 0.54 (B:A 9:1)
MS : *m/z* 511 (M+H⁺, 28%), 493(40), Found : (M+H⁺), 511.2340 C₂₉H₃₉O₄SiS
requires (M+H⁺), 511.2338

¹H NMR (CDCl₃): see Table 11.

10.9.6 ***Threo*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxyphenyl)propan-1-ol (274)**

Method : see paragraph 9.8.7
Reagents : *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxyphenyl)propanoate **270** (215 mg, 0.40 mmol), LiAlH₄ (152 mg, 4.00 mmol, 10 equiv.), Et₂O (5ml)
Reaction time: 10 minutes at 10°C
Yield : 198 mg, 97% (yellow oil)

R_f : 0.52 (B:A 9:1)
MS : *m/z* 511 (M+H⁺, 38%), 493(44), Found : (M+H⁺), 511.2338 C₂₉H₃₉O₄SiS
requires (M+H⁺), 511.2338

¹H NMR (CDCl₃): see Table 11.

10.9.7 ***Erythro*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (275)**

Method : see paragraph 9.8.7
Reagents : *erythro*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate **271** (229 mg, 0.40 mmol), LiAlH₄ (152 mg, 4.00 mmol, 10 equiv.), Et₂O (5ml)
Reaction time: 10 minutes at 10°C
Yield : 174 mg, 80% (yellow oil)

R_f : 0.47 (B:A 9:1)

MS : *m/z* 541 (M+H⁺, 40%), 523(50), Found : (M+H⁺), 541.2443 C₃₀H₄₁O₅SiS
requires (M+H⁺), 541.2444

¹H NMR (CDCl₃, plate 13): see Table 11.

10.9.8 *Threo*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (275)

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate 271 (226 mg, 0.40 mmol), LiAlH₄ (152 mg, 4.00 mmol, 10 equiv.), Et₂O (5ml)

Reaction time: 10 minutes at 10°C

Yield : 168 mg, 78% (yellow oils)

R_f : 0.47 (B:A 9:1)

MS : *m/z* 541 (M+H⁺, 25%), 523(64), Found : (M+H⁺), 541.2444 C₃₀H₄₁O₅SiS
requires (M+H⁺), 541.2444

¹H NMR (CDCl₃, plate 14): see Table 11.

10.10 SYNTHESIS OF 4-BENZYL SULFANYLISOFLAVANS (279-286)

10.10.1 *Cis*-4-benzylsulfanyl-2'-*O*-isopropylisoflavan (279)

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-*O*-isopropylphenyl)propan-1-ol 262 (67 mg, 0.16 mmol), TPP (430 mg, 1.64 mmol, 10 equiv.), DEAD (143 mg, 0.82 mmol, 5 equiv.), THF (3ml).

Reaction time: 4 hours at room temperature.

Yield : 59 mg, 92 % (light yellow oil)

R_f : 0.83 (B)

MS : *m/z* 421 (M+H⁺, 55%), 395(38), Found : (M+H⁺), 421.1837 C₂₆H₂₉O₃S
requires (M+H⁺), 421.1837

¹H NMR (CDCl₃): see Table 13.

10.10.2 *Cis*-4-benzylsulfanyl-2'-*O*-isopropyl-7-methoxyisoflavan (280)

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-*O*-isopropylphenyl)propan-1-ol **263** (248 mg, 0.56 mmol), TPP (1.483 g, 5.65 mmol, 10 equiv.), DEAD (492 mg, 2.83 mmol, 5 equiv.), THF (6ml).

Reaction time: 4 hours at room temperature.

Yield : 210 mg, 92 % (light yellow oil)

R_f : 0.77 (B)

¹H NMR (CDCl₃): see Table 13.

10.10.3 *Cis*-4-benzylsulfanyl-2'-*O*-isopropyl-4'-methoxyisoflavan (281)

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-3-(2'-hydroxyphenyl)-2-(2''-*O*-isopropyl-4''-methoxyphenyl)propan-1-ol **264** (248 mg, 0.58 mmol), TPP (1.531 g, 5.84 mmol, 10 equiv.), DEAD (508 mg, 2.92 mmol, 5 equiv.), THF (6ml).

Reaction time: 4 hours at room temperature.

Yield : 204 mg, 83 % (light yellow oil)

R_f : 0.74 (B)

¹H NMR (CDCl₃): see Table 13.

10.10.4 *Cis-4-benzylsulfanyl-2'-O-isopropyl-4',7-dimethoxyisoflavan (282)*

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-3-(2'-hydroxy-4'-methoxyphenyl)-2-(2''-*O*-isopropyl-4''-methoxyphenyl)propan-1-ol **265** (156 mg, 0.33 mmol), TPP (873 mg, 3.33 mmol, 10 equiv.), DEAD (290 mg, 1.66 mmol, 5 equiv.), THF (3ml).

Reaction time: 4 hours at room temperature.

Yield : 146 mg, 97 % (light yellow oil)

R_f : 0.56 (B)

¹H NMR (CDCl₃): see Table 13.

10.10.5 *Cis-4-benzylsulfanyl-2'-O-t-butyldimethylsilylisoflavan (283)*

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxyphenyl)propan-1-ol **272** (96 mg, 0.20 mmol), TPP (525 mg, 2.00 mmol, 10 equiv.), DEAD (174 mg, 1.00 mmol, 5 equiv.), THF (3ml)

Reaction time: 4 hours at room temperature.

Yield : 75 mg, 81% (white needles), m.p. 117°C

R_f : 0.78 (B)

MS : *m/z* 463 (M+H⁺, 28%), 348(15), Found : (M+H⁺), 463.2127 C₂₈H₃₅O₂SiS requires (M+H⁺), 463.2127

¹H NMR (CDCl₃): see Table 14.

10.10.6 ***Cis*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-7-methoxyisoflavan (284)**

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-2-(2"-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol **273** (101 mg, 0.20 mmol), TPP (525 mg, 2.00 mmol, 10 equiv.), DEAD (174 mg, 1.00 mmol, 5 equiv.), THF (3ml)

Reaction time: 4 hours at room temperature.

Yield : 80 mg, 82% (yellow oil)

R_f : 0.79 (B)

MS : *m/z* 493 (M+H⁺, 28%), 378(23), Found : (M+H⁺), 493.2233 C₂₉H₃₇O₃SiS requires (M+H⁺), 493.2233

¹H NMR (CDCl₃): see Table 14.

10.10.7 ***Trans*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-7-methoxyisoflavan (284)**

Method : see paragraph 9.8.8

Reagents : *erythro*-3-benzylsulfanyl-2-(2"-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol **273** (98 mg, 0.19 mmol), TPP (498 mg, 1.90 mmol, 10 equiv.), DEAD (165 mg, 0.95 mmol, 5 equiv.), THF (3ml)

Reaction time: 4 hours at room temperature.

Yield : 76 mg, 80% (yellow oil)

R_f : 0.79 (B)

MS : *m/z* 493 (M+H⁺, 37%), 378(18), Found : (M+H⁺), 493.2230 C₂₉H₃₇O₃SiS requires (M+H⁺), 493.2233

¹H NMR (CDCl₃): see Table 14.

10.10.8 ***Cis*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4'-methoxyisoflavan (285)**

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxy-phenyl)-3-(2'-hydroxyphenyl)propan-1-ol **274** (101 mg, 0.2 mmol), TPP (525 mg, 2.0 mmol, 10 equiv.), DEAD (174 mg, 1.00 mmol, 5 equiv.), THF (3ml)

Reaction time: 4 hours at room temperature.

Yield : 91 mg, 93% (white needles), m.p. 92°C

R_f : 0.79 (B)

MS : *m/z* 493 (M+H⁺, 32%), 378(19), Found : (M+H⁺), 493.2234 C₂₉H₃₇O₃SiS requires (M+H⁺), 493.2233

¹H NMR (CDCl₃): see Table 14.

10.10.9 ***Cis*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan (286)**

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxy-phenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol **275** (107 mg, 0.20 mmol), TPP (525 mg, 2.00 mmol, 10 equiv.), DEAD (174 mg, 1.00 mmol, 5 equiv.), THF (3ml)

Reaction time: 4 hours at room temperature.

Yield : 89 mg, 86% (yellow oil)

R_f : 0.68 (B)

MS : *m/z* 523 (M+H⁺, 24%), 408(33), Found : (M+H⁺), 523.2340 C₃₀H₃₉O₄SiS requires (M+H⁺), 523.2338

¹H NMR (CDCl₃, plate 15): see Table 14.

10.10.10 ***Trans*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan (286)**

Method : see paragraph 9.8.8

Reagents : *erythro*-3-benzylsulfanyl-2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol **275** (84 mg, 0.19 mmol), TPP (498 mg, 1.90 mmol, 10 equiv.), DEAD (165 mg, 0.95 mmol, 5 equiv.), THF (3ml)

Reaction time: 4 hours at room temperature.

Yield : 84 mg, 85% (yellow oil)

R_f : 0.68 (B)

MS : *m/z* 523 (M+H⁺, 34%), 408(25), Found : (M+H⁺), 523.2338 C₃₀H₃₉O₄SiS requires (M+H⁺), 523.2338

¹H NMR (CDCl₃, plate 16): see Table 14.

10.11 **CLEAVAGE OF THE 2'-*O*-ISOPROPYL ETHERS (279-282)**

10.11.1 **BBr₃**

Method : A solution of 2'-*O*-isopropylisoflavan in dry DCM (5ml) was carefully treated with BBr₃ (1 equiv.) at room temperature. The reaction mixture was stirred for 1 hour after which a 10% NaOH solution (*ca.* 10ml) was added dropwise until the reaction mixture turned milky. Using diluted HCl the mixture was acidified to pH = 6. Following extraction with EtOAc (3x20ml) the combined organic layer was washed with water (3x50ml), dried (Na₂SO₄) and evaporated. The product was purified by PLC.

10.11.1.1 Cis-4-benzylsulfanyl-2'-hydroxyisoflavan (294)

Method : see paragraph 10.11.1

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropylisoflavan **279** (102 mg, 0.26 mmol),
BBr₃ (65 mg, 0.26 mmol, 1 equiv.), DCM (5ml).

Reaction time: 1 hour at room temperature.

Yield : 86 mg, 94 % (yellow oil)

R_f : 0.33 (B)

MS : *m/z* 349 (M+H⁺, 65%), 331(28), Found : (M+H⁺), 349.1260; C₂₂H₂₁O₂S
(M+H⁺) requires 349.1262

¹H NMR (CDCl₃): see Table 15.

10.11.1.2 Cis-4-benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan (295)

Method : see paragraph 10.11.1

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropyl-7-methoxyisoflavan **280** (100 mg, 0.24
mmol), BBr₃ (60 mg, 0.24 mmol, 1 equiv.), DCM (5ml).

Reaction time: 1 hour at room temperature.

Yield : 0 mg, 0 %

10.11.1.3 Cis-4-benzylsulfanyl-2'-hydroxy-4'-methoxyisoflavan (296)

Method : see paragraph 10.11.1

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropyl-4'-methoxyisoflavan **281** (98 mg, 0.23
mmol), BBr₃ (58 mg, 0.23 mmol, 1 equiv.), DCM (5ml).

Reaction time: 1 hour at room temperature.

Yield : 0 mg, 0 %

10.11.1.4 Cis-4-benzylsulfanyl-2'-hydroxy-4',7-dimethoxyisoflavan (297)

Method : see paragraph 10.11.1

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropyl-4',7-dimethoxyisoflavan **282** (20 mg, 0.05 mmol), BBr₃ (13 mg, 0.05 mmol, 1 equiv.), DCM (1ml).

Reaction time: 1 hour at room temperature.

Yield : 0 mg, 0 %

10.11.2 **BCl₃ / TiCl₄ / AlCl₃**

Method : Deprotection of isopropylethers employing BCl₃, TiCl₄ or AlCl₃, was attempted *via* the same procedure as used for BBr₃ in paragraph 10.11.1.

10.11.2.1 Cis-4-benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan (295)

Method : see paragraph 10.11.2

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropyl-7-methoxyisoflavan **280** (0.12 mmol), BCl₃ / TiCl₄ / AlCl₃ (±0.12 mmol, 1 equiv.), DCM (5ml).

Reaction time: 1 hour at room temperature.

Yield : 0 mg, 0 %; extensive decomposition occurred in all instances

10.11.2.2 Cis-4-benzylsulfanyl-2'-hydroxy-4'-methoxyisoflavan (296)

Method : see paragraph 10.11.2

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropyl-4'-methoxyisoflavan **281** (0.11 mmol), BCl₃ / TiCl₄ / AlCl₃ (±0.11 mmol, 1 equiv.), DCM (5ml).

Reaction time: 1 hour at room temperature.

Yield : 0 mg, 0 %; extensive decomposition occurred in all instances

10.11.2.3 Cis-4-benzylsulfanyl-2'-hydroxy-4',7-dimethoxyisoflavan (297)

Method : see paragraph 10.11.2

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-isopropyl-4',7-dimethoxyisoflavan **282** (0.09 mmol), BCl₃ / TiCl₄ / AlCl₃ (±0.09 mmol, 1 equiv.), DCM (5ml).

Reaction time: 1 hour at room temperature.

Yield : 0 mg, 0 %; extensive decomposition occurred in all instances

10.12 **TBAF CLEAVAGE OF THE 2'-*O*-TBDMS ETHERS (283-286)**

Method : The respective 2'-*O*-*t*-butyldimethylsilylisoflavans (0.20 mmol) in anhydrous THF (5ml) at 25°C were treated with TBAF suspended on silica (2 equiv.) for 15 minutes. After the addition of moist THF (5ml) the solvent was evaporated and the products separated by PLC affording the 2'-hydroxyisoflavans.

10.12.1 **Cis-4-Benzylsulfanyl-2'-hydroxyisoflavan (294)**

Method : see paragraph 10.12

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilylisoflavan **283** (91 mg, 0.2 mmol), TBAF (silica)(0.4 mmol, 2 equiv.), THF (5ml)

Reaction time: 15 minutes at room temperature.

Yield : 66 mg, 96% (light yellow oil)

R_f : 0.33 (B)

MS : see paragraph 10.11.1.1

¹H NMR (CDCl₃): see Table 15.

10.12.2 *Cis*-4-Benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan (295)

Method : see paragraph 10.12

Reagents : *cis*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-7-methoxyisoflavan **284** (97 mg, 0.20 mmol), TBAF (silica)(0.40 mmol, 2 equiv.), THF (5ml)

Reaction time: 15 minutes at room temperature.

Yield : 74 mg, 99% (light yellow oil)

R_f : 0.41 (B)

MS : *m/z* 379 (M+H⁺, 34%), 361(14), Found : (M+H⁺), 379.1368 C₂₃H₂₃O₃S requires (M+H⁺), 379.1368

¹H NMR (CDCl₃): see Table 15.

10.12.3 *Trans*-4-Benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan (295)

Method : see paragraph 10.12

Reagents : *trans*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-7-methoxyisoflavan **284** (92 mg, 0.19 mmol), TBAF (silica)(0.38 mmol, 2 equiv.), THF (5ml)

Reaction time: 15 minutes at room temperature.

Yield : 70 mg, 99% (light yellow oil)

R_f : 0.41 (B)

MS : *m/z* 379 (M+H⁺, 30%), 361(26), Found : (M+H⁺), 379.1370 C₂₃H₂₃O₃S requires (M+H⁺), 379.1368

¹H NMR (CDCl₃): see Table 15.

10.12.4 ***Cis-4-Benzylsulfanyl-2'-hydroxy-4'-methoxyisoflavan (296)***

Method : see paragraph 10.12

Reagents : *cis-4-benzylsulfanyl-2'-O-t-butyl*dimethylsilyl-4'-methoxyisoflavan **285**
(97 mg, 0.20 mmol), TBAF (silica)(0.40 mmol, 2 equiv.), THF (5ml)

Reaction time: 15 minutes at room temperature.

Yield : 74 mg, 99% (light yellow oil)

R_f : 0.24 (B)

MS : *m/z* 379 (M+H⁺, 32%), 361(20), Found : (M+H⁺), 379.1368 C₂₃H₂₃O₃S
requires (M+H⁺), 379.1368

¹H NMR (CDCl₃): see Table 15.

10.12.5 ***Cis-4-benzylsulfanyl-2'-hydroxy-4',7-dimethoxyisoflavan (297)***

Method : see paragraph 10.12

Reagents : *cis-4-benzylsulfanyl-2'-O-t-butyl*dimethylsilyl-4',7-dimethoxyisoflavan **286**
(103 mg, 0.20 mmol), TBAF (silica)(0.40 mmol, 2 equiv.), THF (5ml)

Reaction time: 15 minutes at room temperature.

Yield : 80 mg, 99% (light yellow oil)

R_f : 0.55 (B)

MS : *m/z* 409 (M+H⁺, 28%), 391(16), Found : (M+H⁺), 409.1473 C₂₄H₂₅O₄S
requires (M+H⁺), 409.1474

¹H NMR (CDCl₃, plate 17): see Table 15.

10.12.6 ***Trans-4-benzylsulfanyl-2'-hydroxy-4',7-dimethoxyisoflavan (297)***

Method : see paragraph 10.12

Reagents : *trans*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan
286 (111 mg, 0.21 mmol), TBAF (silica)(0.41 mmol, 2 equiv.), THF (5ml)

Reaction time: 15 minutes at room temperature.

Yield : 86 mg, 99% (light yellow oil)

R_f : 0.55 (B)

MS : *m/z* 409 (M+H⁺, 36%), 391(49), Found : (M+H⁺), 409.1475 C₂₄H₂₅O₄S
requires (M+H⁺), 409.1474

¹H NMR (CDCl₃, plate 18): see Table 15.

10.13 SYNTHESIS OF PTEROCARPANS

Method A : 2'-Hydroxyisoflavans (0.07→0.12 mmol) were dissolved in anhydrous DCM (5ml) and treated with AgBF₄ (4 equiv.). When no starting material could be detected (TLC), moist DCM (2ml) was added, the solvent evaporated and the mixtures separated by PLC and crystallized from ethanol.

Method B : 2'-Hydroxyisoflavans (0.07→0.1 mmol) were dissolved in anhydrous DCM (2ml) and treated with AgOTf (5 equiv.). When no starting material could be detected on TLC, moist Me₂CO (2ml) was added, the solvent evaporated and the mixtures separated by PLC and crystallized from ethanol.

Method C : 2'-Hydroxyisoflavan (0.1 mmol) was dissolved in anhydrous DCM (2ml) and treated with DMTSF (1.5 equiv.). After the starting material was consumed (TLC) moist DCM (2ml) was added, the solvent evaporated and the mixtures separated on PLC and crystallized from ethanol.

10.13.1 (\pm) **6a,11a-cis-Pterocarpan (298)**

Method A : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxyisoflavan **294** (51 mg, 0.12 mmol), AgBF₄ (23 mg, 0.47 mmol, 4 equiv.), DCM (5ml)

Reaction time: 16 hours at 25°C

Yield : 22 mg, 82% (white plates), m.p. 123°C

Method B : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxyisoflavan **294** (34 mg, 0.10 mmol), AgOTf (128 mg, 0.5 mmol, 5 equiv.), DCM (2ml)

Reaction time: 16 hours at 25°C

Yield : 18 mg, 82% (white plates), m.p. 123°C (lit.,²⁰⁷ m.p. 125-126°)

R_f : 0.75 (B)

MS : *m/z* 225 (M+H⁺, 68%), 207(26), C₁₅H₁₃O₂ (M+H⁺), calcd as 225.0916; found 225.0918

¹H NMR (C₆D₆, plate 19): see Table 18.

¹³C NMR (CDCl₃): δ 40.74 (C-6a), 66.74 (C-6), 78.01 (C-11a), 110.62, 117.85, 120.40, 121.37, 122.16, 125.15, 127.46, 129.64, 130.48, 131.52, 155.87, 159.68.

10.13.2 (\pm)-**6a,11a-cis-3-Methoxypterocarpan (299)**

Method A : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan **295** (30 mg, 0.07 mmol), AgBF₄ (55 mg, 0.28 mmol, 4 equiv.), DCM (5ml)

Reaction time: 16 hours at 25°C

Yield : 4.6 mg, 23% (white plates), m.p. 94°C

Method B : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan **295** (37 mg, 0.09 mmol),
AgOTf (116 mg, 0.45 mmol, 5 equiv.), DCM (2ml)

Reaction time: 2 hours at 25°C

Yield : 14 mg, 57% (white plates), m.p. 94°C (lit.,⁵⁵ m.p. 94-95°)

R_f : 0.65 (B)

MS : *m/z* 255 (M+H⁺, 48%), 237(18), C₁₆H₁₅O₃ (M+H⁺), calcd as 255.1021;
found 255.1022

¹H NMR (C₆D₆, plate 20): see Table 18.

¹³C NMR (CDCl₃): δ 40.54 (C-6a), 55.79 (OCH₃), 66.76 (C-6), 78.11 (C-11a), 102.03,
109.63, 110.62, 112.66, 121.27, 125.12, 127.54, 129.61, 132.31, 156.99, 159.77, 161.45

10.13.3 (±)-6a,11a-cis-9-Methoxypterocarpan (**300**)

Method A : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-4'-methoxyisoflavan **296** (30 mg, 0.08 mmol),
AgBF₄ (58 mg, 0.30 mmol, 4 equiv.), DCM (5ml)

Reaction time: 16 hours at 25°C

Yield : 0 mg, 0%

Method B : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-4'-methoxyisoflavan **296** (25 mg, 0.07 mmol),
AgOTf (90 mg, 0.35 mmol, 5 equiv.), DCM (2ml)

Reaction time: 2 hours at 25°C

Yield : 0 mg, 0%

Method C : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-4'-methoxyisoflavan **296** (34 mg, 0.09 mmol),
DMTSF (27 mg, 0.14 mmol, 1.5 equiv.), DCM (2ml)

Reaction time: 1 hour at -10°C

Yield : 9 mg, 39% (white plates), m.p. 112°C

R_f : 0.53 (B)

MS : *m/z* 255 (M+H⁺, 42%), 237(35), Found : (M+H⁺), 255.1021 C₁₆H₁₅O₃
requires (M+H⁺), 255.1021

¹H NMR (C₆D₆, plate 21): see Table 18.

¹³C NMR (CDCl₃): δ 40.15 (C-6a), 55.92 (OCH₃), 66.98 (C-6), 78.89 (C-11a), 97.31, 106.88, 117.85, 119.46, 120.50, 122.12, 125.19, 130.48, 131.47, 155.90, 161.05, 161.56.

10.13.4 (±)-6a,11a-cis-3,9-dimethoxypterocarpan (301)

Method A : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan **297** (30 mg, 0.07 mmol),
AgBF₄ (56 mg, 0.29 mmol, 4 equiv.), DCM (5ml)

Reaction time: 16 hours at 25°C

Yield : 3 mg, 14%

Method B : see paragraph 10.13

Reagents : 4-benzylsulfanyl-2'-hydroxy-7-methoxyisoflavan **297** (40 mg, 0.10 mmol),
AgOTf (128 mg, 0.5 mmol, 5 equiv.), DCM (2ml)

Reaction time: 7 minutes at 0°C

Yield : 14 mg, 50% (white plates), m.p. 125°C (lit.,¹⁶³ m.p. 123-125°)

R_f : 0.48 (B)

MS : *m/z* 285 (M+H⁺, 54%), 267(39), Found : C₁₇H₁₇O₄ (M+H⁺), calcd as
285.1127; found 285.1127

¹H NMR (C₆D₆, plate 22): see Table 18.

¹³C NMR (CDCl₃): δ 39.94 (C-6a), 55.79 (3-OCH₃), 55.91 (9-OCH₃), 67.00 (C-6), 78.99

(C-11a), 97.30, 102.02, 106.75, 109.58, 112.75, 119.53, 125.15, 132.24, 157.02, 161.12, 161.43, 161.53.

10.14 SHORTENED APPROACH TO PTEROCARPANS

10.14.1 Aldol condensation

Erythro- and *threo-*methyl 3-hydroxy-2,3-di(2'-*O*-methoxymethylphenyl)-propanoates (303)

Method : see paragraph 9.8.5

Reagents : methyl 2-*O*-methoxymethylphenylacetate **223** (493 mg, 2.35 mmol), diisopropylamine (262 mg, 2.59 mmol, 1.1 equiv.), *n*BuLi (0.90 mmol, 1.1 equiv.), Et₂O (3ml), 2-*O*-methoxymethylbenzaldehyde **216** (391 mg, 2.35 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by another 30 minutes and then 2 hours at 0°C

Yield : *erythro* : 289 mg, (light yellow oil)
threo : 353 mg, (yellow needles), m.p. 80°C
total yield : 73 %
de : 10 %

R_f : *erythro* : 0.60 (B:A 9:1)
threo : 0.46 (B:A 9:1)

IR : *erythro* : ν_{\max} 2954, 1732 (CO), 1549 and 1386 cm⁻¹
threo : ν_{\max} 2964, 1716 (CO), 1556 and 1380 cm⁻¹

¹H NMR (CDCl₃):

[*erythro*]: δ 3.35, 3.57 (2xOCH₂OCH₃, 2xs, 2x3H), 3.69 (OCH₃, s, 3H), 3.70 (OH, d, J = 4.1 Hz, 1H), 4.65, 4.76 (OCH₂OCH₃, 2xd, J = 6.8 Hz, 2x1H), 4.70 (2-H, d, J = 4.1 Hz, 1H), 5.26, 5.31 (OCH₂OCH₃, 2xd, J = 6.8 Hz, 2x1H), 5.75 (3-H, dd, J = 4.1, 4.1 Hz, 1H), 6.80 (5'-H, ddd, J = 1.1, 7.1, 7.1 Hz, 1H), 6.92 (3"-H, dd, J = 1.1, 7.9 Hz, 1H), 6.97 (5"-H,

ddd, J = 1.1, 7.1, 7.1 Hz, 1H), 7.04 (6'-H, dd, J = 1.9, 7.1 Hz, 1H), 7.07 (3'-H, dd, J = 1.1, 8.1 Hz, 1H), 7.15 (4''-H, ddd, J = 1.9, 7.1, 7.9 Hz, 1H), 7.21 (4'-H, ddd, J = 1.9, 7.1, 8.1 Hz, 1H), 7.30 (6''-H, dd, J = 1.9, 7.1 Hz, 1H),

[*threo*]: δ 3.41 (2xOCH₂OCH₃, 2xs, 2x3H), 3.71 (OCH₃, s, 3H), 3.96 (OH, d, J = 5.9 Hz, 1H), 4.49 (2-H, d, J = 8.9 Hz, 1H), 4.86, 4.87, 4.95, 4.98 (4xOCH₂OCH₃, 4xd, J = 6.8 Hz, 4x1H), 5.58 (3-H, dd, J = 5.9, 8.9 Hz, 1H), 6.83-7.00 (ArH, m, 4H), 7.09-7.15 (ArH, m, 2H), 7.24 (ArH, dd, J = 1.9, 7.5 Hz, 1H), 7.31 (ArH, dd, J = 1.9, 7.5 Hz, 1H).

10.14.2 SnCl₂/BnSH cleavage of the 2-O-MOM ethers

Erythro- and *threo*-methyl 3-benzylsulfanyl-2,3-di(2-hydroxyphenyl)-propanoate (304)

Method : see paragraph 9.8.6

Reagents : methyl 3-hydroxy-2,3-di(2-O-methoxymethylphenyl)propanoate **303** (280 mg, 0.74 mmol), BnSH (370 mg, 2.98 mmol, 4 equiv.), SnCl₄ (292 mg, 1.12 mmol, 1.5 equiv.), DCM (10ml).

Reaction time: 15 minutes at -15°C, then 15 minutes at 5°C

Yield : *erythro* : 12 mg, (yellow oil)

threo : 186 mg, (yellow oil)

total yield : 65 %

de : 88 %

R_f : *erythro* : 0.43 (B:A 9:1)

threo : 0.38 (B:A 9:1)

¹H NMR (CDCl₃):

[*erythro*]: δ 3.39, 3.52 (ArCH₂S, 2xd, J = 13.0 Hz, 2x1H), 3.52 (OCH₃, s, 3H), 4.52-4.68 (2-H, m, 1H), 4.79-4.93 (3-H, m, 1H), 6.80-7.12 (ArH, m, 6H), 7.18-7.30 (ArH; ArOH, m, 3H), 7.36-7.40 (ArH, m, 5H), 7.49-7.53 (ArOH, m, 1H),

[*threo*]: δ 3.62, 3.67 (ArCH₂S, 2xd, J = 13.1 Hz, 2x1H), 3.83 (OCH₃, s, 3H), 4.23 (2-

H, d, J = 11.9 Hz, 1H), 4.77 (3-H, d, J = 11.9 Hz, 1H), 6.56-6.65 (ArH, m, 2H), 6.71-6.83 (ArH, m, 4H), 6.90-6.95 (ArOH, m, 1H), 6.99-7.06 (ArH, m, 2H), 7.18-7.22 (ArH, m, 2H), 7.26-7.35 (ArH, m, 3H), 8.33-8.36 (ArOH, m, 1H).

10.14.3 **LiAlH₄ reduction of benzylsulfanylpropanoate (304)**

Threo-3-benzylsulfanyl-2,3-di(2-hydroxyphenyl)propan-1-ol (305)

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-benzylsulfanyl-2,3-di(2-hydroxyphenyl)propanoate **304** (32 mg, 0.09 mmol), Et₂O (2ml), LiAlH₄ (34 mg, 0.9 mmol, 10 equiv.).

Reaction time: 10 minutes at 10°C

Yield : 21 mg, 70 % (yellow oil)

R_f : 0.27 (B:A 9:1)

¹H NMR (CDCl₃): δ 2.51-2.59 (C₁-OH, m, 1H), 3.35 (2-H, ddd, J = 2.0, 4.5, 11.2 Hz, 1H), 3.53, 3.65 (ArCH₂S, 2xd, J = 13.1 Hz, 2x1H), 4.00 (1-H, d, J = 2.0, 11.2 Hz, 1H), 4.45 (1-H, d, J = 4.5, 11.2 Hz, 1H), 4.60 (3-H, d, J = 11.2 Hz, 1H), 6.54 (ArH, ddd, J = 1.1, 6.9, 7.0 Hz, 1H), 6.60 (ArH, dd, J = 1.9, 7.8 Hz, 1H), 6.68 (ArH, ddd, J = 1.1, 7.2, 7.2 Hz, 1H), 6.77 (ArH, dd, J = 1.1, 8.1 Hz, 1H), 6.81-6.86 (ArOH, m, 1H), 6.90 (ArH, dd, J = 1.1, 8.1 Hz, 1H), 6.99 (ArH, ddd, J = 1.9, 7.1, 8.0 Hz, 1H), 7.04 (ArH, ddd, J = 1.5, 7.1, 8.0 Hz, 1H), 7.20-7.38 (ArH, m, 6H), 8.32-8.38 (ArOH, m, 1H).

10.14.4 **Mitsunobu cyclisation**

3-(α-Benzylsulfanyl-2'-hydroxybenzyl)-2,3-dihydrobenzofuran (306)

Method : see paragraph 9.8.8

Reagents : 3-benzylsulfanyl-2,3-di(2-hydroxyphenyl)propan-1-ol **305** (21 mg, 0.06 mmol), TPP (149 mg, 0.57 mmol, 10 equiv.), DEAD (50 mg, 0.29 mmol, 5 equiv.), THF (2ml).

Reaction time: 4 hours at room temperature.

Yield : 13 mg, 65 % (light yellow oil)

R_f : 0.67 (B)

MS : *m/z* 349 (M+H⁺, 10%), 331(42), Found : (M+H⁺), 349.1260; C₂₂H₂₁O₂S
(M+H⁺) requires 349.1262

¹H NMR (CDCl₃, plate 23): δ 3.53, 3.64 (ArCH₂S, 2xd, J = 13.2 Hz, 2x1H), 3.86 (α-H,d, J = 11.0 Hz, 1H), 3.99 (3-H, ddd, J = 5.5, 8.0, 11.0 Hz, 1H), 4.58 (2-H, dd, J = 5.5, 9.5 Hz, 1H), 4.63 (2-H, dd, J = 8.0, 9.5 Hz, 1H), 5.96-6.00 (4-H, m, 1H), 6.54 (5-H, ddd, J = 1.0, 7.5, 7.5 Hz, 1H), 6.72-6.76 (3'-;5'-H, m, 2H), 6.85 (4'-H, ddd, J = 1.1, 7.5, 7.5 Hz, 1H), 7.00 (7-H, dd, J = 1.0, 7.5 Hz, 1H), 7.02 (ArOH, s, 1H), 7.05 (6-H, ddd, J = 1.5, 7.5, 7.5 Hz, 1H), 7.18 (6'-H, dd, J = 1.1, 7.5 Hz, 1H), 7.25-7.34 (ArH, m, 5H).

CHAPTER 11

SYNTHESIS OF RACEMIC *TRANS*-PTEROCARPANS

11.1 CYCLISATION OF THE PTEROCARPAN C-RING

2-(2'-Hydroxyphenyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran (308)

Method : A solution of *threo*-methyl 3-benzylsulfanyl-2,3-di(2-hydroxyphenyl)-propanoate **304** (141 mg, 0.36 mmol) in anhydrous DCM (5ml) was treated with AgBF₄ (70 mg, 0.36 mmol, 1 equiv.) for 24 hours at room temperature. When no starting material could be detected (TLC), moist DCM (5ml) was added, the solvent evaporated and the mixture separated by PLC to yield the benzofuran **308**.

Yield : 45 mg, 47 % (yellow oil)

R_f : 0.53 (B:A 9:1)

IR : ν_{\max} 1738 (CO), 1717, 1696 and 1609 cm⁻¹

MS : *m/z* 271 (M+H⁺, 36%), 212(38), Found : (M+H⁺), 271.0973; C₁₆H₁₅O₄
(M+H⁺) requires 271.0970

¹H NMR (CDCl₃, plate 24): δ 3.89 (OCH₃, s, 3H), 4.40 (2-H, d, J = 8.5 Hz, 1H), 6.28 (3-H, d, J = 8.5 Hz, 1H), 6.66-6.72 (ArOH, m, 1H), 6.90-7.01 (ArH, m, 4H), 7.21-7.42 (ArH, m, 4H).

11.2 REDUCTION OF THE METHYLPHENYLACETATES

2-(2'-Hydroxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzofuran (309)

Method : see paragraph 9.8.7

Reagents : 2-(2'-hydroxyphenyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran **308** (41 mg, 0.15 mmol), Et₂O (2ml), LiAlH₄ (57 mg, 1.50 mmol, 10 equiv.).

Reaction time: 10 minutes at 25°C

Yield : 34 mg, 93 % (yellow oil)

R_f : 0.27 (B:A 9:1)

MS : *m/z* 243 (M+H⁺, 18%), 225(36), Found : (M+H⁺), 243.1021; C₁₅H₁₅O₃
(M+H⁺) requires 243.1021

¹H NMR (CDCl₃, plate 25): δ 2.51-2.62 (C₁-OH, m, 1H), 3.64 (3-H, ddd, J = 4.5, 5.1, 10.0 Hz, 1H), 3.95 (CH₂OH, dd, J = 9.9, 10.0 Hz, 1H), 4.13 (CH₂OH, dd, J = 4.5, 9.9 Hz, 1H), 5.92 (2-H, d, J = 5.1 Hz, 1H), 6.89-6.96 (ArH, m, 3H), 6.99-7.03 (ArH, m, 1H), 7.14-7.34 (ArH; ArOH, m, 5H).

11.3 MITSUNOBU CYCLISATION

Trans-pterocarpan (307)

Method : see paragraph 9.8.8

Reagents : 2-(2'-hydroxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzofuran **309** (34 mg, 0.14 mmol), TPP (368 mg, 1.40 mmol, 10 equiv.), DEAD (38% in THF, 120 mg, 0.70 mmol, 5 equiv.), THF (2ml).

Reaction time: 16 hours at room temperature.

Yield : 22 mg, 58 % (white needles), m.p. 89°C

R_f : 0.75 (B)

MS : m/z 225 ($M+H^+$, 38%), 208(40); Found : ($M+H^+$), 225.0916; $C_{15}H_{13}O_2$
($M+H^+$) requires 225.0916

1H NMR ($CDCl_3$, plate 26): δ 3.36 (6a-H, ddd, $J = 4.9, 12.1, 13.5$ Hz, 1H), 4.01 (6- H_{ax} ,
dd, $J = 10.0, 12.1$ Hz, 1H), 4.41 (6- H_{eq} , dd, $J = 4.9, 10.0$ Hz, 1H), 4.99 (11a-H, d, $J = 13.5$
Hz, 1H), 6.72-6.76 (ArH, m, 1H), 6.80-6.95 (ArH, m, 2H), 7.05-7.16 (ArH, m, 4H), 7.69-
7.74 (ArH, m, 1H).

CHAPTER 12

ASYMMETRIC SYNTHESIS OF *CIS*-PTEROCARPANS

12.1 ALDOL CONDENSATION EMPLOYING BORON TRIFLATE

Method : The methyl phenylacetate, dissolved in the minimum volume of anhydrous Et₂O, was transferred to a solution of *n*Bu₂OTf (1M in hexanes)(1.15 equiv.) and diisopropylethylamine (1.1 equiv.), in dry Et₂O (5-10ml) at -78°C. After stirring for one hour at -78°C the benzaldehyde (1 equiv.), dissolved in the minimum volume of dry Et₂O, was added. The mixture was stirred for 30 minutes at -78°C and then at 0°C for one hour followed by addition of a 0.4M phosphate buffer (30ml, pH=7) and extraction of the water layer with Et₂O (2x50ml). The ether was evaporated and the residue redissolved in MeOH (6ml) and treated with 30% H₂O₂ (2ml) at 0°C for 2 hours. After addition of water (25ml) and subsequent extraction with Et₂O (2x50ml), the combined ether layer was washed with water (3x100ml), dried (Na₂SO₄) and evaporated. The product was separated by PLC and crystallized from ethanol to give the 2,3-diphenylpropanoates.

12.1.1 Methyl 3-hydroxy-2,3-diphenylpropanoate (316)

Method : see paragraph 12.1

Reagents : methyl phenylacetate **220** (313 mg, 2.08 mmol), *n*Bu₂OTf (658 mg, 2.40mmol, 1.15 equiv.), diisopropylethylamine (296 mg, 2.29 mmol, 1.1 equiv.), Et₂O (10ml), benzyldehyde **314** (221 mg, 2.08 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : 376 mg, 70% (white flakes), mp. 88°C

R_f : 0.61 (B:A 9:1)

IR : ν_{\max} 1732 (CO), 1542, 1534, 1440 and 1252 cm⁻¹

¹H NMR (CDCl₃): δ 2.60 (OH, d, J = 2.5 Hz, 1H), 3.56 (COOCH₃, s, 3H), 3.90 (H-2, d, J = 7.2 Hz, 1H), 5.33 (H-3, dd, J = 2.5, 7.2 Hz), 7.25-7.40 (ArH, m, 10H).

12.1.2 *Threo*-methyl 3-hydroxy-3-(4'-methoxyphenyl)-2-phenylpropanoate (317)

Method : see paragraph 12.1

Reagents : methyl phenylacetate **220** (308 mg, 2.05 mmol), *n*Bu₂OTf (647 mg, 2.36 mmol, 1.15 equiv.), diisopropylethylamine (291 mg, 2.26 mmol, 1.1 equiv.), Et₂O (10ml), 4-methoxybenzaldehyde **315** (279 mg, 2.05 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : 147 mg, 25% (light yellow plates), mp. 82 °C

R_f : 0.44 (B:A 9:1)

IR : ν_{\max} 1732 (CO), 1614, 1516, 1306 and 1254 cm⁻¹

¹H NMR (CDCl₃): δ 3.03 (OH, d, J = 3.8 Hz, 1H), 3.75 (2xOCH₃, s, 6H), 3.88 (2-H, d, J = 9.5 Hz, 1H), 5.16 (3-H, dd, J = 3.8, 9.5 Hz, 1H), 6.73 (3'-;5'-H, d, J = 9.0 Hz, 2H), 7.04 (2'-;6'-H, d, J = 9.0 Hz, 2H), 7.08-7.13 (ArH, m, 2H), 7.16-7.23 (ArH, m, 3H).

12.1.3 *Erythro*- and *threo*-methyl 3-hydroxy-3-(4'-methoxyphenyl)-2-phenylpropanoates (317)

Method : see paragraph 12.1: note Et₂O was replaced by DCM as solvent.

Reagents : methyl phenylacetate **220** (312 mg, 2.08 mmol), *n*Bu₂OTf (655 mg, 2.39 mmol, 1.15 equiv.), diisopropylethylamine (326 mg, 2.52 mmol, 1.1 equiv.), DCM (20ml), 4-methoxybenzaldehyde **315** (283 mg, 2.08 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : *erythro* : 5 mg, (yellow oil)
threo : 459mg, (light yellow plates), mp. 82°C
total yield : 78 %
de : 98 %

R_f : *erythro* : 0.54 (B:A 9:1)

threo : 0.44 (B:A 9:1)

IR : *erythro* : ν_{max} 1734 (CO), 1623, 1512 and 1252 cm^{-1}

threo : see paragraph 12.1.2

$^1\text{H NMR}$ (CDCl_3):

[*erythro*]: δ 2.47 (OH, d, $J = 2.2\text{ Hz}$, 1H), 3.55, 3.81 (2xOCH₃, 2xs, 2x3H), 3.87 (2-H, d, $J = 7.8\text{ Hz}$, 1H), 5.26 (3-H, dd, $J = 2.2, 7.8\text{ Hz}$, 1H), 6.86 (3'-;5'-H, d, $J = 8.2\text{ Hz}$, 2H), 7.26 (2'-;6'-H, d, $J = 8.2\text{ Hz}$, 2H), 7.33-7.40 (ArH, m, 5H),

[*threo*]: see paragraph 12.1.2.

12.1.4 *Threo*-methyl 3-hydroxy-3-(2'-*O*-methoxymethylphenyl)-2-phenylpropanoate (318)

Method : see paragraph 12.1

Reagents : methyl phenylacetate **220** (300 mg, 2.00 mmol), *n*Bu₂OTf (630 mg, 2.30 mmol, 1.15 equiv.), diisopropylethylamine (284 mg, 2.20 mmol, 1.1 equiv.), Et₂O (10ml), 2-*O*-methoxymethylbenzaldehyde **216** (332 mg, 2.00 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : 164 mg, 26% (light yellow plates), mp. 80°C

R_f : 0.48 (B:A 9:1)

IR : ν_{max} 1732 (CO), 1496, 1458, 1266 and 1252 cm^{-1}

^1H NMR (CDCl_3): δ 3.45, 3.74 ($2\times\text{OCH}_3$, 2xs, $2\times 3\text{H}$), 3.59 (OH , d, $J = 7.0$ Hz, 1H), 4.13 (2-H, d, $J = 8.2$ Hz, 1H), 4.98, 5.06 (OCH_2OCH_3 , 2xd, $J = 6.9$ Hz, $2\times 1\text{H}$), 5.48 (3-H, dd, $J = 7.0, 8.2$ Hz, 1H), 6.92 (5'-H, ddd, $J = 1.1, 7.2, 7.2$ Hz, 1H), 7.00 (3'-H, dd, $J = 1.1, 8.1$ Hz, 1H), 7.16 (4'-H, ddd, $J = 1.9, 7.2, 8.1$ Hz, 1H), 7.18-7.21 (ArH, m, 5H), 7.23 (5'-H, dd, $J = 1.9, 7.2$ Hz, 1H).

12.1.5 *Erythro- and threo-methyl 3-hydroxy-3-(2'-O-methoxymethylphenyl)-2-phenylpropanoate (318)*

Method : see paragraph 12.1: note Et_2O was replaced with DCM as solvent.

Reagents : methyl phenylacetate **220** (303 mg, 2.02 mmol), $n\text{Bu}_2\text{OTf}$ (639 mg, 2.33mmol, 1.15 equiv.), diisopropylethylamine (287 mg, 2.22 mmol, 1.1 equiv.), DCM (10ml), 2-*O*-metoxymethylbenzaldehyde **216** (335 mg, 2.02 mmol, 1 equiv.), 30% H_2O_2 (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : *erythro* : 26 mg, (yellow oil),
threo : 408 mg (light yellow plates), mp. 80°C
total yield : 68 %
de : 88 %

R_f : *erythro* : 0.56 (B:A 9:1)
threo : 0.48 (B:A 9:1)

IR : *erythro* : ν_{max} 1730 (CO), 1500, 1464, 1254 and 1242 cm^{-1}
threo : see paragraph 12.1.4

^1H NMR (CDCl_3):

[*erythro*]: δ 3.52 (OH , d, $J = 5.0$ Hz, 1H), 3.56, 3.65 ($2\times\text{OCH}_3$, 2xs, $3\times 3\text{H}$), 4.15 (2-H, d, $J = 5.5$ Hz, 1H), 5.28, 5.31 (OCH_2OCH_3 , 2xd, $J = 6.9$ Hz, $2\times 1\text{H}$), 5.63 (3-H, dd, $J = 5.0, 5.5$ Hz, 1H), 6.86 (5'-H, ddd, $J = 1.1, 7.5, 7.5$ Hz, 1H), 7.02 (3'-H, dd, $J = 2.0, 7.5$ Hz, 1H), 7.11 (6'-H, dd, $J = 1.1, 8.1$ Hz, 1H), 7.15-7.28 (ArH, m, 6H),

[*threo*]: see paragraph 12.1.4.

12.1.6 *Erythro*- and *threo*-methyl 3-hydroxy-3-(2'-*O*-methoxymethylphenyl)-2-(2''-*O*-methoxyphenyl)propanoates (319)

Method : see paragraph 12.1: note Et₂O was replaced with DCM as solvent.

Reagents : methyl 2-*O*-methoxyphenylacetate **221** (110 mg, 0.61 mmol), *n*Bu₂OTf (192 mg, 0.70 mmol, 1.15 equiv.), diisopropylethylamine (87 mg, 0.67 mmol, 1.1 equiv.), DCM (3ml), 2-*O*-methoxymethylbenzaldehyde **216** (101 mg, 0.61 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : *erythro* : 27 mg (light yellow oil)

threo : 70 mg (light yellow crystals), mp. 84°C

total yield : 46 %

de : 44 %

R_F : *erythro* : 0.58 (B:A 9:1)

threo : 0.43 (B:A 9:1)

IR : *erythro* : ν_{\max} 1724 (CO), 1602, 1540 and 1516 cm⁻¹

threo : ν_{\max} 1732 (CO), 1618, 1536 and 1502 cm⁻¹

¹H NMR (CDCl₃):

[*erythro*]: δ 3.45, 3.57, 3.69 (3xOCH₃, 3xs, 3x3H), 3.69 (OH, d, J = 4.0 Hz, 1H), 4.69 (2-H, d, J = 4.0 Hz, 1H), 5.29 (OCH₂OCH₃, s, 2x1H), 5.71 (3-H, dd, J = 4.0, 4.0 Hz, 1H), 6.71-6.81 (ArH, m, 2H), 6.88-6.94 (ArH, m, 2H), 7.06-7.26 (ArH, m, 4H),

[*threo*]: δ 3.45, 3.61, 3.72 (3xOCH₃, 3xs, 3x3H), 3.89 (OH, d, J = 6.1 Hz, 1H), 4.55 (2-H, d, J = 8.9 Hz, 1H), 4.93, 5.00 (OCH₂OCH₃, 2xd, J = 6.9 Hz, 2x1H) 5.51 (3-H, dd, J = 6.1, 8.9 Hz, 1H), 6.69 (3''-H, dd, J = 1.0, 8.2 Hz, 1H), 6.82 (5''-H, ddd, J = 1.0, 7.0, 7.2 Hz, 1H), 6.89 (5'-H, ddd, J = ddd, J = 1.0, 7.0, 7.0 Hz, 1H), 6.95 (3'-H, dd, J = 1.0, 8.2 Hz, 1H), 7.11 (4''-H, ddd, J = 1.9, 7.0, 8.2 Hz, 1H), 7.14 (4'-H, ddd, J = 1.9, 7.0, 8.2 Hz, 1H), 7.26 (6'-H, dd, J = 1.9, 7.0 Hz, 1H), 7.27 (6''-H, dd, J = 1.9, 7.2 Hz, 1H).

12.1.7 ***Erythro*- and *threo*-methyl 3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoates (248)**

Method : see paragraph 12.1: note Et₂O was replaced with DCM as solvent.
Reagents : methyl 2-*O*-isopropylphenylacetate **224** (250 mg, 1.20 mmol), *n*Bu₂OTf (378 mg, 1.38 mmol, 1.15 equiv.), diisopropylethylamine (134 mg, 1.32 mmol, 1.1 equiv.), DCM (10ml), 2-*O*-methoxymethylbenzaldehyde **216** (199 mg, 1.20 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : *erythro* : 35 mg (light yellow oil)
threo : 40 mg (white crystals), mp. 44°C
total yield : 17 %
de : 6%

R_f : *erythro* : 0.63 (B:A 9:1)

threo : 0.53 (B:A 9:1)

IR : see paragraph 10.4.1

¹H NMR (CDCl₃):

[*erythro*]: see Table 4,

[*threo*] : see Table 4.

12.1.8 ***Threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate (252)**

Method : see paragraph 12.1: note Et₂O was replaced with DCM as solvent.
Reagents : methyl 2-*O*-*t*-butyldimethylsilylphenylacetate **225** (193 mg, 0.69 mmol), *n*Bu₂OTf (216 mg, 0.79mmol, 1.15 equiv.), diisopropylethylamine (98 mg, 0.76 mmol, 1.1 equiv.), DCM (3ml), 2-*O*-methoxymethylbenzaldehyde **216** (114 mg, 0.69 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : 43 mg, 14% (yellow crystals), mp. 113°C

R_f : 0.57 (B:A 9:1)

IR : see paragraph 10.4.5

¹H NMR (CDCl₃): see Table 5.

12.1.9 ***Threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate (253)**

Method : see paragraph 12.1: note Et₂O was replaced with DCM as solvent.

Reagents : methyl 2-*O*-*t*-butyldimethylsilylphenylacetate **225** (200 mg, 0.72 mmol), *n*Bu₂OTf (225 mg, 0.82mmol, 1.15 equiv.), diisopropylethylamine (102 mg, 0.79 mmol, 1.1 equiv.), DCM (3ml), 2-*O*-methoxymethylbenzaldehyde **217** (140 mg, 0.72 mmol, 1 equiv.), 30% H₂O₂ (2ml)

Reaction time: 30 minutes at -78°C followed by 1 hour at 0°C

Yield : 31 mg, 9% (yellow crystals), mp. 113°C

R_f : 0.57 (B:A 9:1)

IR : see paragraph 10.4.6

¹H NMR (CDCl₃): see Table 5.

12.2 **SYNTHESIS OF CHIRAL PROPANOATE DERIVATIVES (338-340, 342)**

12.2.1 **Direct synthesis of amide (326)**

Method : Methyl 2-*O*-*t*-butyldimethylsilylphenylacetate **225** (268 mg, 0.96 mmol) was dissolved in anhydrous CH₃CN (10ml) and treated with NaI (286 mg, 1.91 mmol, 2 equiv.) and TMSCl (208 mg, 1.91 mmol, 2 equiv.) at 25°C.

The reaction mixture was stirred for 1½ hours, after which diisopropylamine (193 mg, 1.91 mmol, 2 equiv.) was added. The mixture was stirred for a further 2 hours at 25°C before the addition of water (20 ml). Following extraction with EtOAc (3x25ml), the combined organic layer was washed with water (2x50ml), dried (Na₂SO₄), evaporated and the products separated by PLC.

Yield : 0 mg, 0%; The starting material was recovered (ca. 100%)

12.2.2 Hydrolysis of methyl phenylpropanoates

Method : To a stirred suspension of potassium *t*-butoxide (KOC(CH₃)₃)(8.0 equiv.) in anhydrous THF (10ml) at 0°C, H₂O (2.0 equiv.) was added and the mixture stirred for 5 minutes. The methyl propanoate, dissolved in the minimum volume of dry THF, was added and the reaction mixture warmed to room temperature and stirred for 4 hours. When no starting material could be detected (TLC), ice was added, the aqueous layer acidified with 1M HCl to pH = 7 and extracted with EtOAc (3x25ml). The combined organic layer was washed with water (2x50ml), dried (Na₂SO₄) and evaporated. The product was purified by PLC and crystallized from ethanol.

12.2.2.1 2-*O*-Methoxymethylphenylacetic acid (330)

Method : see paragraph 12.2.2

Reagents : methyl 2-*O*-methoxymethylphenylacetate **223** (533 mg, 2.54 mmol), KOC(CH₃)₃ (2.28 g, 20.32 mmol, 8.0 equiv.), H₂O (91 mg, 5.07 mmol, 2.0 equiv.), THF (10ml)

Reaction time: 4 hours at room temperature.

Yield : 446 mg, 90% (yellow needles), m.p. 76°C

R_f : 0.60 (B:A 9:1)

IR : ν_{\max} 1725 (CO), 1620, 1590 and 1510 cm⁻¹

¹H NMR (CDCl₃): δ 3.49 (OCH₂OCH₃, s, 3H), 3.75 (ArCH₂, s, 2H), 5.20 (OCH₂OCH₃, s, 2H), 6.97 (4-H, ddd, J = 1.5, 7.5, 7.5 Hz, 1H), 7.10 (6-H, dd, J = 1.5, 8.1 Hz, 1H), 7.22 (5-H, ddd, J = 2.0, 7.5, 8.1 Hz, 1H), 7.30 (3-H, dd, J = 2.0, 7.5 Hz, 1H).

12.2.2.2 2-O-*t*-Butyldimethylsilylphenylacetic acid (331)

Method : see paragraph 12.2.2

Reagents : methyl 2-*O-t*-butyldimethylsilylphenylacetate **225** (237 mg, 0.85 mmol), KOC(CH₃)₃ (763 mg, 6.80 mmol, 8.0 equiv.), H₂O (30 mg, 1.70 mmol, 2.0 equiv.), THF (10ml)

Reaction time: 4 hours at room temperature.

Yield : 158 mg, 70% (white crystals), m.p. 140°C

R_f : 0.62 (B:A 9:1)

IR : ν_{\max} 1720 (CO), 1620, 1595 and 1514 cm⁻¹

¹H NMR (CDCl₃): δ 0.10 (Si(CH₃)₂, s, 6H), 1.01 (^{*t*}Bu, s, 9H), 3.67 (ArCH₂, bs, 2H), 6.88-6.98 (ArH, m, 2H), 7.11-7.30 (ArH;COOH, m, 3H).

12.2.2.3 2-O-Benzyl-4-methoxyphenylacetic acid (332)

Method : see paragraph 12.2.2

Reagents : methyl 2-*O*-benzyl-4-methoxyphenylacetate **246** (1.496 g, 5.22 mmol), KOC(CH₃)₃ (4.686 g, 41.76 mmol, 8.0 equiv.), H₂O (188 mg, 10.44 mmol, 2.0 equiv.), THF (25ml)

Reaction time: 4 hours at room temperature.

Yield : 1.346 mg, 95% (light orange flakes), m.p. 98°C

R_f: 0.72 (B:A 6:4)

IR: ν_{\max} 1715 (CO), 1616, 1595 and 1514 cm⁻¹

¹H NMR (CDCl₃): δ 3.64 (ArCH₂, bs, 2H), 3.76 (OCH₃, s, 3H), 5.02 (ArCH₂O, bs, 2H), 6.46 (5-H, dd, J = 2.1, 7.9 Hz, 1H), 6.51 (3-H, d, J = 2.1 Hz, 1H), 7.11 (6-H, d, J = 7.9 Hz, 1H), 7.26-7.40 (ArH;COOH, m, 6H).

12.2.2.4 2-O-Benzylphenylacetic acid (333)

Method: see paragraph 12.2.2

Reagents: methyl 2-O-benzylphenylacetate **327** (270 mg, 1.05 mmol), KOC(CH₃)₃ (943 mg, 8.40 mmol, 8.0 equiv.), H₂O (38 mg, 2.10 mmol, 2.0 equiv.), THF (10ml)

Reaction time: 4 hours at room temperature.

Yield: 230 mg, 90% (light yellow oil)

R_f: 0.70 (B:A 6:4)

IR: ν_{\max} 1720 (CO), 1616, 1602 and 1514 cm⁻¹

¹H NMR (CDCl₃): δ 3.73 (ArCH₂, bs, 2H), 5.08 (ArCH₂O, bs, 2H), 6.91-6.98 (ArH, m, 2H), 7.20-7.27 (ArH, m, 2H), 7.28-7.42 (ArH;COOH, m, 6H).

12.2.3 **Synthesis of the phenylacetyl chlorides**

Method: The phenylacetic acid was dissolved in anhydrous benzene and treated with oxalyl chloride (4 equiv.) at 0°C. After stirring for 1 hour, the benzene was evaporated, the residue redissolved in dry benzene (20ml) and evaporated. In all instances product formation was determined *via* NMR and directly used without purification.

12.2.3.1 2(3H)-Benzofuranone (334)

Method : see paragraph 12.2.3

Reagents : 2-*O-t*-butyldimethylsilylphenylacetic acid **331** (192 mg, 0.72 mmol),
C₂O₂Cl₂ (367 mg, 2.89 mmol, 4.0 equiv.), benzene (15ml)

Reaction time: 1 hour at 0°C

Yield : 65 mg, 67% (dark yellow oil)

¹H NMR (CDCl₃): δ 3.77 (ArCH₂, s, 2H), 7.09-7.18 (ArH, m, 2H), 7.26-7.35 (ArH, m, 2H).

12.2.3.2 2-O-Methoxymethylphenylacetyl chloride (335)

Method : see paragraph 12.2.3

Reagents : 2-*O*-methoxymethylphenylacetic acid **330** (100 mg, 0.51 mmol), C₂O₂Cl₂
(259 mg, 2.04 mmol, 4.0 equiv.), benzene (15ml)

Reaction time: 1 hour at 0°C

Yield : 109 mg, 100% (light yellow oil)

¹H NMR (CDCl₃): δ 3.51 (OCH₂OCH₃, s, 3H), 4.26 (ArCH₂, s, 2H), 5.28 (OCH₂OCH₃,
s, 2H), 7.02 (4-H, ddd, J = 1.9, 7.5, 8.0 Hz, 1H), 7.11 (6-H, dd, J = 1.9, 8.1 Hz, 1H), 7.26
(5-H, ddd, J = 2.0, 7.5, 8.1 Hz, 1H), 7.34 (3-H, dd, J = 2.0, 8.0 Hz, 1H).

12.2.3.3 2-O-Benzyl-4-methoxyphenylacetyl chloride (336)

Method : see paragraph 12.2.3

Reagents : 2-*O*-benzyl-4-methoxyphenylacetic acid **332** (125 mg, 0.46 mmol),
C₂O₂Cl₂ (233 mg, 1.84 mmol, 4.0 equiv.), benzene (10ml)

Reaction time: 1 hour at 0°C

Yield : 133 mg, 100% (yellow oil)

$^1\text{H NMR}$ (CDCl_3): δ 3.81 (OCH_3 , s, 3H), 4.12 (ArCH_2 , s, 2H), 5.09 (ArCH_2O , s, 2H), 6.50 (5-H, dd, $J = 2.2, 8.1$ Hz, 1H), 6.55 (3-H, d, $J = 2.2$ Hz, 1H), 7.11 (6-H, d, $J = 8.1$ Hz, 1H), 7.35-7.43 (ArH, m, 5H).

12.2.3.4 2-O-Benzylphenylacetyl chloride (337)

Method : see paragraph 12.2.3

Reagents : 2-*O*-benzylphenylacetic acid **333** (100 mg, 0.41 mmol), $\text{C}_2\text{O}_2\text{Cl}_2$ (209 mg, 1.65 mmol, 4.0 equiv.), benzene (10ml)

Reaction time: 1 hour at 0°C

Yield : 108 mg, 100% (light yellow oil)

$^1\text{H NMR}$ (CDCl_3): δ 4.23 (ArCH_2 , s, 2H), 5.16 (ArCH_2O , s, 2H), 7.94-7.02 (ArH, m, 2H), 7.26-7.38 (ArH, m, 7H).

12.2.4 **Synthesis of chiral derivatives**

Method : (4*R*,5*S*)-(-)-1,5-Dimethyl-4-phenyl-2-imidazolidinone was dissolved in anhydrous THF, cooled to 0°C , treated with *n*BuLi (1.2 equiv.) and stirred for 15 minutes. The phenylacetyl chloride (4 equiv.), dissolved in dry THF was transferred to the reaction mixture. After stirring for 2 hours at 0°C , water was added and the aqueous layer extracted with EtOAc (3x20ml). The combined organic layer was washed with water (2x50ml), dried (Na_2SO_4), evaporated and the product purified by PLC.

12.2.4.1 (4*S*,5*R*)-3-(2-*O*-Methoxymethylphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (338)

Method : see paragraph 12.2.4

Reagents : 2-*O*-methoxymethylphenylacetyl chloride **335** (221 mg, 1.03 mmol, 4 equiv.), (4*R*,5*S*)-(-)-1,5-dimethyl-4-phenyl-2-imidazolidinone **320** (49 mg, 0.26 mmol), *n*BuLi (0.31 mmol, 1.2 equiv.), THF (2ml).

Reaction time: 2 hours at 0°C

Yield : 12 mg, 13% (light yellow oil)

R_f : 0.33 (B:A 9:1)

IR : ν_{\max} 1730 (CO), 1652, 1607 and 1538 cm⁻¹

MS : *m/z* 368 (M+H⁺, 17%), 177(41), Found : (M+H⁺), 368.1736 C₂₁H₂₄N₂O₄ requires (M+H⁺), 368.1736

¹H NMR (CDCl₃): δ 0.84 (4-CH₃, d, J = 6.5 Hz, 3H), 2.88 (3-NCH₃, s, 3H), 3.24 (OCH₂OCH₃, s, 3H), 3.95 (4-H, dq, J = 6.5, 8.5 Hz, 1H), 4.21, 4.48 (ArCH₂O, 2xd, J = 17.5 Hz, 2x1H), 4.98, 5.02 (OCH₂OCH₃, 2xd, J = 6.5 Hz, 2x1H), 5.33 (5-H, d, J = 8.5 Hz, 1H), 6.88-6.94 (ArH, m, 1H), 7.00-7.04 (ArH, m, 1H), 7.09-7.21 (ArH, m, 2H), 7.26-7.34 (ArH, m, 5H).

12.2.4.2 (4*S*,5*R*)-3-(2'-*O*-Benzyl-4'-methoxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (339)

Method : see paragraph 12.2.4

Reagents : 2-*O*-benzyl-4-methoxyphenylacetyl chloride **336** (361 mg, 1.24 mmol, 4 equiv.), (4*R*,5*S*)-(-)-1,5-dimethyl-4-phenyl-2-imidazolidinone **320** (59 mg, 0.31 mmol), *n*BuLi (0.37 mmol, 1.2 equiv.), THF (2ml).

Reaction time: 2 hours at 0°C

Yield : 103 mg, 75% (light yellow oil)

R_f : 0.73 (B:A 9:1)

IR : ν_{\max} 1697 (CO), 1604 and 1535 cm⁻¹

MS : *m/z* 445 (M+H⁺, 21%), 256(34); Found : (M+H⁺), 445.3243 C₂₇H₂₉N₂O₄ requires (M+H⁺), 445.2127

$^1\text{H NMR}$ (CDCl_3 , plate 27): δ 0.78 (4- CH_3 , d, $J = 6.8$ Hz, 3H), 2.83 (3- NCH_3 , s, 3H), 3.75 (OCH_3 , s, 3H), 3.76 (4-H, dq, $J = 6.8, 8.1$ Hz, 1H), 4.25, 4.40 (ArCH_2O , 2xd, $J = 17.0$ Hz, 2x1H), 4.88 ($\alpha\text{-H}_2$, s, 2H), 5.23 (5-H, d, $J = 8.1$ Hz, 1H), 6.42 (5'-H, dd, $J = 2.5, 8.1$ Hz, 1H), 6.45 (3'-H, d, $J = 2.5$ Hz, 1H), 7.02 (6'-H, d, $J = 8.1$ Hz, 1H), 7.09-7.13 (ArH, m, 2H), 7.19-7.25 (ArH, m, 3H), 7.29-7.37 (ArH, m, 5H).

12.2.4.3 *N*-(2-*O*-Benzylphenylcarbonyl)-10,2-camphorsultam (340)

Method : (+)-10,2-Camphorsultam **321** (135 mg, 0.63 mmol) dissolved in anhydrous THF (10ml) at 0°C was treated with NaH (23 mg, 0.94 mmol, 1.5 equiv.) for 2 hours. 2-*O*-Benzylphenylacetyl chloride **337** (245 mg, 0.94 mmol, 1.5 equiv.) was dissolved in dry THF (1ml) and transferred to the reaction mixture. The mixture was allowed to warm to room temperature and stirred for 2 hours, water (15ml) was added and the aqueous layer extracted with EtOAc (3x20ml). The organic layer was washed with water (2x50ml), dried (Na_2SO_4), evaporated and the product purified by PLC and crystallized from ethanol.

Yield : 264 mg, 96% (white needles), m.p. 105°C

R_f : 0.53 (B:A 95:5)

IR : ν_{max} 1706 (CO), 1607, 1538 and 1523 cm^{-1}

MS : m/s 440 ($\text{M}+\text{H}^+$, 18%), 226(41); Found : ($\text{M}+\text{H}^+$), 440.1896 $\text{C}_{25}\text{H}_{30}\text{O}_4\text{NS}$ requires ($\text{M}+\text{H}^+$), 440.1896

$^1\text{H NMR}$ (CDCl_3): δ 0.96, 1.08 (2x CH_3 , 2xs, 2x3H), 1.27-1.45 (CH_2 , m, 2H), 1.79-1.93 (CH_2 ;CH, m, 3H), 2.00-2.12 (CH_2 , m, 2H), 3.45, 3.53 (ArCH_2 , 2xd, $J = 13.8$ Hz, 2x1H), 3.86 (NCHR_2 , dd, $J = 5.0, 7.1$ Hz, 1H), 4.01, 4.26 (SO_2CH_2 , 2xd, $J = 14.0$ Hz, 2x1H), 5.10 (ArCH_2O , s, 2H), 6.90-6.97 (ArH, m, 2H), 7.18-7.28 (ArH, m, 2H), 7.30-7.44 (ArH, m, 5H).

12.2.4.4 Synthesis of (1R,2R)-N-(p-toluenesulfonyl)-2-amino-1-phenylpropyl 2-O-benzylphenylacetate (342)

12.2.4.4.1 *(1R,2R)-N-(p-toluenesulfonyl)norephedrine (322)*

Method : (1R,2S)-(-)-Norephedrine **341** (200 mg, 1.32 mmol), dissolved in anhydrous DCM (5ml), was treated with *p*-toluenesulfonyl chloride (265 mg, 1.39 mmol, 1.05 equiv.) and triethylamine (174 mg, 1.72 mmol, 1.3 equiv.). After stirring at room temperature for 20 hours, water (20ml) was added and the mixture extracted with EtOAc (3x25ml). The combined organic layer was washed with water (2x50ml), dried (Na₂SO₄) and evaporated. The product was purified by PLC.

Yield : 404 mg, 100% (colourless oil)

R_f : 0.63 (B:A 7:3)

¹H NMR (CDCl₃): δ 0.86 (3-CH₃, d, J = 7.0 Hz, 3H), 2.44 (ArCH₃, s, 3H), 2.74 (1-OH, d, J = 4.5 Hz, 1H), 3.59 (2-H, qdd, J = 3.0, 7.0, 8.5 Hz, 1H), 4.80 (1-H, dd, J = 3.0, 4.5 Hz, 1H), 4.99 (NH, d, J = 8.5 Hz, 1H), 7.24-7.35 (ArH, m, 7H), 7.79 (ArH, d, J = 8.1 Hz, 2H).

12.2.4.4.2 *(1R,2R)-N-(p-toluenesulfonyl)-2-amino-1-phenylpropyl 2-O-benzylphenylacetate (342)*

Method : (1R,2R)-*N*-(*p*-toluenesulfonyl)norephedrine **322** (109 mg, 0.36 mmol) in anhydrous DCM (5ml) was treated with Et₃N (72 mg, 0.71 mmol, 2.0 equiv.) at room temperature for 30 minutes after which 2-*O*-benzylphenylacetyl chloride **336** (186 mg, 0.71 mmol, 2.0 equiv.), dissolved in the minimum DCM, was added. After stirring for 2 hours at room temperature, water (20ml) was added and the mixture extracted with EtOAc (3x25ml). The combined organic layer was washed with water (2x50ml), dried (Na₂SO₄), evaporated and the product purified by PLC

and crystallized from ethanol.

Yield : 169 mg, 90% (white flakes), m.p. 150°C

R_f : 0.62 (B:A 9:1)

IR : ν_{\max} 1742 (CO), 1604, 1539 and 1529 cm⁻¹

MS : *m/s* 530 (M+H⁺, 27%), 226(45); Found : (M+H⁺), 530.1998 C₃₁H₃₂NO₅S requires (M+H⁺), 530.2001

¹H NMR (CDCl₃): δ 0.79 (3'-CH₃, d, J = 6.5 Hz, 3H), 2.41 (ArCH₃, s, 3H), 3.62 (2'-H, qdd, J = 3.2, 6.5, 9.2 Hz, 1H), 3.74 (ArCH₂, s, 2H), 4.56 (1-H, d, J = 9.2 Hz, 1H), 5.10, 5.16 (ArCH₂O, 2xd, J = 11.9 Hz, 2x1H), 5.51 (NH, d, J = 3.2 Hz, 1H), 6.97-7.04 (ArH, m, 4H), 7.20-7.28 (ArH, m, 6H), 7.30-7.43 (ArH, m, 6H), 7.62 (ArH, d, J = 8.2 Hz, 2H).

12.3 ASYMMETRIC ALDOL CONDENSATION OF CHIRAL DERIVATIVES

12.3.1 (4*S*,5*R*)-3-(2-*O*-Benzyl-4-methoxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (339) and 2-*O*-methoxymethylbenzaldehyde (216)

Method A : see paragraph 9.8.5

Reagents : (4*R*,5*S*)-3-(2-*O*-benzyl-4-methoxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone **339** (49 mg, 0.11 mmol), diisopropylamine (12 mg, 0.12 mmol, 1.1 equiv.), *n*BuLi (0.12 mmol, 1.1 equiv.), Et₂O (1ml), 2-*O*-methoxymethylbenzaldehyde **216** (18 mg, 0.11 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : 0 mg, 0%; Starting materials were recovered.

12.3.2 *N*-(2-*O*-Benzylphenylcarbonyl)-10,2-camphorsultam (340) and 2-*O*-methoxymethylbenzaldehyde (216)

Method : see paragraph 9.8.5

Reagents : *N*-(2-*O*-benzylphenylcarbonyl)-10,2-camphorsultam **340** (55 mg, 0.13 mmol), diisopropylamine (14 mg, 0.14 mmol, 1.1 equiv.), *n*BuLi (0.14 mmol, 1.1 equiv.), Et₂O (1ml), 2-*O*-methoxymethylbenzaldehyde **216** (21 mg, 0.13 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : 0 mg, 0%; Starting materials were recovered.

12.3.3 **(1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-2-amino-1-phenylpropyl 2-*O*-benzylphenylacetate (**342**) and 2-*O*-methoxymethylbenzaldehyde (**216**)**

Method : see paragraph 9.8.5

Reagents : (1*R*,2*R*)-*N*-(*p*-Toluenesulfonyl)-2-amino-1-phenylpropyl 2-*O*-benzylphenylacetate **342** (50 mg, 0.09 mmol), diisopropylamine (11 mg, 0.10 mmol, 1.1 equiv.), *n*BuLi (0.10 mmol, 1.1 equiv.), Et₂O (1ml), 2-*O*-methoxymethylbenzaldehyde **216** (16 mg, 0.09 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : 0 mg, 0%; Starting materials were recovered.

12.3.4 **(4*S*,5*R*)-3-(2-*O*-Benzyl-4-methoxyphenylcarbonyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (**339**) and 2-hydroxybenzyl chloride (**343**)**

Method : see paragraph 9.8.5

Reagents : (4*S*,5*R*)-3-(2-*O*-Benzyl-4-methoxyphenylcarbonyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone **339** (55 mg, 0.12 mmol), diisopropylamine (14 mg, 0.14 mmol, 1.1 equiv.), *n*BuLi (0.14 mmol, 1.1 equiv.), Et₂O (1ml), 2-hydroxybenzyl chloride **343** (19 mg, 0.12 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : 10 mg, 23 %; as a dynamic mixture of the enol and enolate.

R_f : 0.72 (B:A 9:1)

¹H NMR (CDCl₃):

[enol]: δ 0.79 (5"-CH₃, d, J = 6.5 Hz, 3H), 2.79 (1"-NCH₃, s, 3H), 3.66 (OCH₃, s, 3H), 4.00 (5"-H, dq, J = 6.5, 8.9 Hz, 1H), 5.11, 5.16 (ArCH₂O, 2xd, J = 8.0 Hz, 2x1H), 5.44 (4"-H, d, J = 8.9 Hz, 1H), 6.37 (6'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.43 (3'-H, d, J = 2.5 Hz, 1H), 6.75-6.83 (ArH, m, 1H), 6.94-6.97 (ArH, m, 3H), 6.96 (6'-H, d, J = 8.5 Hz, 1H), 7.06-7.11 (ArH, m, 1H), 7.15-7.26 (ArH, m, 3H), 7.19 (OCHCO, s, 1H), 7.34-7.49 (ArH; ArOH, m, 6H), 7.80-7.84 (6-H, m, 1H)

[enolate]: δ 0.79 (5"-CH₃, d, J = 6.5 Hz, 3H), 2.76 (1"-NCH₃, s, 3H), 3.71 (OCH₃, s, 3H), 3.81 (5"-H, dq, J = 6.5, 8.9 Hz, 1H), 5.04, 5.19 (ArCH₂O, 2xd, J = 12.5 Hz, 2x1H), 5.17 (1-OH, s, 1H), 5.26 (4"-H, d, J = 8.9 Hz, 1H), 6.37 (6'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.53 (3'-H, d, J = 2.5 Hz, 1H), 6.75-6.83 (ArH, m, 1H), 6.94-6.97 (ArH, m, 3H), 6.97 (6'-H, d, J = 8.5 Hz, 1H), 7.06-7.11 (ArH, m, 1H), 7.15-7.26 (ArH, m, 3H), 7.34-7.49 (ArH; ArOH, m, 6H), 7.80-7.84 (6-H, m, 1H).

12.4 SYNTHESIS OF PHENOLIC CHIRAL DERIVATIVES (346 and 347)

12.4.1 (4*S*,5*R*)-3-(2'-Hydroxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (346)

Method : see paragraph 9.8.6

Reagents : (4*S*,5*R*)-3-(2'-*O*-methoxymethylphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone **338** (20 mg, 0.05 mmol), BnSH (27 mg, 0.22 mmol, 4 equiv.), SnCl₄ (18 mg, 0.07 mmol, 1.2 equiv.), DCM (1 ml).

Reaction time: 15 minutes at -15°C, then 15 minutes at 5°C

Yield : 0 mg, 0%

12.4.2 (4*S*,5*R*)-3-(2'-Hydroxy-4'-methoxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (347)

Method : see paragraph 9.8.3

Reagents : (4*S*,5*R*)-3-(2'-*O*-benzyl-4'-methoxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone **339** (35 mg, 0.08 mmol), 10% Pd (4 mg), acetone (20 ml).

Reaction time: 1 hours

Yield : 0 mg, 0%

12.5 ASYMMETRIC ALDOL CONDENSATION EMPLOYING CHIRAL BASES

Erythro- and *threo*-methyl 2-(2''-*t*-butyldimethylsilyloxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoates **252**

Method : Methyl 2-*O*-*t*-butyldimethylsilylphenylacetate **225** (100 mg, 0.36 mmol) and (-)-sparteiene **348** (92 mg, 0.39 mmol, 1.1 equiv.), dissolved in anhydrous Et₂O (2ml) was cooled to -78°C and treated with *s*BuLi (0.39 mmol, 1.1 equiv.). The reaction was warmed to -20°C for 20 minutes and again cooled to -78°C before 2-*O*-methoxymethylbenzaldehyde **216** (59 mg, 0.36 mmol, 1 equiv.) was added. The reaction mixture was stirred for 1 hour at -78°C before water (10ml) was added and the mixture extracted with EtOAc (3x25ml). The combined organic layer was washed with water (2x50ml), dried (Na₂SO₄), evaporated and the products purified by PLC and crystallized from ethanol.

Yield : *erythro* : 45 mg, (light yellow oil)
threo : 794 mg, (yellow needles), m.p. 113°C
total yield : 78 %
de : 28 %
ee : 0 %

R_f : *erythro*: 0.69 (B:A 9:1)
threo: 0.53 (B:A 9:1)

IR and MS : see paragraph 10.4.5

¹H NMR (CDCl₃):

[*erythro*, plate 3] : see table 5,

[*threo*, plate 4] : see table 5.

12.6 SYNTHESIS OF METHYL 2,3-DIARYL-2-PROPENOATES

12.6.1 Dehydration of methyl propanoates

12.6.1.1 *p*-Toluenesulfonic acid

Method : Methyl 3-hydroxy-2,3-diphenylpropanoates **252-255** (*ca.* 0.10 mmol) were dissolved in anhydrous benzene (2ml) and treated with *p*-toluenesulfonic acid (0.20 mmol, 2 equiv.) at 50°C. The reaction mixture was stirred for *ca.* 30 minutes until no starting material could be detected (TLC). After the addition of water (10ml), the mixture was extracted with EtOAc (3x10ml). The combined organic layer was washed with water, dried (Na₂SO₄) and evaporated. The products were purified by PLC.

Yield : 0 mg, 0%; Extensive decomposition occurred in all instances.

12.6.1.2 Camphorsulfonic acid

Method : Methyl 3-hydroxy-2,3-diphenylpropanoates **252-255** (*ca.* 0.10 mmol) were dissolved in dry benzene (2ml) and treated with camphor-10-sulfonic acid (0.12 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature until no starting material could be detected (TLC). After 48 hours water (10ml) was added and the mixture extracted with EtOAc (3x20ml). The combined organic layer was washed with water (2x30ml), dried (Na₂SO₄), evaporated and the products purified by PLC.

12.6.1.2.1 *Methyl propenoates (353-355)*

Method : see paragraph 12.6.1.2
Reagents : Methyl 3-hydroxy-2,3-diphenylpropanoates **252-254** (ca. 0.10 mmol), camphor-10-sulfonic acid (ca. 0.12 mmol, 1.2 equiv.).
Yield : 0 mg, 0%; Decomposition occurred in all instances.

12.6.1.2.2 *Methyl 2-(2''-O-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-O-methoxymethyl-4'-methoxyphenyl)propanoate* **356**

Method : see paragraph 12.6.1.2
Reagents : methyl 2-(2''-O-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-O-methoxymethyl-4'-methoxyphenyl)propanoate **255** (49 mg, 0.10 mmol), camphor-10-sulfonic acid (27 mg, 0.12 mmol, 1.2 equiv.), benzene (2ml).
Yield : 14 mg, 30%

R_f : 0.81 (B:A 9:1)
IR : ν_{\max} 1734 (CO), 1412 and 1092 cm⁻¹
MS : *m/z* 489 (M+H⁺, 8%), 431 (25); Found : (M+H⁺), 489.2310; C₂₆H₃₇O₇Si (M+H⁺) requires 489.2308

¹H NMR (CDCl₃, plate 28): δ 0.19 (Si(CH₃)₂, bs, 6H), 0.90 (^tBu, s, 9H), 3.54, 3.75, 3.76, 3.81 (4xOCH₃, 4xs, 4x3H), 5.25 (OCH₂OCH₃, s, 2H), 6.26 (5''-H, dd, J = 2.5, 8.9 Hz, 1H), 6.46 (3'-H, d, J = 2.5 Hz, 1H), 6.49 (5'-H, dd, J = 2.5, 7.9 Hz, 1H), 6.69 (3''-H, d, J = 2.5 Hz, 1H), 6.79 (6''-H, d, J = 8.9 Hz, 1H), 6.95 (6'-H, d, J = 7.9 Hz, 1H), 8.11 (3-H, s, 1H).

12.6.2 *via Methyl 2,3-diphenyl-3-chloropropanoates*

Method A : Methyl 2-(2''-O-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-O-methoxymethyl-4'-methoxyphenyl)propanoate **255** (100 mg, 0.20 mmol) was dissolved in anhydrous benzene (5ml) and cooled to 0°C.

SOCl₂ (47 mg, 0.40 mmol, 2 equiv.) was added and the reaction mixture heated to room temperature. Using ¹H NMR the reaction was monitored until completion (2 hours). The benzene and excess SOCl₂ was evaporated and the chlorinated product dissolved in Et₃N (2ml) and stirred at room temperature for 2 hours. Water (10ml) was added and the mixture extracted with EtOAc (3x20ml). The combined organic layer was washed with water (2x30ml), dried (Na₂SO₄), evaporated and the product purified by PLC.

Yield : 0 mg, 0%; Starting material was recovered.

Method B : Methyl 2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **255** (114 mg, 0.23 mmol), converted to the chloride as in method A, was dissolved in anhydrous THF (5ml) and treated with NaH (8 mg, 0.34 mmol, 1.5 equiv.) at room temperature for 2 hours. After the addition of crushed ice and extraction with EtOAc (3x20ml), the combined organic layer was washed with water (2x30ml), dried (Na₂SO₄) and evaporated. The product was purified by PLC.

Yield : 14 mg, 13%, as a 1:1 mixture of *cis*- and *trans*-products **356**.

R_f : 0.81 (B:A 9:1), for both *cis*- and *trans*-products

¹H NMR (CDCl₃):

[*cis*]: δ 0.21 (Si(CH₃)₂, s, 6H), 0.93 (^tBu, s, 9H), 3.46, 3.67, 3.80, 3.82 (4xOCH₃, 4xs, 4x3H), 5.17 (OCH₂OCH₃, s, 2H), 6.43 (3'-H, d, J = 2.2 Hz, 1H), 6.49 (6"-H, d, J = 8.1 Hz, 1H), 6.54 (5"-H, dd, J = 2.2, 8.1 Hz, 1H), 6.56 (5'-H, dd, J = 2.2, 8.1 Hz, 1H), 6.72 (3"-H, d, J = 2.2 Hz, 1H), 7.05 (3-H, s, 1H), 7.23 (6'-H, d, J = 8.1 Hz, 1H);

[*trans*]: see paragraph 12.6.1.2.2

12.6.3 *via* Methyl 2,3-diphenyl-3-*O*-tosylpropanoate

Method A : Methyl 2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **255** (20 mg, 0.04 mmol) in anhydrous benzene (1ml) was treated with pyridine (13 mg, 0.16 mmol, 4 equiv.) and TsCl (11 mg, 0.06 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 20 hours after which water was added. The aqueous phase was extracted with EtOAc (3x10ml) and dried (Na₂SO₄). The EtOAc was evaporated and the product separated by PLC.

Yield : 0 mg, 0%; The starting material was recovered.

Method B : Methyl 2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **255** (34 mg, 0.07 mmol) was dissolved in Et₃N (2ml) and treated with TsCl (19 mg, 0.10 mmol, 1.5 equiv.). After stirring at room temperature for 24 hours, water was added and the mixture extracted with EtOAc (3x10ml), the organic layer was washed with water (2x20ml) and dried (Na₂SO₄). The EtOAc was evaporated and the product separated by PLC.

Yield : 0 mg, 0%; The starting material was recovered.

Method C : Methyl 2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **255** (25 mg, 0.05 mmol) was dissolved in anhydrous THF (1ml) and treated with NaH (2 mg, 0.05 mmol, 1.1 equiv.) at 0°C. After 5 minutes, TsCl (14 mg, 0.07 mmol, 1.5 equiv.) was added and the mixture stirred at room temperature for 1 hour. After addition of crushed ice and extraction with EtOAc (3x10ml), the organic layer was washed with water (2x20ml), dried (Na₂SO₄), evaporated and the products separated by PLC.

Yield : 0 mg, 0%; Only *retro*-aldol products could be isolated.

12.6.4 *via* Methyl 2,3-diphenyl-3-*O*-mesylpropanoate

Method A : Methyl 2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoate **255** (100 mg, 0.20 mmol) was dissolved in anhydrous DCM (5ml) and treated with methanesulfonic anhydride (38 mg, 0.22 mmol, 1.1 equiv.) and pyridine (17 mg, 0.22 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 24 hours. Complete conversion to the mesylate was confirmed by ¹H NMR. The DCM was evaporated under a stream of nitrogen and the product redissolved in dry benzene. DBU (45 mg, 0.30 mmol, 1.5 equiv.) was added and the mixture stirred for a further 24 hours at room temperature, followed by the addition of water (20ml). The mixture was extracted with EtOAc (3x10ml) and the combined organic layer washed with water (2x20ml), dried (Na₂SO₄), evaporated and the product separated by PLC.

Yield : 0 mg, 0%; The starting material was recovered.

Method B : As above. DBU was replaced with Et₃N.

Yield : 0 mg, 0%; The starting material was recovered.

12.6.5 *via* Oxidative elimination of methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate (**271**)

Method : Methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate **271** (100 mg, 0.18 mmol) dissolved in MeOH (10ml) was treated with 0.4M NaIO₄ (1ml) at room temperature for 24 hours. After filtration, the residue was washed with MeOH (2x30ml) and the combined filtrate evaporated. This residue was redissolved in EtOAc (40ml), dried (Na₂SO₄) and the solvent evaporated. The sulfoxide was dissolved in CHCl₃ (20ml) and stirred at 60°C for 24

hours, followed by evaporation of the CHCl_3 and separation of the products by PLC.

Yield : 9 mg, 12%

R_f : 0.65 (B)

IR : ν_{max} 1728 (CO), 1394 and 1162 cm^{-1}

$^1\text{H NMR}$ (CDCl_3): δ 0.19 ($\text{Si}(\text{CH}_3)_2$, s, 6H), 0.95 (^tBu , s, 9H), 3.78, 3.79, 3.80 ($3 \times \text{OCH}_3$, 3xs, 3x3H), 6.37 (5''-H, dd, $J = 2.9, 8.9$ Hz, 1H), 6.41 (3'-H, d, $J = 2.5$ Hz, 1H), 6.52 (5'-H, dd, $J = 2.5, 8.0$ Hz, 1H), 6.60 (3''-H, d, $J = 2.9$ Hz, 1H), 6.77 (3-H, s, 1H), 7.03 (6''-H, d, $J = 8.9$ Hz, 1H), 7.11 (6'-H, d, $J = 8.0$ Hz, 1H), 8.38 (ArOH, bs, 1H).

CHAPTER 13

STEREOSELECTIVE SYNTHESIS OF 6a-HYDROXY-PTEROCARPANS

13.1 SYNTHESIS OF ISOFLAV-3-ENES (373 and 374)

13.1.1 Synthesis of 2'-*O*-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflavan (370)

13.1.1.1 2-Hydroxy-3,4-dimethoxybenzophenone (364)

Method : see paragraph 9.8.2.3.1

Reagents : 2,3,4-trihydroxybenzophenone (1.0 g, 5.95 mmol.), *N*-methyl-*N*-nitroso-*p*-toluene sulphonamide (15 g).

Reaction time: 30 minutes at 0°C

Yield : 1.155 g, 99% (dark yellow oil)

R_f : 0.25 (B)

IR : ν_{\max} 1675 (CO), 1310, 1225, 1180 and 965 cm⁻¹

¹H NMR (CDCl₃): δ 2.60 (COCH₃, s, 3H), 3.91, 3.95 (2xOCH₃, 2xs, 2x3H), 6.51 (6-H, d, J = 9.0 Hz, 1H), 7.52 (5-H, d, J = 9.0 Hz, 1H), 12.59 (ArOH, m, 1H).

13.1.1.2 2-*O*-Benzyl-3,4-dimethoxybenzophenone (365)

Method : see paragraph 9.8.2.5

Reagents : 2-hydroxy-3,4-dimethoxybenzophenone **364** (1.739 g, 8.86 mmol.), 80% NaH (532 mg, 17.73 mmol, 2 equiv.), DMF (30ml), benzyl chloride (4.488 g, 35.45 mmol, 4 equiv.).

Reaction time: 1 hour at 0°C

Yield : 2.204 g, 87% (dark orange oil)

R_f : 0.71 (B:A 9:1)

IR : ν_{\max} 1680 (CO), 1313, 1224, 1122 and 980 cm⁻¹

¹H NMR (CDCl₃): δ 2.54 (COCH₃, s, 3H), 3.90, 3.95 (2xOCH₃, 2xs, 2x3H), 5.16 (ArCH₂, s, 2H), 6.76 (6-H, d, J = 9.0 Hz, 1H), 7.35-7.50 (Ar-H, m, 5H), 7.54 (5-H, d, J = 9.0 Hz, 1H).

13.1.1.3 Methyl 2-O-benzyl-3,4-dimethoxyphenylacetate

Method : see paragraph 9.8.4

Reagents : 2-O-benzyl-3,4-dimethoxybenzophenone **365** (735 mg, 2.57 mmol.), thallium(III)nitrate (1.002 g, 2.57 mmol, 1 equiv.), 60% perchloric acid (3ml), MeOH (10ml).

Reaction time: 12 hours at room temperature

Yield : 710 mg, 87% (yellow oil)

R_f : 0.71 (B:A 9:1)

IR : ν_{\max} 1740 (CO), 1492, 1232, 1178 and 1127 cm⁻¹

¹H NMR (CDCl₃): δ 3.56 (ArCH₂, s, 2H), 3.64, 3.89, 3.90 (3xOCH₃, 3xs, 3x3H), 5.10 (ArCH₂O, s, 2H), 6.67 (5-H, d, J = 8.5 Hz, 1H), 6.92 (6-H, d, J = 8.5 Hz, 1H), 7.34-7.50 (Ar-H, m, 5H).

13.1.1.4 Methyl 2-hydroxy-3,4-dimethoxyphenylacetate

Method : see paragraph 9.8.3

Reagents : methyl 2-*O*-benzyl-3,4-dimethoxyphenylacetate (1.0 g, 3.16 mmol), 10% Pd-C (100 mg), acetone (20ml).

Reaction time: 5 hours at room temperature

Yield : 715 mg, 100% (colourless oil)

R_f : 0.32 (B:A 95:5)

IR : ν_{\max} 1730 (CO), 1498, 1249, 1042 and 906 cm⁻¹

¹H NMR (CDCl₃): δ 3.63 (ArCH₂, s, 2H), 3.73, 3.86, 3.92 (3xOCH₃, 3xs, 3x3H), 6.07 (ArOH, bs, 1H), 6.46 (5-H, d, J = 8.9 Hz, 1H), 6.87 (6-H, d, J = 8.9 Hz, 1H).

13.1.1.5 Methyl 2-*O*-*t*-butyldimethylsilyl-3,4-dimethoxyphenylacetate (366)

Method : see paragraph 9.8.2.6

Reagents: methyl 2-hydroxy-3,4-dimethoxyphenylacetate (684 mg, 3.02 mmol.), imidazole (515 mg, 7.56 mmol, 2.5 equiv.), TBDMSCl (684 mg, 4.54 mmol, 1.5 equiv.), DMF (3ml).

Reaction time: 16 hours at room temperature

Yield : 908 mg, 88% (yellow oil)

R_f : 0.70 (B:A 9:1)

IR : ν_{\max} 1756 (CO), 1470, 1338, 1297 and 1178 cm⁻¹

¹H NMR (CDCl₃): δ 0.21 (Si(CH₃)₂, s, 6H), 1.00 (^tBu, s, 9H), 3.62 (ArCH₂, s, 2H), 3.70, 3.76, 3.86 (3xOCH₃, 3xs, 3x3H), 6.55 (5-H, d, J = 8.5 Hz, 1H), 6.89 (6-H, d, J = 8.5 Hz, 1H).

13.1.1.6 Erythro- and threo-methyl 2-(2"-O-t-butyldimethylsilyl-3",4"-dimethoxyphenyl)-3-hydroxy-3-(2'-O-methoxymethyl-4'-methoxyphenyl)-propanoates (367)

Method : see paragraph 9.8.5

Reagents : methyl 2-O-t-butyldimethylsilyl-3,4-dimethoxypropanoate **366** (497 mg, 1.46 mmol), diisopropylamine (163 mg, 1.61 mmol, 1.1 equiv.), *n*BuLi (1.61 mmol, 1.1 equiv.), Et₂O (3ml), 2-O-methoxymethyl-4-methoxybenzaldehyde **217** (286 mg, 1.46 mmol, 1 equiv.).

Reaction time: 1 hour at -78°C followed by 2 hours at 0°C

Yield : *erythro* : 352 mg, (light yellow needles), m.p. 76°C
threo : 263 mg, (light yellow needles), m.p. 102°C
total yield : 76 %
de : 18 %

R_f : *erythro* : 0.59 (B:A 9:1)
threo : 0.50 (B:A 9:1)

IR : *erythro* : ν_{\max} 2930, 1729 (CO), 1490, 1258 cm⁻¹
threo : ν_{\max} 2928, 1702 (CO), 1496, 1242 cm⁻¹

MS : *erythro* : *m/z* 537 (M+H⁺, 18%), 519 (34%); Found : (M+H⁺), 537.2522
C₂₇H₄₁O₉Si requires (M+H⁺), 537.2520
threo : *m/z* 537 (M+H⁺, 32%), 519 (18%); Found : (M+H⁺), 537.2520
C₂₇H₄₁O₉Si requires (M+H⁺), 537.2520

¹H NMR (CDCl₃):

[*erythro*]: δ 0.14, 0.16 (2xSiCH₃, 2xs, 2x3H), 0.95 (^tBu, s, 9H), 3.20 (3-OH, d, J = 4.1 Hz, 1H), 3.50, 3.59, 3.61, 3.74, 3.87 (5xOCH₃, 5xs, 5x3H), 4.54 (2-H, d, J = 5.5 Hz, 1H), 5.15, 5.25 (OCH₂OCH₃, 2xd, J = 6.5 Hz, 2x1H), 5.60 (3-H, dd, J = 4.1, 5.5 Hz, 1H), 6.36 (5'-H, dd, J = 2.2, 8.5 Hz, 1H), 6.61 (5"-H, d, J = 8.9 Hz, 1H), 6.64 (3'-H, d, J = 2.2 Hz, 1H), 6.77 (6'-H, d, J = 8.5 Hz, 1H), 7.24 (6"-H, d, J = 8.9 Hz, 1H),

[*threo*]: δ 0.16, 0.18 (2xSiCH₃, 2xs, 2x3H), 1.04 (¹Bu, s, 9H), 3.26 (3-OH, d, J = 5.0 Hz, 1H), 3.40, 3.42, 3.71, 3.74, 3.79 (5xOCH₃, 5xs, 5x3H), 4.54 (2-H, d, J = 10.0 Hz, 1H), 4.85, 4.99 (OCH₂OCH₃, 2xd, J = 6.5 Hz, 2x1H), 5.49 (3-H, dd, J = 5.0, 10.0 Hz, 1H), 6.43 (5'-H, dd, J = 2.2, 8.2 Hz, 1H), 6.45 (5''-H, d, J = 8.9 Hz, 1H), 6.50 (3'-H, d, J = 2.2 Hz, 1H), 7.11 (6''-H, d, J = 8.9 Hz, 1H), 7.24 (6'-H, d, J = 8.2 Hz, 1H).

13.1.1.7 *Erythro*- and *threo*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-3'',4''-dimethoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoates (368)

Method : see paragraph 9.8.6

Reagents : methyl 2-(2''-*O*-*t*-butyldimethylsilyl-3'',4''-dimethoxyphenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propanoates **367** (489 mg, 0.82 mmol), BnSH (406 mg, 3.27 mmol, 4 equiv.), SnCl₄ (318 mg, 1.22 mmol, 1.5 equiv.), DCM (10ml).

Reaction time: 15 minutes at -15°C followed by 15 minutes at 5°C

Yield : *erythro* : 312 mg, (light yellow flakes), m.p. 40°C

threo : 224 mg, (light yellow flakes), m.p. 40°C

total yield : 98 %

de : 16 %

R_f : *erythro* : 0.58 (B:A 95:5)

threo : 0.47 (B:A 95:5)

MS : *erythro* : *m/z* 599 (M+H⁺, 28%), 540 (23%); Found : (M+H⁺), 599.2500
C₃₂H₄₃O₇SiS requires (M+H⁺), 599.2499

threo : *m/z* 599 (M+H⁺, 34%), 540 (46%); Found : (M+H⁺), 599.2597

C₃₂H₄₃O₇SiS requires (M+H⁺), 599.2499

¹H NMR (CDCl₃):

[*erythro*]: δ 0.23, 0.32 (2xSiCH₃, 2xs, 2x3H), 1.08 (¹Bu, s, 9H), 3.30, 3.42 (ArCH₂S,

2xd, J = 13.1 Hz, 2x1H), 3.42, 3.77, 3.81, 3.89 (4xOCH₃, 4xs, 4x3H), 4.37 (2-H, d, J = 11.5 Hz, 1H), 4.71 (3-H, d, J = 11.5 Hz, 1H), 6.48 (5'-H, dd, J = 2.9, 8.5 Hz, 1H), 6.52 (3'-H, d, J = 2.9 Hz, 1H), 6.54 (5''-H, d, J = 8.9 Hz, 1H), 6.99 (6'-H, d, J = 8.5 Hz, 1H), 7.04-7.07 (ArH, m, 2H), 7.11 (6''-H, d, J = 8.9 Hz, 1H), 7.21-7.27 (ArH, m, 3H), 7.34-7.36 (ArOH, m, 1H),

[*threo*]: δ 0.16, 0.20 (2xSiCH₃, 2xs, 2x3H), 1.05 (^tBu, s, 9H), 3.41, 3.69, 3.71, 3.79 (4xOCH₃, 4xs, 4x3H), 3.55, 3.64 (ArCH₂S, 2xd, J = 12.9 Hz, 2x1H), 4.35 (2-H, d, J = 11.0 Hz, 1H), 4.67 (3-H, d, J = 11.0 Hz, 1H), 6.12 (5'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.34 (3'-H, d, J = 2.5 Hz, 1H), 6.43 (5''-H, d, J = 8.9 Hz, 1H), 7.48 (6'-H, d, J = 8.5 Hz, 1H), 7.05 (6''-H, d, J = 8.9 Hz, 1H), 7.16-7.32 (ArH, ArOH, m, 6H).

13.1.1.8 *Erythro*-3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-3''-4''-dimethoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (369)

Method : see paragraph 9.8.7

Reagents : *erythro*-methyl 3-benzylsulfanyl-2-(2''-*O*-*t*-butyldimethylsilyl-3''-4''-dimethoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate **368** (312 mg, 0.52 mmol), LiAlH₄ (197 mg, 5.20 mmol, 10 equiv.), Et₂O (5ml)

Reaction time: 10 minutes at 10°C

Yield : 229 mg, 77% (yellow oil)

R_f : 0.57 (B:A 9:1)

MS : *m/z* 571 (M+H⁺, 14%), 553(40); Found : (M+H⁺), 571.2550 C₃₁H₄₃O₆SiS requires (M+H⁺), 571.2550

¹H NMR (CDCl₃): δ 0.22, 0.26 (2xSiCH₃, 2xs, 2x3H), 1.00 (^tBu, s, 9H), 1.45-1.55 (C₁-OH, m, 1H), 3.35, 3.49 (ArCH₂S, 2xd, J = 13.5 Hz, 2x1H), 3.38-3.56 (1-CH₂, m, 2H), 3.69-3.77 (2-H, m, 1H), 3.75, 3.84, 3.88 (3xOCH₃, 3xs, 3x3H), 4.27 (3-H, d, J = 11.5 Hz, 1H), 6.51 (5''-H, d, J = 9.0 Hz, 1H), 6.54 (5'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.55 (3'-H, d, J = 2.5 Hz, 1H), 6.68 (6'-H, d, J = 8.5 Hz, 1H), 7.10-7.14 (ArH, m, 2H), 7.19 (6''-H, d, J = 9.0 Hz, 1H), 7.24-7.33 (ArH, m, 3H), 7.45-7.51 (ArOH, m, 1H).

13.1.1.9 Threo-3-benzylsulfanyl-2-(2"-O-t-butyl dimethylsilyl-3",4"-dimethoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (369)

Method : see paragraph 9.8.7

Reagents : *threo*-methyl 3-benzylsulfanyl-2-(2"-O-t-butyl dimethylsilyl-3",4"-dimethoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate **368** (272 mg, 0.45 mmol), LiAlH₄ (171 mg, 4.50 mmol, 10 equiv.), Et₂O (5ml)

Reaction time: 10 minutes at 10°C

Yield : 202 mg, 78% (yellow oil)

R_f : 0.57 (B:A 9:1)

MS : *m/z* 571 (M+H⁺, 24%), 553(36); Found : (M+H⁺), 571.2576 C₃₁H₄₃O₆SiS requires (M+H⁺), 571.2550

¹H NMR (CDCl₃): δ 0.12, 0.20 (2xSiCH₃, 2xs, 2x3H), 1.03 (^tBu, s, 9H), 1.79-1.87 (C₁-OH, m, 1H), 3.45, 3.59 (ArCH₂S, 2xd, J = 13.0 Hz, 2x1H), 3.55, 3.74, 3.80 (3xOCH₃, 3xs, 3x3H), 3.89-3.97 (1-CH₂;2-H, m, 3H), 4.20 (3-H, d, J = 8.5 Hz, 1H), 6.25 (5'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.37 (3'-H, d, J = 2.5 Hz, 1H), 6.42 (5"-H, d, J = 8.9 Hz, 1H), 6.66 (6'-H, d, J = 8.5 Hz, 1H), 6.67 (6"-H, d, J = 8.9 Hz, 1H), 7.15-7.19 (ArH, m, 2H), 7.21-7.32 (ArH, ArOH, m, 4H).

13.1.1.10 Cis-4-benzylsulfanyl-2'-O-t-butyl dimethylsilyl-3',4',7-trimethoxyisoflavan (370)

Method : see paragraph 9.8.8

Reagents : *threo*-3-benzylsulfanyl-2-(2"-O-t-butyl dimethylsilyl-3",4"-dimethoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol **369** (150 mg, 0.26 mmol), TPP (689 mg, 2.63 mmol, 10 equiv.), DEAD (229 mg, 1.31 mmol, 5 equiv.), THF (5ml)

Reaction time: 4 hours at room temperature.

Yield : 127 mg, 88% (yellow oil)

R_f : 0.63 (B)

MS : *m/z* 553 (M+H⁺, 32%), 438(20); Found : (M+H⁺), 553.2441 C₃₁H₄₁O₅SiS
requires (M+H⁺), 553.2444

¹H NMR (CDCl₃): δ 0.15, 0.35 (SiCH₃, 2xs, 2x3H), 0.86 (^tBu, s, 9H), 2.76, 3.05
(ArCH₂S, 2xd, J = 13.0 Hz, 2x1H), 3.75, 3.84, 3.91 (3xOCH₃, 3xs, 3x3H), 3.88 (3-H, ddd,
J = 3.0, 3.8, 11.5 Hz, 1H), 4.19 (4-H, dd, J = 2.0, 3.8 Hz, 1H), 4.33 (2-H_{eq}, ddd, J = 2.0,
3.0, 10.1 Hz, 1H), 4.65 (2-H_{ax}, dd, J = 10.1, 11.5 Hz, 1H), 6.33 (8-H, d, J = 2.5 Hz, 1H),
6.40 (6-H, dd, J = 2.5, 8.2 Hz, 1H), 6.66 (5'-H, d, J = 8.9 Hz, 1H), 6.67 (6'-H, d, J = 8.9
Hz, 1H), 6.88 (5-H, d, J = 8.2 Hz, 1H), 7.17-7.34 (ArCH₂S, m, 5H).

13.1.1.11 Trans-4-benzylsulfanyl-2'-O-*t*-butyldimethylsilyl-3',4',7-trimethoxy-
isoflavan (370)

Method : see paragraph 9.8.8

Reagents : *erythro*-3-benzylsulfanyl-2-(2''-O-*t*-butyldimethylsilyl-3'',4''-dimethoxy-
phenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol **369** (257 mg, 0.45
mmol), TPP (1.179 g, 4.50 mmol, 10 equiv.), DEAD (392 mg, 2.25 mmol,
5 equiv.), THF (10ml)

Reaction time: 4 hours at room temperature.

Yield : 213 mg, 86% (yellow oil)

R_f : 0.63 (B)

MS : *m/z* 553 (M+H⁺, 42%), 438(26); Found : (M+H⁺), 553.2445 C₃₁H₄₁O₅SiS
requires (M+H⁺), 553.2444

¹H NMR (CDCl₃): δ 0.30, 0.32 (SiCH₃, 2xs, 2x3H), 1.07 (^tBu, s, 9H), 3.70, 3.83
(ArCH₂S, 2xd, J = 12.9 Hz, 2x1H), 3.78, 3.81, 3.82 (3xOCH₃, 3xs, 3x3H), 3.87 (3-H, ddd,
J = 3.0, 3.9, 4.5 Hz, 1H), 3.96 (4-H, dd, J = 1.1, 3.9 Hz, 1H), 4.24 (2-H_{eq}, ddd, J = 1.1, 4.5,
11.0 Hz, 1H), 4.55 (2-H_{ax}, dd, J = 3.0, 11.0 Hz, 1H), 6.37 (8-H, d, J = 2.5 Hz, 1H), 6.40

(5'-H, d, J = 8.9 Hz, 1H), 6.50 (6'-H, d, J = 8.9 Hz, 1H), 6.52 (6-H, dd, J = 2.5, 8.5 Hz, 1H), 7.22 (5-H, d, J = 8.5 Hz, 1H), 7.22-7.30 (ArCH₂S, m, 5H).

13.1.2 Oxidative elimination of 4-benzylsulfanylisoflavans (286 and 370)

13.1.2.1 Oxidation of 4-benzylsulfanylisoflavans

Method : 4-Benzylsulfanylisoflavan, dissolved in MeOH, was treated with 4M NaIO₄ (4 equiv.) and stirred for 16 hours at room temperature, after which a further 0.5 equiv. NaIO₄ was added and the mixture stirred for 30 minutes. After filtration the solvent was evaporated and the residue redissolved in EtOAc (50ml). The organic layer was washed with water, dried (Na₂SO₄) and evaporated under reduced pressure. The products were purified by PLC.

13.1.2.1.1 *Cis-4-benzylsulfoxide-2'-O-t-butyltrimethylsilyl-4',7-dimethoxyisoflavan* (371)

Method : see paragraph 13.1.2.1

Reagents : *cis*-4-benzylsulfanyl-2'-O-t-butyltrimethylsilyl-4',7-dimethoxyisoflavan **286** (166 mg, 0.32 mmol), 0.4 M NaIO₄ (1.28 mmol, 4 equiv.), MeOH (5ml).

Reaction time: 16.5 hours at room temperature

Yield : 137 mg, 80% (yellow oil)

R_f : 0.40 (B:A 9:1)

¹H NMR (CDCl₃, plate 29): δ 0.21, 0.33 (SiCH₃, 2xs, 2x3H), 0.92 (tBu, s, 9H), 3.25, 3.56 (ArCH₂SO, 2xd, J = 13.0 Hz, 2x1H), 3.79, 3.84 (2xOCH₃, 2xs, 2x3H), 3.94 (3-H, ddd, J = 3.5, 4.0, 12.0 Hz, 1H), 4.23 (4-H, dd, J = 2.0, 4.0 Hz, 1H), 4.46 (2-H_{eq}, ddd, J = 2.0, 3.5, 10.5 Hz, 1H), 4.91 (2-H_{ax}, dd, J = 10.5, 12.0 Hz, 1H), 6.46-6.51 (6-,8-,3'-H, m, 3H), 6.57 (5'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.61 (5-H, d, J = 8.5 Hz, 1H), 7.02 (6'-H, d, J = 8.5 Hz, 1H), 7.07-7.12 (ArH, m, 2H), 7.28-7.32 (ArH, m, 3H).

13.1.2.1.2 *Trans-4-benzylsulfoxide-2'-O-t-butyltrimethylsilyl-4',7-dimethoxyisoflavan*
(371)

Method : see paragraph 13.1.2.1

Reagents : *trans-4-benzylsulfanyl-2'-O-t-butyltrimethylsilyl-4',7-dimethoxyisoflavan*
286 (135 mg, 0.26 mmol), 0.4 M NaIO₄ (1.04 mmol, 4 equiv.), MeOH
(5ml).

Reaction time: 16.5 hours at room temperature

Yield : 109 mg, 78% (yellow oil)

R_f : 0.44 (B:A 9:1)

¹H NMR (CDCl₃, plate 30): δ 0.34, 0.35 (SiCH₃, 2xs, 2x3H), 1.06 (^tBu, s, 9H), 3.71-3.76 (3-H, m, 1H), 3.76, 3.80 (2xOCH₃, 2xs, 2x3H), 3.84, 4.08 (ArCH₂SO, 2xd, J = 13.0 Hz, 2x1H), 3.95-3.97 (4-H, m, 1H), 4.24 (2-H_{eq}, dm, J = 11.0 Hz, 1H), 4.43 (2-H_{ax}, dd, J = 3.8, 11.0 Hz, 1H), 6.39 (5'-H, dd, J = 2.5, 8.5 Hz, 1H), 6.45 (8-H, d, J = 2.5 Hz, 1H), 6.49 (3'-H, d, J = 2.5 Hz, 1H), 6.57 (6-H, dd, J = 2.5, 8.5 Hz, 1H), 6.88 (6'-H, d, J = 8.1 Hz, 1H), 7.09 (5-H, d, J = 8.5 Hz, 1H), 7.21-7.26 (ArH, m, 2H), 7.30-7.35 (ArH, m, 3H).

13.1.2.1.3 *Cis-4-benzylsulfoxide-2'-O-t-butyltrimethylsilyl-3',4',7-trimethoxyisoflavan*
(372)

Method : see paragraph 13.1.2.1

Reagents : *cis-4-benzylsulfanyl-2'-O-t-butyltrimethylsilyl-3',4',7-trimethoxyisoflavan*
370 (156 mg, 0.28 mmol), 0.4 M NaIO₄ (1.12 mmol, 4 equiv.), MeOH
(5ml).

Reaction time: 16.5 hours at room temperature

Yield : 96 mg, 60% (yellow oil)

R_f : 0.24 (B:A 9:1)

¹H NMR (CDCl₃): δ 0.14, 0.34 (SiCH₃, 2xs, 2x3H), 0.89 (^tBu, s, 9H), 3.10, 3.65 (ArCH₂SO, 2xd, J = 13.1 Hz, 2x1H), 3.78, 3.80, 3.92 (3xOCH₃, 3xs, 3x3H), 4.00 (3-H,

ddd, J = 4.0, 4.0, 12.0 Hz, 1H), 4.28 (4-H, dd, J = 2.5, 4.0 Hz, 1H), 4.46 (2-H_{eq}, ddd, J = 2.5, 4.0, 10.9 Hz, 1H), 4.87 (2-H_{ax}, dd, J = 10.9, 12.0 Hz, 1H), 6.45 (ArH, m, 3H), 6.61 (5-H, d, J = 8.5 Hz, 1H), 6.79 (6'-H, d, J = 8.5 Hz, 1H), 7.15-7.20 (ArH, m, 2H), 7.33-7.36 (ArH, m, 3H).

13.1.2.1.4 *Trans-4-benzylsulfoxide-2'-O-t-butyltrimethylsilyl-3',4',7-trimethoxy-isoflavan (372)*

Method : see paragraph 13.1.2.1

Reagents : *trans*-4-benzylsulfanyl-2'-O-t-butyltrimethylsilyl-3',4',7-trimethoxy-isoflavan **370** (187 mg, 0.34 mmol), 0.4 M NaIO₄ (1.36 mmol, 4 equiv.), MeOH (5ml).

Reaction time: 16.5 hours at room temperature

Yield : 127 mg, 66% (yellow oil)

R_f : 0.47 (B:A 9:1)

¹H NMR (CDCl₃): δ 0.28, 0.33 (SiCH₃, 2xs, 2x3H), 1.06 (tBu, s, 9H), 3.79, 3.79, 3.82 (3xOCH₃, 3xs, 3x3H), 3.83 (3-H, ddm, J = 2.5, 3.5 Hz, 1H), 3.84, 4.11 (ArCH₂S, 2xd, J = 12.8 Hz, 2x1H), 3.92-3.95 (4-H, m, 1H), 4.24 (2-H_{eq}, ddd, J = 1.2, 2.5, 11.1 Hz, 1H), 4.42 (2-H_{ax}, dd, J = 3.5, 11.1 Hz, 1H), 6.43 (5'-H, d, J = 8.9 Hz, 1H), 6.49 (8-H, d, J = 2.5 Hz, 1H), 6.57 (6-H, dd, J = 2.5, 8.5 Hz, 1H), 6.64 (6'-H, d, J = 8.9 Hz, 1H), 7.06 (5-H, d, J = 8.5 Hz, 1H), 7.23-7.27 (ArH, m, 2H), 7.30-7.35 (ArH, m, 3H).

13.1.2.2 Thermal elimination of 4-benzylsulfoxide derivatives

Method : The respective sulfoxides **371** and **372** (ca. 0.2 mmol) were dissolved in CHCl₃ (20ml) and stirred for 24 hours at 60°C. After evaporation of the solvent, separation by PLC afforded the isoflav-3-enes.

13.1.2.2.1 *2'-O-t-butyldimethylsilyl-4',7-dimethoxyisoflav-3-ene (373)*

Method : see paragraph 13.1.2.2

Reagents : 4-benzylsulfoxide-2'-*O-t-butyldimethylsilyl-4',7-dimethoxyisoflavan* **371**
(125 mg, 0.23 mmol), CHCl₃ (20ml).

Reaction time: 24 hours at 60°C

Yield : 69 mg, 75% (yellow oil)

R_f : 0.74 (B)

MS : *m/z* 399 (M+H⁺, 10%), 341 (76); Found : (M+H⁺), 399.1955 C₂₃H₃₁O₄Si
requires (M+H⁺), 399.1960

¹H NMR (CDCl₃, plate 31): δ 0.24 (Si(CH₃)₂, s, 6H), 1.00 (^tBu, s, 9H), 3.81, 3.81
(2xOCH₃, 2xs, 2x3H), 5.01 (2-H₂, s, 2H), 6.44 (3'-H, d, J = 2.5 Hz, 1H), 6.47 (8-H, d, J =
2.5 Hz, 1H), 6.49 (6-H, dd, J = 2.5, 8.0 Hz, 1H), 6.54 (4-H, bs, 1H), 6.56 (5'-H, dd, J =
2.5, 8.1 Hz, 1H), 6.98 (5-H, d, J = 8.0 Hz, 1H), 7.19 (6'-H, d, J = 8.1 Hz, 1H).

13.1.2.2.2 *2'-O-t-butyldimethylsilyl-3',4',7-trimethoxyisoflav-3-ene (374)*

Method : see paragraph 13.1.2.2

Reagents : 4-benzylsulfoxide-2'-*O-t-butyldimethylsilyl-3',4',7-trimethoxyisoflavan*
372 (128 mg, 0.23 mmol), CHCl₃ (20ml).

Reaction time: 24 hours at 60°C

Yield : 92 mg, 95% (light yellow oil)

R_f : 0.56 (B)

MS : *m/z* 429 (M+H⁺, 13%), 341 (60); Found : (M+H⁺), 429.2095 C₂₄H₃₃O₅Si
requires (M+H⁺), 429.2097

¹H NMR (CDCl₃): δ 0.15 (Si(CH₃)₂, s, 6H), 0.98 (^tBu, s, 9H), 3.80, 3.81, 3.89 (3xOCH₃,
3xs, 3x3H), 5.00 (2-H₂, s, 2H), 6.46 (3-H, d, J = 2.2 Hz, 1H), 6.49 (6-H, dd, J = 2.2, 8.0

Hz, 1H), 6.54 (4-H, bs, 1H), 6.59 (5'-H, d, J = 8.5 Hz, 1H), 6.94 (6'-H, d, J = 8.5 Hz, 1H), 6.96 (5-H, d, J = 8.0 Hz, 1H).

13.2 DIHYDROXYLATION OF ISOFLAV-3-ENES (373 and 374).

13.2.1 Asymmetric dihydroxylation via AD-mix- α or - β

Method : A 10 ml round-bottomed flask, equipped with a magnetic stirrer, was charged with *t*-butyl alcohol (2ml), water (2ml) and AD-mix- α or - β (67 mg). Stirring of the mixture at room temperature produced two clear phases; the lower aqueous phase appeared bright yellow. Methanesulfonamide (5 mg, 0.05 mmol, 1 equiv.) was added to the mixture which was then cooled to 0°C and treated at once with the respective isoflav-3-enes **373** or **374** (0.05 mmol). The resulting heterogeneous slurry was stirred vigorously at 0°C for 48 hours. Sodium sulfite (80 mg) was added to the mixture which was then allowed to warm to room temperature and stirred for 30-60 minutes. Ethyl acetate (10ml) was added to the reaction mixture and the organic layer was separated; the aqueous phase was then further extracted with the same solvent (3x10ml). The combined extracts were dried (Na₂SO₄) and evaporated and the crude extract was purified by PLC.

Yield : 0 mg; 0%; In both instances the starting materials were recovered.

13.2.2 Asymmetric dihydroxylation employing chiral ligands DHQ-CLB and DHQD-CLB

Method : The isoflav-3-ene and chiral ligands DHQ-CLB **375** or DHQD-CLB **376** (1.5 equiv.) were dissolved in anhydrous DCM, cooled to -78°C and treated with OsO₄ (1 equiv.) for 24 hours. The resulting dark green solution was treated with aqueous 20%-Na₂SO₃ / 20%-NaHSO₄ for 1 hour at room temperature. Water (5ml) was added and the mixture extracted with Et₂O

(3x20ml). The combined organic layer was washed with water (2x25ml), dried (Na₂SO₄), evaporated and the products purified *via* PLC.

13.2.2.1 (-)-(3*R*,4*S*)-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diol
(377a)

Method : see paragraph 13.2.2

Reagents : 2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflav-3-ene **373** (80 mg, 0.20 mmol), DHQ-CLB **375** (140 mg, 0.30 mmol, 1.5 equiv.), OsO₄ (51 mg, 0.20 mmol, 1 equiv.), DCM (2ml).

Reaction time: 24 hours at -78°C

Yield : 56 mg, 65% (yellow oil)

R_F : 0.40 (B:A 9:1)

CD : $\Delta\epsilon_{\max} [\lambda \text{ (nm)}]: -3.02 \times 10^3 \text{ (287)}, -5.06 \times 10^3 \text{ (268)}, +1.77 \times 10^3 \text{ (238)}$

$[\alpha]_D^{25}$: -28.7 (c 0.57, CHCl₃)

¹H NMR (CDCl₃, plate 32): δ 0.39, 0.40 (2xSiCH₃, 2xd, 2x3H), 1.04 (^tBu, s, 9H), 2.84 (4-OH, d, J = 6.0 Hz, 1H), 3.77, 3.79 (2xOCH₃, 2xs, 2x3H), 4.29, 4.39 (2-H₂, 2xd, J = 11.1 Hz, 2x1H), 4.39 (3-OH, s, 1H), 5.18 (4-H, d, J = 6.0 Hz, 1H), 6.42 (8-H, d, J = 2.5 Hz, 1H), 6.46 (3'-H, d, J = 2.2 Hz, 1H), 6.50 (5'-H, dd, J = 2.2, 8.2 Hz, 1H), 6.57 (6-H, dd, J = 2.5, 8.2 Hz, 1H), 7.36 (6'-H, d, J = 8.2 Hz, 1H), 7.43 (5-H, d, J = 8.2 Hz, 1H).

13.2.2.2 (+)-(3*S*,4*R*)-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diol
(377b)

Method : see paragraph 13.2.2

Reagents : 2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflav-3-ene **373** (75 mg, 0.20 mmol), DHQD-CLB **376** (131 mg, 0.28 mmol, 1.5 equiv.), OsO₄ (51 mg, 0.20 mmol, 1 equiv.), DCM (2ml).

Reaction time: 24 hours at -78°C

Yield : 55 mg, 68% (yellow oil)

R_f : 0.40 (B:A 9:1)

CD : $\Delta\epsilon_{\max} [\lambda \text{ (nm)}]$: +3.10 x 10³ (287), +5.00 x 10³ (268), -1.82 x 10³ (238)

[α]_D²⁵ : +28.6 (c 0.49, CHCl₃)

¹H NMR (CDCl₃): see paragraph 13.2.2.1

13.2.2.3 (-)-(3R,4S)-2'-O-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflavan-3,4-diol
(378a)

Method : see paragraph 13.2.2

Reagents : 2'-O-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflav-3-ene 374 (65 mg, 0.15 mmol), DHQ-CLB 375 (106 mg, 0.23 mmol, 1.5 equiv.), OsO₄ (39 mg, 0.15 mmol, 1 equiv.), DCM (2ml).

Reaction time: 24 hours at -78°C

Yield : 46 mg, 66% (yellow oil)

R_f : 0.49 (B:A 9:1)

CD : $\Delta\epsilon_{\max} [\lambda \text{ (nm)}]$: -6.16 x 10³ (281), +1.69 x 10³ (220)

[α]_D²⁵ : -25.8 (c 0.58, CHCl₃)

¹H NMR (CDCl₃): δ 0.34, 0.39 (2xSiCH₃, 2xd, 2x3H), 1.03 (^tBu, s, 9H), 2.91 (4-OH, d, J = 6.5 Hz, 1H), 3.79, 3.80, 3.86 (3xOCH₃, 3xs, 3x3H), 4.26, 4.32 (2-H₂, 2xd, J = 11.5 Hz, 2x1H), 4.82 (3-OH, s, 1H), 5.15 (4-H, d, J = 6.5 Hz, 1H), 6.42 (8-H, d, J = 2.2 Hz, 1H), 6.54 (5'-H, d, J = 8.9 Hz, 1H), 6.57 (6-H, dd, J = 2.2, 8.5 Hz, 1H), 7.12 (6'-H, d, J = 8.9 Hz, 1H), 7.37 (5-H, d, J = 8.5 Hz, 1H).

13.2.2.4 (+)-(3*S*,4*R*)-2'-*O*-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflavan-3,4-diol
(378b)

Method : see paragraph 13.2.2

Reagents : 2'-*O*-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflav-3-ene **374** (80 mg, 0.20 mmol), DHQD-CLB **376** (130 mg, 0.28 mmol, 1.5 equiv.), OsO₄ (51 mg, 0.20 mmol, 1 equiv.), DCM (2ml).

Reaction time: 24 hours at -78°C

Yield : 54 mg, 63% (yellow oil)

R_f : 0.49 (B:A 9:1)

CD : $\Delta\epsilon_{\max} [\lambda \text{ (nm)}]: -6.00 \times 10^3 \text{ (280)}, +1.75 \times 10^3 \text{ (220)}$

$[\alpha]_{\text{D}}^{25}$: +26.0 (c 0.69, CHCl₃)

¹H NMR (CDCl₃): see paragraph 13.2.2.3

13.2.3 **Racemic dihydroxylation of isoflav-3-enes (373 and 374)**

Method : see paragraph 13.2.2: note chiral ligands substituted by pyridine.

13.2.3.1 (±)-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diol (377)

Method : see paragraph 13.2.2

Reagents : 2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflav-3-ene **373** (20 mg, 0.05 mmol), pyridine (6 mg, 0.08 mmol, 1.5 equiv.), OsO₄ (13 mg, 0.05 mmol, 1 equiv.), DCM (1ml).

Reaction time: 24 hours at -78°C

Yield : 12 mg, 55% (yellow oil)

¹H NMR (CDCl₃): see paragraph 13.2.2.1

13.2.3.2 (±)-2'-*O*-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflavan-3,4-diol (378)

Method : see paragraph 13.2.2

Reagents : 2'-*O*-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflav-3-ene **374** (20 mg, 0.05 mmol), pyridine (6 mg, 0.07 mmol, 1.5 equiv.), OsO₄ (12 mg, 0.05 mmol, 1 equiv.), DCM (1ml).

Reaction time: 24 hours at -78°C

Yield : 11 mg, 50% (yellow oil)

¹H NMR (CDCl₃): see paragraph 13.2.2.3

13.3 ACETYLATION OF ISOFLAVAN-3,4-DIOLS

13.3.1 2',3,4-tri-*O*-acetyl-4',7-dimethoxyisoflavans

Method : see paragraph 9.8.2.1

Reagents : 2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diols **377a/b** (*ca.* 10 mg, 0.02 mmol), pyridine (5 drops), acetic anhydride (10 drops)

Reaction time: 48 hours at 35°C

Yield : *ca.* 9 mg, 100%; products were not purified.

R_f : 0.45 (B:A 9:1)

¹H NMR (CDCl₃, plate 33): δ 1.93, 2.13, 2.45 (3xCOCH₃, 3xs, 3x3H), 3.74, 3.74 (2xOCH₃, 2xs, 2x3H), 4.47 (2-H_{ax}, d, J = 10.5 Hz, 1H), 5.44 (2-H_{eq}, dd, J = 1.9, 10.9 Hz, 1H), 6.35 (8-H, d, J = 2.5 Hz, 1H), 6.44 (6-H, dd, J = 2.5, 8.0 Hz, 1H), 6.50 (3'-H, d, J = 2.9 Hz, 1H), 6.68 (5'-H, dd, J = 2.9, 9.0 Hz, 1H), 6.96 (4-H, d, J = 1.9 Hz, 1H), 7.16 (5-H, d, J = 8.0 Hz, 1H), 7.60 (6'-H, d, J = 9.0 Hz, 1H).

13.3.2 2',3,4-tri-*O*-acetyl-3',4',7-trimethoxyisoflavans

Method : see paragraph 9.8.2.1

Reagents : 2'-*O*-*t*-butyldimethylsilyl-3',4',7-trimethoxyisoflavan-3,4-diols **378a/b** (ca. 10 mg, 0.02 mmol), pyridine (5 drops), acetic anhydride (10 drops)

Reaction time: 48 hours at 35°C

Yield : ca. 9 mg, 100%; products were not purified.

R_f : 0.56 (B:A 9:1)

¹H NMR (CDCl₃): δ 1.92, 2.11, 2.48 (3xCOCH₃, 3xs, 3x3H), 3.74, 3.78, 3.82 (3xOCH₃, 3xs, 3x3H), 4.44 (2-H_{ax}, d, J = 11.0 Hz, 1H), 5.31 (2-H_{eq}, dd, J = 1.0, 11.0 Hz, 1H), 6.39 (8-H, d, J = 2.5 Hz, 1H), 6.44 (5'-H, d, J = 8.0 Hz, 1H), 6.48 (6-H, dd, J = 2.5, 8.5 Hz, 1H), 6.51 (4-H, d, J = 1.0 Hz, 1H), 7.05 (6'-H, d, J = 8.0 Hz, 1H), 7.12 (5-H, d, J = 8.5 Hz, 1H).

13.4 CLEAVAGE OF THE 2'-*O*-TBDMS ETHERS (**377a/b** and **378a/b**)

Method : The 2'-*O*-*t*-butyldimethylsilylisoflavan-3,4-diol, dissolved in anhydrous THF, was treated with TBAF suspended on silica (2 equiv.) for 15 minutes at room temperature. After the addition of moist THF, the solvent was evaporated and the products separated by PLC.

13.4.1 (3*R*,4*S*)-2'-hydroxy-4',7-dimethoxyisoflavan-3,4-diol (**379a**)

Method : see paragraph 13.4

Reagents : (3*R*,4*S*)-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diol **377a** (48 mg, 0.11 mmol), TBAF (silica)(0.22 mmol, 2 equiv.), THF (5ml).

Reaction time: 15 minutes at room temperature

Yield : 35 mg, 100% (yellow oil)

R_f : 0.59 (B:A 7:3)

¹H NMR (CDCl₃, plate 34): δ 3.77, 3.80 (2xOCH₃, 2xs, 2x3H), 3.90-3.94 (4-OH, m, 1H),

4.21, 4.30 (2-H₂, 2xd, J = 11.1 Hz, 2x1H), 5.14 (4-H, d, J = 4.1 Hz, 1H), 5.53-5.56 (3-OH, m, 1H), 6.41 (5'-H, dd, J = 2.5, 8.9 Hz, 1H), 6.45 (3'-H, d, J = 2.5 Hz, 1H), 6.50 (8-H, d, J = 2.5 Hz, 1H), 6.61 (6-H, dd, J = 2.5, 8.5 Hz, 1H), 7.02 (6'-H, d, J = 8.9 Hz, 1H), 7.36 (5-H, d, J = 8.5 Hz, 1H), 8.86-8.91 (ArOH, m, 1H).

13.4.2 (3*S*,4*R*)-2'-hydroxy-4',7-dimethoxyisoflavan-3,4-diol (379b)

Method : see paragraph 13.4

Reagents : (3*S*,4*R*)-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diol **377b**
(50 mg, 0.12 mmol), TBAF (silica)(0.23 mmol, 2 equiv.), THF (5ml).

Reaction time: 15 minutes at room temperature

Yield : 37 mg, 100% (yellow oil)

R_f : 0.59 (B:A 7:3)

¹H NMR (CDCl₃): see paragraph 13.4.1

13.4.3 (3*R*,4*S*)-2'-hydroxy-3',4',7-dimethoxyisoflavan-3,4-diol (380a)

Method : see paragraph 13.4

Reagents : (3*R*,4*S*)-2'-*O*-*t*-butyldimethylsilyl-3',4',7-dimethoxyisoflavan-3,4-diol **378a**
(52 mg, 0.11 mmol), TBAF (silica)(0.22 mmol, 2 equiv.), THF (5ml).

Reaction time: 15 minutes at room temperature

Yield : 39 mg, 100% (yellow oil)

R_f : 0.74 (B:A 7:3)

¹H NMR (CDCl₃): δ 3.80, 3.86, 3.94 (3xOCH₃, 3xs, 3x3H), 4.28, 4.40 (2-H₂, 2xd, J = 1.1 Hz, 2x1H), 5.27-5.32 (4-H, m, 1H), 6.44 (8-H, d, J = 2.5 Hz, 1H), 6.49 (5'-H, d, J = 9.0 Hz, 1H), 6.60 (6-H, dd, J = 2.5, 8.1 Hz, 1H), 6.87 (ArOH, s, 1H), 7.16 (6'-H, d, J = 9.0 Hz, 1H), 7.40 (5-H, d, J = 8.1 Hz, 1H).

13.4.4 (3*R*,4*S*)-2'-hydroxy-3',4',7-dimethoxyisoflavan-3,4-diol (380b)

Method : see paragraph 13.4

Reagents : (3*R*,4*S*)-2'-*O*-*t*-butyldimethylsilyl-3',4',7-dimethoxyisoflavan-3,4-diol **378b**
(55 mg, 0.12 mmol), TBAF (silica)(0.24 mmol, 2 equiv.), THF (5ml).

Reaction time: 15 minutes at room temperature

Yield : 41 mg, 100% (yellow oil)

R_f : 0.74 (B:A 7:3)

¹H NMR (CDCl₃): see paragraph 13.4.3

13.5 SYNTHESIS OF 6a-HYDROXYPTEROCARPANS (381a/b and 382 a/b)

13.5.1 Mitsunobu cyclisation

(6*aR*,11*aR*)-*cis*-6a-hydroxy-3,9-dimethoxypterocarpan (variabilin) (381a)

Method : see paragraph 9.8.8

Reagents : (3*R*,4*S*)-2'-hydroxy-4',7-dimethoxyisoflavan-3,4-diol **379a** (10 mg, 0.03 mmol), TPP (79 mg, 0.30 mmol, 10 equiv.), DEAD (26 mg, 0.15 mmol, 5 equiv.), THF (1ml)

Reaction time: 16 hours at room temperature.

Yield : 0 mg, 0%; Starting material was recovered.

13.5.2 Methanesulfonyl anhydride (Ms₂O) / pyridine

Method : A solution of 2'-hydroxyisoflavan-3,4-diol in anhydrous DCM was treated with Ms₂O (1.2 equiv.) and pyridine (5 equiv.). The reaction mixture was stirred at room temperature for 16 hours. After dilution with moist Et₂O,

the organic layer was washed with water (3x25ml), dried (Na₂SO₄), evaporated and the 6a-hydroxypterocarpan purified by PLC.

13.5.2.1 (+)-(6aR,11aR)-cis-6a-hydroxy-3,9-dimethoxypterocarpan [(+)-Variabilin]
(381a)

Method : see paragraph 13.5.2

Reagents : (3R,4S)-2'-hydroxy-4',7-dimethoxyisoflavan-3,4-diol **379a** (25 mg, 0.08 mmol), Ms₂O (16 mg, 0.09 mmol, 1.2 equiv.), pyridine (33 mg, 0.39 mmol, 5 equiv.), DCM (1ml)

Reaction time: 16 hours at room temperature

Yield : *cis*-**381a** : 17 mg, 70% (light yellow oil)
trans-**383a** : 2.3 mg, 10% (light yellow oil)

R_f : *cis* : 0.50 (B:A 9:1)

trans : 0.45 (B:A 9:1)

MS : *cis* : *m/z* 301 (M+H⁺, 18%), 283(96); Found : C₁₇H₁₆O₅ (M+H⁺), calcd as 301.1076; found 301.1076

trans : *m/z* 301 (M+H⁺, 34%), 283(21); Found : (M+H⁺), 301.1070

C₁₇H₁₆O₅ requires (M+H⁺), 301.1076

CD: Δε_{max} [λ (nm)]: *cis* : -3.93 x 10³ (294), +2.45 x 10⁴ (246)

trans : +2.95 x 10² (278), +1.13 x 10³ (222), +7.98 x 10² (208)

[α]_D²⁵ : *cis* : +223.6 (c 0.72, CHCl₃)

trans : -128.6 (c 0.28, CHCl₃)

¹H NMR (CDCl₃):

[*cis*-**381a**, plate 35] : δ 2.48-2.55 (6a-OH, m, 1H), 3.78, 3.79 (2xOCH₃, 2xs, 2x3H),

¹H NMR (CDCl₃):

[*cis*-**381b**] : see paragraph 13.5.2.1

[*trans*-**383b**] : see paragraph 13.5.2.1

13.5.2.3 (+)-(6a*R*,11a*R*)-*cis*-6a-hydroxy-3,9,10-trimethoxypterocarpan (**382a**)

Method : see paragraph 13.5.2

Reagents : (3*R*,4*S*)-2'-hydroxy-3',4',7-trimethoxyisoflavan-3,4-diol **380a** (24 mg, 0.06 mmol), Ms₂O (14 mg, 0.08 mmol, 1.2 equiv.), pyridine (29 mg, 0.34 mmol, 5 equiv.), DCM (1ml)

Reaction time: 16 hours at room temperature

Yield : 17 mg, 75% (light yellow oil)

R_f : 0.40 (B:A 9:1)

MS : *m/z* 331 (M+H⁺, 25%), 313(67); Found : (M+H⁺), 331.1180 C₁₈H₁₉O₆ requires (M+H⁺), 331.1182

CD : Δε_{max} [λ (nm)]: -8.24 × 10³ (285), +9.10 × 10³ (245)

[α]_D²⁵ : +185.6 (c 0.48, CHCl₃)

¹H NMR (CDCl₃, plate 37): δ 2.43-2.46 (6a-OH, m, 1H), 3.80, 3.87, 3.94 (3xOCH₃, 3xs, 3x3H), 4.05 (6-H_{ax}, d, J = 11.5 Hz, 1H), 4.25 (6-H_{eq}, dd, J = 1.0, 11.5 Hz, 1H), 5.36 (11a-H, bs, 1H), 6.48 (4-H, d, J = 2.5 Hz, 1H), 6.57 (8-H, d, J = 8.0 Hz, 1H), 6.67 (2-H, dd, J = 2.5, 8.9 Hz, 1H), 7.04 (7-H, d, J = 8.0 Hz, 1H), 7.48 (1-H, d, J = 8.9 Hz, 1H).

13.5.2.4 (-)-(6a*S*,11a*S*)-*cis*-6a-hydroxy-3,9,10-trimethoxypterocarpan (**382b**)

Method : see paragraph 13.5.2

Reagents : (3*S*,4*R*)-2'-hydroxy-3',4',7-trimethoxyisoflavan-3,4-diol **380b** (27 mg, 0.08 mmol), Ms₂O (16 mg, 0.09 mmol, 1.2 equiv.), pyridine (33 mg, 0.39 mmol, 5 equiv.), DCM (1ml)

Reaction time: 16 hours at room temperature

Yield : 19 mg, 73% (light yellow oil)

R_f : 0.40 (B:A 9:1)

MS : *m/z* 331 (M+H⁺, 21%), 313(53); Found : (M+H⁺), 331.1183 C₁₈H₁₉O₆
requires (M+H⁺), 331.1182

CD : $\Delta\epsilon_{\max}$ [λ (nm)]: +8.20 x 10³ (285), -8.95 x 10³ (245)

[α]_D²⁵ : -186.2 (c 0.58, CHCl₃)

¹H NMR (CDCl₃): see paragraph 13.5.2.3.

APPENDIX A

REPRESENTATIVE NMR SPECTRA

Plate 1: ^1H NMR [CDCl_3]: 2-*O*-Methoxymethyl-4-methoxybenzaldehyde

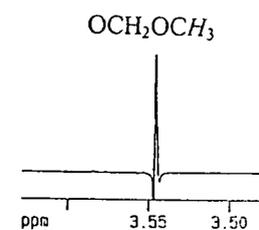
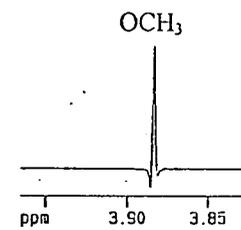
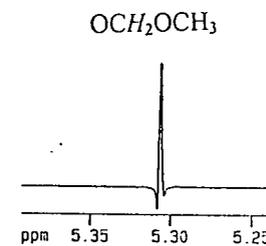
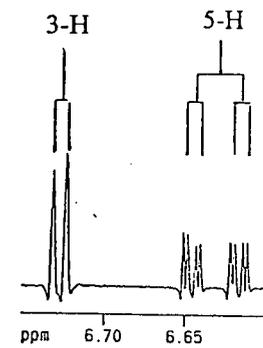
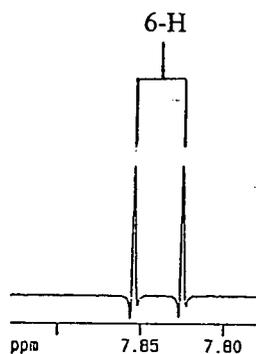
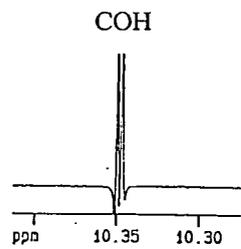
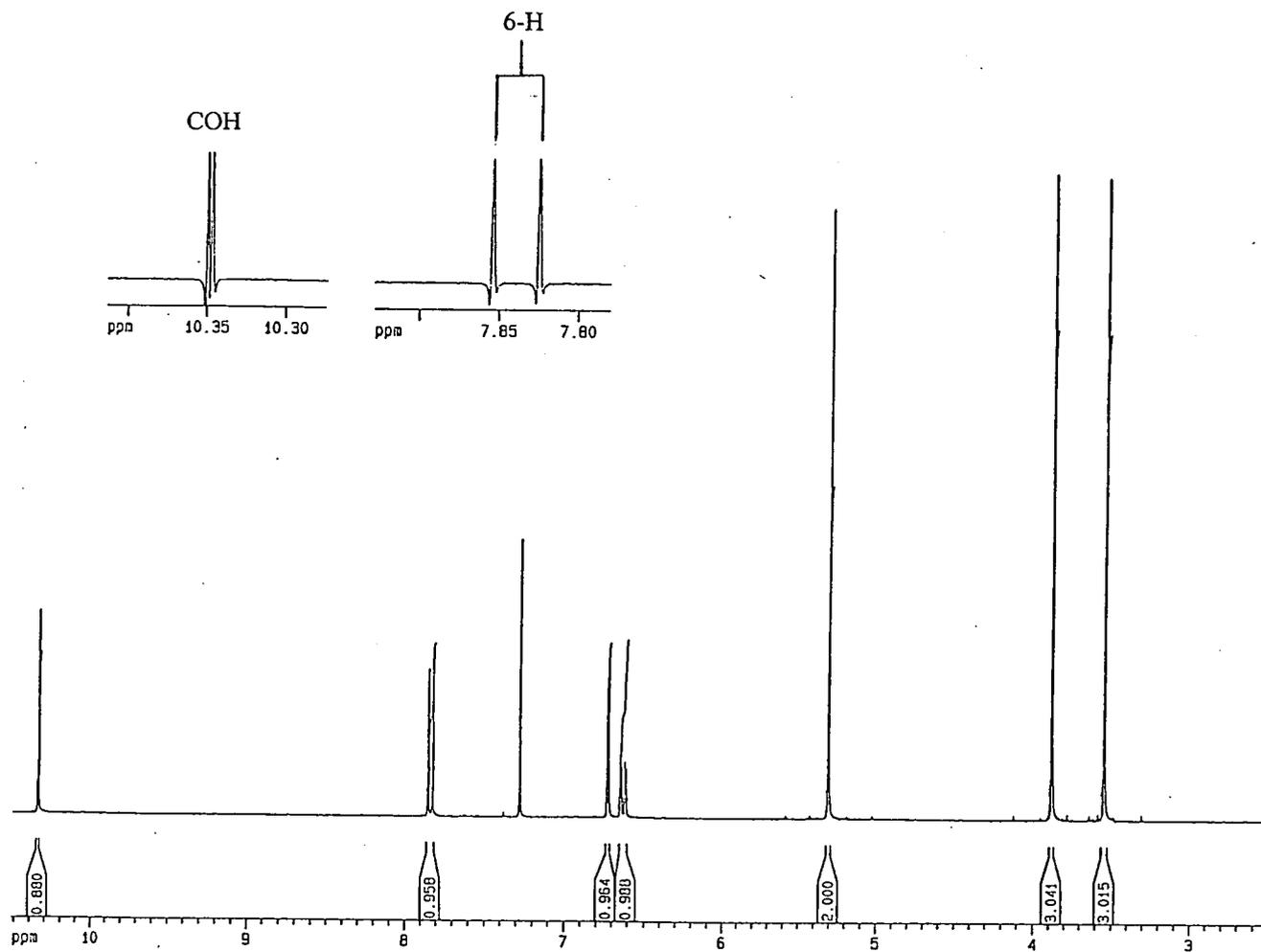
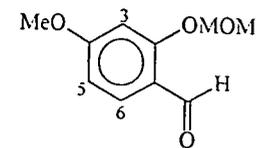


Plate 2: ^1H NMR [CDCl_3]: Methyl 2-*O*-*t*-butyldimethylsilyl-4-methoxyphenylacetate (244)

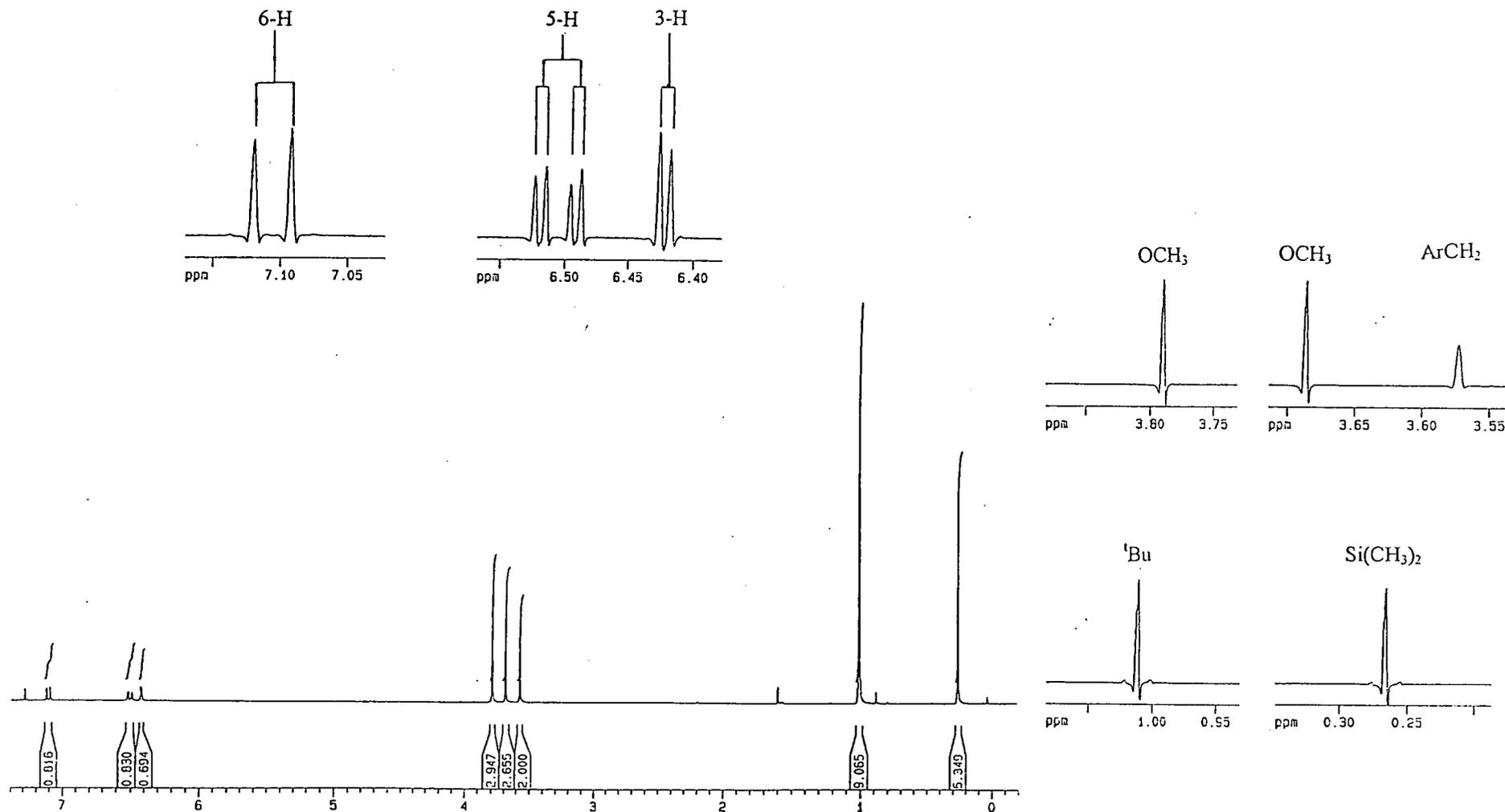
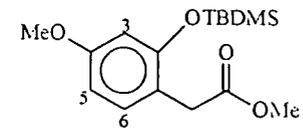


Plate 3: ^1H NMR [CDCl_3]: *Erythro*-methyl 2-(2'-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate (252)

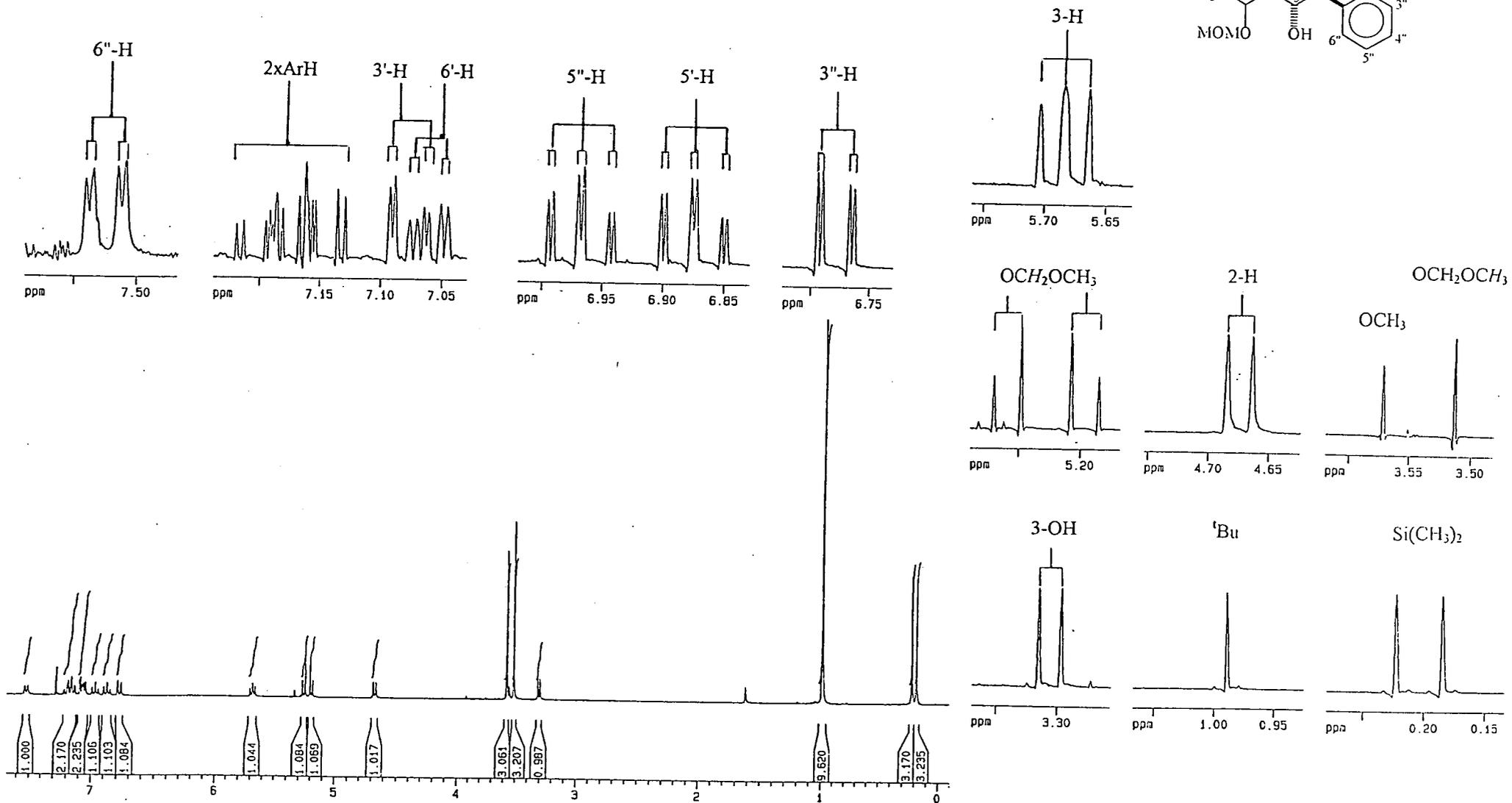
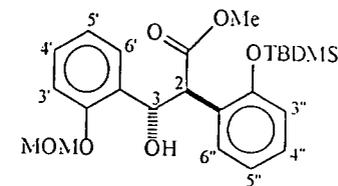


Plate 4: ^1H NMR [CDCl_3]: *Threo*-methyl 2-(2''-*O*-*t*-butyldimethylsilylphenyl)-3-hydroxy-3-(2'-*O*-methoxymethylphenyl)propanoate (252)

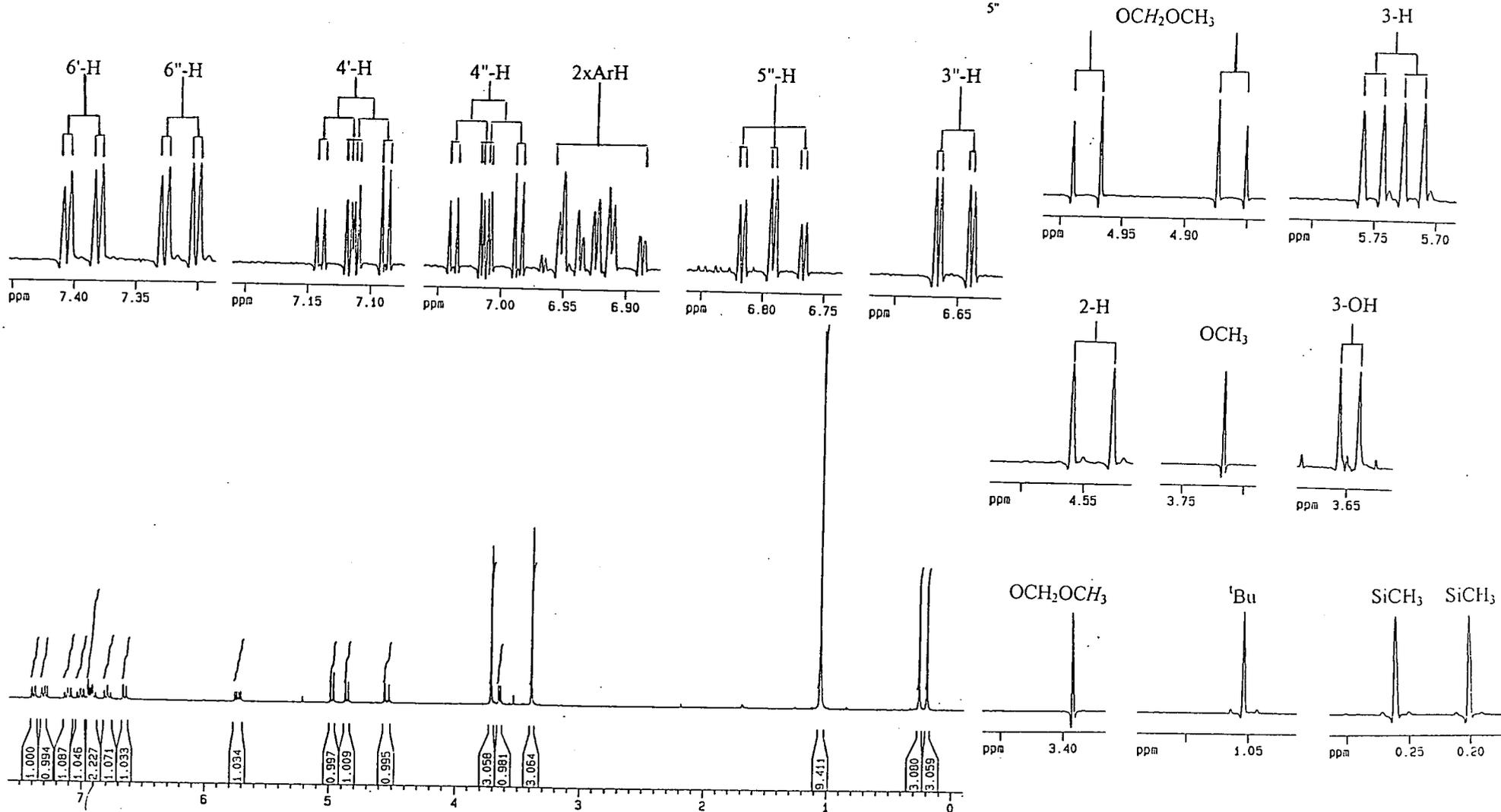
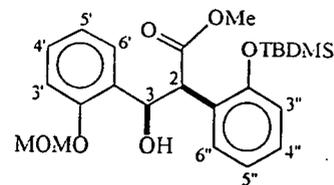


Plate 5: ^1H NMR [CDCl_3]: *Erythro*-methyl 2-(2'-*O*-*t*-butyldimethylsilyl-4''-methoxy-phenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)-propanoate (255)

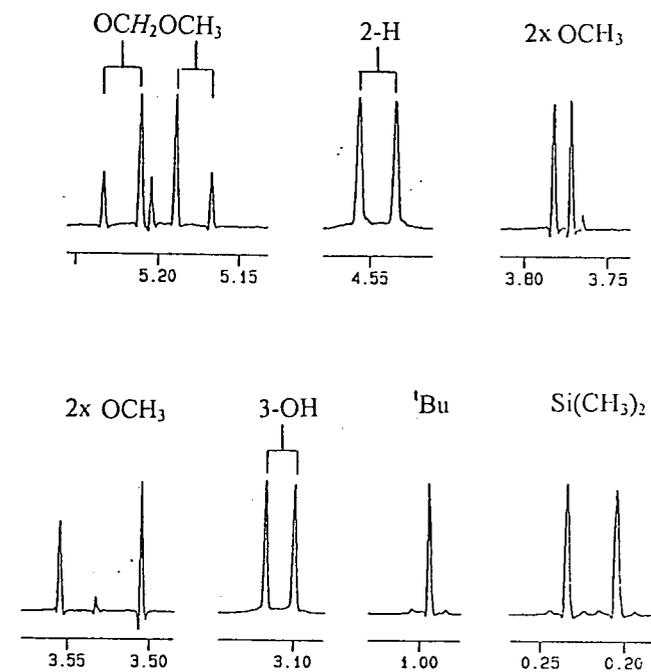
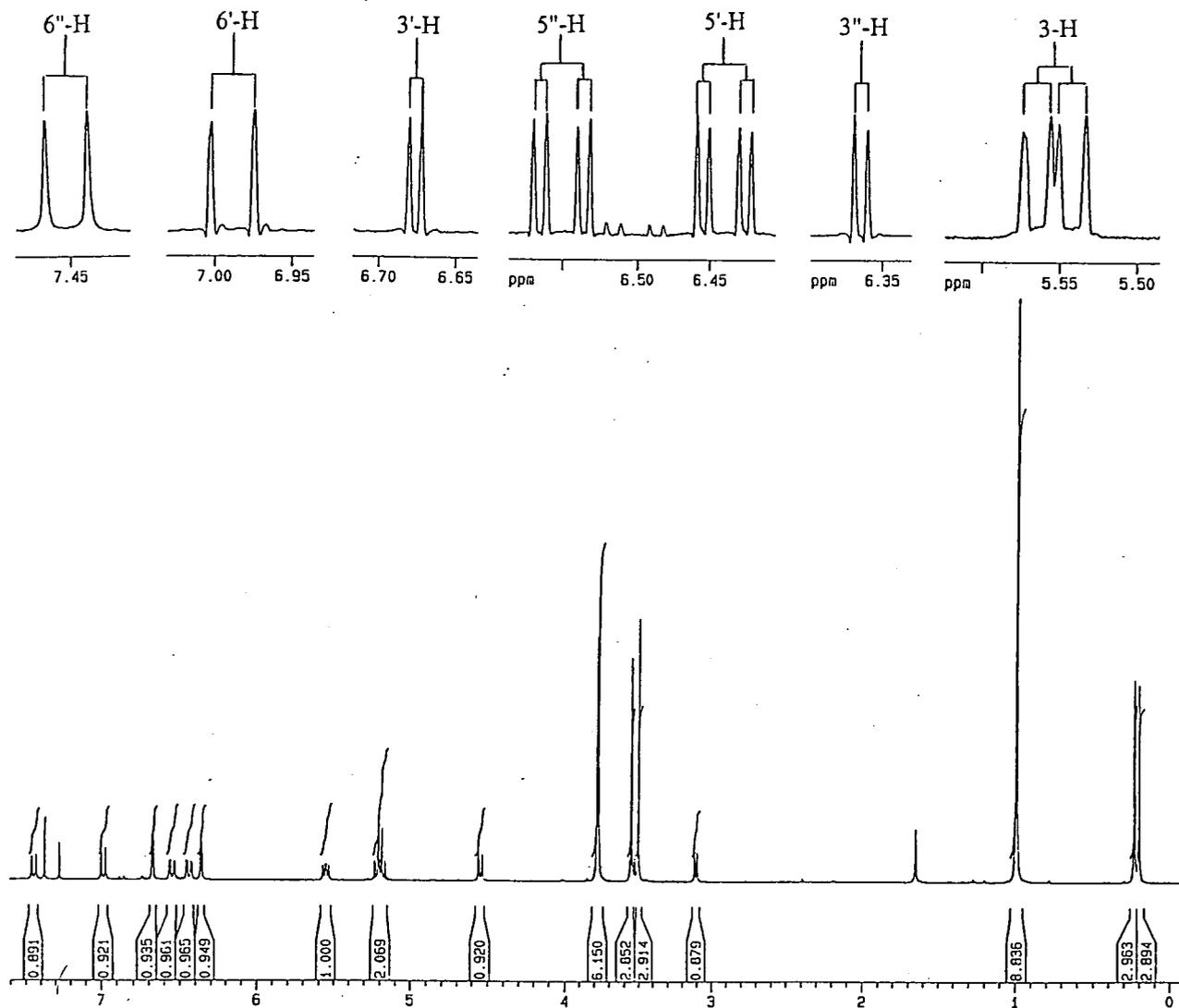
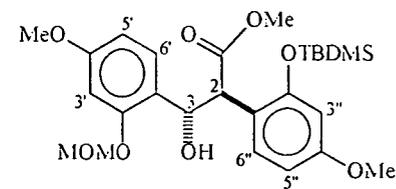


Plate 6: ^1H NMR [CDCl_3]: *Threo*-methyl 2-(2'-*O*-*t*-butyldimethylsilyl-4"-methoxy-phenyl)-3-hydroxy-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)-propanoate (255)

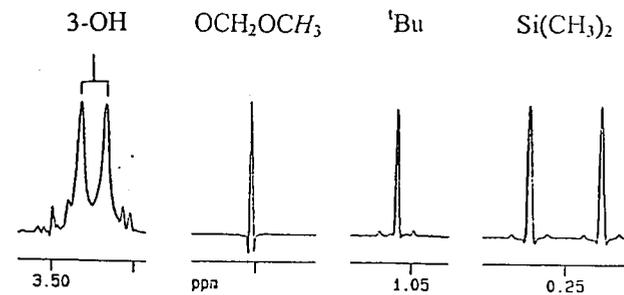
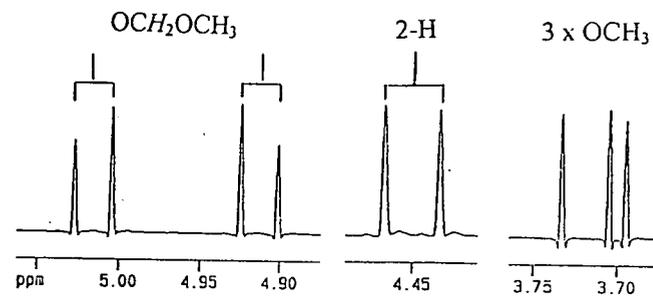
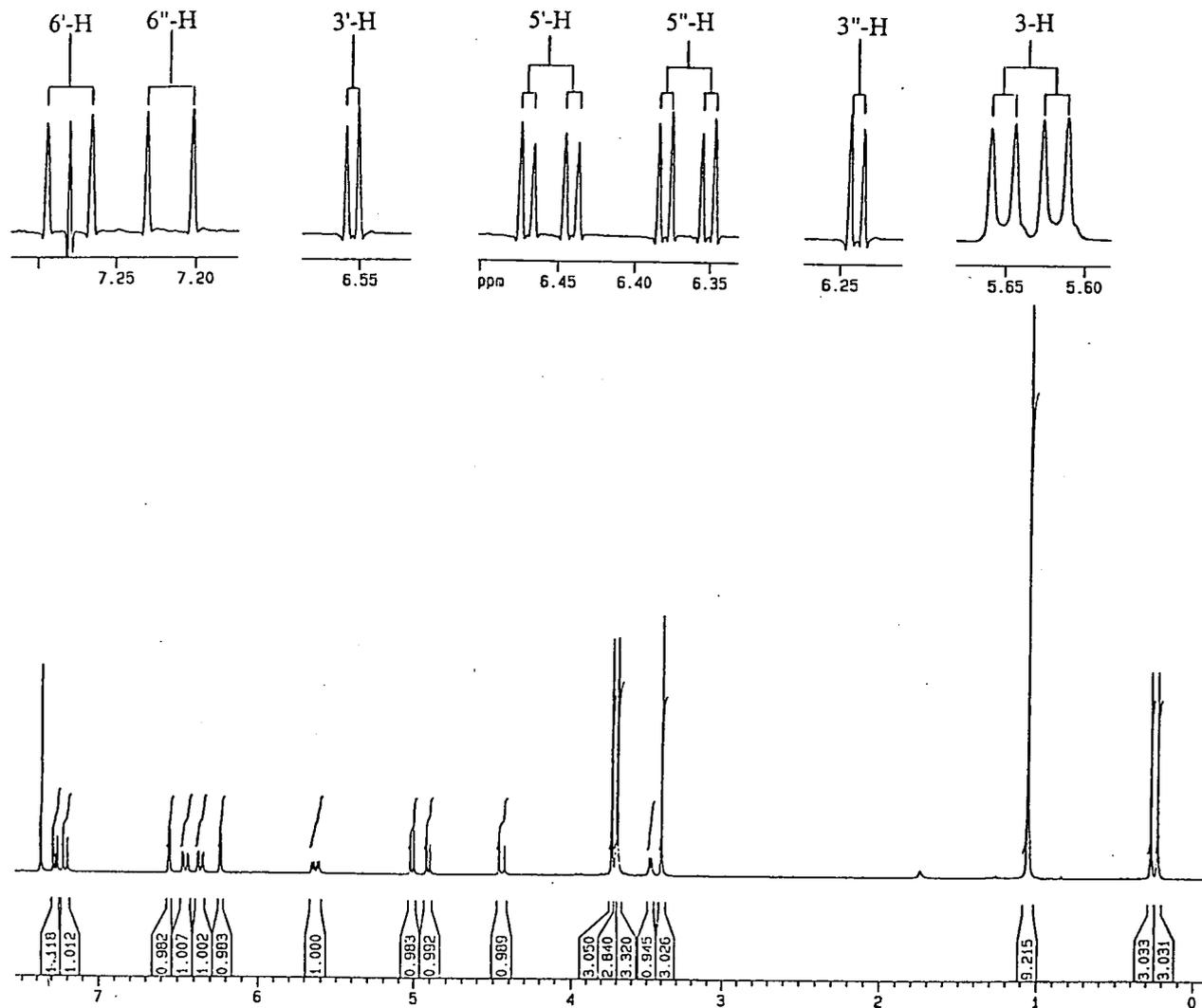
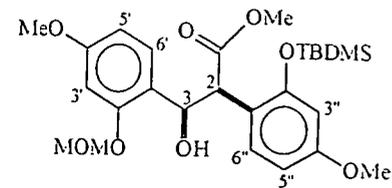


Plate 7: ^1H NMR [CDCl_3]: *Erythro*-methyl 3-acetoxy-2-(2'-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate (256)

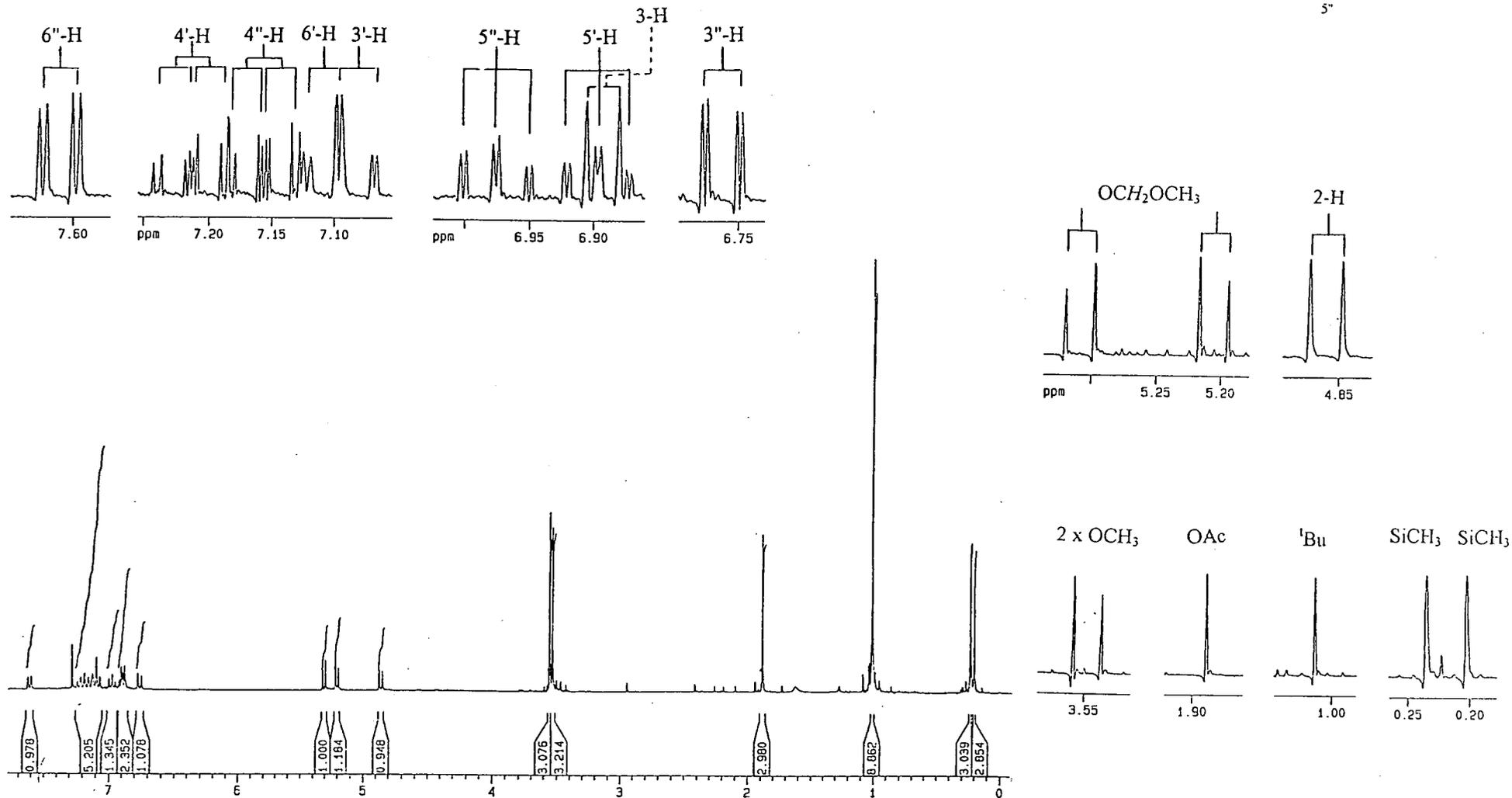
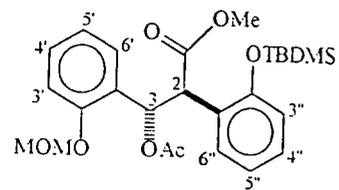


Plate 8: $^1\text{H NMR}$ [CDCl_3]: *Threo*-methyl 3-acetoxy-2-(2"-*O*-*t*-butyldimethylsilylphenyl)-3-(2'-*O*-methoxymethylphenyl)propanoate (257)

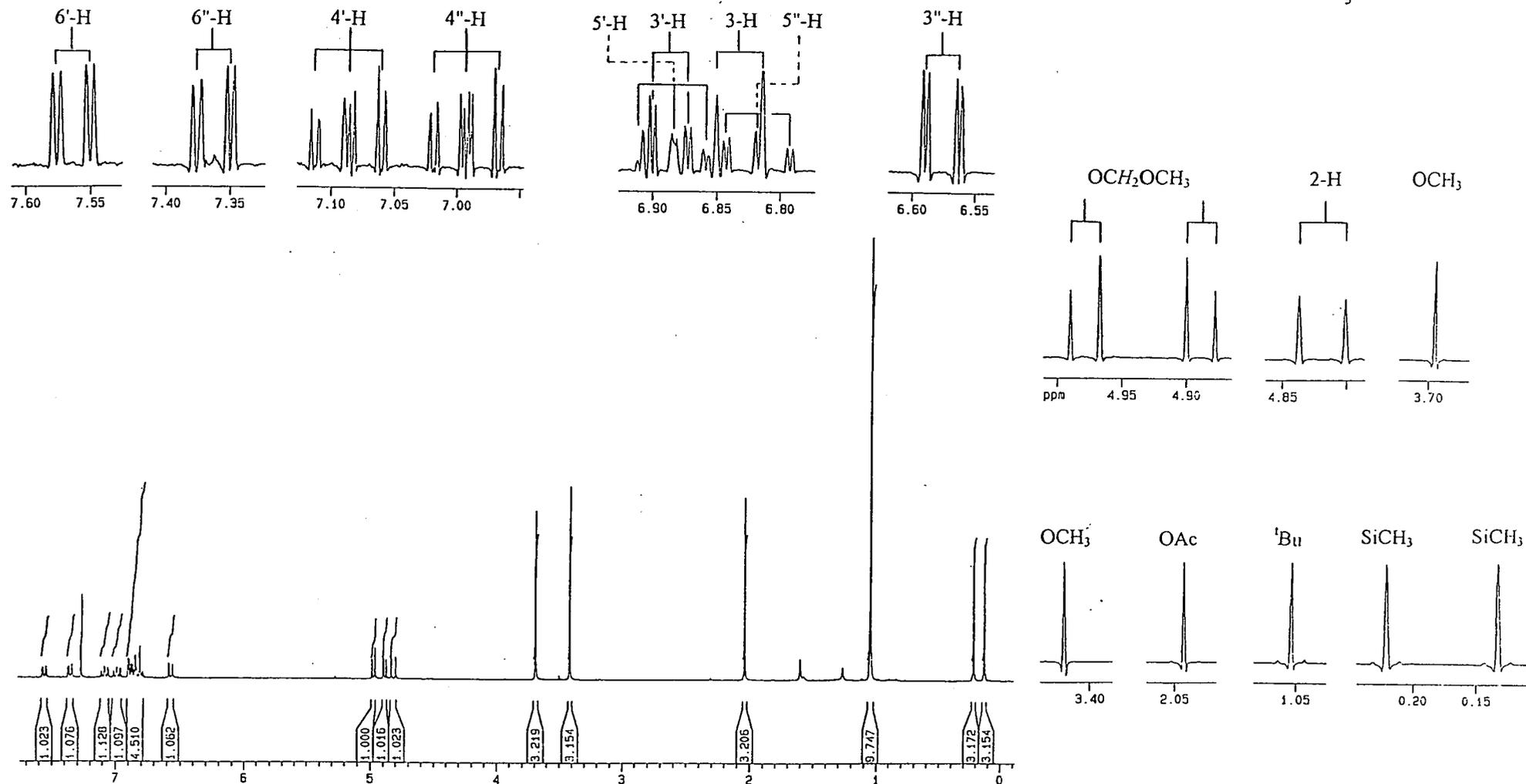
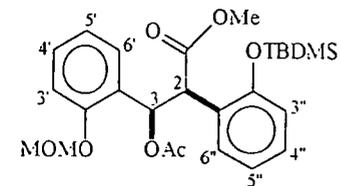


Plate 9: ^1H NMR [CDCl_3]: *Erythro*-3-hydroxy-2-(2'-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propan-1-ol (258)

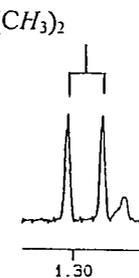
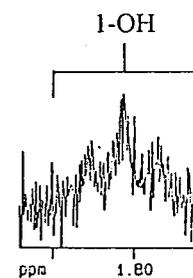
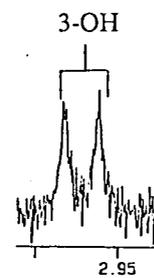
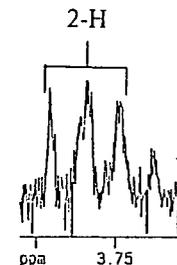
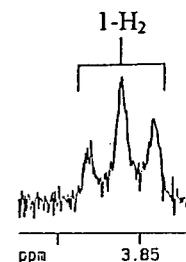
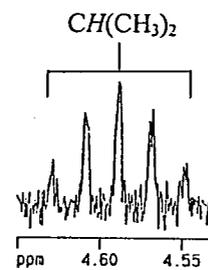
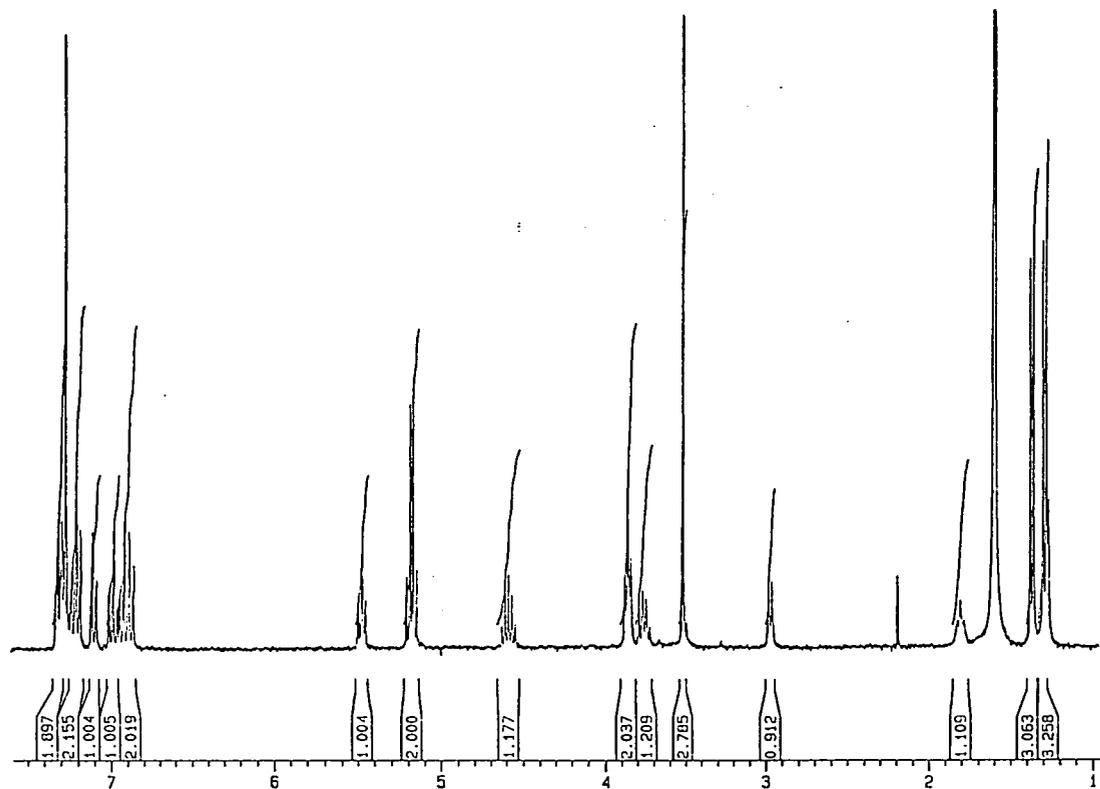
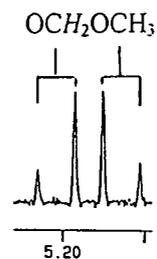
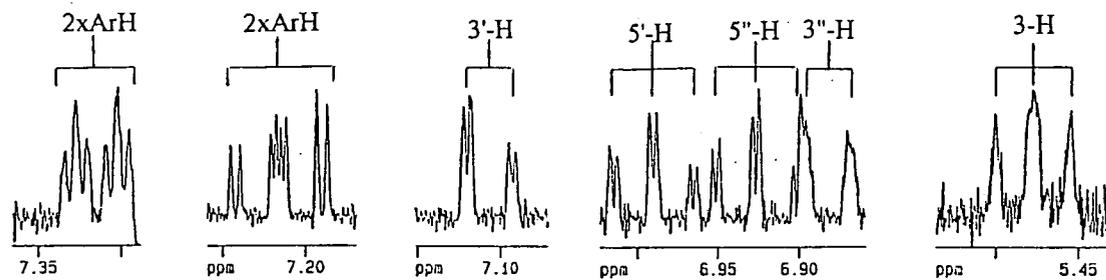
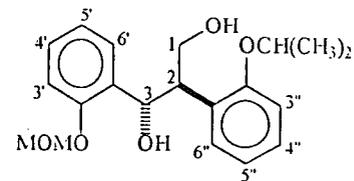


Plate 10: ^1H NMR [CDCl_3]: *Threo*-3-hydroxy-2-(2''-*O*-isopropylphenyl)-3-(2'-*O*-methoxymethylphenyl)propan-1-ol (258)

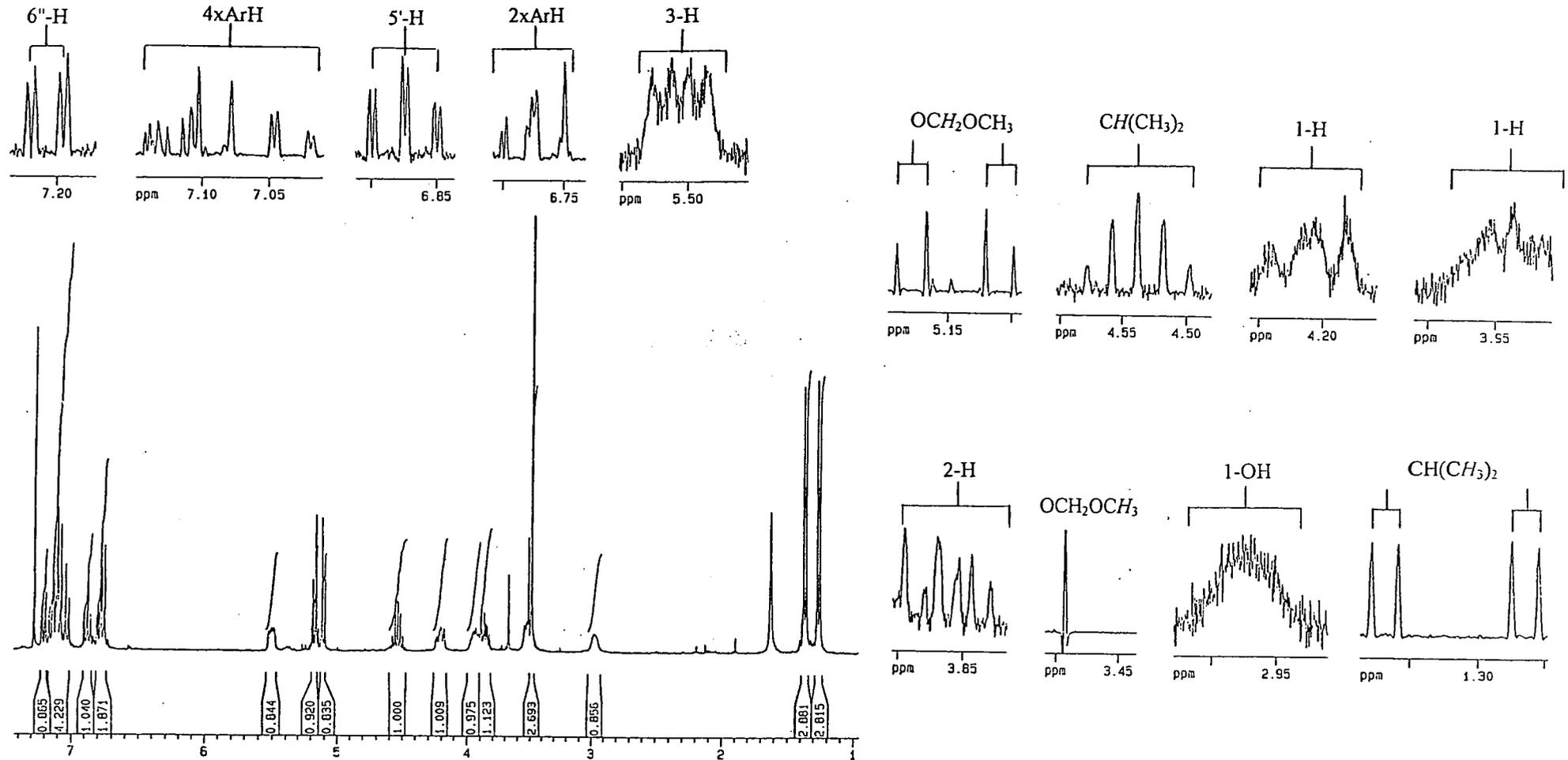
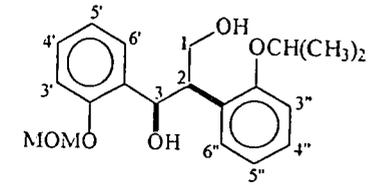


Plate 11: ^1H NMR [CDCl_3]: *Erythro*-methyl 3-benzylsulfanyl-2-(2'-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate (271)

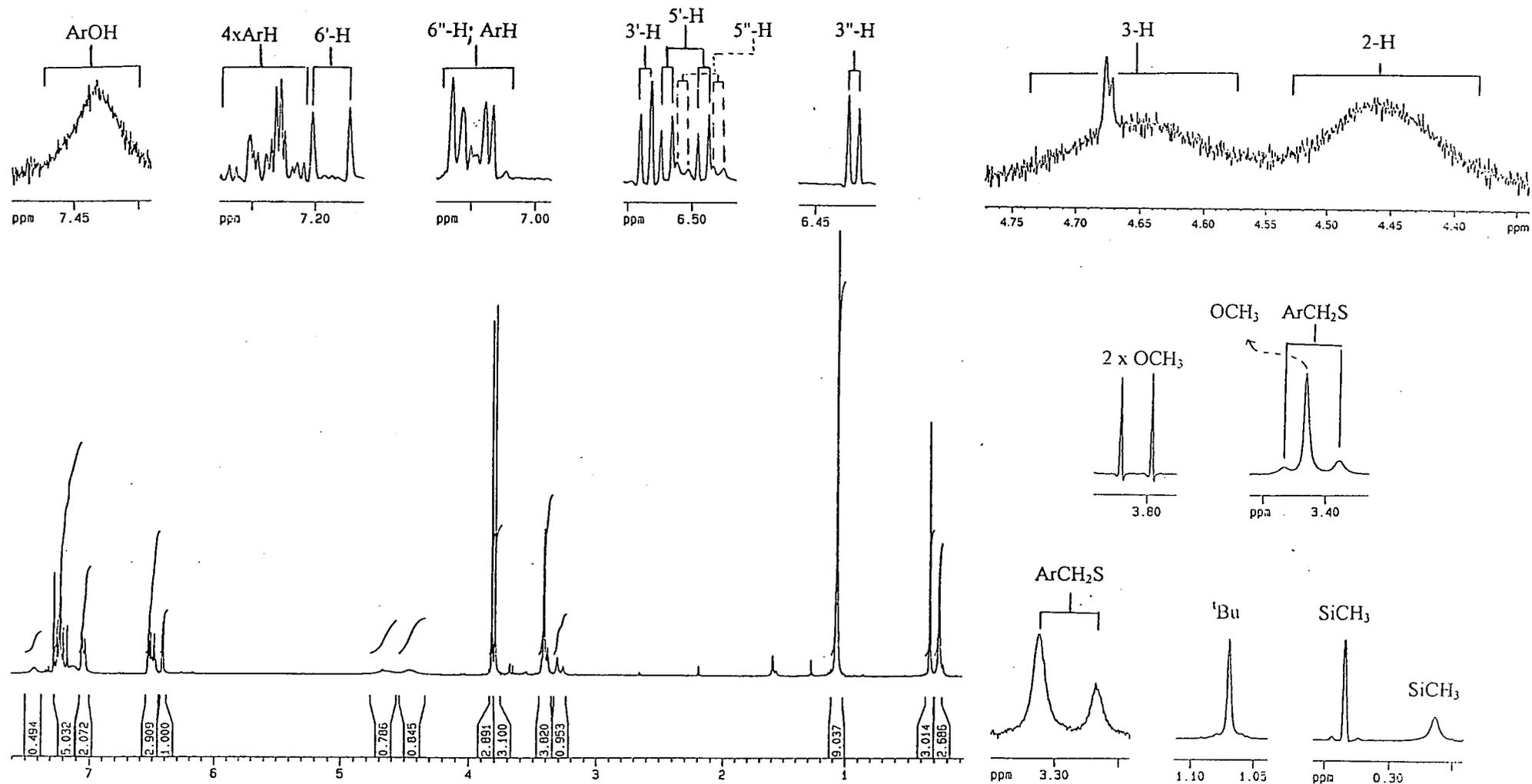
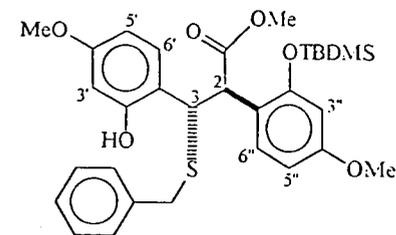


Plate 12: $^1\text{H NMR}$ [CDCl_3]: *Threo*-methyl 3-benzylsulfanyl-2-(2"-*O*-*t*-butyldimethylsilyl-4"-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propanoate (271)

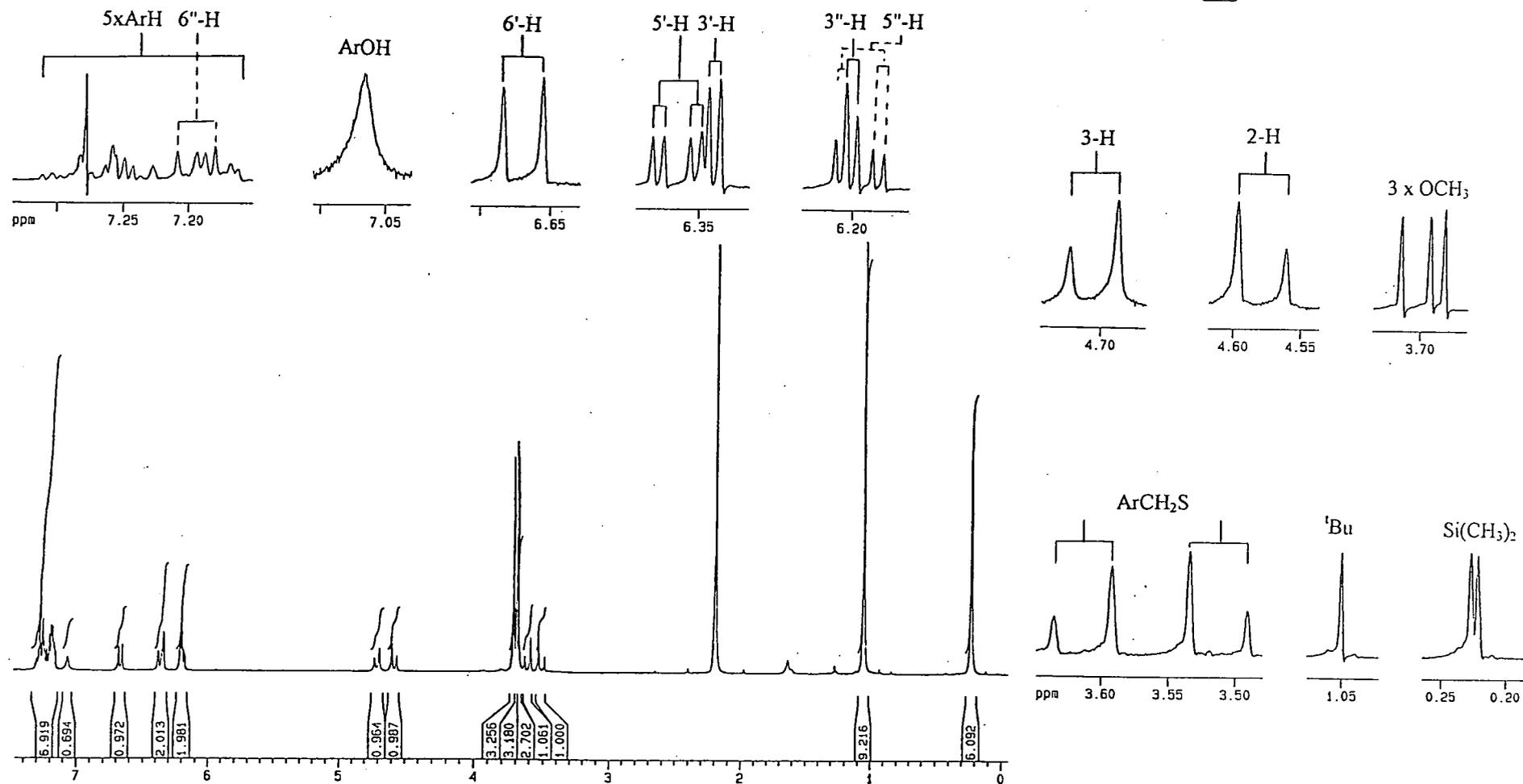
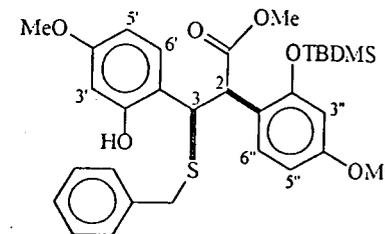


Plate 13: ^1H NMR [CDCl_3]: *Erythro*-3-benzylsulfanyl-2-(2'-*O*-*t*-butyldimethylsilyl-4''-methoxy-phenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (275)

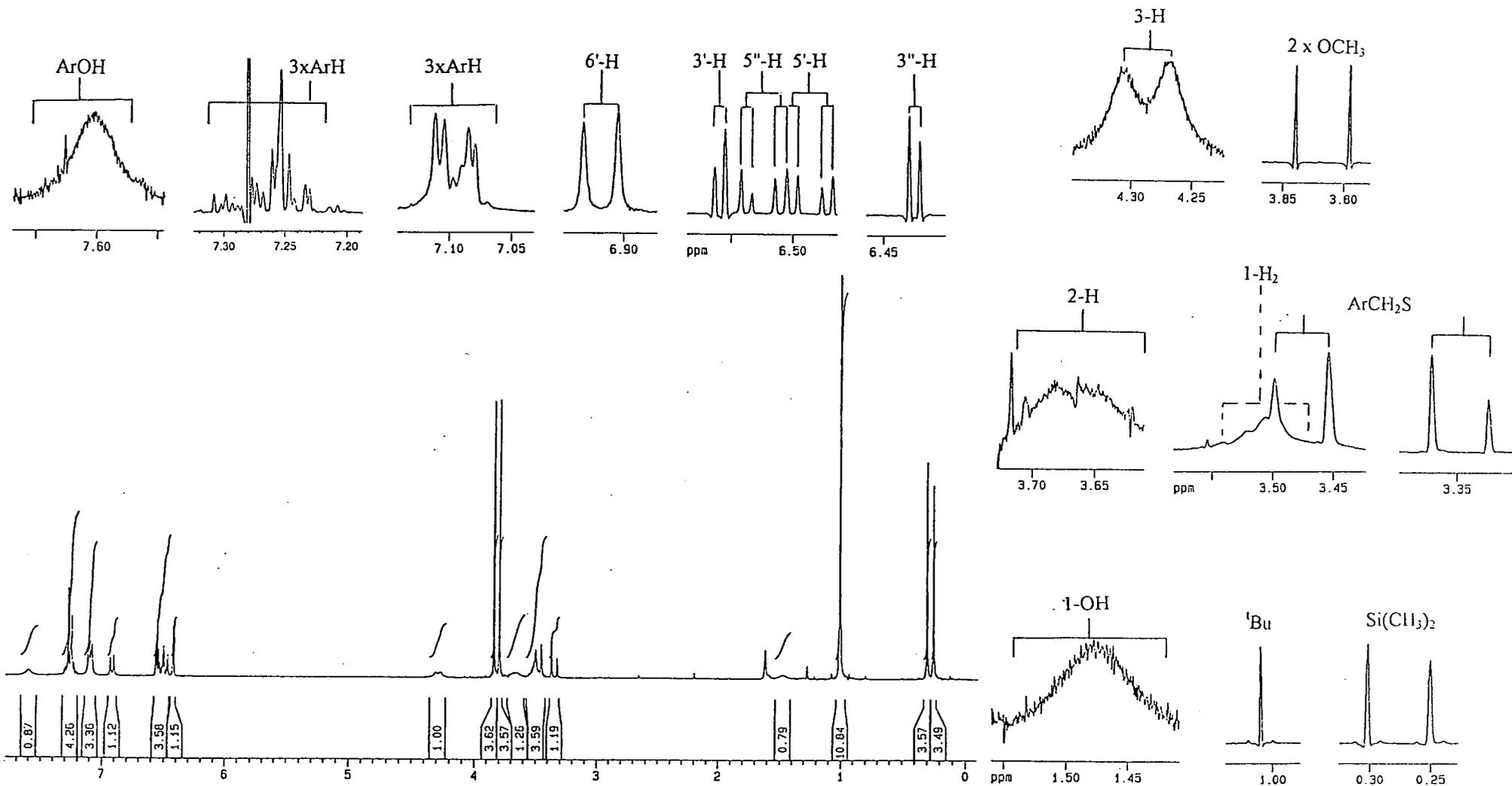
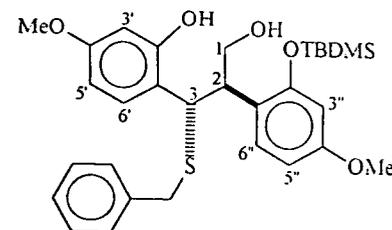


Plate 14: $^1\text{H NMR}$ [CDCl_3]: *Threo*-3-benzylsulfanyl-2-(2'-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-hydroxy-4'-methoxyphenyl)propan-1-ol (275)

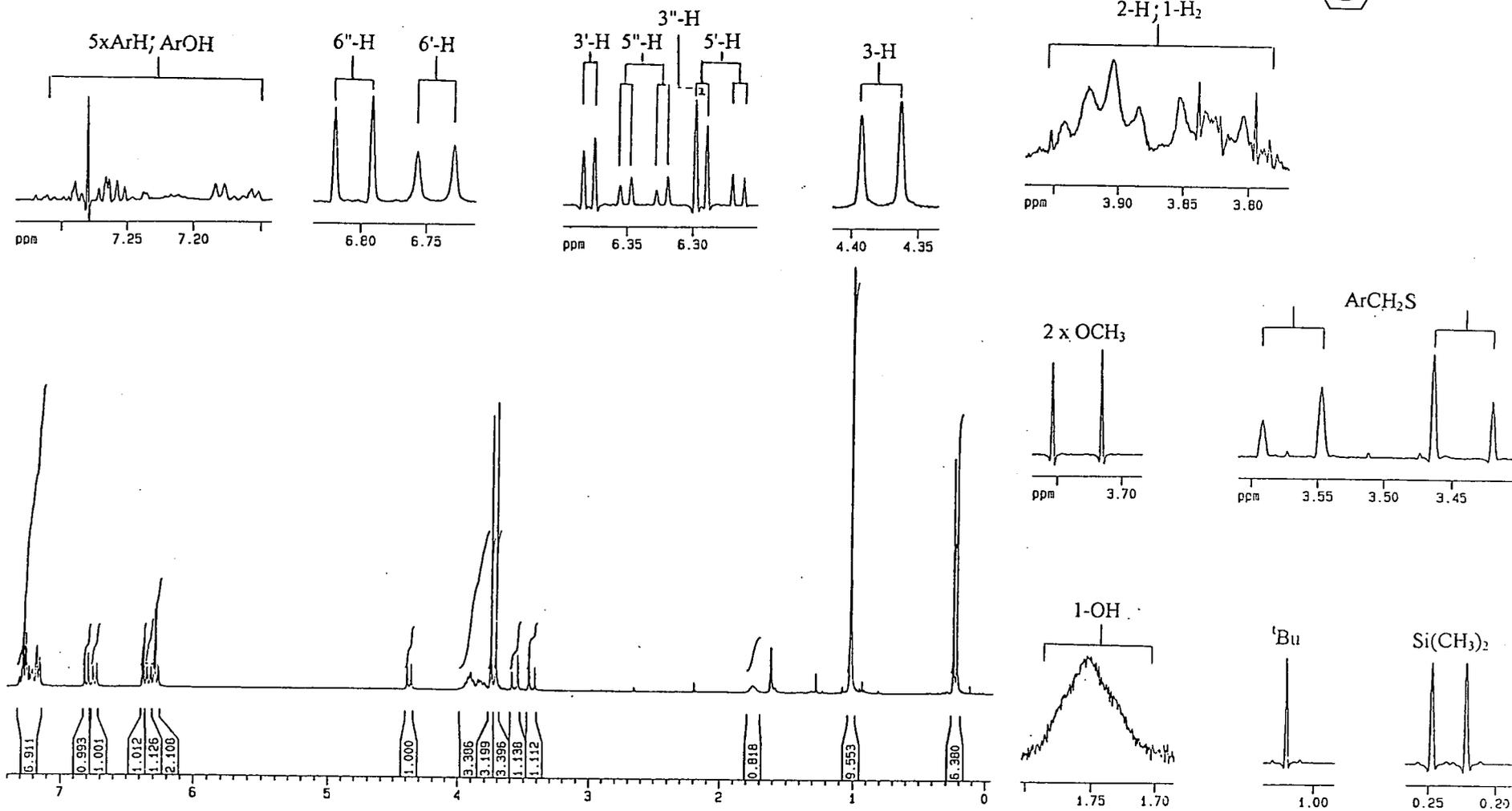
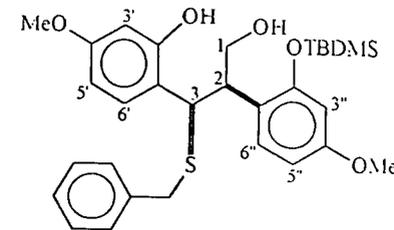


Plate 15: ^1H NMR [CDCl_3]: *Cis*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan (286)

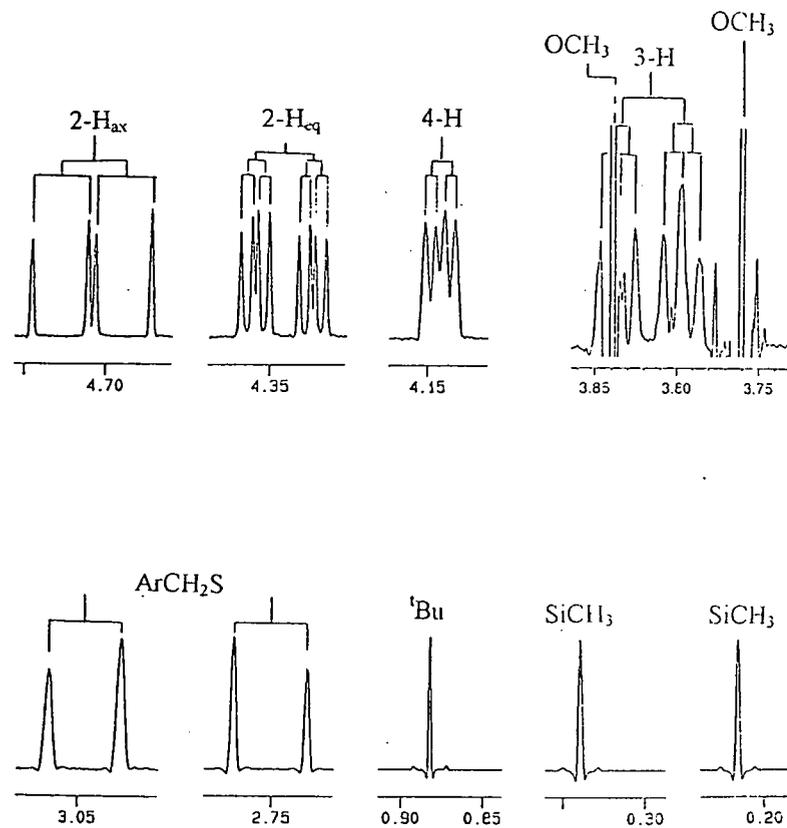
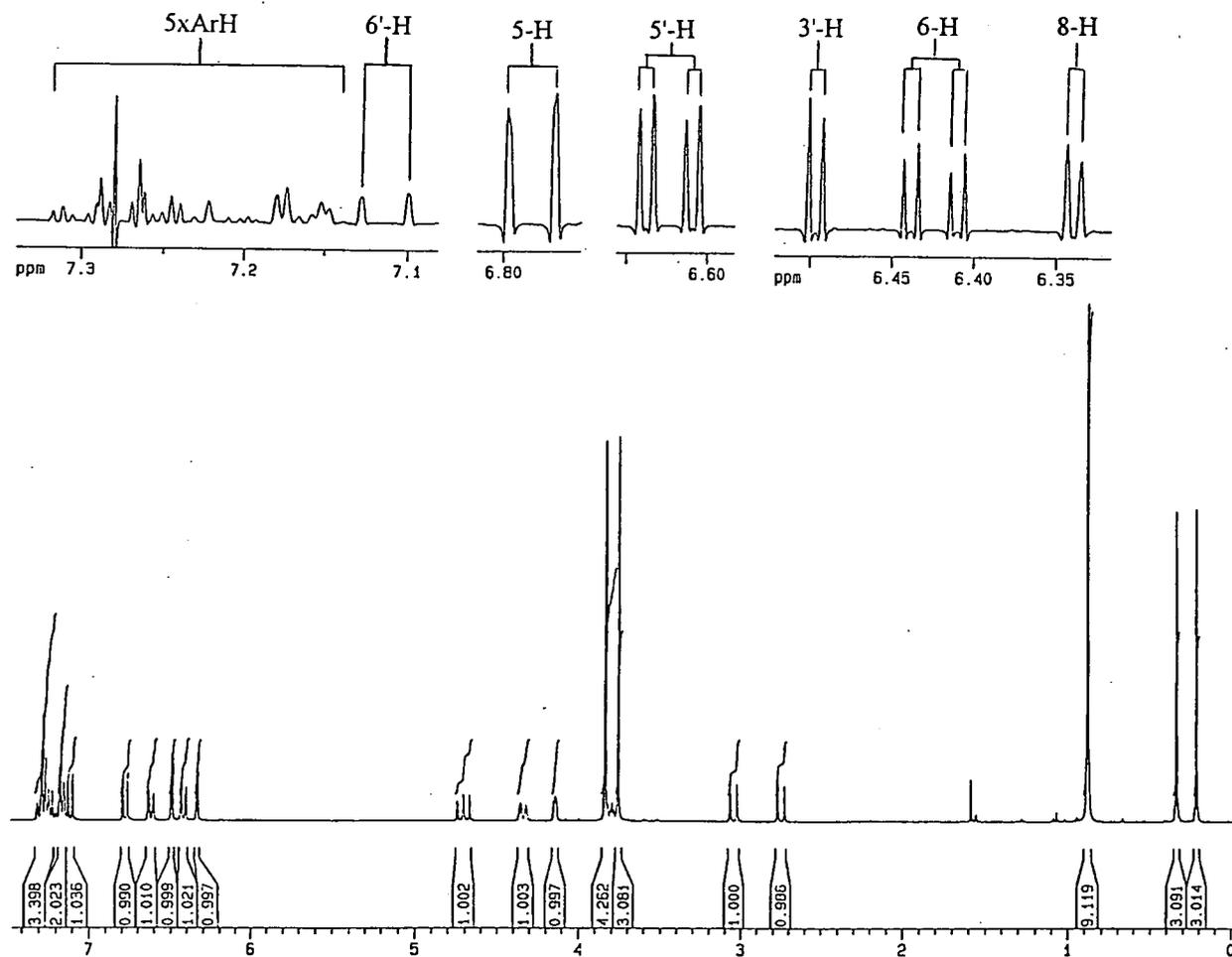
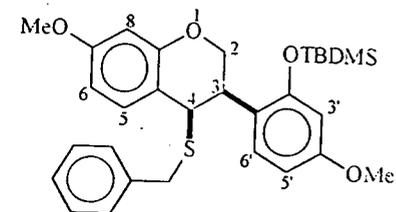


Plate 16: ^1H NMR [CDCl_3]: *Trans*-4-benzylsulfanyl-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan (286)

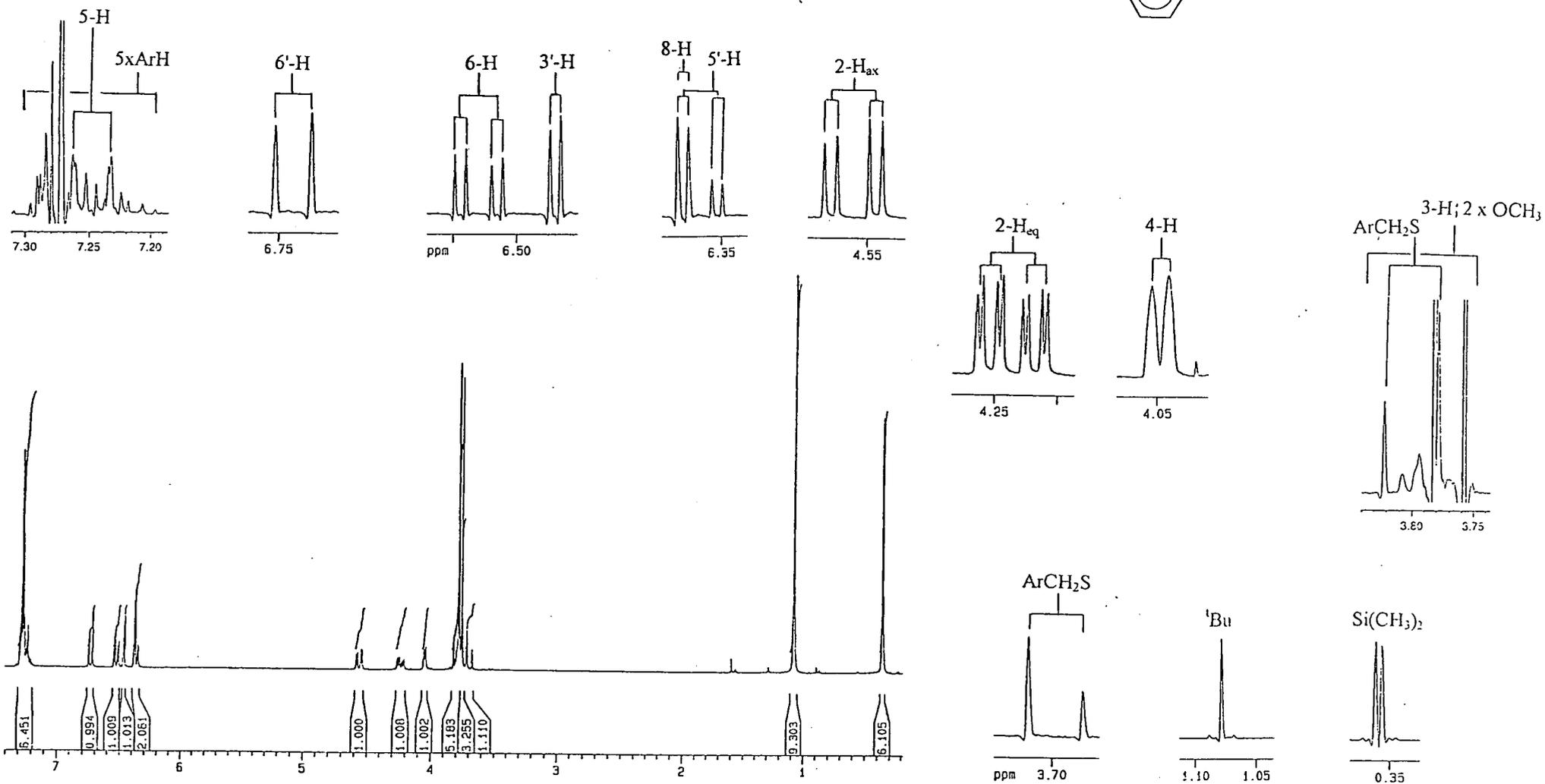
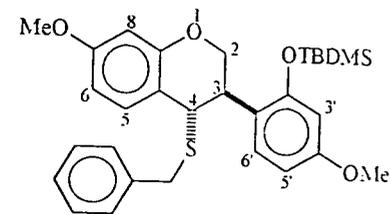


Plate 17: ^1H NMR [CDCl_3]: *Cis*-4-benzylsulfanyl-2'-hydroxy-4',7-dimethoxyisoflavan (297)

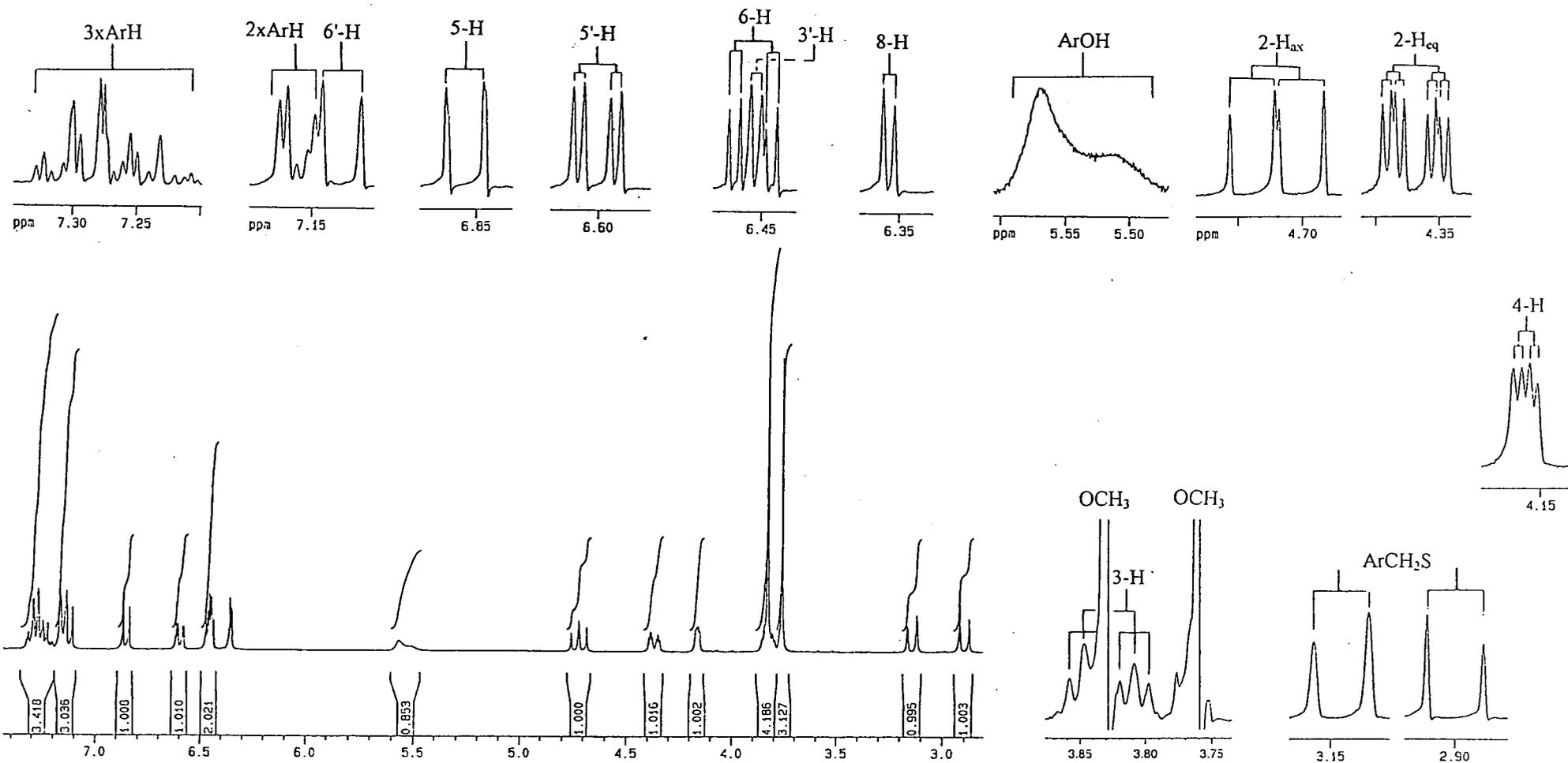
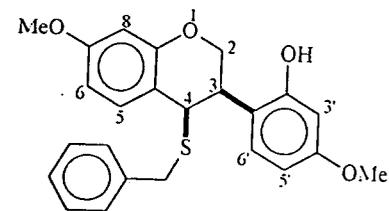


Plate 18: ^1H NMR [CDCl_3]: *Trans*-4-benzylsulfanyl-2'-hydroxy-4',7-dimethoxyisoflavan (297)

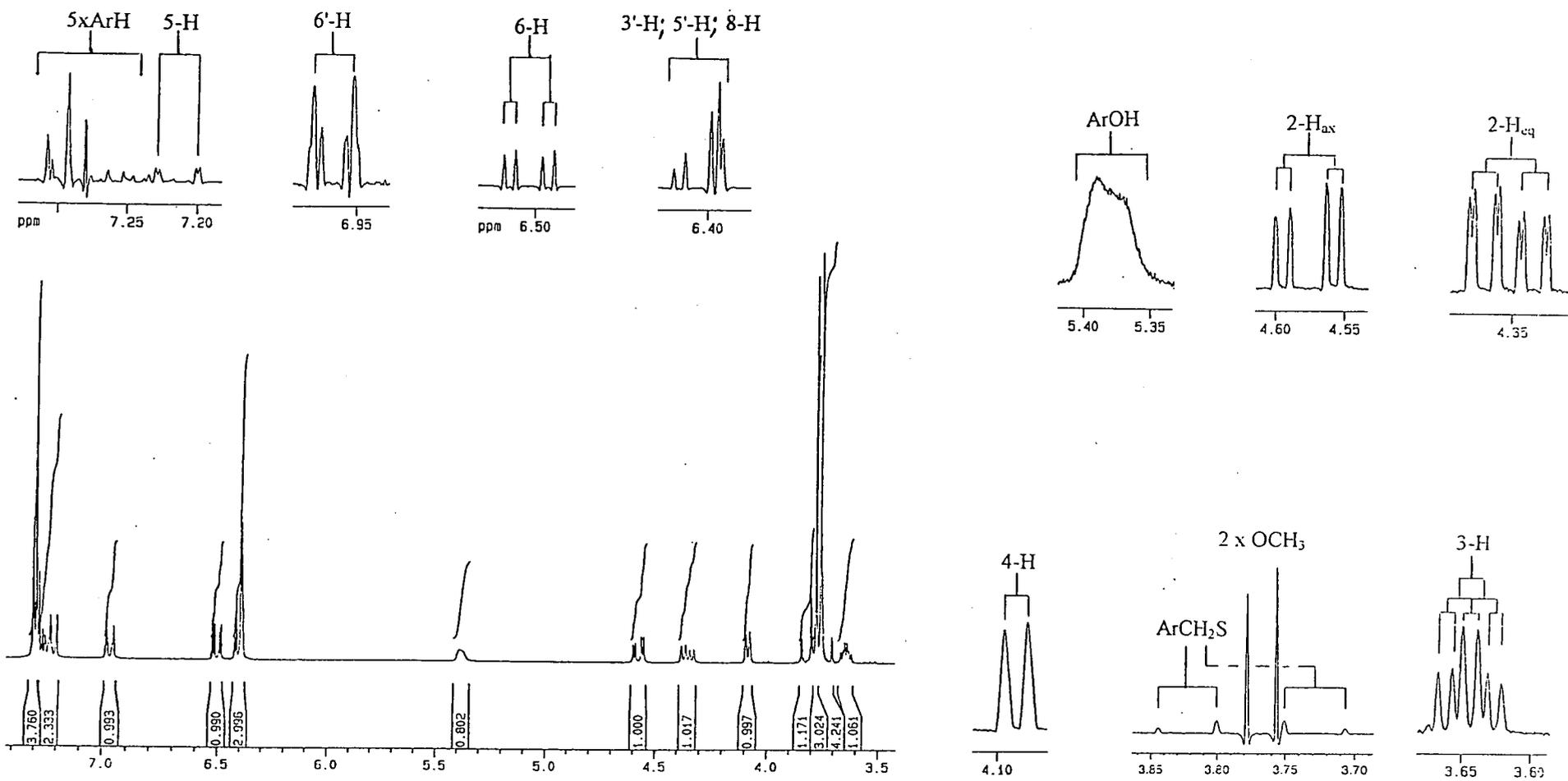
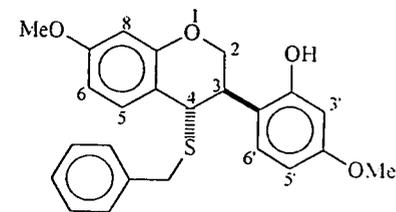


Plate 19: ^1H NMR [C_6D_6]: (\pm)-6a,11a-*cis*-Pterocarpan (298)

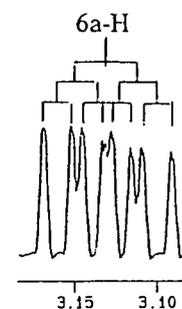
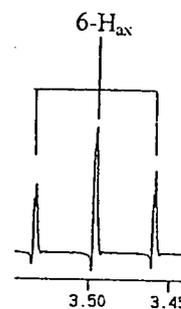
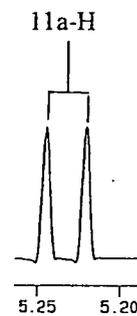
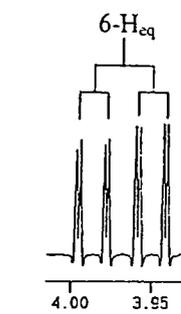
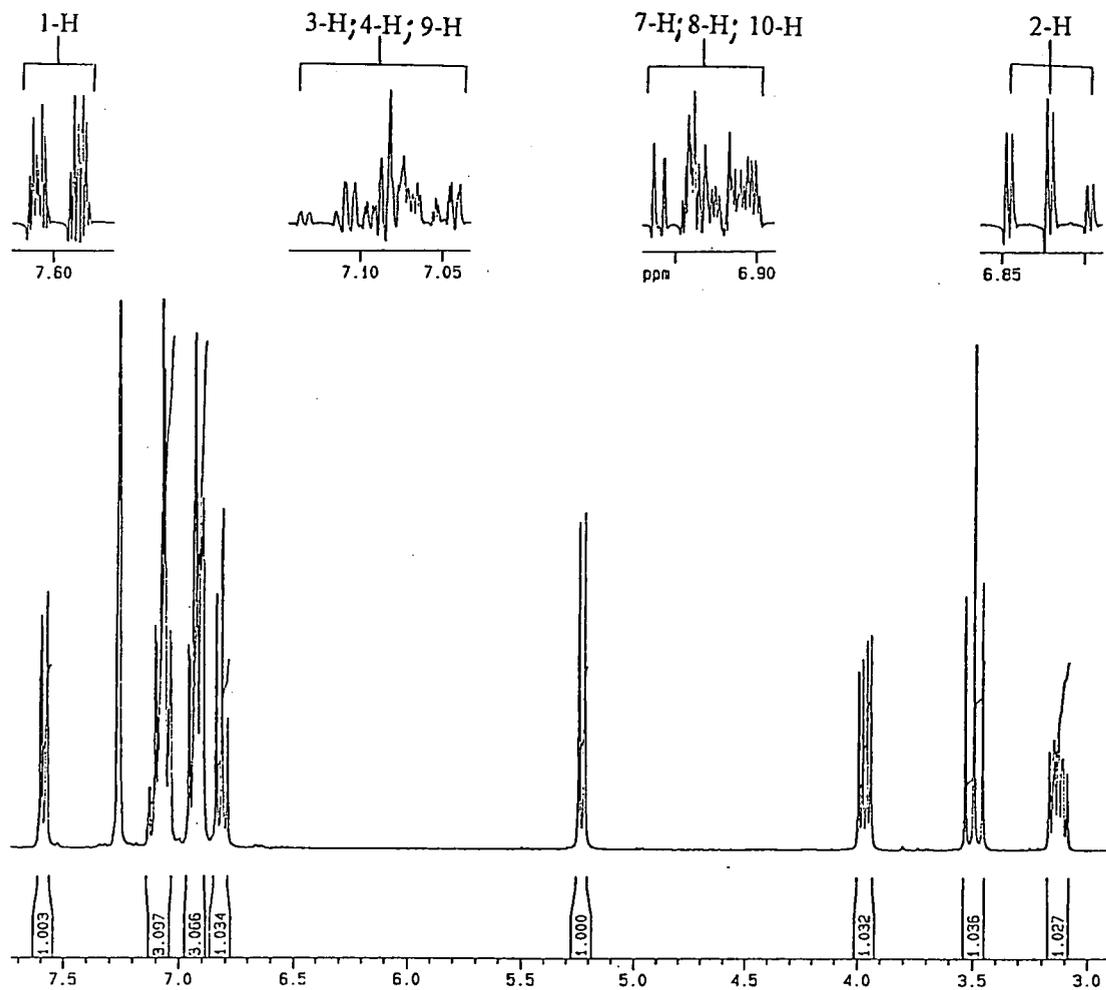
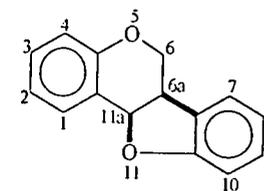


Plate 20: $^1\text{H NMR}$ [C_6D_6]: (\pm)-6a,11a-*cis*-3-Methoxytercarpan (299)

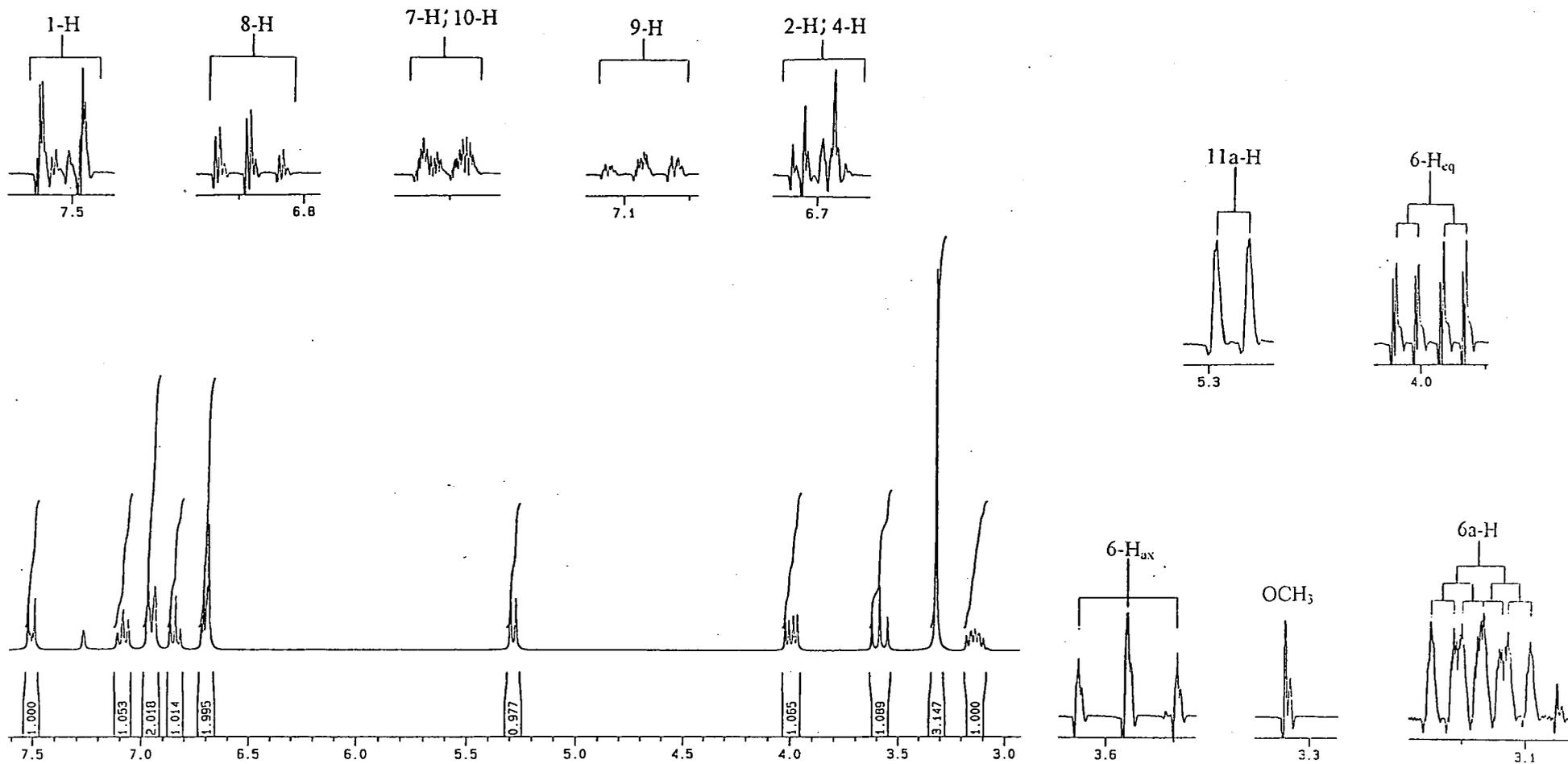
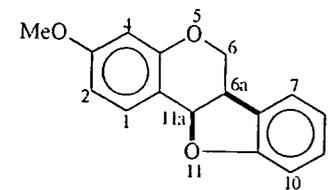


Plate 22: ^1H NMR [C_6D_6]: (\pm)-6a,11a-*cis*-3,9-dimethoxypterocarpan (301)

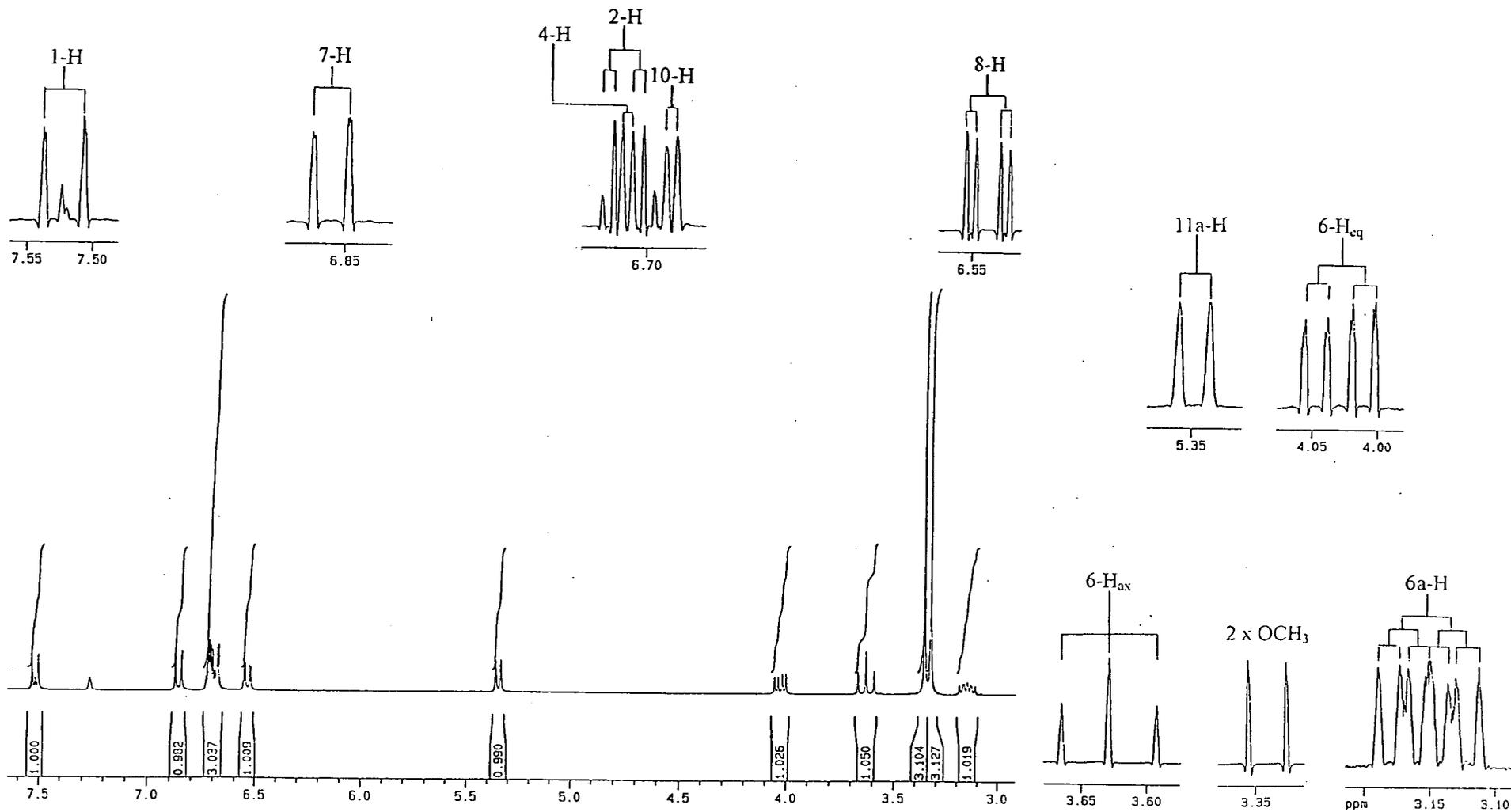
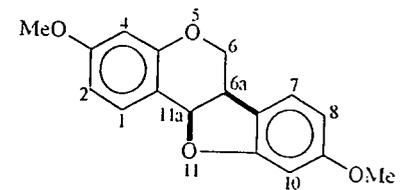


Plate 23: ^1H NMR [CDCl_3]: 3-(α -Benzylsulfanyl-2'-hydroxybenzyl)-2,3-dihydrobenzofuran (306)

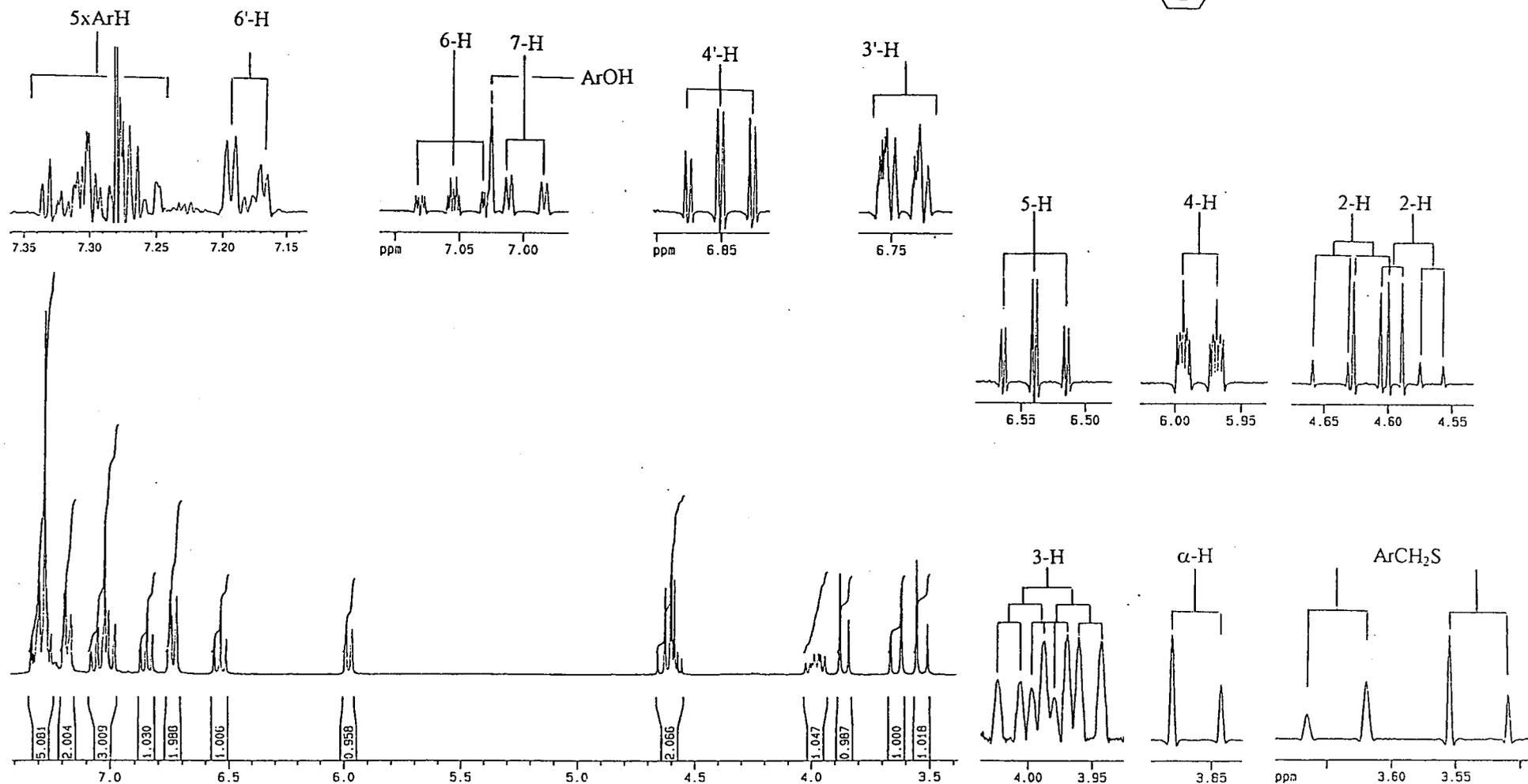
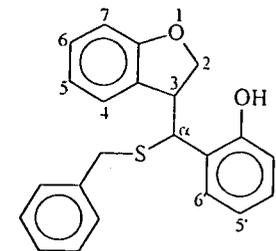


Plate 24: ^1H NMR [CDCl_3]: 2-(2'-Hydroxyphenyl)-3-methoxycarbonyl-2,3-dihydrobenzofuran (308)

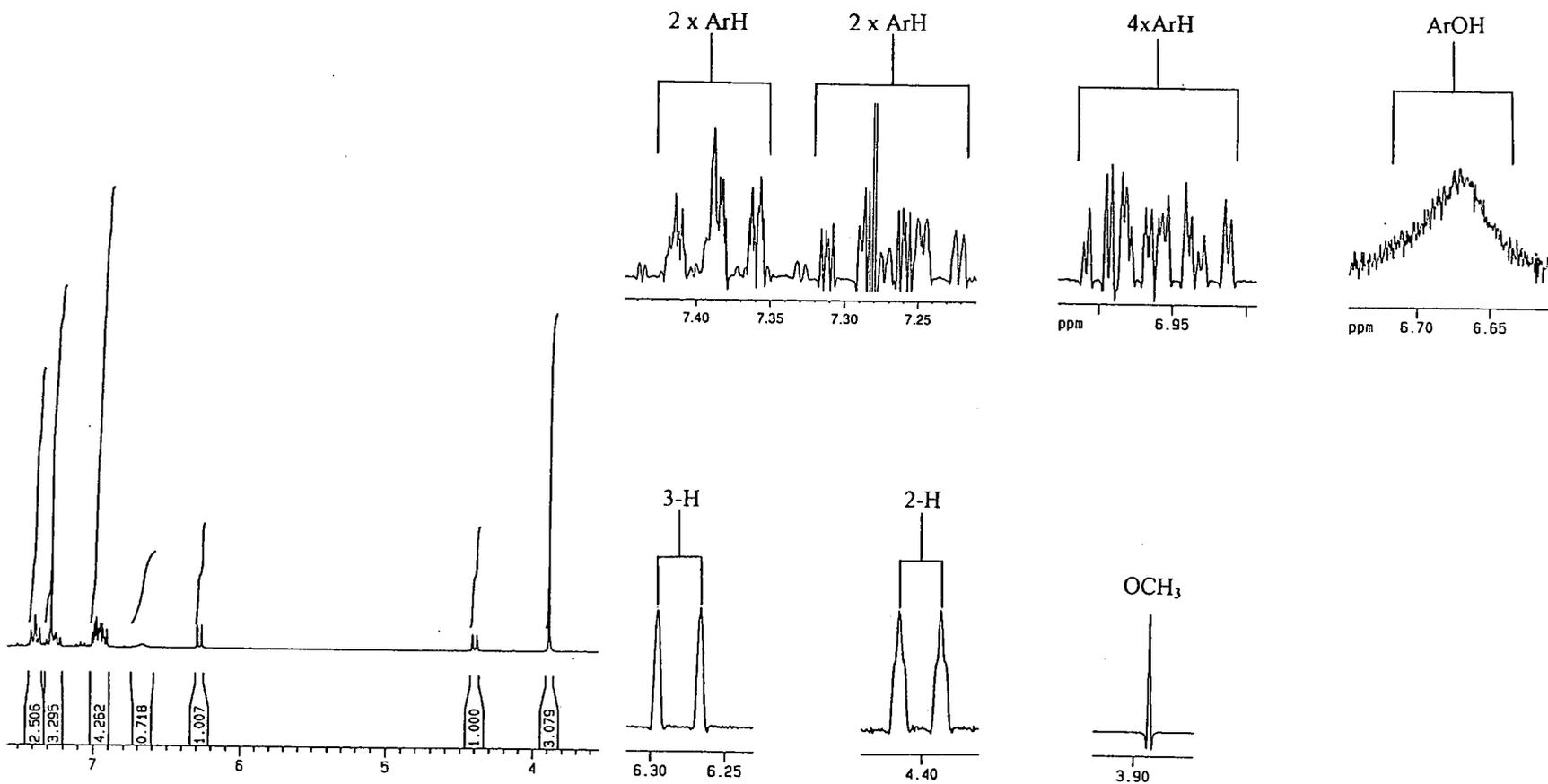
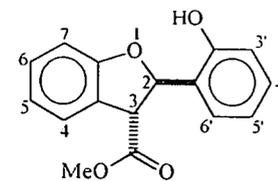


Plate 25: ^1H NMR [CDCl_3]: 2-(2'-Hydroxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzofuran (309)

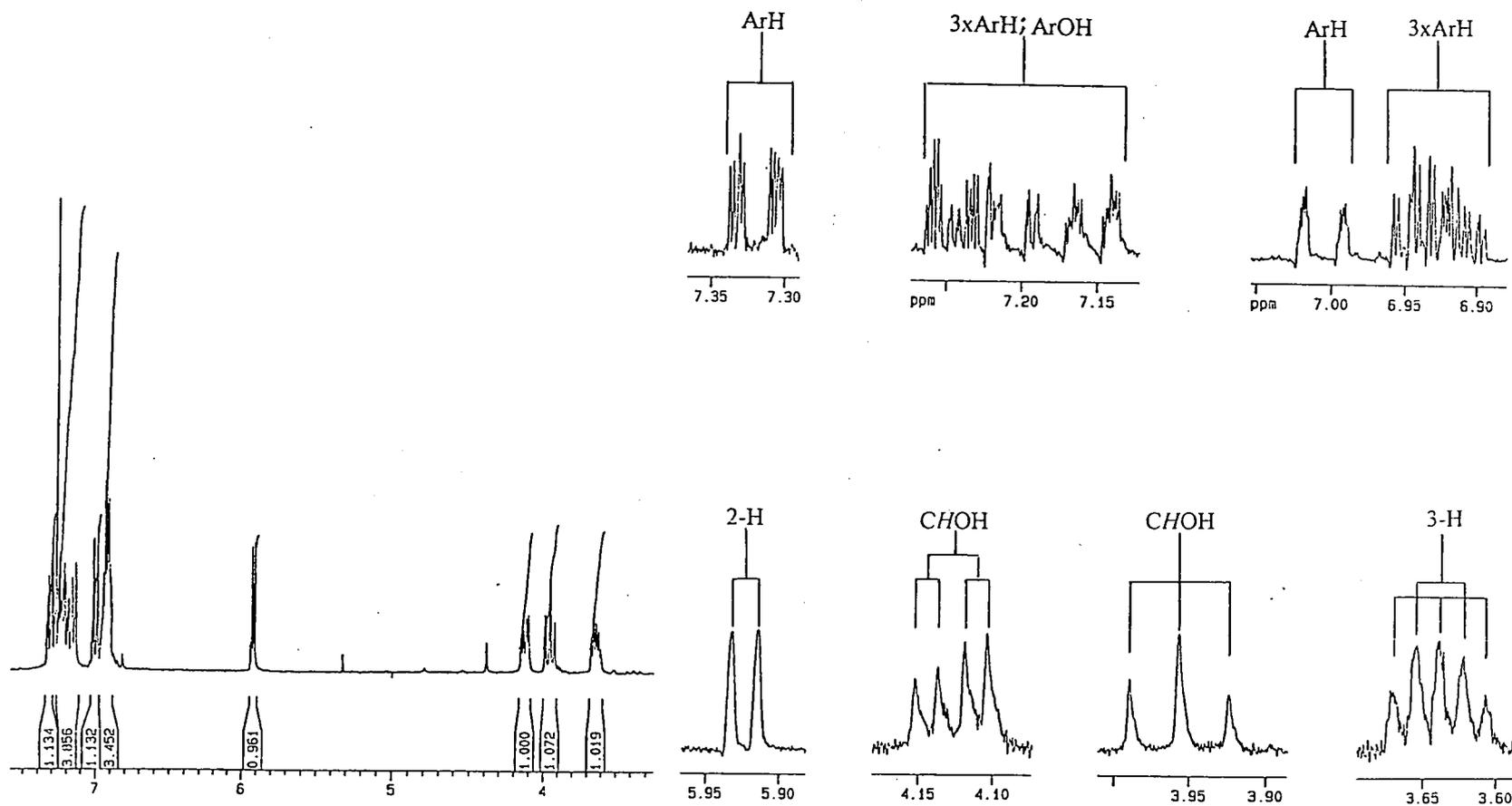
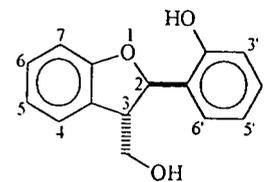


Plate 26: ^1H NMR [CDCl_3]: *Trans*-pterocarpan (307)

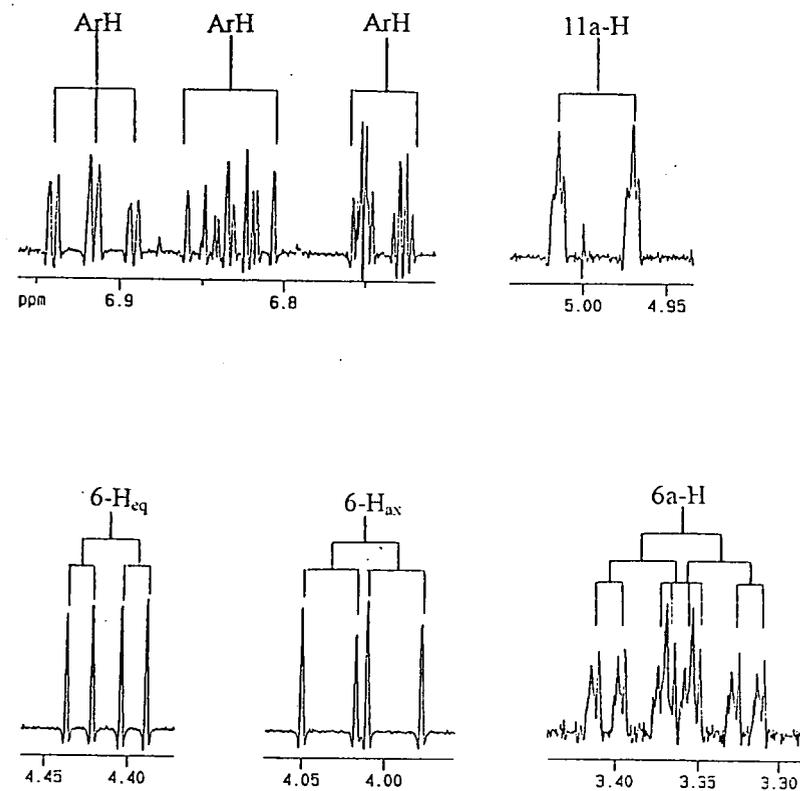
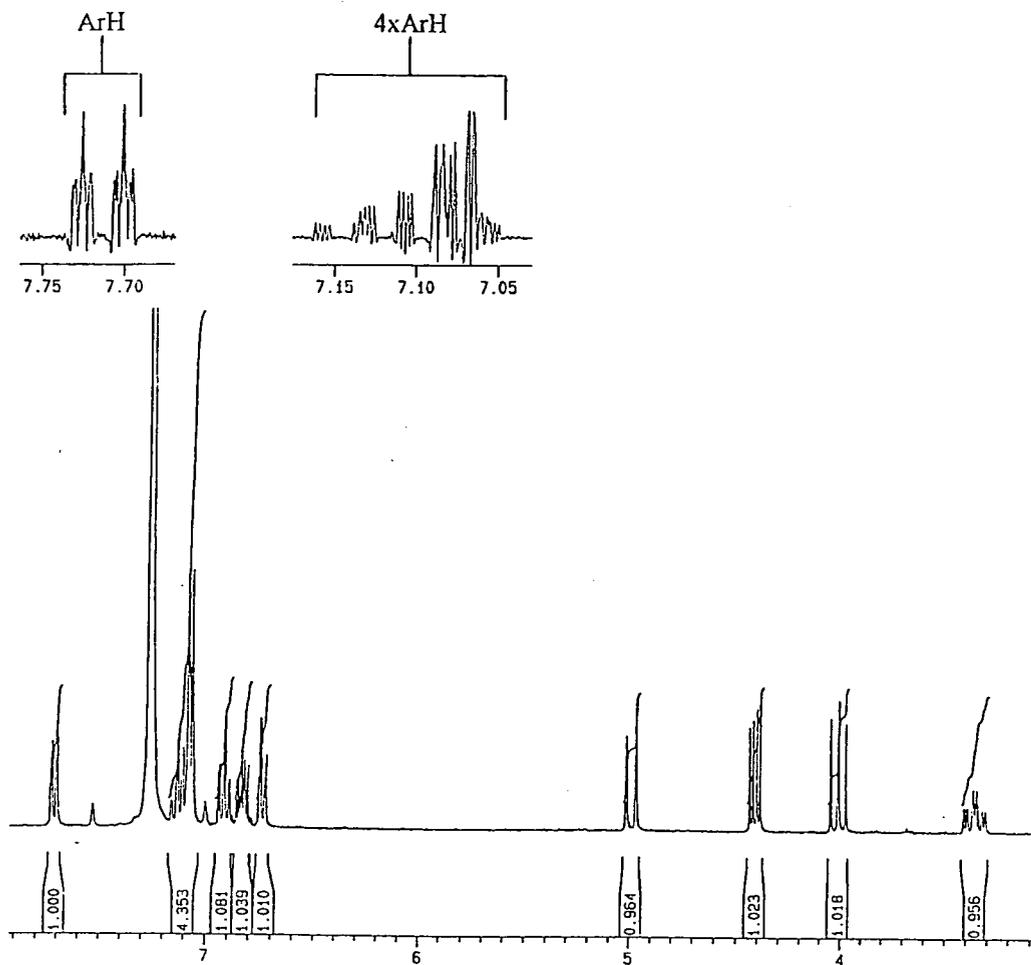
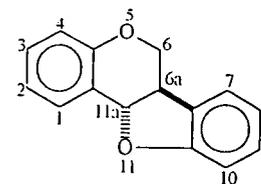


Plate 27: ^1H NMR [CDCl_3]: (4*S*,5*R*)-3-(2-*O*-Benzyl-4-methoxyphenylacetyl)-3,4-dimethyl-5-phenyl-2-imidazolidinone (339)

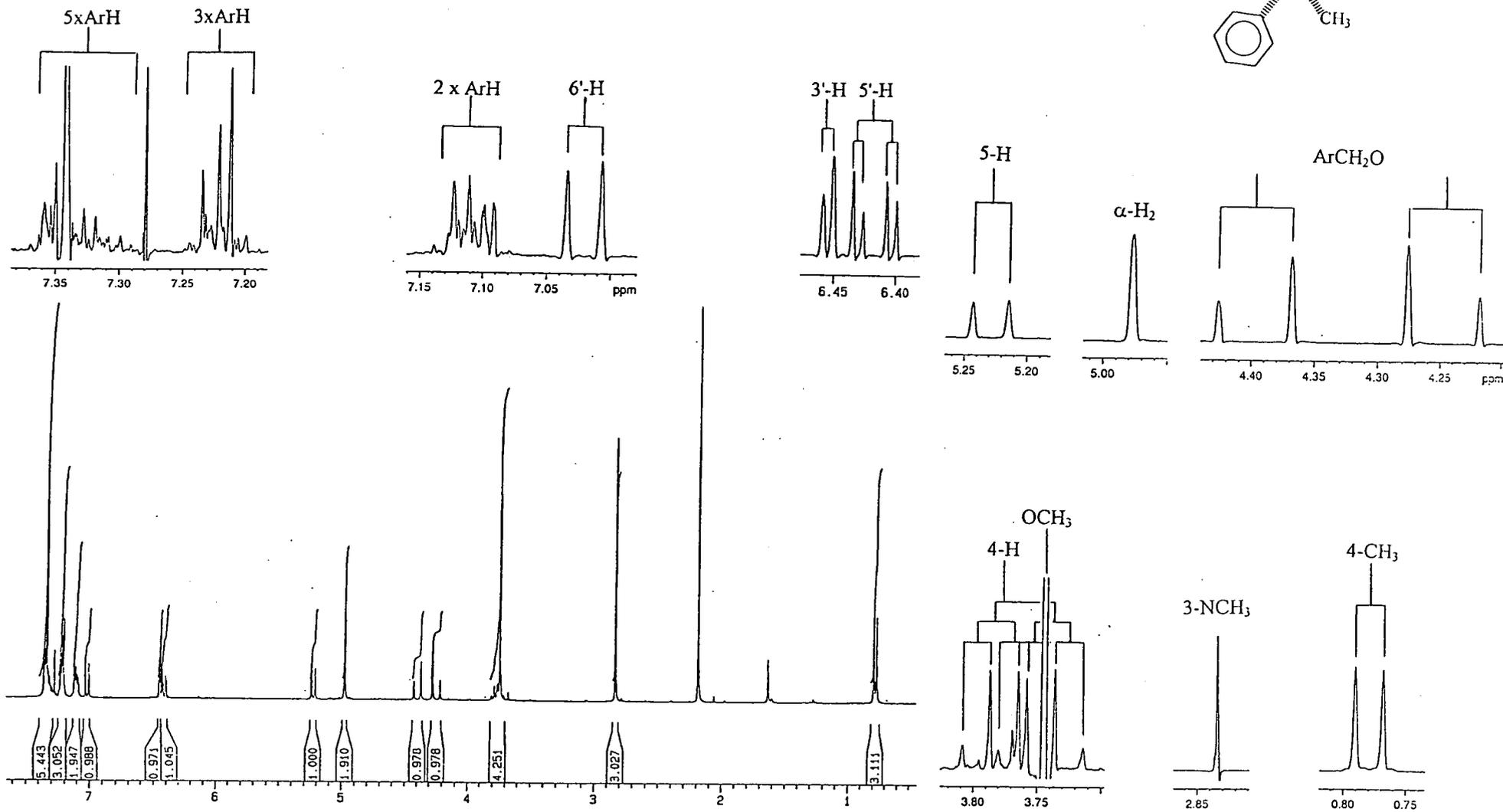
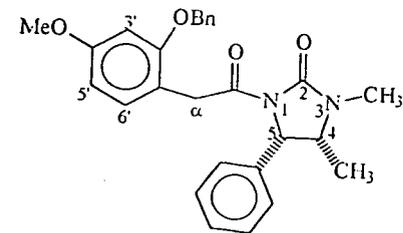


Plate 28: $^1\text{H NMR}$ [CDCl_3]: Methyl 2-(2''-*O*-*t*-butyldimethylsilyl-4''-methoxyphenyl)-3-(2'-*O*-methoxymethyl-4'-methoxyphenyl)propenoate (356)

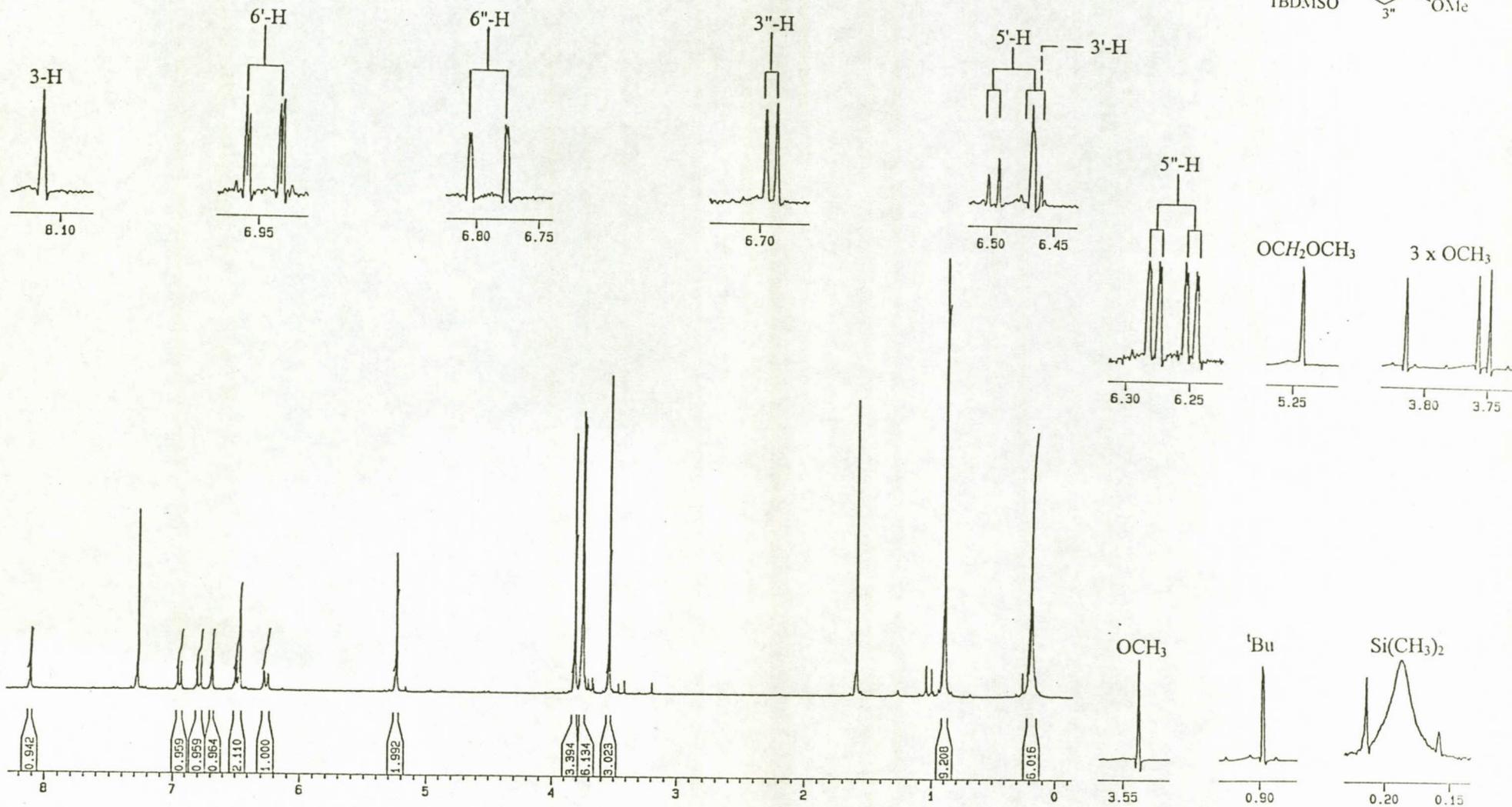
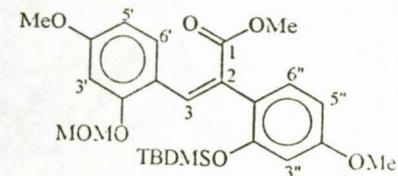


Plate 29: ^1H NMR [CDCl_3]: *Cis*-4-benzylsulfoxide-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan (371)

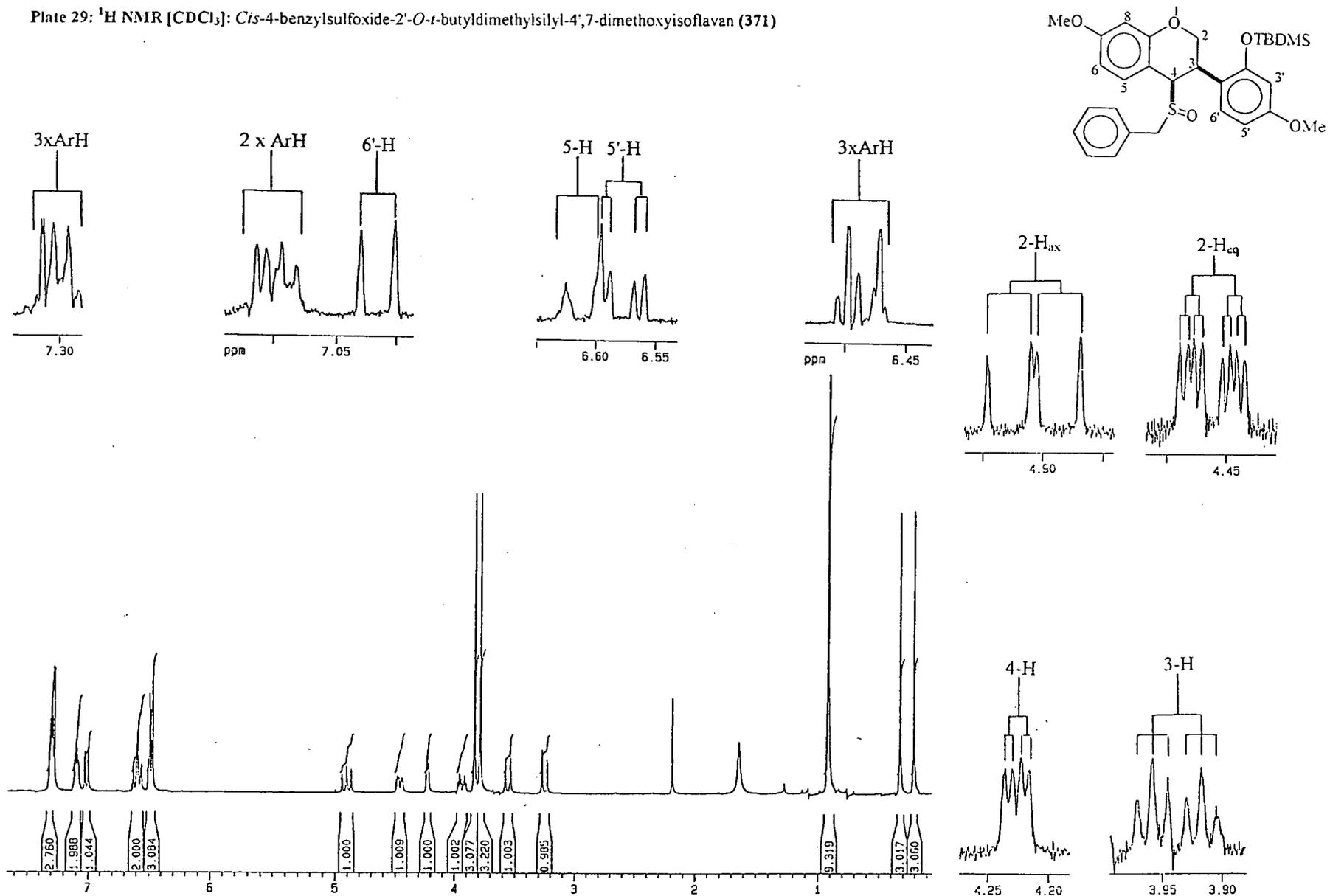


Plate 29 : (continue)

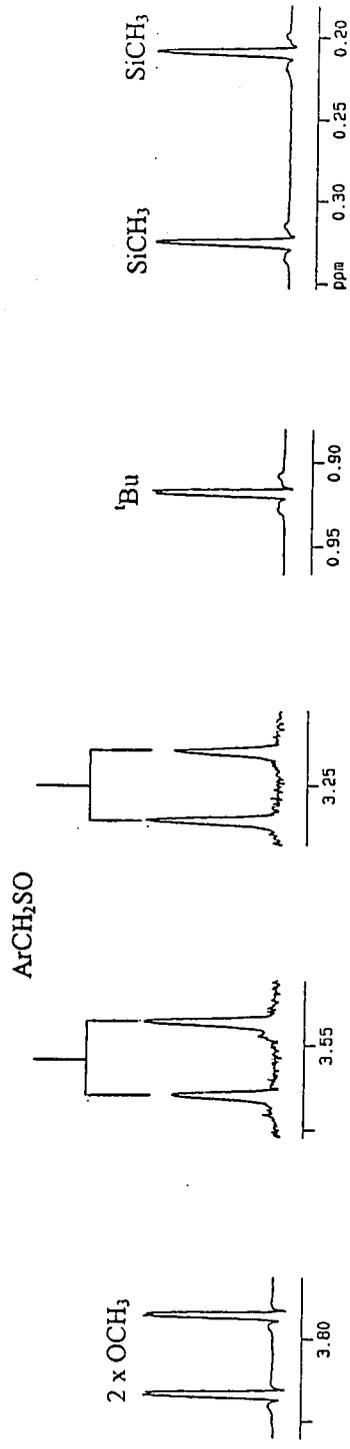


Plate 30: ^1H NMR [CDCl_3]: *Trans*-4-benzylsulfoxide-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan (371)

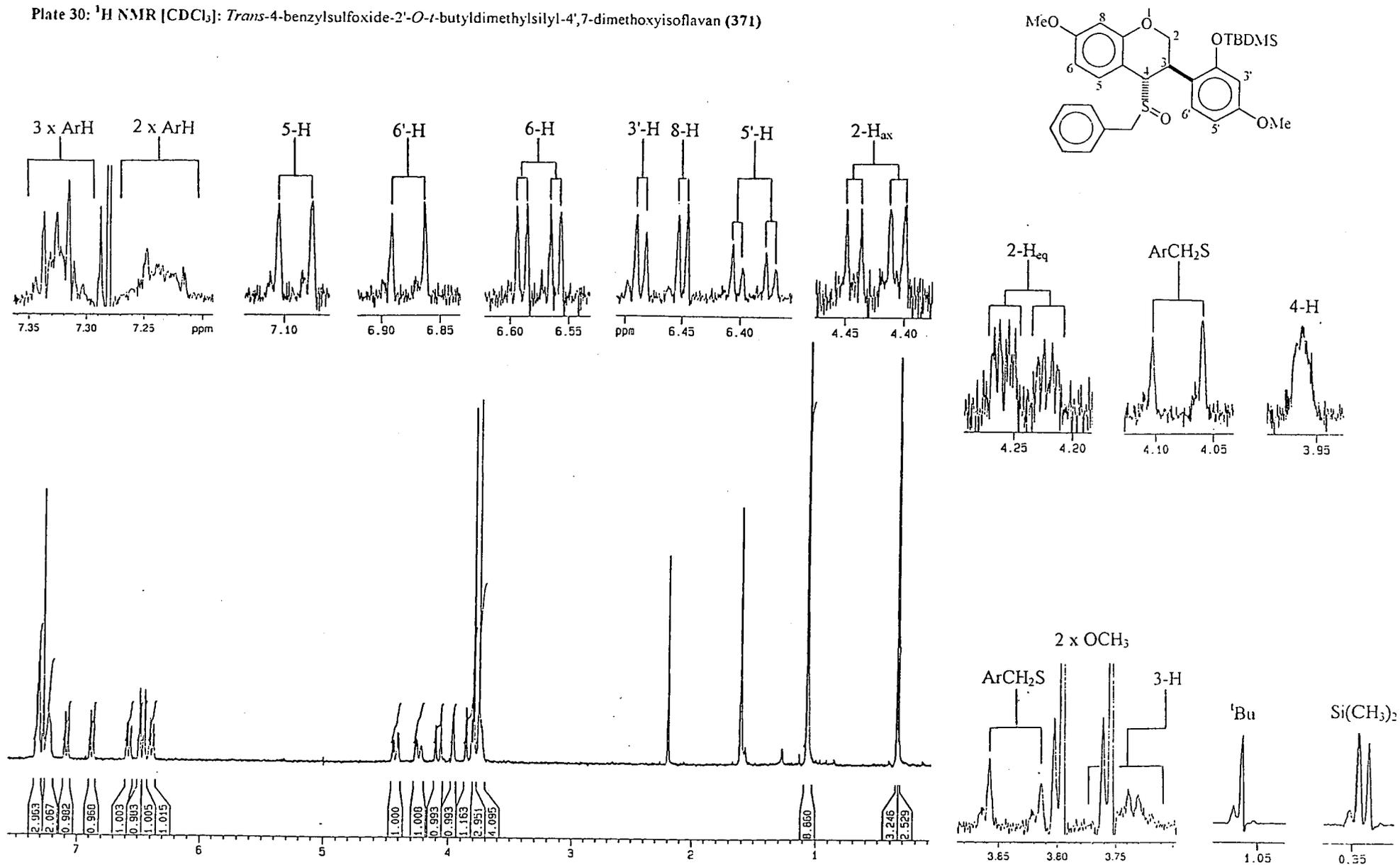


Plate 31: ^1H NMR [CDCl_3]: 2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflav-3-ene (373)

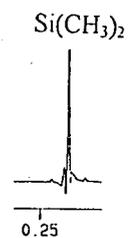
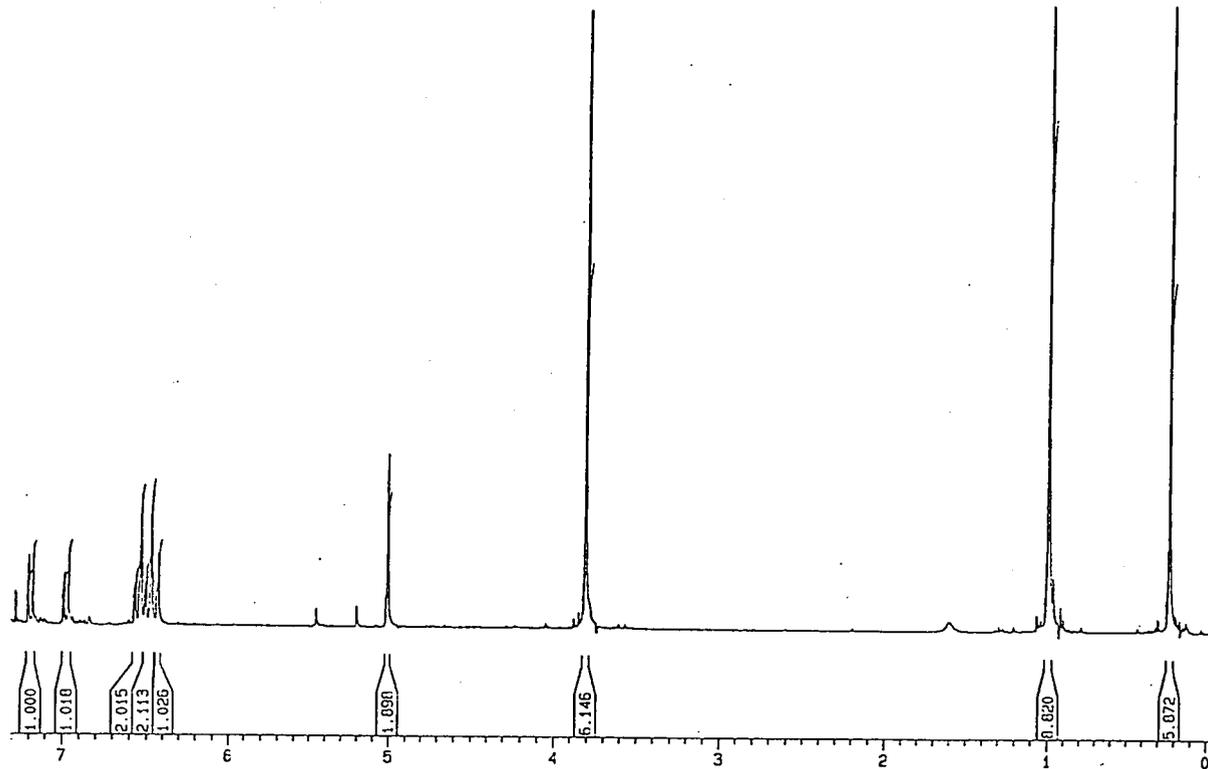
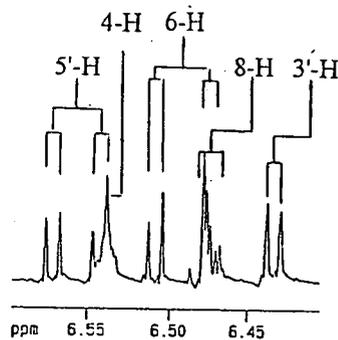
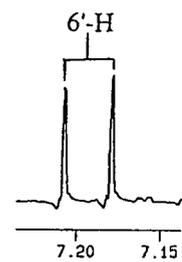
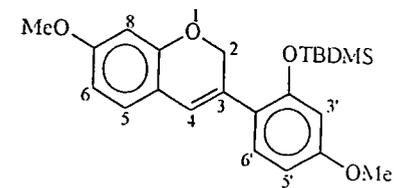


Plate 32: ^1H NMR [CDCl_3]: (-)-(3*R*,4*S*)-2'-*O*-*t*-butyldimethylsilyl-4',7-dimethoxyisoflavan-3,4-diol (377a)

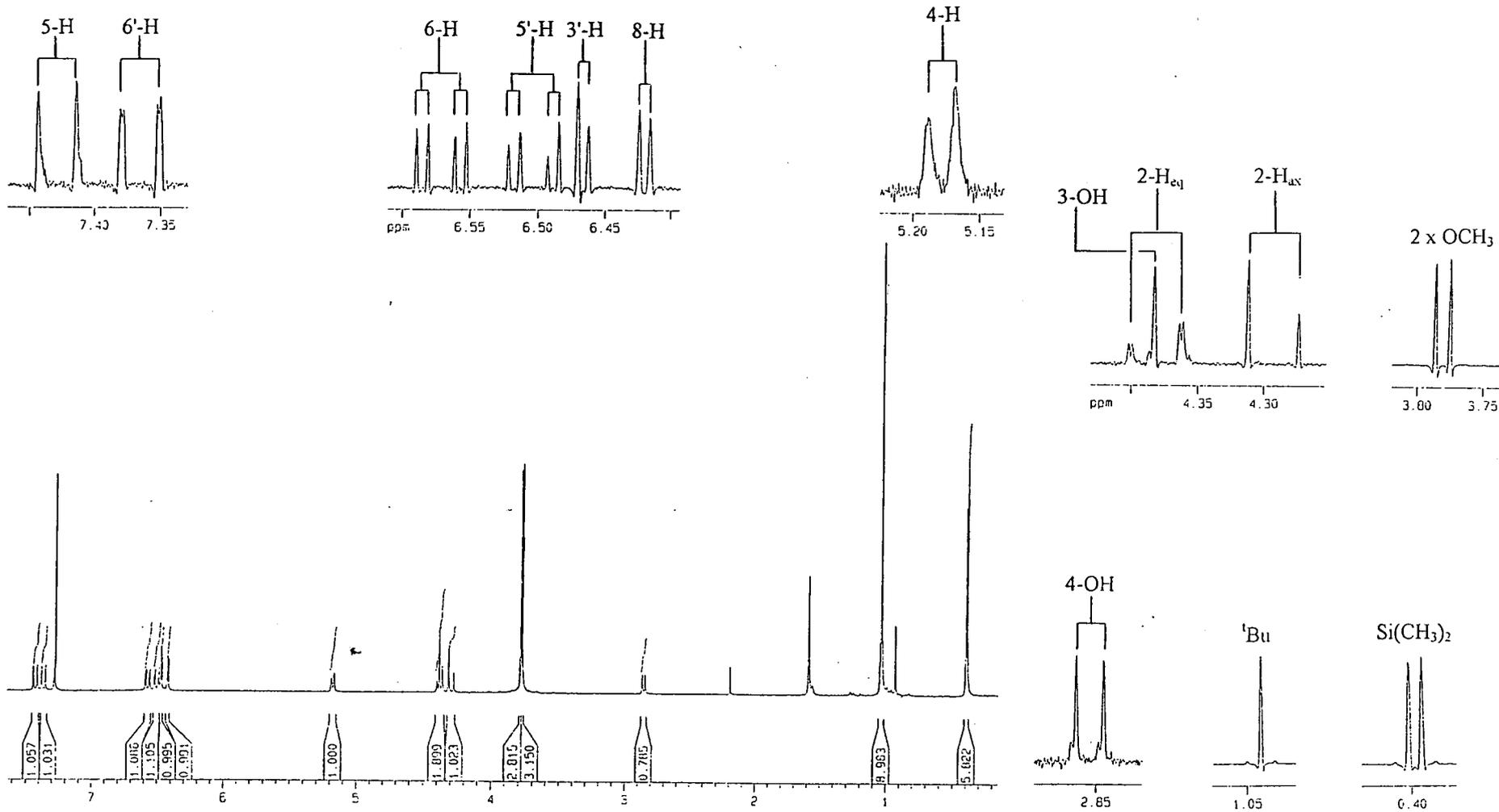
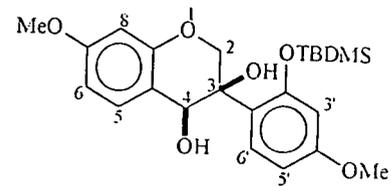


Plate 33: ^1H NMR [CDCl_3]: 2',3,4-tri-*O*-acetyl-4',7-dimethoxyisoflavan

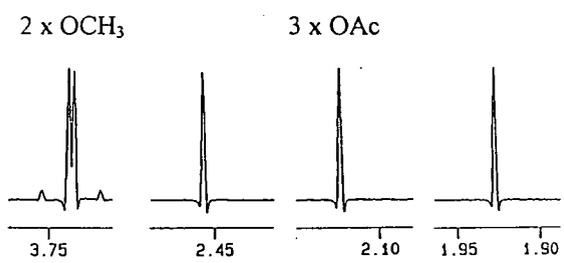
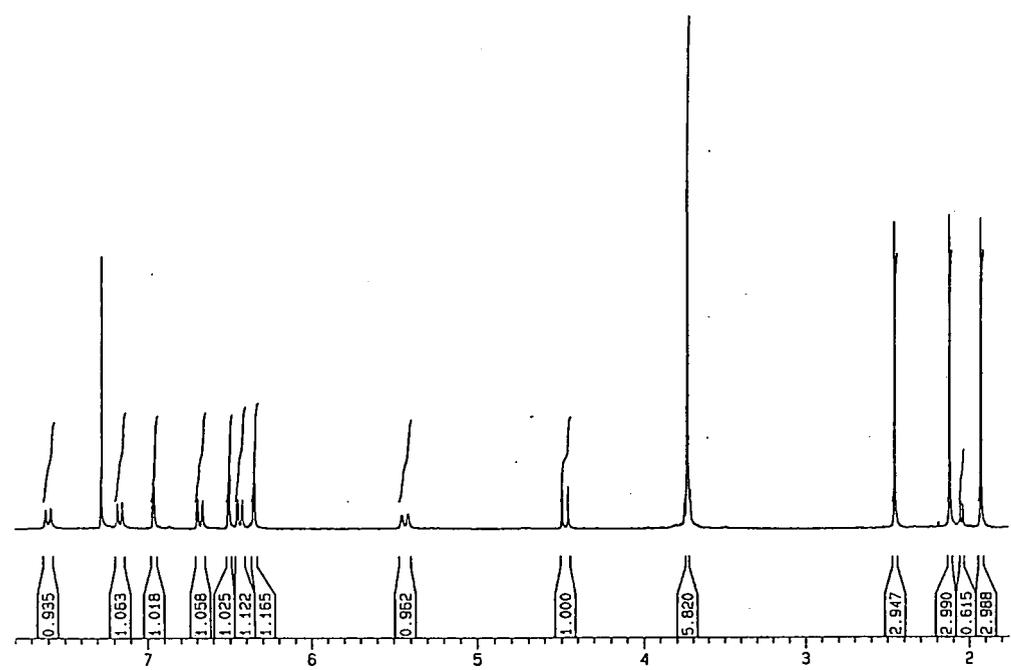
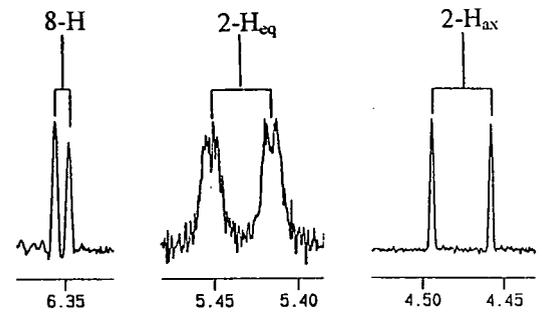
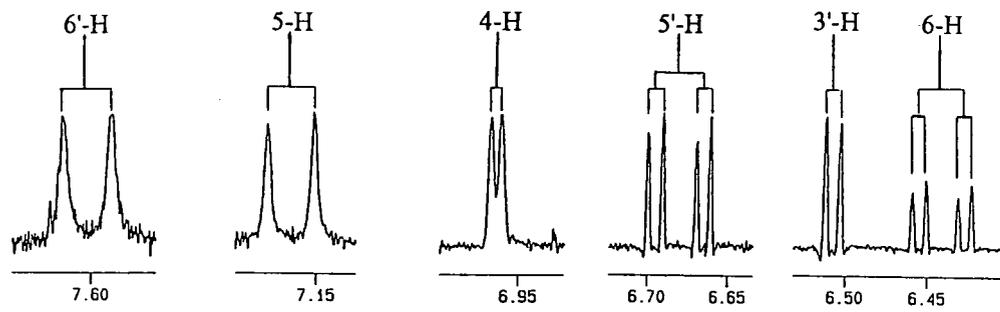
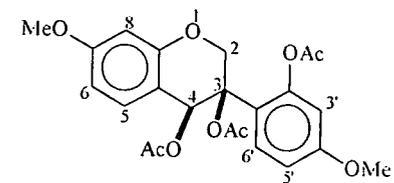
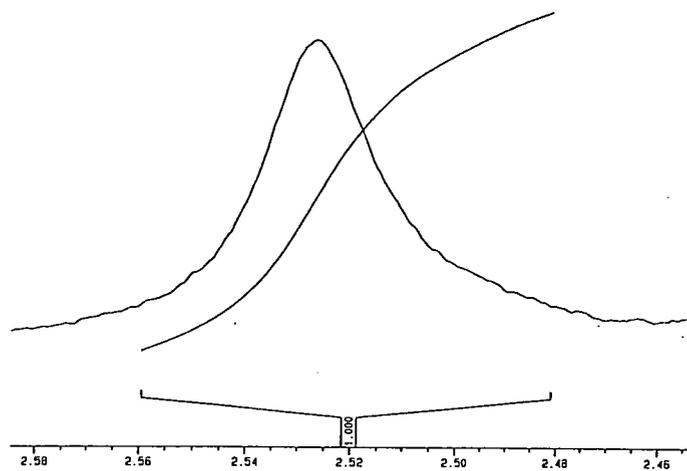
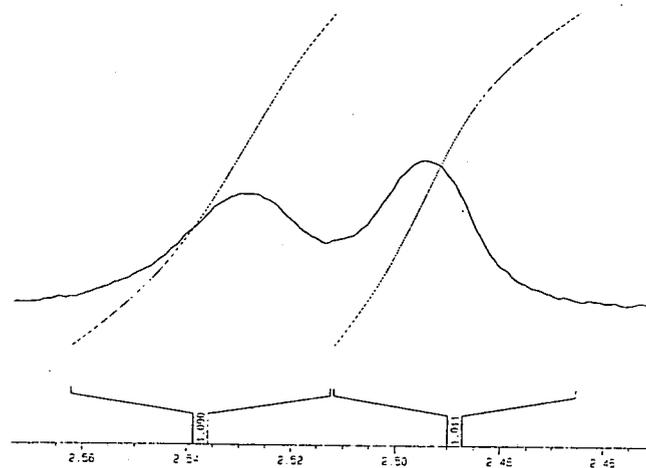


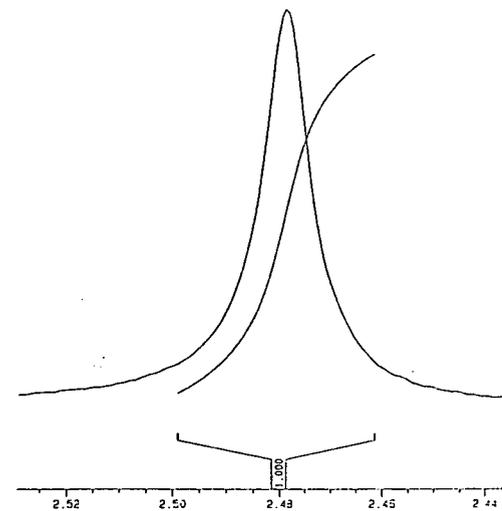
Plate 33: (continue) Assessment of enantiomeric excess



(+)-(3*S*,4*R*)-isomer



racemic mixture



(-)-(3*R*,4*S*)-isomer

Plate 34: $^1\text{H NMR}$ [CDCl_3]: (3*R*,4*S*)-2'-hydroxy-4',7-dimethoxyisoflavan-3,4-diol (379a)

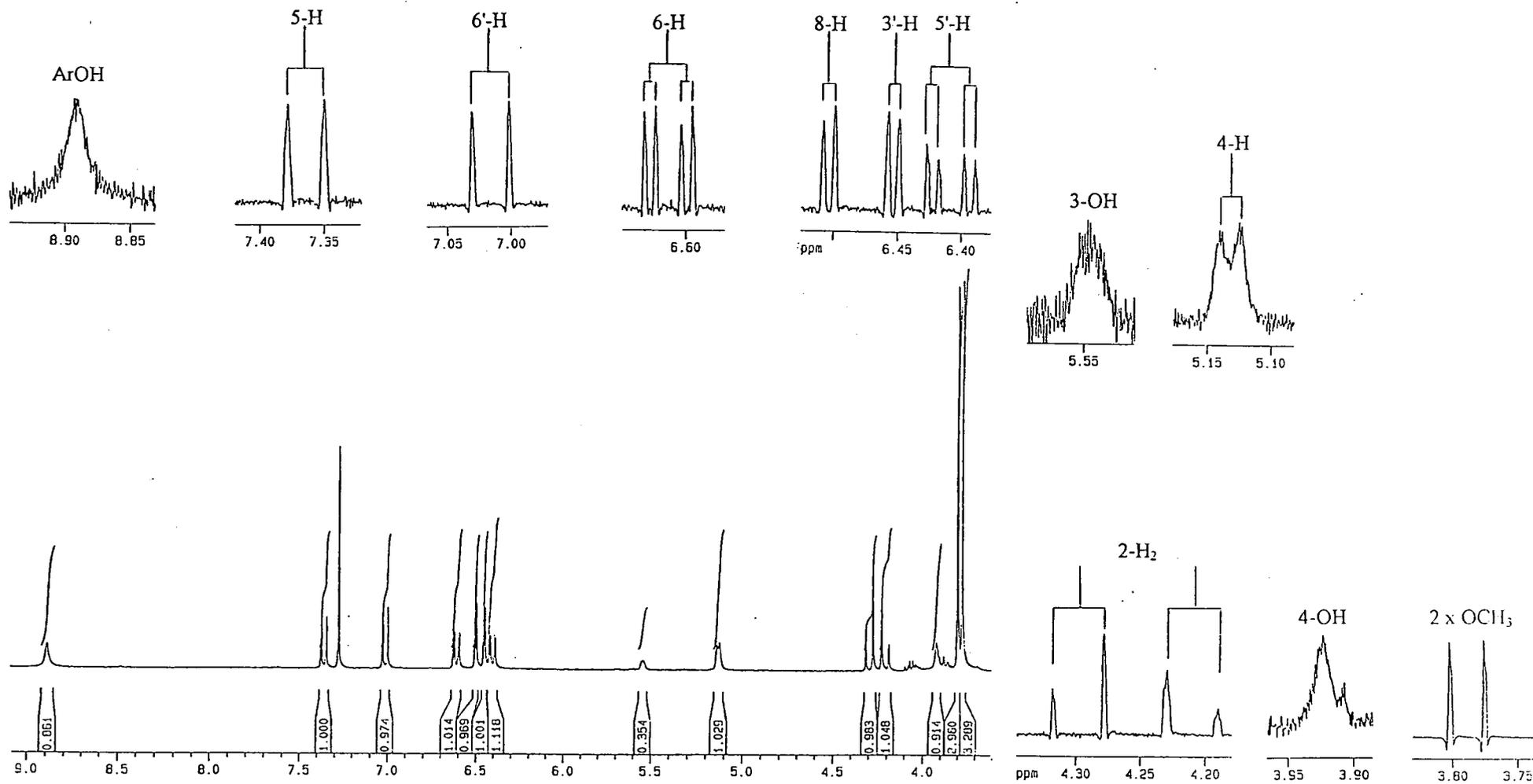
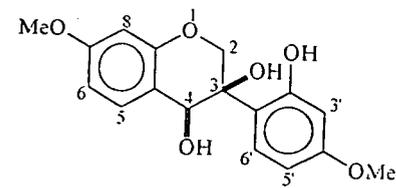


Plate 35: ¹H NMR [CDCl₃]: (+)-(6a*R*, 11a*R*)-*c/s*-6a-hydroxy-3,9-dimethoxypterocarpan (381n)

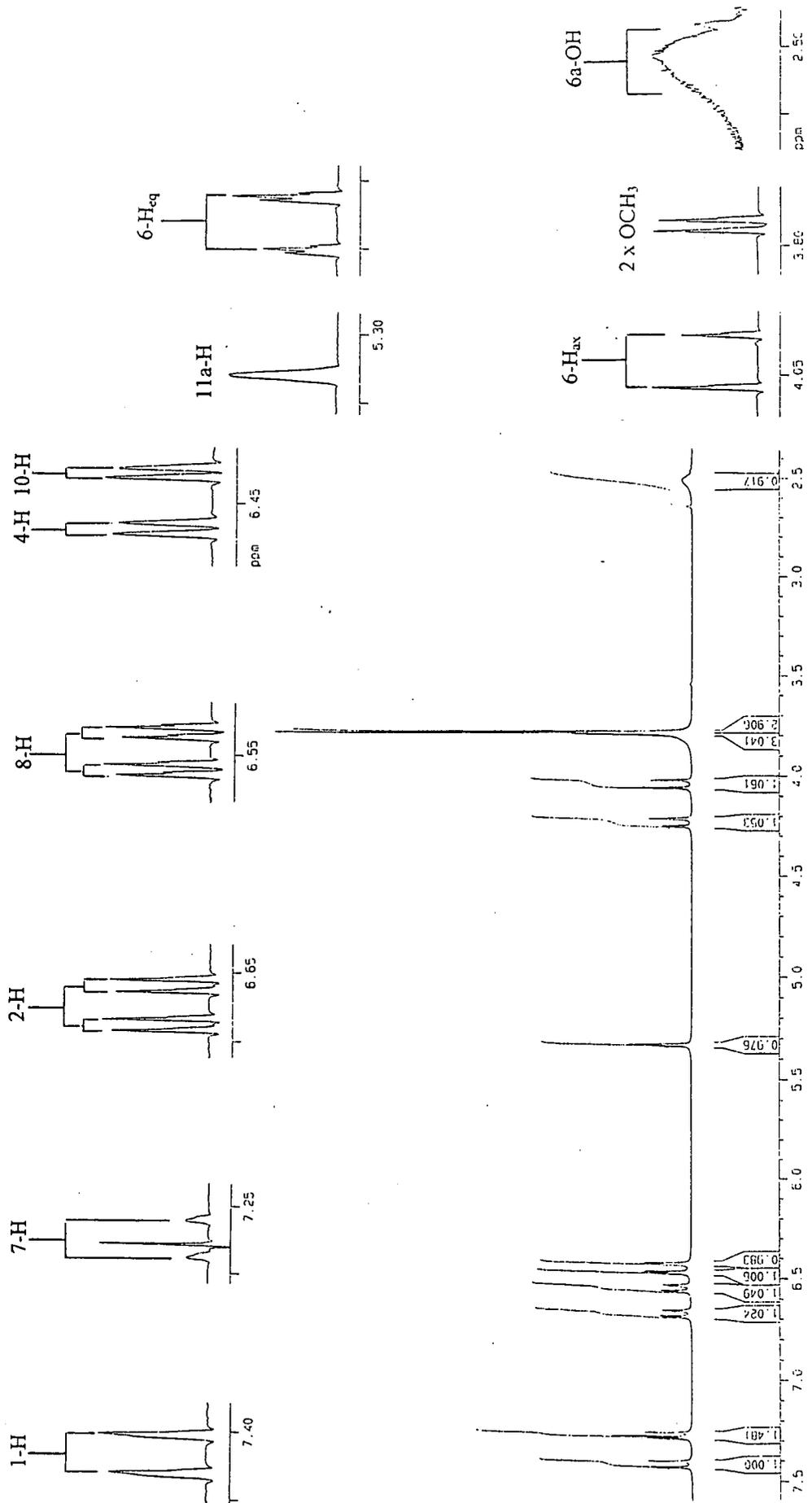
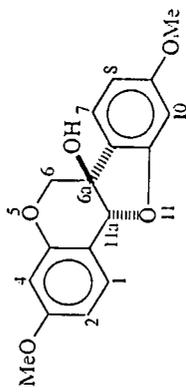


Plate 36: $^1\text{H NMR}$ [CDCl_3]: (-)-(6*aR*,11*aS*)-*trans*-6*a*-hydroxy-3,9-dimethoxyptero-*carpan* (383*a*)

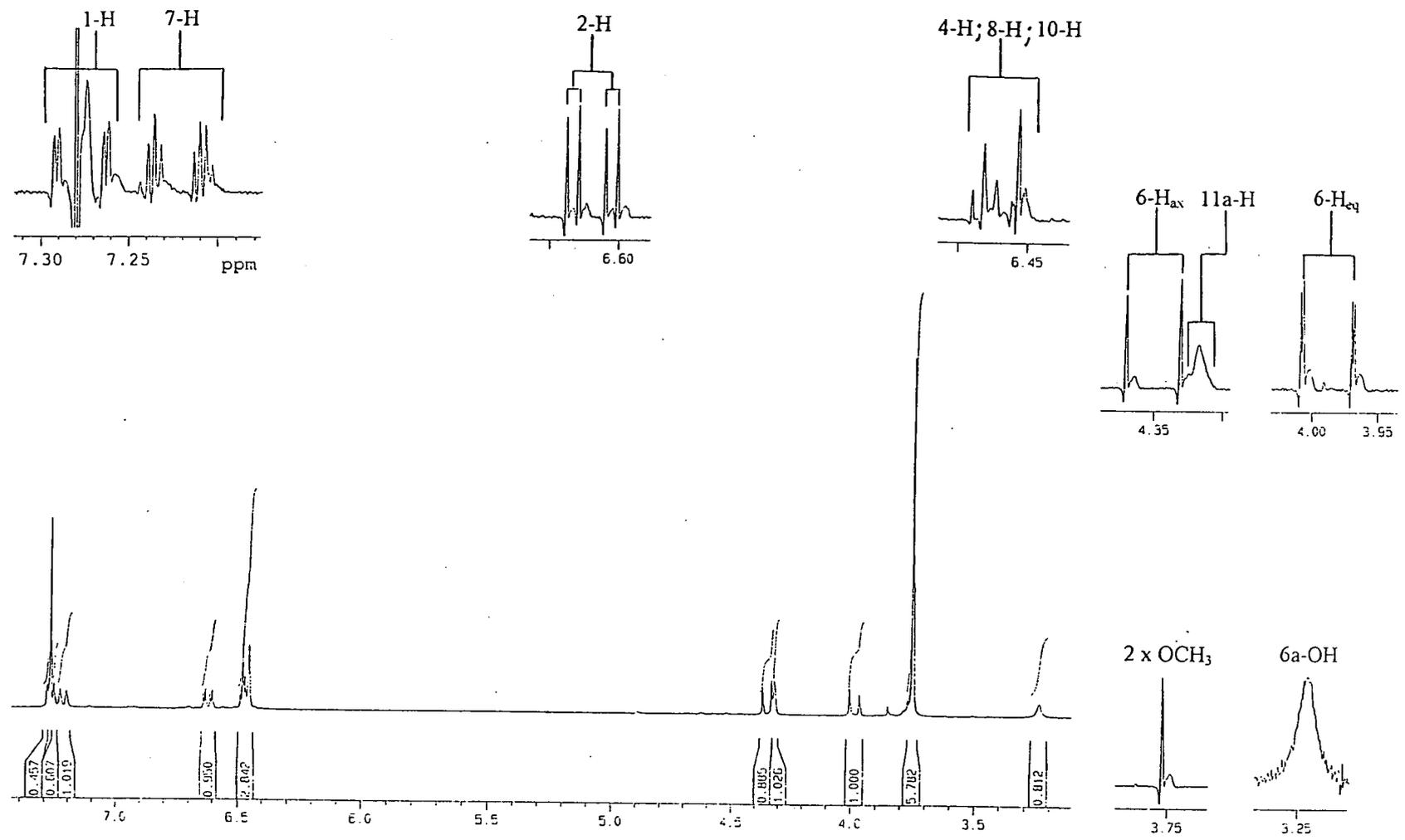
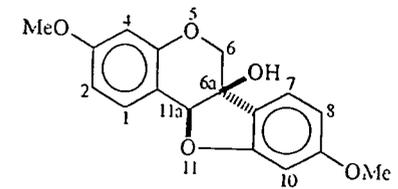
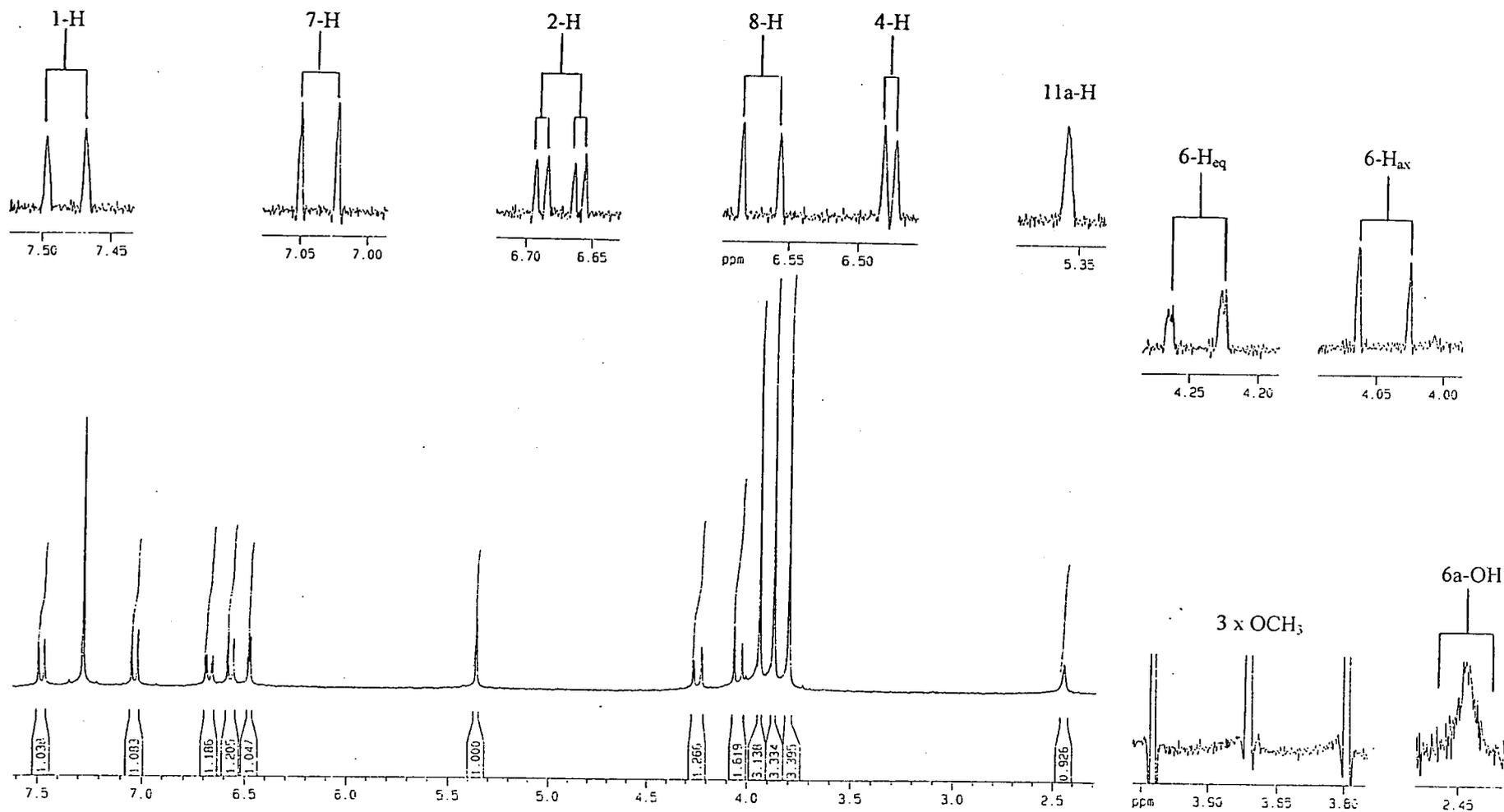
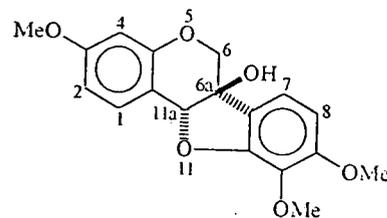


Plate 37: ^1H NMR [CDCl_3]: (+)-(6a*R*,11a*R*)-*cis*-6a-hydroxy-3,8,9-trimethoxyptero-carpan (382a)



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SUMMARY

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Key Terms: flavonoids, isoflavonoids, phytoalexins, aldol condensation, Mitsunobu, pterocarpan, oxidative elimination, isoflav-3-enes, asymmetric dihydroxylation, 6a-hydroxypterocarpan.

Pterocarpan, representing the second largest group of natural isoflavonoids, have received considerable interest on account of their medicinal properties over the last few years. These phytoalexins not only serve as antitoxins but also display antifungal, antiviral and antibacterial properties. Despite this, the study of these metabolites are restricted by their limited availability from natural sources. Furthermore, synthetic protocols allowing ready access to these compounds are restricted by the lack of availability of suitable starting materials and the potential introduction of stereoselectivity. Owing to the demand for enantiopure pterocarpan a direct stereoselective synthetic approach, based on the aldol condensation between appropriate phenylacetates and benzaldehydes, was developed.

2-Hydroxybenzaldehydes, protected as 2-*O*-methoxymethyl ethers, and 2-hydroxyphenylacetates, protected as TBDMS ethers, were subjected to aldol condensation employing lithium diisopropylamide, to afford the 2,3-diphenyl-3-hydroxypropanoates (40-76%, de = 22-100%). Subsequent reduction (LiAlH_4), followed by Lewis acid (SnCl_4 , BnSH) deprotection of the 2'-*O*-MOM ethers, yielded the 3-benzylsulfanyl-2,3-diphenylpropanols (29-56%). Improved yields of these propanols were obtained by simply reversing the order of reactions (54-81%). B-ring formation using Mitsunobu conditions (TPP-DEAD) afforded the isoflavan silyl ethers in good yields (80-97%). The 2'-*O*-TBDMS derivatives were smoothly deprotected (TBAF) to yield the 2'-hydroxyisoflavans in excellent yields (96-99%). Finally, thiophilic Lewis acid (AgBF_4 , AgOTf or DMTSF) cyclisation produced the *cis*-pterocarpan in moderate to good yields (39-82%).

Initial C-ring cyclisation (AgBF_4) of the methyl 3-benzylsulfanyl-2,3-di(2-hydroxyphenyl)propanoates, followed by reduction (LiAlH_4) and Mitsunobu (TPP-DEAD) B-ring formation, afforded for the first time a *trans*-pterocarpan in a moderate overall yield of 12%.

In order to address the issue of stereocontrol, we first attempted to introduce stereoselectivity during the aldol condensation. Stereoselective aldolisation employing diisopropylethylamine and chiral boron triflates, was evaluated utilizing achiral dibutylborontriflate. This system, though capable of effecting aldolisation, was ineffective to incorporate a broad range of substrates. Secondly, we converted the methyl propanoates to chiral derivatives of imidazolidin-2-one, bornane-10,2-sultam and (1*R*,2*S*)-*p*-tol-*N*-norephedrine. Steric shielding of the enolates generated from these derivatives, prevented aldol condensation. Thirdly, using (-)-sparteine as chiral base afforded achiral products. Finally, in an effort to employ stereoselective epoxidation, attempts were made to synthesize 2-propenoates. All attempts to introduce the double bond gave disappointing yields. Although our attempts to introduce chirality failed, several alternatives still needs to be investigated in future endeavours.

6a-Hydroxypterocarpan, although less common than pterocarpan, are equally cherished as health promoting supplements. Oxidative thermal elimination (NaIO_4 , 60°C) of 4-benzylsulfanylisoflavans followed by asymmetric dihydroxylation, utilizing stoichiometric amounts of OsO_4 and DHQ-CLB or DHQD-CLB as chiral ligands, afforded the respective (+)- and (-)-diols (38-43% yields, ee > 99%). Subsequent deprotection of the 2'-*O*-TBDMS ethers (TBAF) and cyclisation (Ms_2O , pyridine) produced the *cis*-6a-hydroxypterocarpan in excellent yields and essentially optically pure form (70-75%, ee > 99%).

We have thus developed a highly efficient synthesis of *cis*-pterocarpan and succeeded in modifying this protocol to the novel synthesis of *trans*-pterocarpanoids. Also, this synthetic protocol was modified to permit the stereoselective synthesis of 6a-hydroxypterocarpan in high overall yields. The ease with which these protocols accommodate highly oxygenated substrates, featured by most natural pterocarpan,

should contribute substantially to assess the chemical and physiological characteristics that may promote application of this class of phenolics as pharmaceutical or agricultural chemicals.

SAMEVATTING

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Gedurende die afgelope paar jaar het pterokarpane, die tweede grootste groep isoflavanoïede, vanweë hul medisinale eienskappe aansienlik aandag ontvang. Hierdie fito-aleksiene dien nie alleen as antitoksiene nie, maar vertoon ook swamdodende, antivirale en antibakteriese eienskappe. Ten spyte hiervan word die studie van hierdie metaboliëte gestrem deur hul beperkte natuurlike beskikbaarheid. Verder word sintetiese toegang tot hierdie verbindings gekortwiek deur beskikbaarheid van uitgangstowwe en die potensiaal om stereoselektiwiteit te bewerkstellig. Vanweë die aanvraag na enantiomeries suiwer pterokarpane is 'n direkte stereoselektiewe sintetiese roete, gebaseer op aldolkondensasie tussen geskikte fenielasetate en bensaldehyede, ontwikkel.

Litiumdiisopropielamied gekataliseerde aldolkondensasie tussen 2-hidroksibensaldehyede, beskerm as 2-*O*-metoksiemetielelers, en 2-hidroksifenielasetate, beskerm as TBDMS-eters, het die 2,3-difeniel-3-hidroksipropanoate gelewer (40-76% opbrengs, de = 22-100%). Daaropvolgende reduksie (LiAlH_4) en Lewissuur gekataliseerde (SnCl_4 , BnSH) ontskering van die 2'-*O*-MOM eters, het gelei tot die 3-bensielsulfaniël-2,3-difenielpropanole (29-56%). Verhoogde opbrengste (54-81%) van laasgenoemde propanole is verkry deur wysiging van die reaksievolgorde. B-ring vorming onder Mitsunobu kondisies (TPP-DEAD) het gelei tot goeie opbrengste van die isoflawaan silieleters (80-97%). Die 2'-*O*-TBDMS derivate is maklik ontskerm (TBAF) om 2'-hidroksi-isoflavane in uitstekende opbrengste te lewer (96-99%). Laastens is tiofiliese Lewissuur (AgBF_4 , AgOTF of DMTSF) siklisering gebruik om die *cis*-pterokarpane in redelike tot goeie opbrengste te lewer (39-82%).

Aanvanklike C-ring siklisering (AgBF_4) van die metiel-3-bensielsulfaniël-2,3-di(2-hidrosifeniel)propanoate, gevolg deur reduksie (LiAlH_4) en Mitsunobu (TPP-DEAD) B-ring vorming, het gelei tot die eerste sintese van 'n *trans*-pterokarpaan in 'n redelike totale opbrengs van 12%.

Ten einde die kwessie van stereobeheer aan te spreek, is eerstens gepoog om stereoselektiwiteit gedurende die aldolkondensasie teweeg te bring. Die benutting van diisopropietielamien en chirale borontriflate in stereoselektiewe aldolreaksies is geëvalueer m.b.v. achirale dibutielborontriflaat. Alhoewel die sisteem aldolprodukte gelewer het, was dit oneffektief om 'n wye reeks substrate te akkommodeer. Tweedens is die metielpropanoate na chirale derivate van imidasolidien-2-oon, bornaan-10,2-sultam en (1*R*,2*S*)-*p*-toliel-*N*-norefedrien omgeskakel. Steriese skerming van die enolate verkry vanaf hierdie derivate het egter aldolkondensasie verhoed. Derdens het (-)-sparteien as chirale basis ook gelei tot die vorming van achirale produkte. Laastens, in 'n poging om stereoselektiewe epoksidasie te benut, is daar gepoog om 2,3-diariel-2-propenoate te sintetiseer. Alle pogings om die dubbelbinding daar te stel het teleurstellende resultate opgelewer. Ten spyte daarvan dat pogings om chiraliteit te induseer misluk het, verskaf dit rigtingwysers vir verskeie alternatiewe wat toekomstig ondersoek kan word.

6a-Hidroksipterokarpane, hoewel minder algemeen as pterokarpane, word ook hoog geag as gesondheidsaanvullende middels. Oksidatiewe termiese eliminasië (NaIO₄, 60°C) van 4-bensielsulfanielisoflavane, gevolg deur asimmetriese dihidroksilering, m.b.v. stoïgiometriese hoeveelhede OsO₄ en DHQ-CLB of DHQD-CLB as chirale ligande, het die onderskeie (+)- en (-)-dióle (38-43% opbrengs, ee > 99%) gelewer. Daaropvolgende ontskerming van die 2'-*O*-TBDMS-eters (TBAF) en siklisering (Ms₂O, piridien) het die *cis*-6a-hidroksipterokarpane in uitstekende opbrengs en essensieel opties suiwer vorm (70-75% opbrengs, ee > 99%) daargestel.

'n Hoogs effektiewe sintese van *cis*-pterokarpane is dus ontwikkel en is verder daarin geslaag om hierdie protokol aan te pas vir die sintese van unieke *trans*-pterokarpanoïede. Hierdie sintetiese protokol is ook gewysigom die hoë opbrengs stereoselektiewe sintese van 6a-hidroksipterokarpane te bewerkstellig. Die toepaslikheid van bogenoemde protokolle op hoogs geoksigeneerde substrate, soos algemeen onder natuurlike pterokarpane aangetref, behoort 'n nuttige bydrae te lewer tot die bepaling van die chemiese en fisiologiese eienskappe wat die gebruik van hierdie klas verbindings as farmaseutiese of landbou chemikalieë kan bevorder.