THE UNIVERSITY OF CALGARY

Improved Syntheses and Resolutions of *cis,cis*-Spiro[4.4]nonane-1,6-diol and *cis,cis*-2,2′-Spirobiindane-1,1′-diol: Applications as Chiral Auxiliaries

by

James A. Nieman

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Abstract

The first chapter describes the importance of enantiopure compounds in the pharmaceutical industry and summarises the methods for their production. Two of the main methods use chiral auxiliaries which are attached to either the substrate, or to a metal, reagent or catalyst. Many of the chiral auxiliaries employed are diols and have C_2-symmetry. Chapter one also provides a review of the literature where C_2-symmetric diols have been employed as chiral auxiliaries. This review shows that at the outset of this project one class of dissymmetric diols that had not been examined as chiral auxiliaries were spirodiols, although a few examples were reported later. *cis,cis*-Spiro[4.4]nonane-1,6-diol and *cis,cis*-2,2′-spirobiindane-1,1′-diol are two spirodiols that were investigated further.

Chapter two delineates a four step stereoselective synthesis of (±)-*cis,cis*-spiro[4.4]nonane-1,6-diol in 55% yield beginning with ethyl 2-oxocyclopentanecarboxylate. A new resolution of (±)-*cis,cis*-spiro[4.4]nonane-1,6-diol by preparing diastereomeric ketals of (1*R*)-(+)-camphor is reported. The absolute stereochemistry was assigned by an X-ray crystal structure of the ketal from (+)-5α-cholestan-3-one and (-)-*cis,cis*-spiro[4.4]nonane-1,6-diol. From the X-ray crystal data the levorotatory enantiomer was assigned the 1*R*,5*R*,6*R* stereochemistry.

Chapter three describes various attempts to convert the hydroxyl groups in (±)-*cis,cis*-spiro[4.4]nonane-1,6-diol and the ketones in spiro[4.4]nonane-1,6-dione to diamines or diphosphines.

Chapter four focusses on a four step (68% overall yield) stereoselective synthesis of (±)-*cis,cis*-2,2′-spirobiindane-1,1′-diol starting with 1-indanone. (2*S*)-*O*-(*tert*-Butyldimethylsilyl)mandeloyl chloride was used as a novel auxiliary to resolve (±)-*cis,cis*-2,2′-spirobiindane-1,1′-diol, by producing diastereomers, with better yields than previously reported. A solution to unexpected epimerisation during resolution is reported.

Chapter five summarises applications of *cis,cis*-spiro[4.4]nonane-1,6-diol and *cis,cis*-2,2′-spirobiindane-1,1′-diol as chiral auxiliaries. The investigation of these diols as ligands bound to Lewis acids gave poor results in both the yield and the percent enantiomeric excesses (ee's). Better results were obtained when the spirodiols were employed as substrate bound chiral auxiliaries in diastereoselective cyclopropanation reactions. Excellent results were obtained when the diester of *cis,cis*-spiro[4.4]nonane-1,6-diol (where one alcohol was reacted with pivaloyl chloride and one with acryloyl chloride) underwent a Diels-Alder reaction with cyclopentadiene in the presence of boron trichloride. Diastereomeric excesses greater than 97% (97% ee after adduct cleavage) were obtained.

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To the members of my family

(past, present and future)

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List of Abbreviations

2,4-DNP	2,4-dinitrophenylhydrazine	Et	ethyl
4Å MS	4Å molecular sieves	FGA	functional group addition
abs.	absolute	FGI	functional group interconversion
Ar	aromatic group		
BINOL	binaphthol	GC	gas chromatography
Bn	benzyl	GC/MS	gas chromatography/ mass spectrometry
Bu	butyl		
Bz	benzoyl	h	hours
c	cyclo	hυ	light
calc'd	calculated	Hex	hexyl
cat.	catalytic	hfc	3-(heptafluoropropyl hydroxymethylene)-*d*-camphorato
CI	chemical ionisation		
conj.	conjugated		
DCC	dicyclohexylcarbodiimide	HPLC	high performance liquid chromatography
de	diastereomeric excess		
dec.	decomposition	i	iso
DEPT	distortionless enhancement by polarisation transfer	L	leaving group
		L*	chiral ligand
DET	diethyl tartrate	L.A.	Lewis acid
Dibal-H	diisobutylaluminium hydride	L.A.*	chiral Lewis acid
		LAH	lithium aluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine	LDA	lithium diisopropylamide
		LHMDS	lithium hexamethyldisilylazide
DMF	*N*,*N*-dimethylformamide		
DMSO	dimethyl sulfoxide	M	metal
ee	enantiomeric excess	*m*	*meta*
eq.	equivalents	Me	methyl

mesyl	methanesulfonyl
min	minutes
MTPA	2-methoxy-2-trifluoro methylphenylacetic acid
MTPA-Cl	2-methoxy-2-trifluoro methylphenylacetyl chloride
MVK	methyl vinyl ketone
n	normal
NMR	nuclear magnetic resonance
Np	naphthyl
o	*ortho*
[O]	oxidation
ODS	octadecylsiloxane
OIT	orbital interaction theory
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPA	polyphosphoric acid
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
Pra-Opt®	Tris[3-(trifluoromethyl)-hydroxymethylene-(+)-camphorato], praseodymium derivative
Py	pyridine
R	various alkyl and aryl substituents (unless otherwise stated)
ref	reference
rt	room temperature
rxn	reaction
salen	*N,N'*-bis-(salicylideneamino)ethane
s.m.	starting material
S_N2	substitution, nucleophilic, bimolecular
t	*tert*
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydrogen peroxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tosyl	*para*-toluenesulfonyl
Ts	*para*-toluenesulfonyl
unsat.	unsaturated
wrt	with respect to
w.u.	work up
X	halogen, RO or R_2N

Chapter 1

1. Induction of Chirality by Substrate or Lewis Acid Bound C_2-Symmetric Diols

We became interested in undertaking research in the area of C_2-symmetric chiral diol auxiliaries. A search of the literature in July 1992 on C_2-symmetric chiral diol auxiliaries revealed that C_2-symmetric spirodiols had not been used as auxiliaries in organic transformations. We became interested, therefore, in investigating the utility of spirodiols as auxiliaries for asymmetric transformations. This chapter explains the importance of and various methods for performing enantioenriched syntheses and subsequently provides a review of the literature on the various types of C_2-symmetric diols that have been used in synthesis as chiral auxiliaries up until the end of 1995. This review of the literature will:

1) display the novelty of spirodiols prior to 1992;

2) summarise the results for other types of C_2-symmetric diols; and

3) show the limited utilisation of spirodiols since 1992.

1.1 Introduction

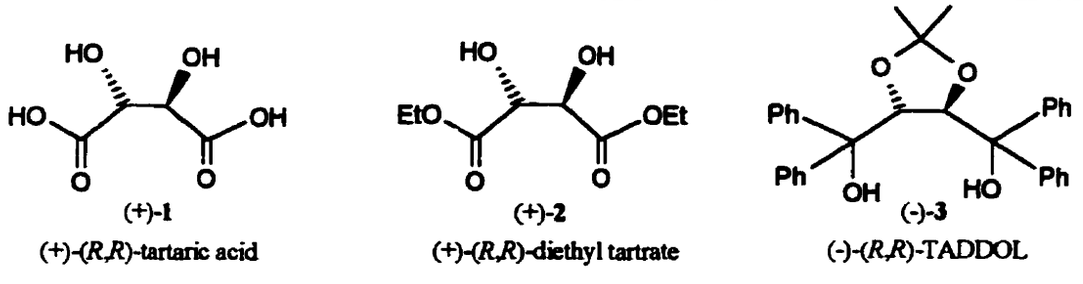


Figure 1.1 Some Common C_2-Symmetric Chiral Molecules

Isolation of natural products has been an important part of organic chemistry for over a hundred years. Over this time a vast array of compounds have been isolated, some of which are enantiomerically pure (enantiopure). If an optically pure natural product is abundant and inexpensive, it is part of what has been termed the "chiral pool".[1] This "chiral pool" is important for modern organic synthesis because it is almost exclusively[2] the source of chirality, directly or indirectly[3] for a synthetic sequence. For example, Figure 1.1 shows (+)-(*R*,*R*)-tartaric acid (**1**), a member of the "chiral pool" (direct), and

two commonly used chiral auxiliaries, (+)-**2** and (-)-**3**, which are derived from (+)-**1** (indirectly).

The majority of chiral molecules have no symmetry elements and therefore are called asymmetric; however, some chiral compounds are not devoid of symmetry. The only symmetry element(s) that can be present in a chiral compound is one or more axes of symmetry (C_n, where n>1). Thus chiral molecules can be assigned the point groups C_n or D_n (where n>1). Chiral compounds in these point groups have been called dissymmetric.[4] The majority of synthesised dissymmetric molecules belong to the C_2 point group. Some examples of C_2-symmetric diols are shown in Figure 1.1. Chiral auxiliaries with C_2-symmetry are important to chemists because they reduce the number of non-identical orientations possible in the transition state to chiral product by 50%. This typically allows for an easier stereochemical analysis to predict or explain the outcome of a stereoselective transformation.

1.1.1 Importance of Enantioselective Syntheses

Prior to 1960, the biological activity of a racemate versus each individual enantiomer was ignored. One of the main tragic events that changed this was the introduction of (±)-thalidomide in 1961 (in Europe).[5] (±)-Thalidomide was introduced as a sedative and antinausea agent for use in early pregnancy; however, it was soon determined that the (-)-(*S*)-thalidomide (Figure 1.2) was a potent teratogen. Children born to women who had used thalidomide had a higher incidence of limb deformities. Later it was shown that (+)-(*R*)-thalidomide does not cause birth defects in animals even in high dosage.[5] The thalidomide incident is not the only example in biological systems where two enantiomers have different physiological properties. Figure 1.2 displays some other examples of biodiscriminating stereoisomers. As a result of cases where the human body showed severe biodiscrimination of enantiomers, federal drug administrations around the world have recently changed their policies, for example:

> "...the [US] Food and Drug Administration explicitly requires the submission of information about the enantiomer composition of chiral substrates in new drug applications."[5a]

With federal drug administrations around the world tightening restrictions on new drugs, the percentage of enantiopure drugs sold to the public continues to rise. The increase in sales of enantiopure drugs quoted in "Chemical and Engineering News" from 1993 to 1994 was 35.6 to 45.2 billion US dollars world wide.[6] This corresponds to a 27.0% increase in sales over a one year period. The same article also predicts that the amount of single enantiomer drugs sold, which have been prepared synthetically, will also

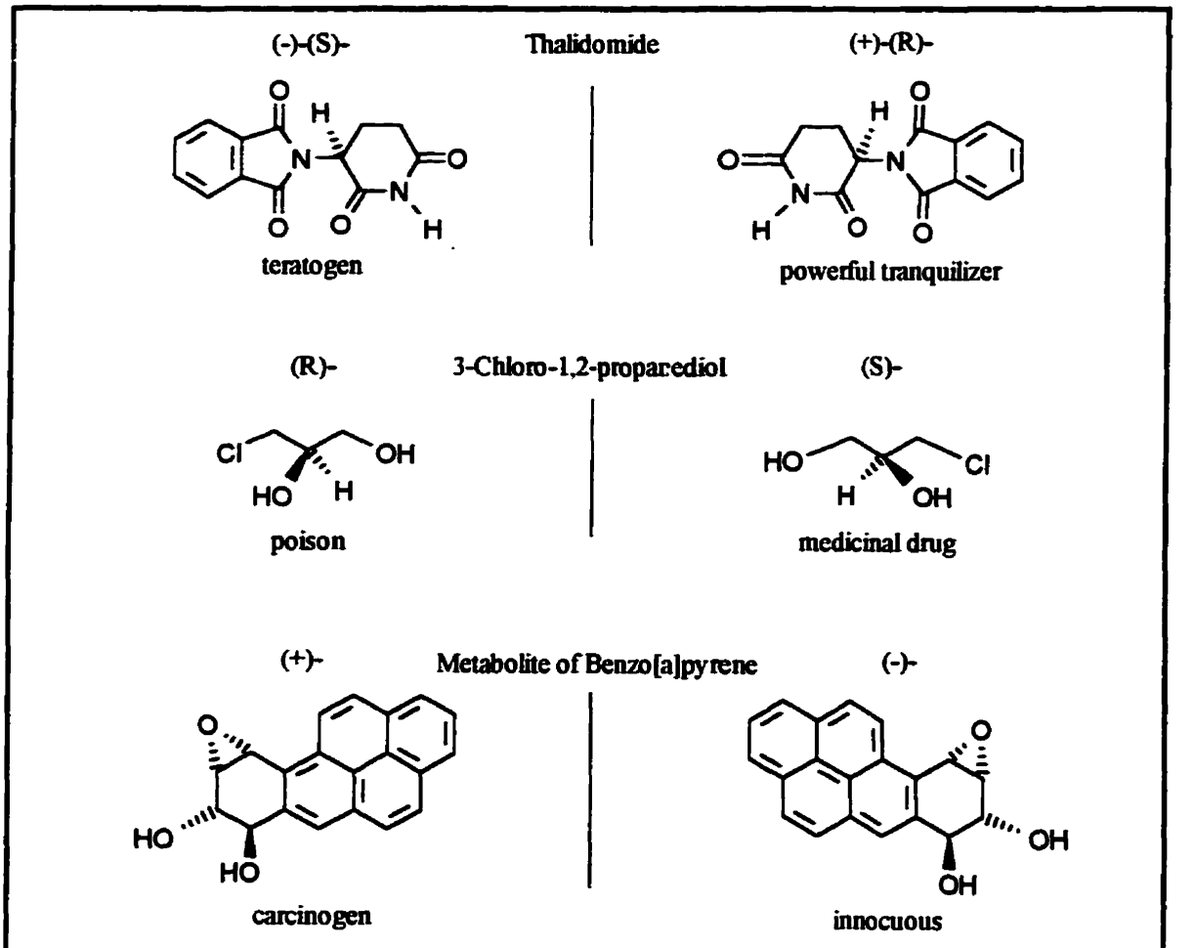


Figure 1.2 Some Examples of Biodiscriminating Enantiomers[5b]

continue to increase with respect to other drugs (single enantiomers from natural sources, racemic mixtures, and achiral compounds).[6] Organic chemists, therefore, must continue to find new and better methods for the synthesis of enantiopure products.

1.1.2 Methods for the Production of Enantiopure Products

This section reviews the five known methods of producing enantioenriched or enantiopure products. These five methods are not absolute divisions and in some cases an enantioenriching technique involves two different methods. These five methods are:

1) **Resolution** - Involves placing a racemic or scalemic (one enantiomer is enriched) mixture in a chiral environment which results in the formation of diastereomers or diastereotopic interactions. Diastereotopic interactions are important for the separation of enantiomers by either kinetic or thermodynamic resolution. The separation of enantiomers by the formation of either diastereomers or by diastereotopic interactions which have different physical properties is called racemate resolution.

2) **Chiral Template**[7a] - Involves the formation of a new optically pure product by using the stereogenic centre(s) of previously synthesised or isolated chiral molecules. Molecules used in this manner are commonly from the "chiral pool". Any of the stereogenic centre(s) in the template can be inverted, maintained or destroyed in order to synthesise the desired enantiopure product.

3) **Chiral Influence** - Involves the diastereotopic interaction of circularly polarised light or substances (which are not reagents or catalysts) with the substrate causing the reaction to proceed enantioselectively (*e.g.* chiral solvent, circularly polarised photochemical excitation, spontaneous resolution).[7b]

4) **Metal, Reagent or Catalyst Bound Chiral Auxiliaries** - Involves the use of a chiral ligand(s) bound to a catalyst, reagent or metal, which is involved in the transition state of a reaction, thereby creating diastereotopic interactions which lead to the product(s) being formed enantioselectively. This is also referred to as Lewis acid or Lewis base bound chiral auxiliaries, and these will be the terms used in this dissertation to describe this method.

5) **Substrate Bound Chiral Auxiliaries** - Involves attaching a chiral auxiliary to the prochiral substrate, by a covalent bond which then influences the stereochemical outcome of a reaction. This influence results in the formation of diastereomers. Removal of the chiral auxiliary then results in the product being enantiomerically enriched.

There are many examples in the literature[8] that illustrate the usefulness of the above five methods for the preparation of enantiopure or enantioenriched products, although the use of the Chiral Influence technique (number 3) is very rare. For the purpose of this dissertation, examples of 4) and 5) using C_2-symmetric diols will be reviewed. We became interested in chiral C_2-symmetric diols because they are extremely versatile moieties, as demonstrated by their use in the literature.[8] These diols can be used as Lewis acid bound chiral auxiliaries (Section 1.2), as substrate bound chiral auxiliaries (Section 1.3), or the alcohols can be converted into other functionalities. There are many examples in the literature where the alcohol functionalities in C_2-symmetric diols are changed and the resulting compounds were used as chiral sources,[9] but the following review will concentrate on C_2-symmetric diols as auxiliaries.

1.2 Enantioselective Reactions Promoted by Lewis Acid Bound Auxiliaries

1.2.1 Introduction

A chiral auxiliary bound to a Lewis acid influences the preferred conformation of a prochiral substrate in the transition state *en route* to a chiral product. This preferred conformation hopefully results in the formation of one enantiomer over the other. The larger the preference for one conformation in the transition state, the higher the enantioselectivity of a reaction under kinetic control.

Frequently, the formation of the chiral Lewis acid is performed in a separate step and then introduced into the reaction mixture. In this section of the review, however, the various C_2-symmetric diols used in creating the chiral Lewis acids will not always be displayed, but in order to conserve space, the chiral Lewis acid will be shown instead.

One diol that is included in this review, even though it is not C_2-symmetric, is the diol corresponding to compound **20** (Scheme 1.4). This diol and the complexes derived

from it are included because it belongs to the TADDOL family of diols, most of which are C_2-symmetric.

1.2.2 Addition of Organometallics to Aldehydes and Ketones

For forty years the addition of organometallics to diastereotopic faces of carbonyl groups has been the subject of intense study by many groups.[10] Recently there has been much interest in the addition of chiral organometallic reagent to enantiotopic faces of aldehydes and ketones. These studies have focussed on the development of suitable organometallics that would create a new stereogenic centre with a high ee.[11-20]

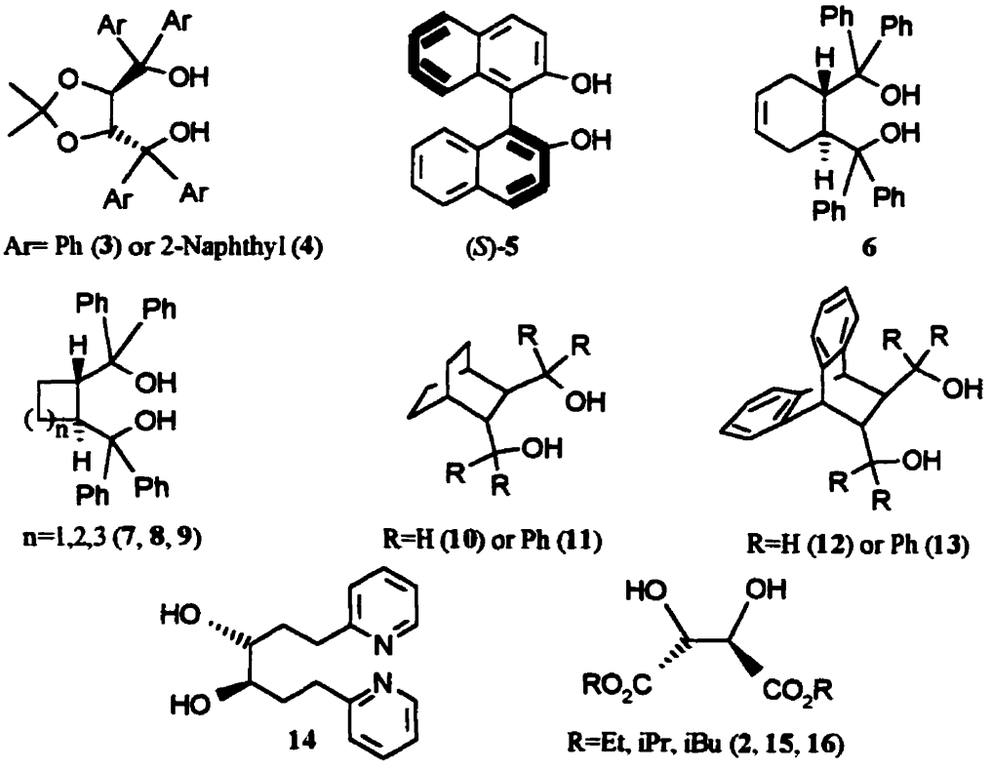
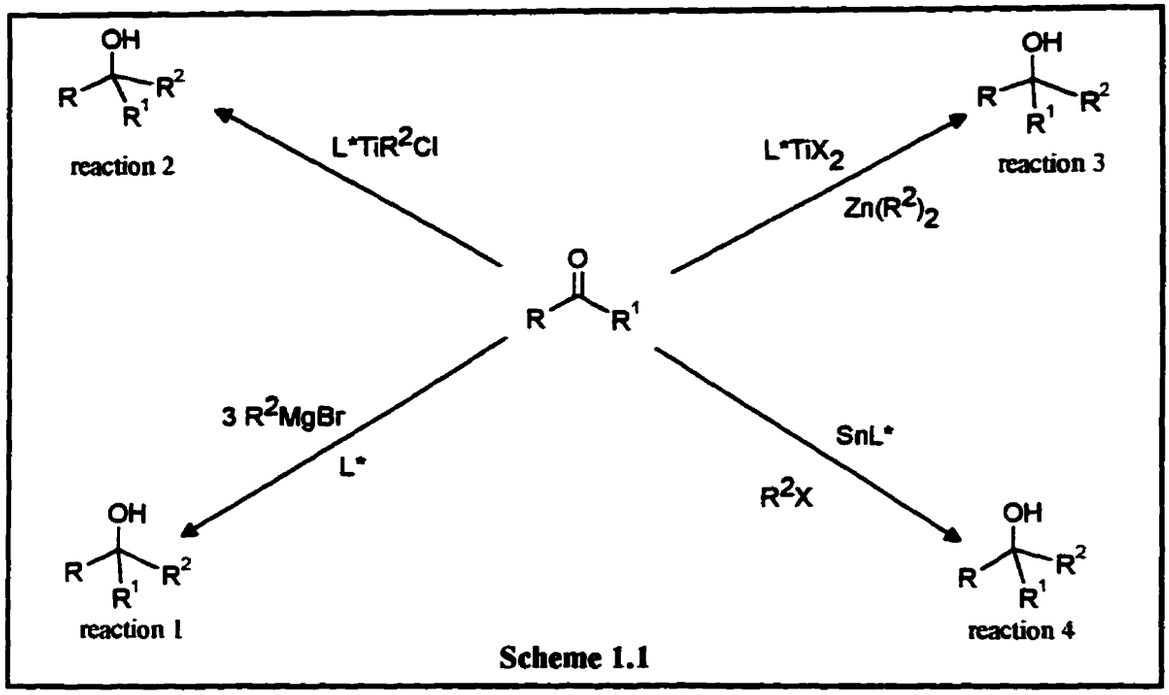


Figure 1.3 Auxiliaries (L*) used for Addition of Organometallics to Aldehydes and Ketones in Scheme 1.1 and Table 1.1

The most common metals studied in the asymmetric addition of organometallics to carbonyl groups are magnesium (Grignard), titanium, and zinc. Many C_2-symmetric diols (Figure 1.3) have been tested for their chirotopic influence in a variety of organometallic additions to carbonyl groups (Scheme 1.1). Table 1.1 summarises the results and shows

the ee's range from poor to excellent for a variety of aldehydes, but only a small amount of research has been done on the addition of organometallic reagents to ketones.[12]



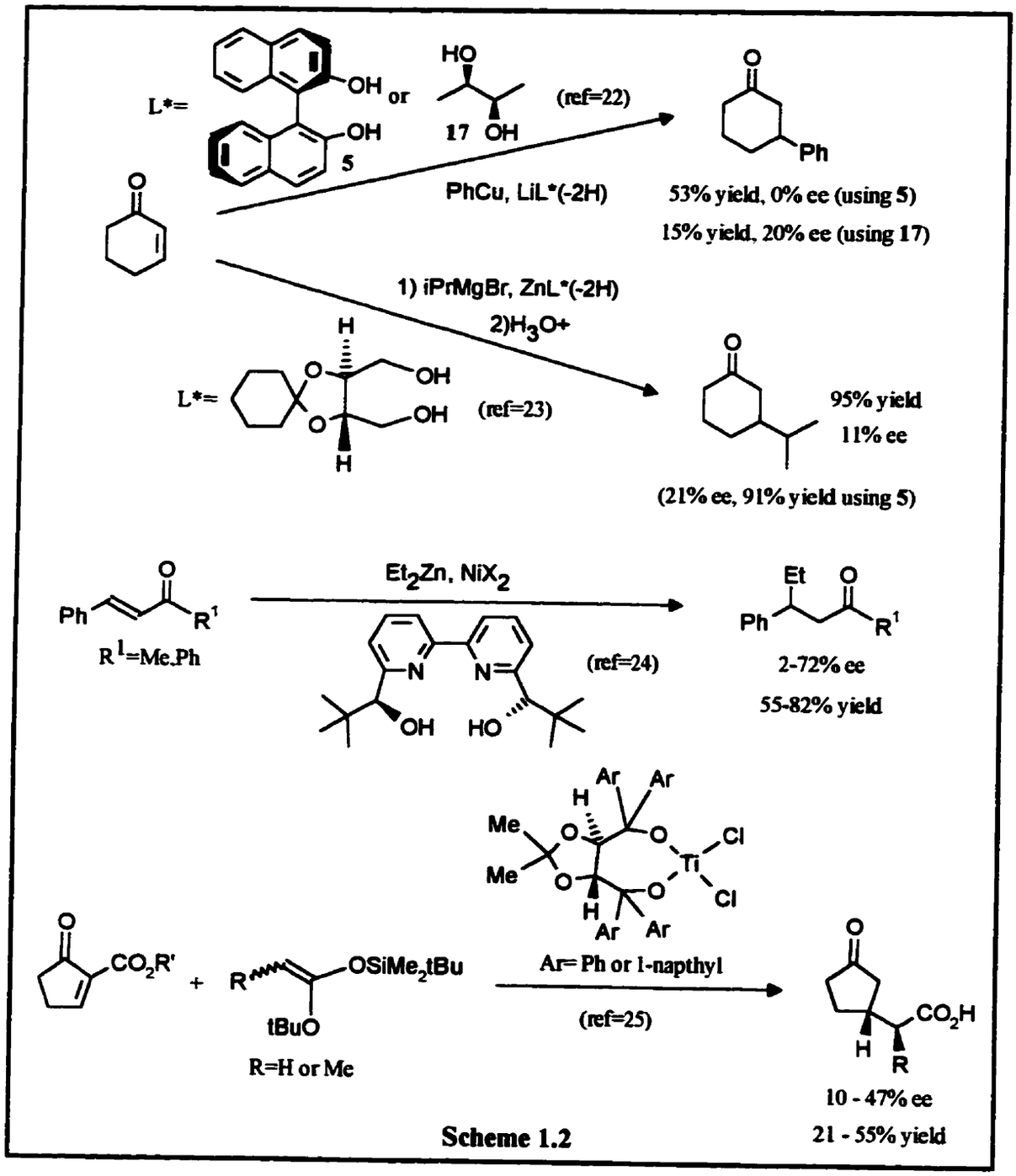
Scheme 1.1

Table 1.1 Results From the Use of Ligands in Figure 1.3 in the Reaction in Scheme 1.1

Rxn	L*	R	R^1	R^2	% yield	% ee	Ref
1	5	alkyl,aryl	H	alkyl,aryl	40-90	6-92	11
1	3, 4	alkyl,aryl	alkyl	alkyl	trace-90	24-98	12
2	3	alkyl, Ph	H	Me	35-91	35-83	13
2	3	Ph, alkyl	H	allyl	69-94	94-97	14
2	3, 6-13	Ph	H	Me	43-81	66-98	15
2	3	iBu, Ph	H	allyl,α-ester	20-95	18-95	16
3	3	Ph, alkyl	H	alkyl	30-95	80-99	17
3	3, 6-13	Ph	H	Et	53-99	20-98	15
3	10-13	Ph	H	Et	81-89	0-86	18
3	14	Ph	H	Et	83-94	9-40	19
4	2, 15, 16	Ph, alkyl	H	allyl	38-84	16-65	20

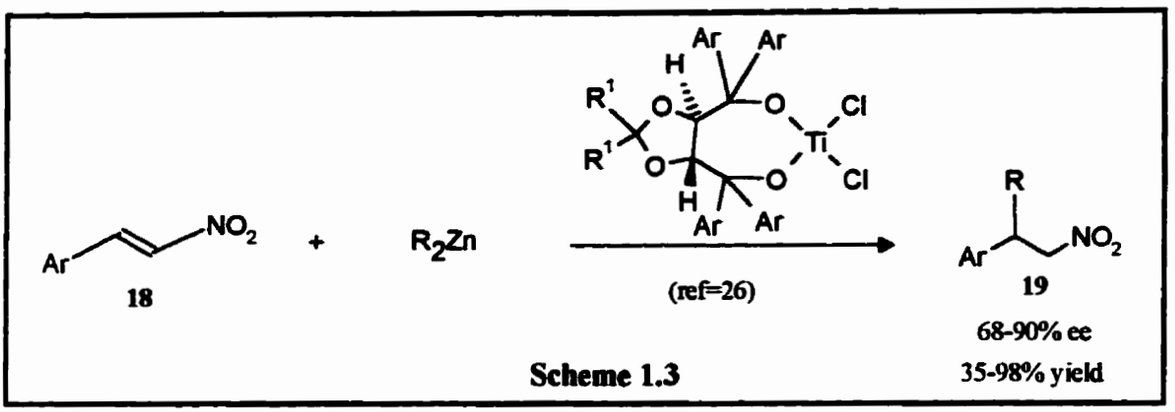
1.2.3 Conjugate Addition Reaction

A large volume of research has been done on the asymmetric conjugate addition reaction;[21] however, only a few examples have used chiral C_2-symmetric diols (Scheme



Scheme 1.2

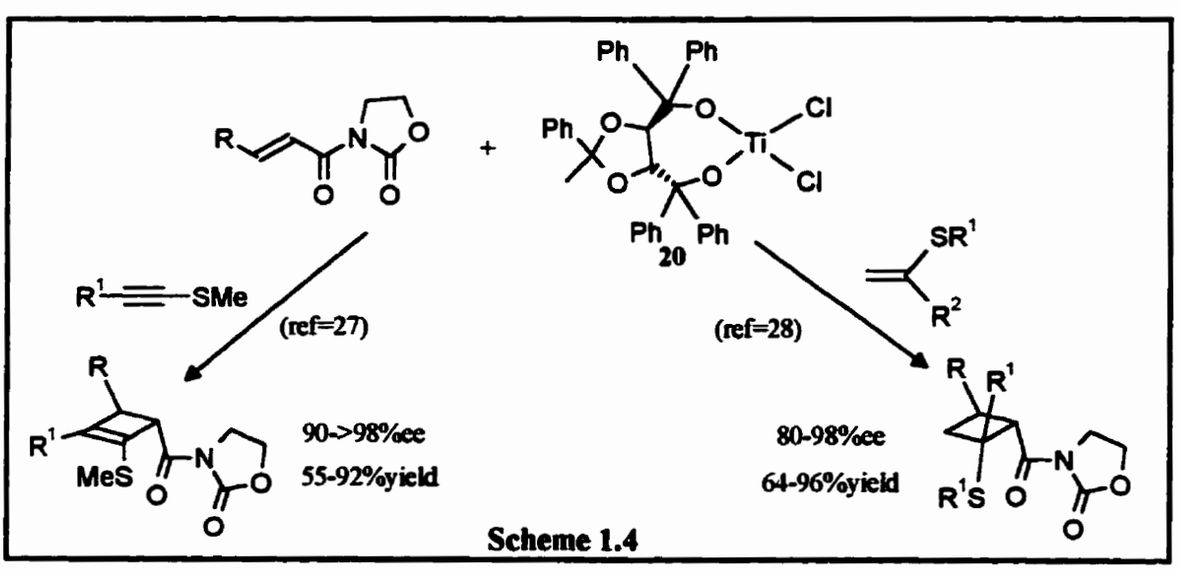
1.2).[22-25] Results for the 1,4-addition of organometallics to enones in the presence of C_2-symmetric diol Lewis acid complexes are mediocre at best, and many other types of chiral auxiliaries have provided products with much higher ee's.



Scheme 1.3

1,4-Addition to α,β-unsaturated carbonyls was not the only type of conjugate addition reaction. Schafer and Seebach[26] reported the conjugate addition of dialkylzinc species to conjugated nitro compounds (**18**) in the presence of titanium TADDOLates (Scheme 1.3). The aryl nitro products (**19**) were obtained with good to excellent ee's.

1.2.4 Cycloaddition [2+2] Reaction

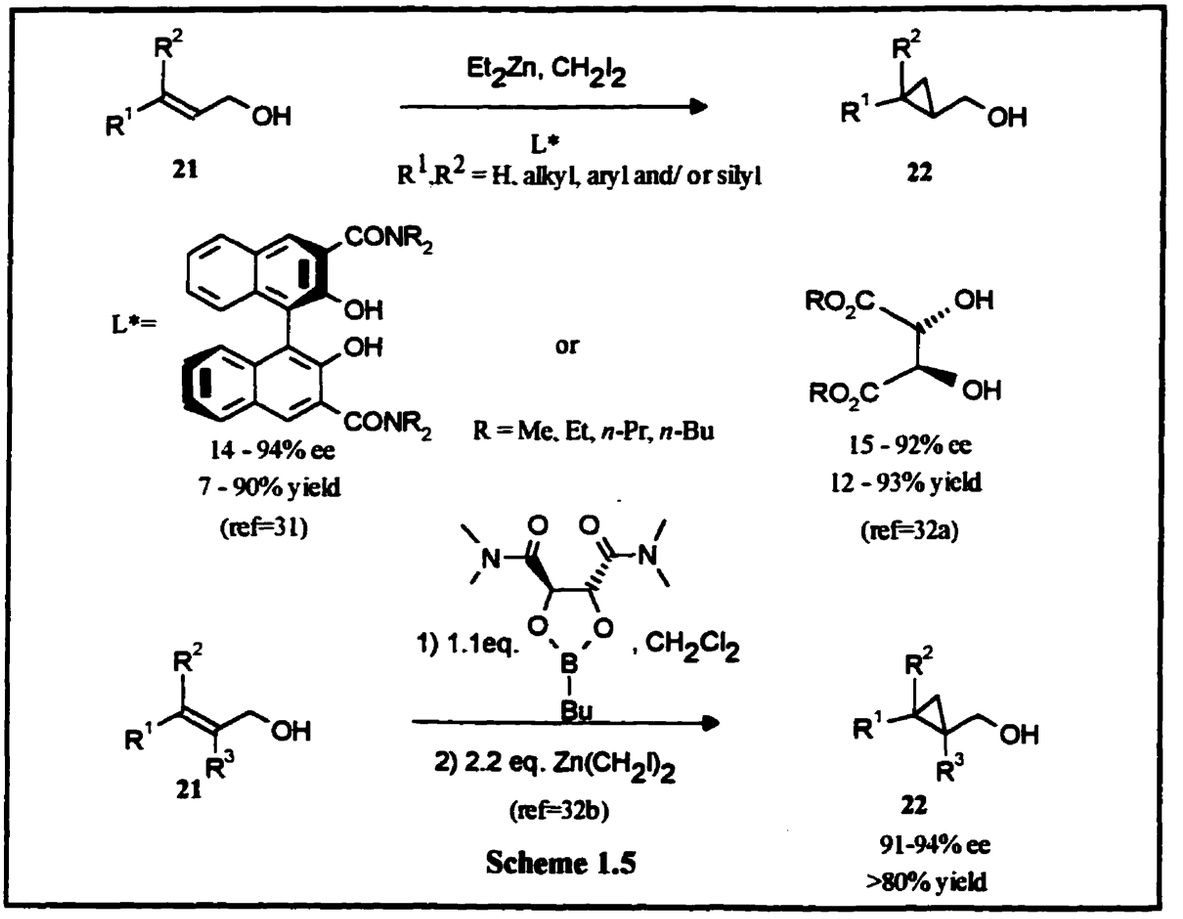


Scheme 1.4

One of the fundamental methods for the formation of cyclobutane derivatives is *via* the [2+2] cycloaddition; however, very little has been reported using metal or catalyst bound chiral auxiliaries. Hayashi and Narasaka[27,28] reported two examples, both using

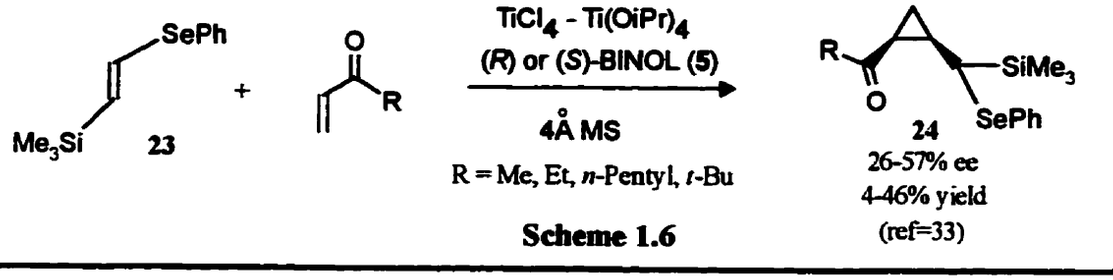
titanium TADDOLate (**20**). The cyclobutane products were formed in good to excellent yield and ee's (Scheme 1.4). In addition to this example, Narasaka reported, in a Diels-Alder reaction (section 1.2.6), a 21% yield of a [2+2] by-product.[29] The above examples are limited to sulfur substituted alkynes and alkenes and therefore the overall utility of this reaction is limited.

1.2.5 Cyclopropanation Reaction



Scheme 1.5

Due to the discovery of natural products containing cyclopropyl rings[30] there has been an interest in developing an asymmetric cyclopropanation reaction. Most of the work in the area of asymmetric cyclopropanation has been done using prochiral allylic alcohols (**21**). Scheme 1.5 shows the results with a (*R*)-BINOL amide derivative,[31] (*R*,*R*)-tartrate esters[32a] and amides[32b] in the presence of diethylzinc. The yield and ee of **22** ranges from poor to excellent with both auxiliaries.



Scheme 1.6

Recently, Yamazaki *et al.*[33] reported a cyclopropanation reaction they claim to be an asymmetric [2+1] cycloaddition. The addition of (*E*)-1-(phenylseleno)-2-(trimethylsilyl)ethene (**23**) to various enones provided cyclopropyl products **24** in low to

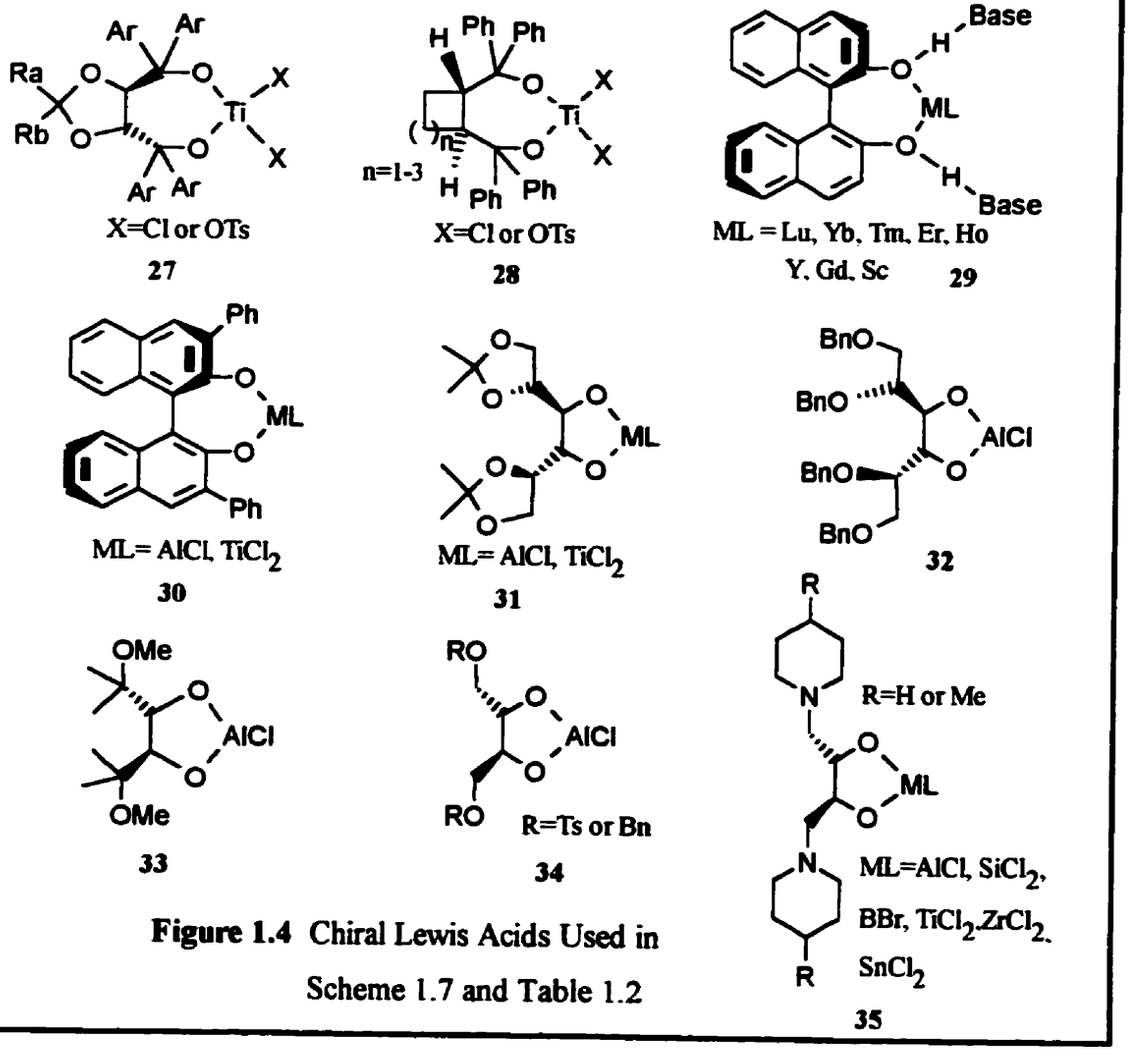
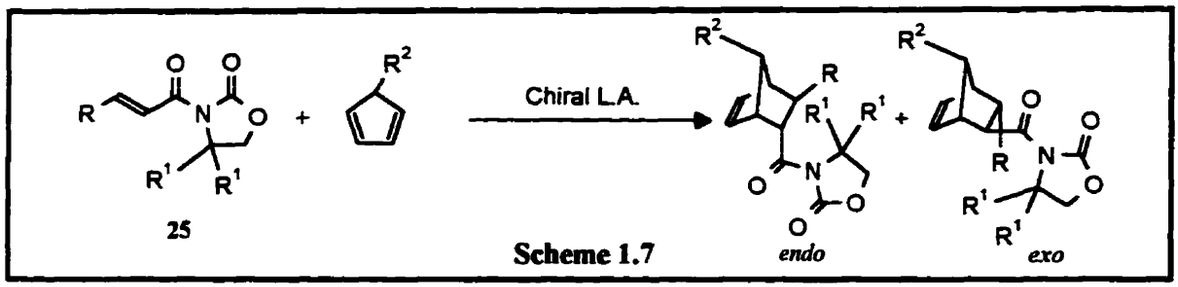


Figure 1.4 Chiral Lewis Acids Used in Scheme 1.7 and Table 1.2

moderate yield and ee's (Scheme 1.6).[33]

1.2.6 Diels-Alder Reaction

The Diels-Alder reaction is one of the most studied and useful transformations in organic chemistry. The goal of using chiral Lewis acids for the Diels-Alder reaction is to control not only the regioisomers, but also the ratio of stereoisomers produced. The chiral Lewis Acid promoted asymmetric Diels-Alder reaction has been studied for over 20 years.[34]



Scheme 1.7

Table 1.2 Summary of Diels-Alder Reactions in Scheme 1.7 with Chiral Lewis Acids in Figure 1.4

L.A.*	Ra	Rb	R	R^1	R^2	*endo* (%)	yield (%)	ee (%)	Ref
27	Me	Me,Ph	Ph,Me	H	H	0-89	50-91	31-86	35
27	Me	Ph	Me,H, *n*-Pr	H	H	88-96	72-93	64-91	36
27,28	alkyl,Ph	alkyl,Ph	Me	H	H	74-90	7-99	0-88	37
27	Me,Et	Ph	Me,H, Ph	H	H,Bn-OCH_2-	81->91	72-93	44-95	38
27	alkyl	alkyl,Ph	alkyl, BOR^3, Ph	H	H	50-92	47-100	22-97	29, 39
29	-	-	Me,Ph, *n*-Pr	H	H	6-90	0-99	20-97	40
30-35	-	-	H,Me	Me	H	71-94	5-99	19->98	41

The main focus of the numerous published studies involving chiral Lewis acids in (Figures 1.4 and 1.5) Diels-Alder reactions is with either oxazolidinones **25** (Scheme 1.7, Table 1.2)[29,35-41] or enones and enals **26** (Scheme 1.8, Table 1.3).[13,42-47] The standard diene used to evaluate the chiral Lewis acid catalysed Diels-Alder reaction is cyclopentadiene, which is used in both Schemes 1.7 and 1.8.

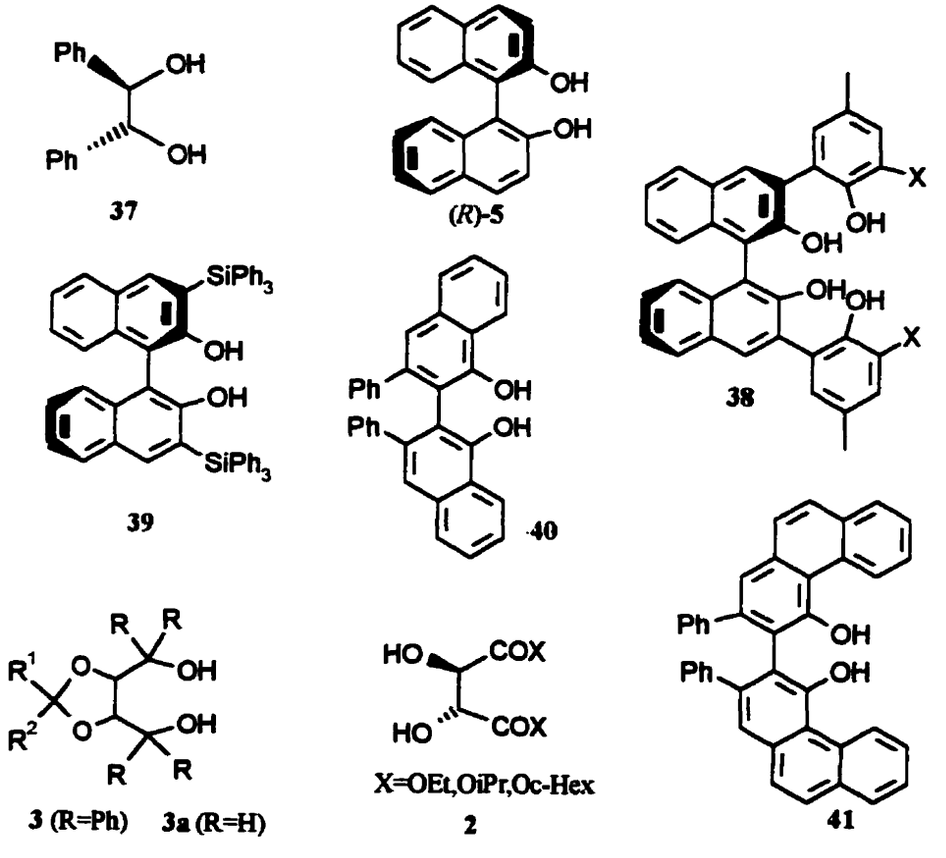
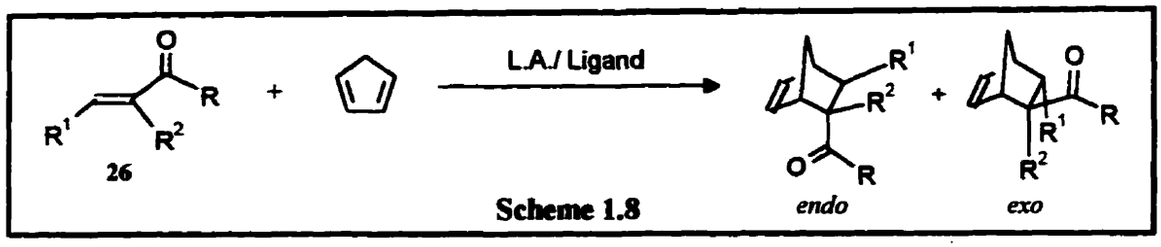


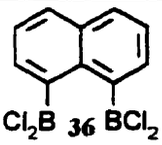
Figure 1.5 C_2-Symmetric Diols Used in Scheme 1.8 and with Lewis Acids in Table 1.3

The results for the reactions in Scheme 1.7 and 1.8 with cyclopentadiene have begun to yield excellent results over the last few years. For example, Seebach's group[37] has reported good results (96% yield, 90% *endo*, 88% ee) for Scheme 1.7, while Wulff's



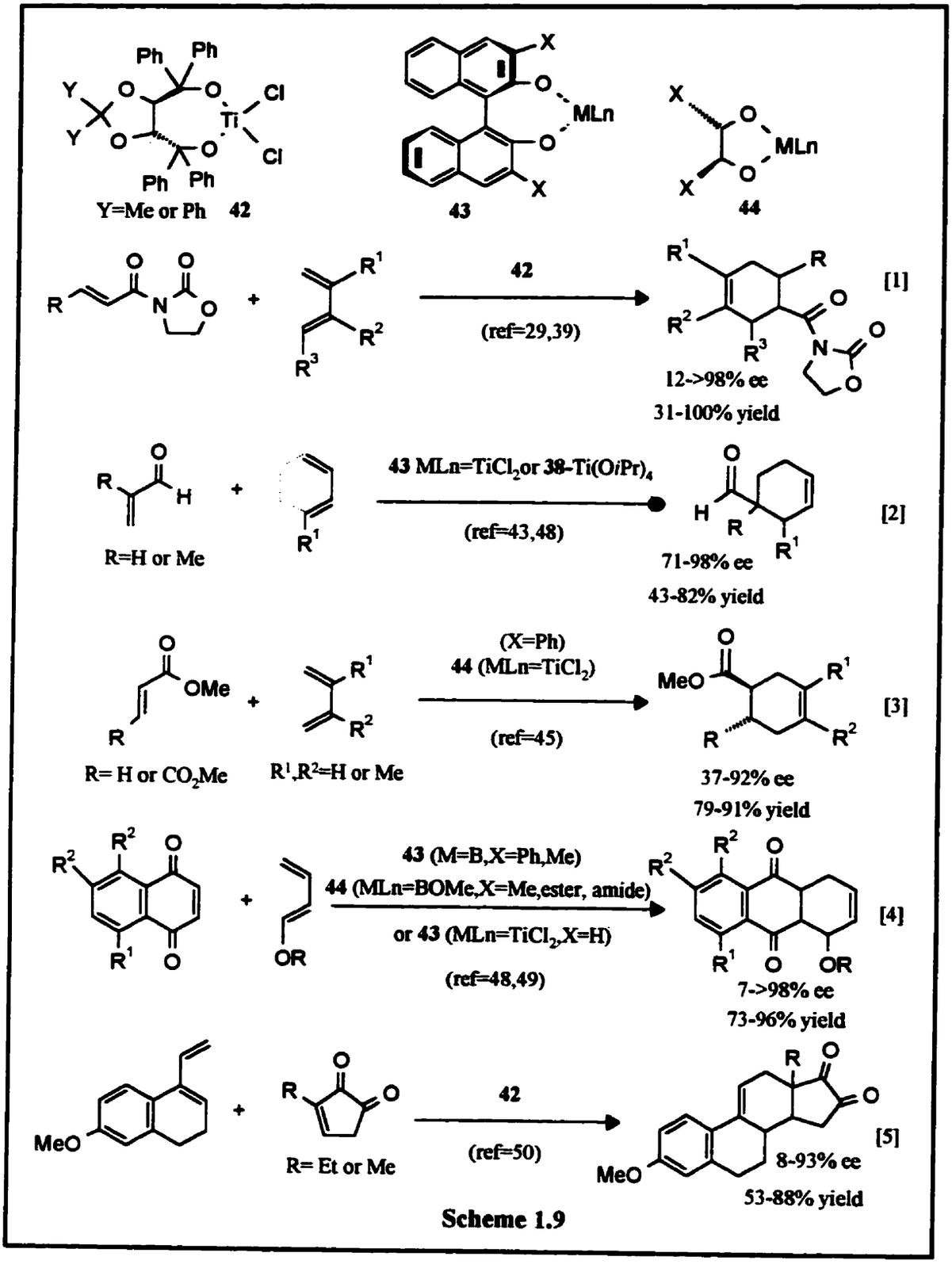
Scheme 1.8

Table 1.3 Diels-Alder (Scheme 1.8) Reactions using Auxiliaries in Figure 1.5

L.A.	Ligand	R	R^1	R^2	*exo* (%)	yield (%)	ee (%)	Ref
$TiCl_4$	(*R*)-**5**	H	H	Me	90	56	16	42
$Ti(OiPr)_4$	**38**	H	H,Me	H,Me	7-99	36-84	29-84	43
Et_2AlCl	(*R*)-**5**,**39-41**	H	H	Me	92-98	5-100	5-97	44
$TiCl_2(OiPr)_4$	(*R*)-**5**,**2**,**3**	OMe	H	H	2	30-87	1-50	13
$TiCl_2(OiPr)_4$	(*R*)-**5**	OMe	MeO_2C,H	H	-	85	36	45
Al, Ti, Sn	**2**,**3a**,(*R*)-**5**	OAlk	H	H	2-10	11-70	13-91	46
	**37**,(*R*)-**5**	H	H	Br	80-86	81-83	81-83	47

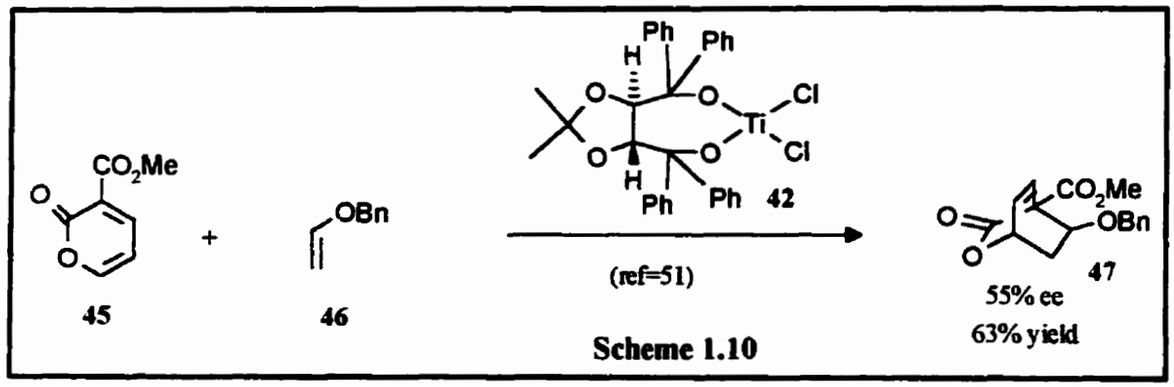
group[44] reported excellent results (100% yield, 98% *exo*, 98% ee) for Scheme 1.8. Continued research, however, is needed to broaden the number of dienes and dienophiles to which these methodologies can be applied.

Other studies with a variety of dienes and dienophiles have been reported in the literature and the results are summarised in Scheme 1.9.[29,39,43,45,47-50] These results range from poor to excellent for both the yield and ee's. In equation 1 (Scheme 1.9) if R^2 is a thioether, a 21% yield of [2+2] cycloaddition (Section 1.2.4) by-product was observed.[29]


Y=Me or Ph 42
43
44
42
(ref=29,39)
12->98% ee
31-100% yield
[1]
43 MLn=TiCl2or 38-Ti(OiPr)4
(ref=43,48)
R=H or Me
71-98% ee
43-82% yield
[2]
(X=Ph)
44 (MLn=TiCl2)
(ref=45)
R= H or CO2Me
R1,R2=H or Me
37-92% ee
79-91% yield
[3]
43 (M=B,X=Ph,Me)
44 (MLn=BOMe,X=Me,ester, amide)
or 43 (MLn=TiCl2,X=H)
(ref=48,49)
7->98% ee
73-96% yield
[4]
42
(ref=50)
R= Et or Me
8-93% ee
53-88% yield
[5]

Scheme 1.9

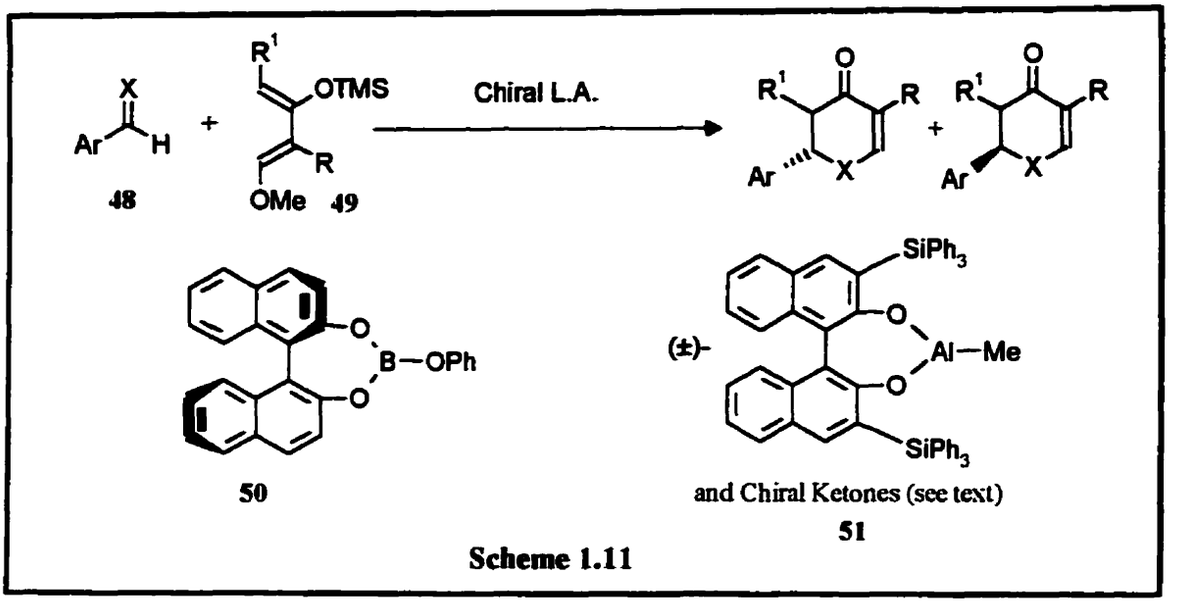
Also reported in the literature were reverse demand (Scheme 1.10) and hetero Diels-Alder reactions (Scheme 1.11 and Table 1.4) using chiral Lewis acids. Other examples of hetero Diels-Alder reactions are mentioned in Section 1.2.8, but the products were obtained as by-products. Posner *et al.*[51] found that the reverse demand reaction between lactone **45** and vinyl benzyl ether **46** in the presence of titanium TADDOLate **42** produced adduct **47** in 63% yield and 55% ee. For the hetero Diels-Alder reaction between imines **48** and Danishefsky's diene **49** (Scheme 1.11 and Table 1.4) Hattori and Yamamoto[52-54] found they obtained good yields and ee's (or de's).



Scheme 1.10

An interesting example of a hetero Diels-Alder reaction was published by Maruoka and Yamamoto (Scheme 1.11),[55] which involved the use of racemic **51** in the presence of chiral ketones. Maruoka and Yamamoto postulated that one of the enantiomers (*R* or *S*) of racemic Lewis acid **51** was complexing to the chiral ketone (*e.g. d*-camphor) which allowed the other uncomplexed enantiomer to promote the reaction. The results obtained were as high as 75% yield and 82% ee.

In a glyoxylate-ene reaction between isoprene and methyl glyoxylate (Scheme 1.14, reaction 2) Mikami *et al.*[48] reported a 20% yield (97% ee) of a cyclic by-product that was obtained as the result of a hetero Diels-Alder side-reaction.



48 49 50 51

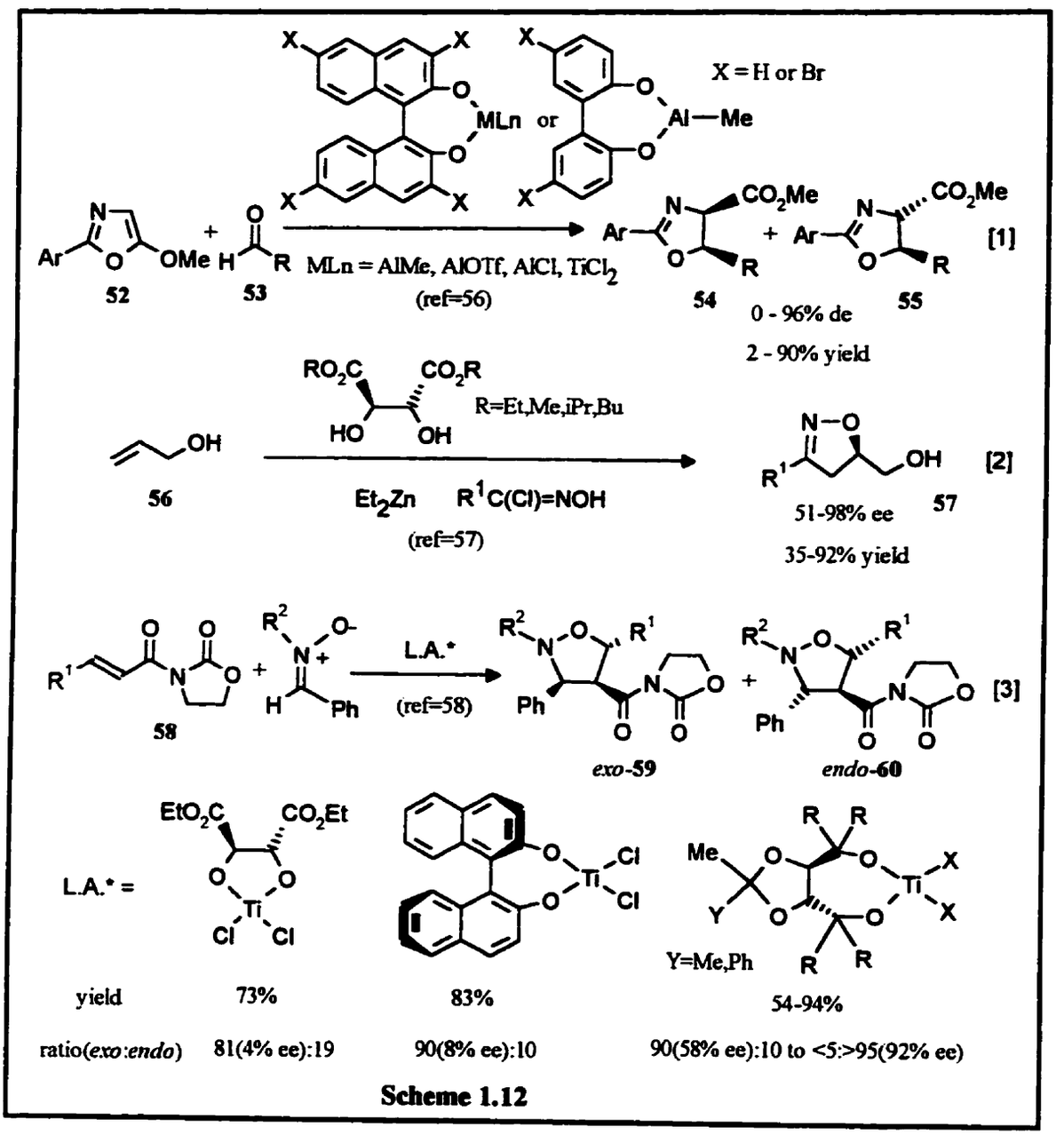
Scheme 1.11

Table 1.4 Hetero Diels-Alder Results for the Reactions in Scheme 1.11

Chiral L.A.	X	Ar	R	R^1	%yield	%ee(de)	Ref
50	NBn	varies	H	H,Me	31-82	72-90	53,54
(+),(-)-50	NCHMePh	Ph	Me	H	30-63	(72-98)	52,53
51	O	Ph	Me	Me	53-84	2-82	55

1.2.7 Dipolar Cycloaddition Reaction

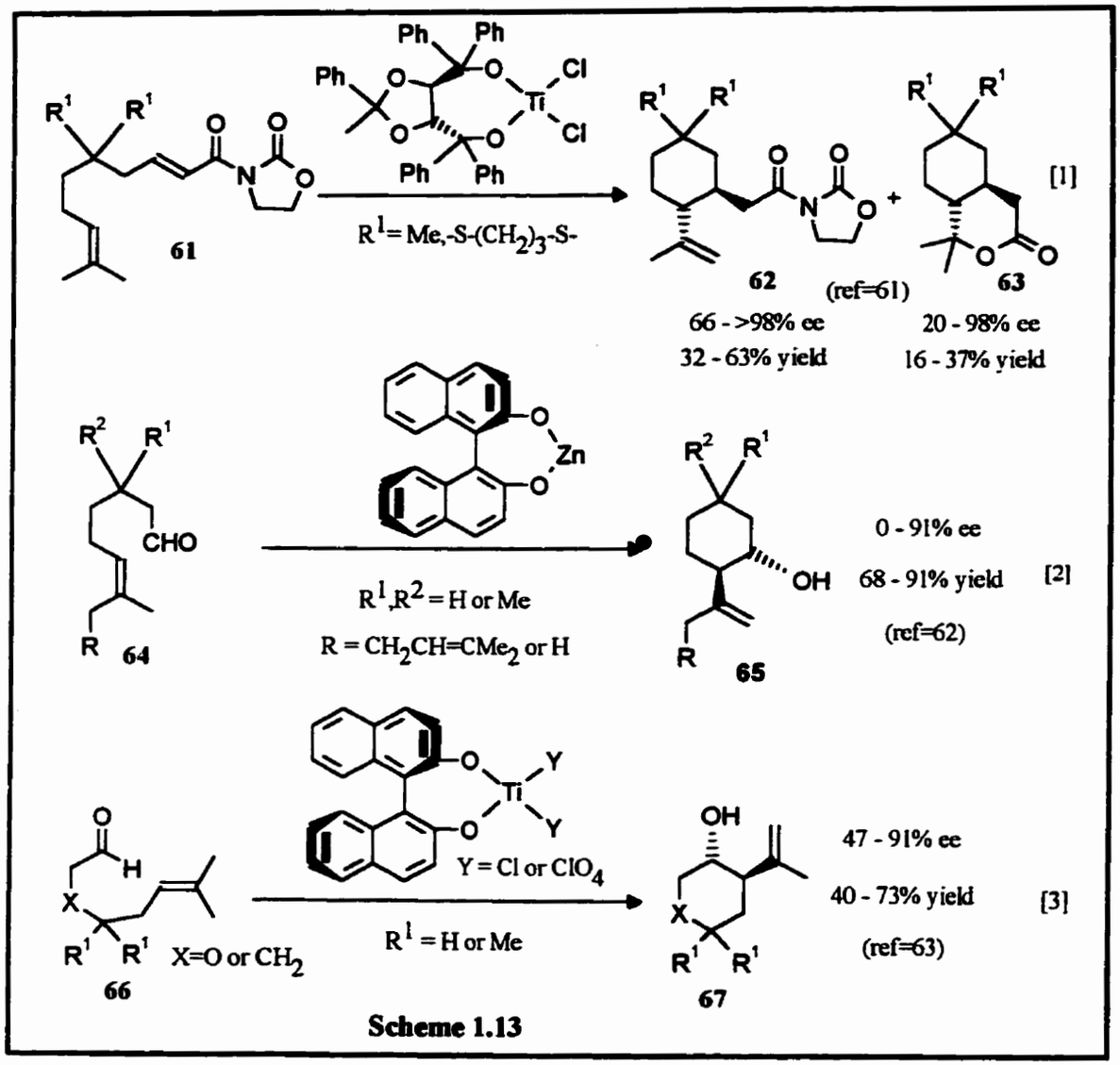
Racemic BINOL and biphenol were used as auxiliaries bound to a variety of Lewis acids to increase the diastereoselectivity of the reaction between oxazoles **52** and aldehydes **53** (Scheme 1.12).[56] The products (racemic) ranged in diastereoselectivity from zero to almost exclusively *cis*-**54**. The use of allylic alcohol **56** and oxazolidinone **58** produced poor to excellent ee's of the corresponding adducts **57** and **59** or **60**, respectively.[57,58]



Scheme 1.12

1.2.8 Ene Reaction

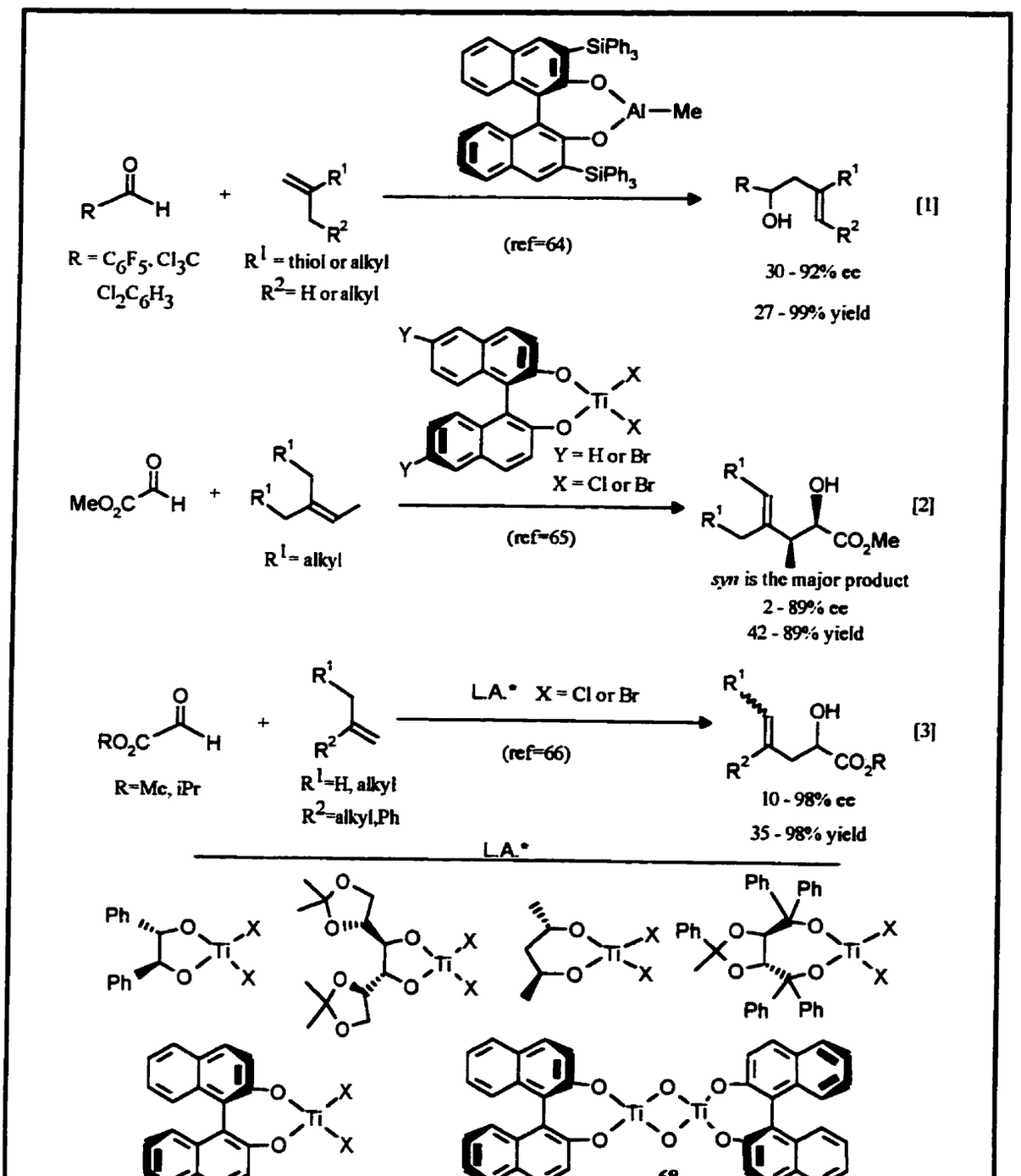
Most of the research in this area has focussed on the carbonyl-ene reaction (also known as the Prins reaction[59]). For a recent review on the carbonyl-ene reaction, see Mikami *et al.*[60] There are two main paths an ene or carbonyl-ene reaction can take; these are *via* intramolecular (Scheme 1.13) or intermolecular reactions (Scheme 1.14).



Scheme 1.13

In Scheme 1.13, reactions 2 and 3 are asymmetric carbonyl-ene reactions while reaction 1 (Scheme 1.13) is the only asymmetric ene reaction reported that uses a C_2-symmetric diol. In reaction 1, a chiral titanium TADDOLate is used to induce the asymmetry for the conversion of oxazolidinone **61** into cycloadduct **62**.[61] Bicyclo compound **63**, which is produced from a hetero Diels-Alder side-reaction was a significant by-product. Reactions 2 and 3 in Scheme 1.13 are intramolecular enantioselective carbonyl-ene reactions of aldehydes **64** and **66** which produce cyclic products **65** and **67**

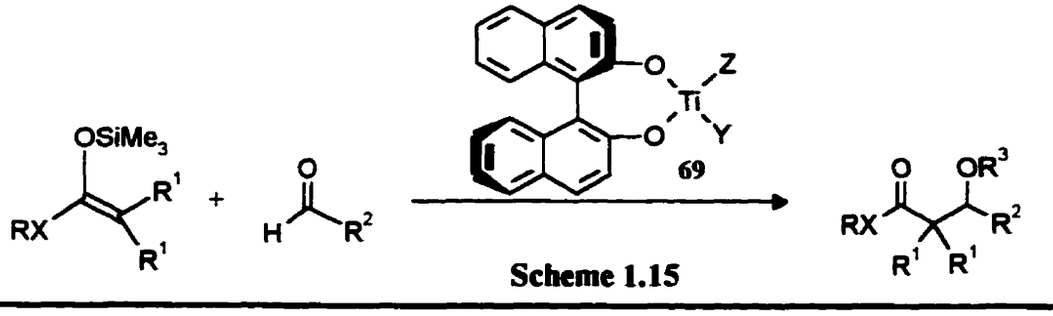
respectively.[62,63] These two methods produce good results, but have had limited use in synthesis.



Scheme 1.14

The intermolecular carbonyl-ene reaction has only been used with aldehydes containing no α-hydrogens (Scheme 1.14). Maruoka *et al.* (reaction 1) showed that chloro and fluoro aldehydes reacted with a variety of alkenes to provide allylic alcohols with good yields and ee's; however, the reaction requires no α-H and therefore will not likely be of much synthetic use.[64] Mikami and Nakai have focussed on the glyoxylate-ene reaction.[65,66] Their results are shown in equations 2 and 3 (Scheme 1.14) which range from poor to excellent depending on the conditions, chiral auxiliary and substrate used. If isoprene (R^1= H and R^2 = -CH=CH_2) was used in reaction 3, a 20% isolated yield of a hetero Diels-Alder side-reaction was obtained.[48]

Another type of ene reaction that has recently been investigated is the silatropic-ene reaction (Scheme 1.15), which is also called the Mukaiyama-aldol reaction.[67] The summary of these investigations is shown in Table 1.5. The results ranged from poor to excellent.[42,66,67,68]



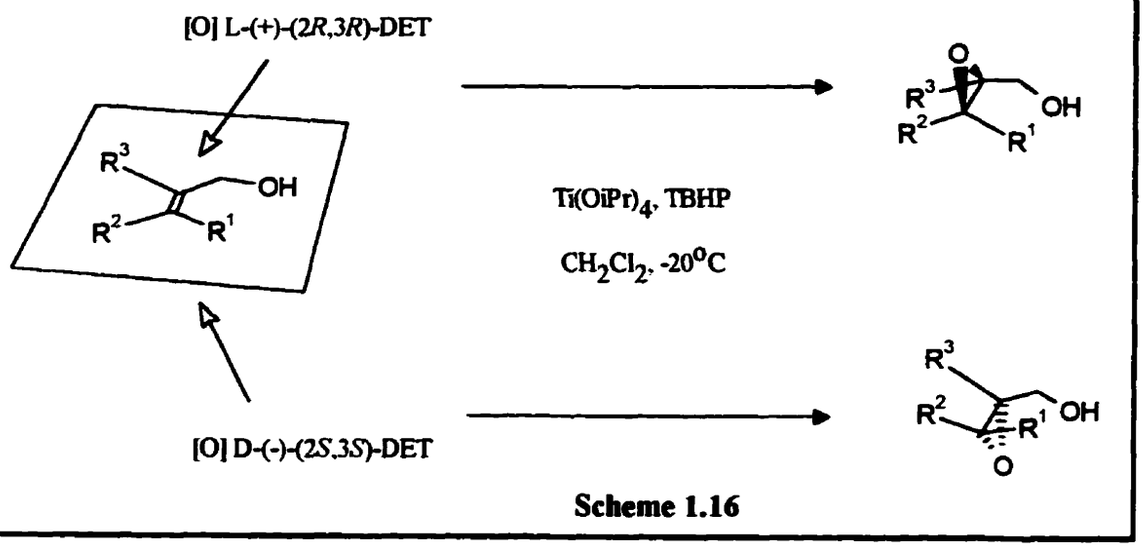
Scheme 1.15

Table 1.5 Summary of Silatropic-Ene Reactions in Scheme 1.15

L.A.*	Z	Y	RX	R^1	R^2	R^3	% yield	% ee	Ref
68	-	-	*t*-BuS	H	Ph	Me_3Si	70	70	66a
69	Cl	Cl	MeO	Me	iBu	H	60	8	42
69	Cl	Cl	alkylS	H	alkyl	Me_3Si	47-96	60-98	68
69	ArO	iPrO	*t*-BuS	H	*n*-Octyl	H	40-62	91-97	67

1.2.9 Epoxidation Reaction

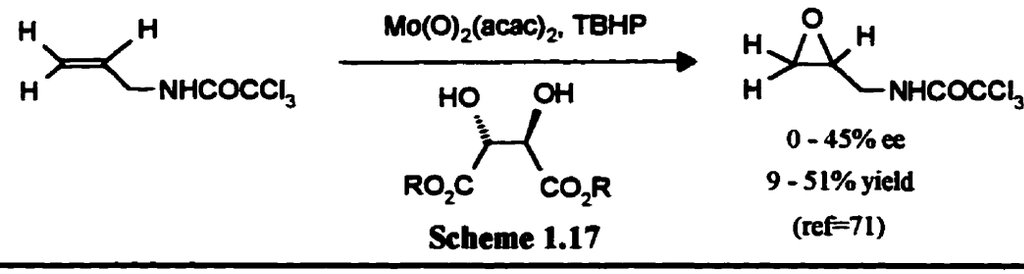
The first practical method for asymmetric epoxidation was the Sharpless epoxidation. This famous method for the asymmetric epoxidation of allylic alcohols has set the standard for the production of enantioenriched epoxides from prochiral allylic alcohols. Scheme 1.16[69] summarises the known stereochemical outcome based on which enantiomer of diethyl tartrate (DET) is employed. This method is inexpensive, easy to repeat, produces a known stereochemical outcome, and results in high enantiomeric excesses. Although extensions of this methodology continue to be reported,[70] the majority



Scheme 1.16

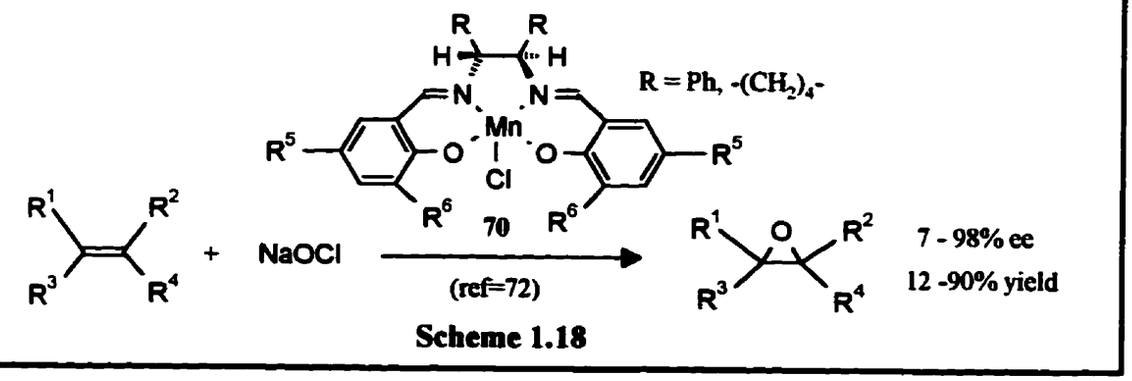
of publications appeared in the early 1980's, and are reviewed in a paper by Pfenninger in 1986.[69]

One of the shortcomings of the Sharpless epoxidation is that it needs an allylic alcohol in order to produce excellent enantiomeric excesses. Recently a report using dialkyl tartrate and molybdenum oxide in the presence of allylic amides produced the corresponding epoxy-amide in mediocre yields and ee's (Scheme 1.17).[71] This methodology still uses an adjacent functional group to direct the epoxidation.



Scheme 1.17

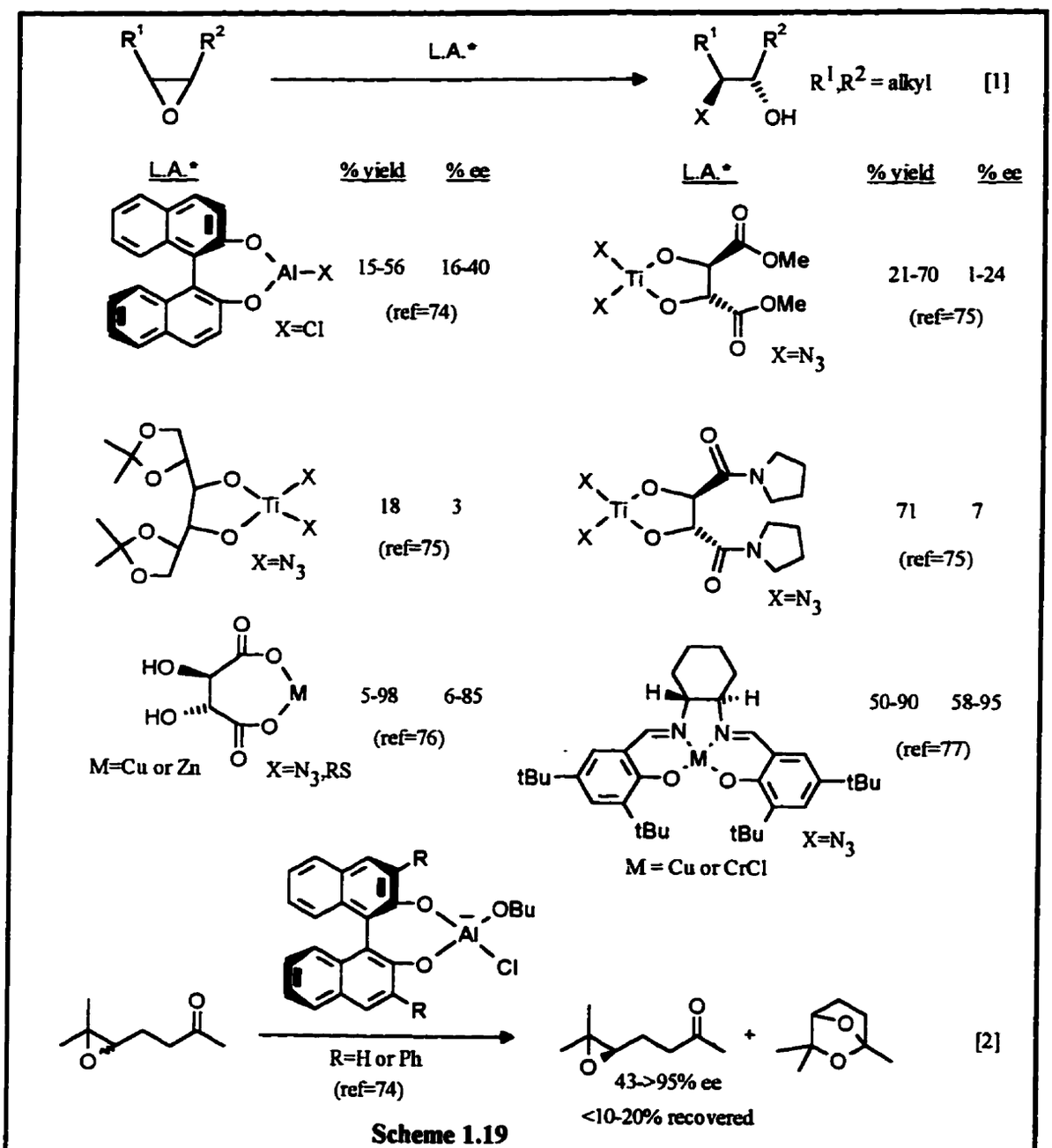
Epoxidation of unfunctionalised double bonds is of considerable interest, and at the beginning of this decade a method to epoxidise unfunctionalised double bonds was introduced by Jacobsen. His reagent, a chiral (salen)Mn(III) catalyst **70**, was voted Reagent of the Year for 1994 by Fluka (Scheme 1.18).[72] The majority of work by Jacobsen's group has focused on the epoxidation of conjugated double bonds, so the overall utility of this reaction to epoxidise unfunctionalised double bonds has not yet been fully explored. He did, however, apply this important methodology to the synthesis of the side-arm of Taxol.[73]



Scheme 1.18

1.2.10 Epoxide Opening

Selective opening of epoxides are potentially useful methods for the synthesis of optically active compounds. Reaction 1 (Scheme 1.19) shows a review of the Lewis acid complexes of C_2-symmetric diols which have been used. The nucleophiles reported thus far are thiols, chloride ion and azide ions, and the results obtained with these ranged from poor to excellent depending on the auxiliary and Lewis acid.[74-77]

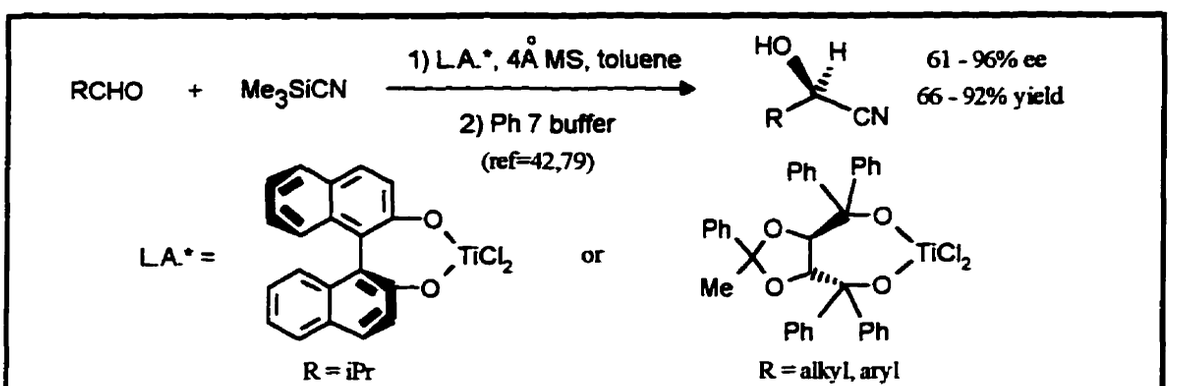


Scheme 1.19

In addition to the reactions reported in reaction 1 (Scheme 1.19), Nause *et al.* reported a kinetic resolution (reaction 2) by selective epoxide opening of a racemic epoxy ketone. This methodology was then applied to the synthesis of Juvenile hormone.[74]

1.2.11 Hydrocyanation Reaction

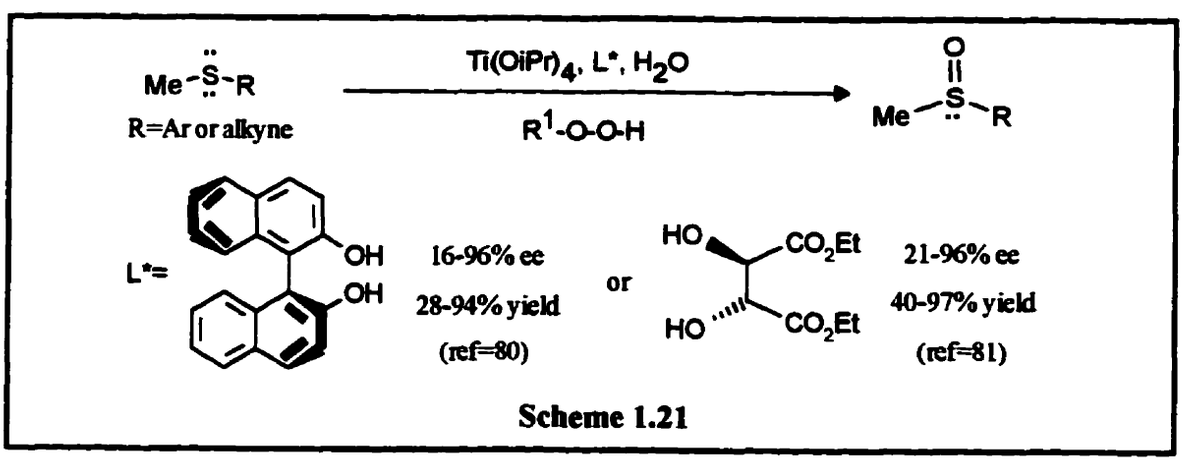
Recently a review entitled "Catalytic Asymmetric Cyanohydrin Synthesis" was published by North.[78] The only examples which used a C_2-symmetric diol were with a titanium binaphtholate complex[42] and a titanium TADDOLate complex[79] (Scheme 1.20). The results obtained ranged from good to excellent for both the yield and ee's.



Scheme 1.20

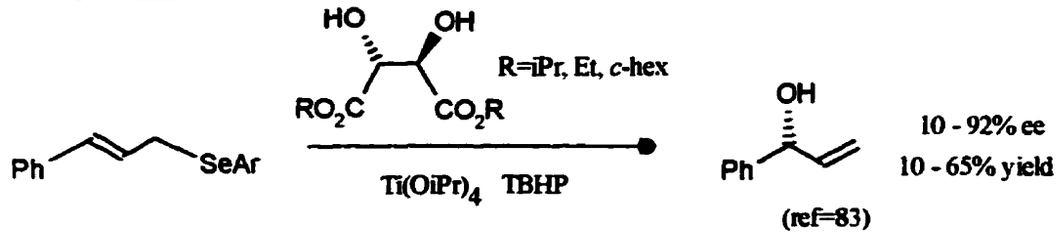
1.2.12 Oxidation of Sulfides and Selenides to Sulfoxides and Selenoxides

Since a sulfur and selenium atom can form hypervalent oxide species, which have a high barrier to inversion, reactions have been developed to enable chemists to form chiral sulfoxides and selenoxides. For the case of sulfur, the sulfoxides can be produced enantioselectively using a chiral diol and an oxidising agent (Scheme 1.21).[80,81] Both Komatsu *et al.*[80b] and Zhao *et al.*[81] found that the amount of water added significantly affected the enantiomeric excess observed.



Scheme 1.21

The group of Choudary[82] has used titanium catalysts on montmorillonite clays with chiral auxiliaries in the presence of a stoichiometric amount of TBHP to asymmetrically oxidize sulfides. Choudary *et al.* tried a variety of thioethers, montmorillonite clays and chiral auxiliaries (TADDOL, diethyl tartrate, diisopropyl tartrate). Enantiomeric excesses ranged from 9 to 92% and yields from 5 to 92%.[82]



Scheme 1.22

As with sulfur, selenium can also be asymmetrically oxidized. Uemara's group oxidised an allyl aryl selenides atom to selenoxides, which immediately underwent a [2,3]-sigmatropic rearrangement to produce chiral allylic alcohols (Scheme 1.22) in moderate yield with poor to excellent ee.[83] Uemara *et al.* also tried (+)-(*R*)-BINOL, but found the results were inferior to those obtained with dialkyl tartrates.

1.2.13 Reduction of Ketones

The application of aluminium binaphtholate (**71**) as a chiral auxiliary to induce asymmetry in the reduction of ketones was studied over a decade ago (Scheme 1.23, Figure 1.6 and Table 1.6).[84] Recently, new aluminium complexes of C_2-symmetric biaryl diols (**72**[85] and **73**[86]) have also been used in the enantioselective reductions of ketones with excellent results.[87]

After the outset of the project covered in chapter 2 of this dissertation, the use of the aluminium complex of *cis,cis*-spiro[4.4]nonane-1,6-diol (**74**) in the asymmetric reduction of ketones was reported with good yields and excellent enantiomeric excesses.[88] Interestingly, attempts by both our and Seebach's[89] laboratory to repeat the results with **74** were unsuccessful.

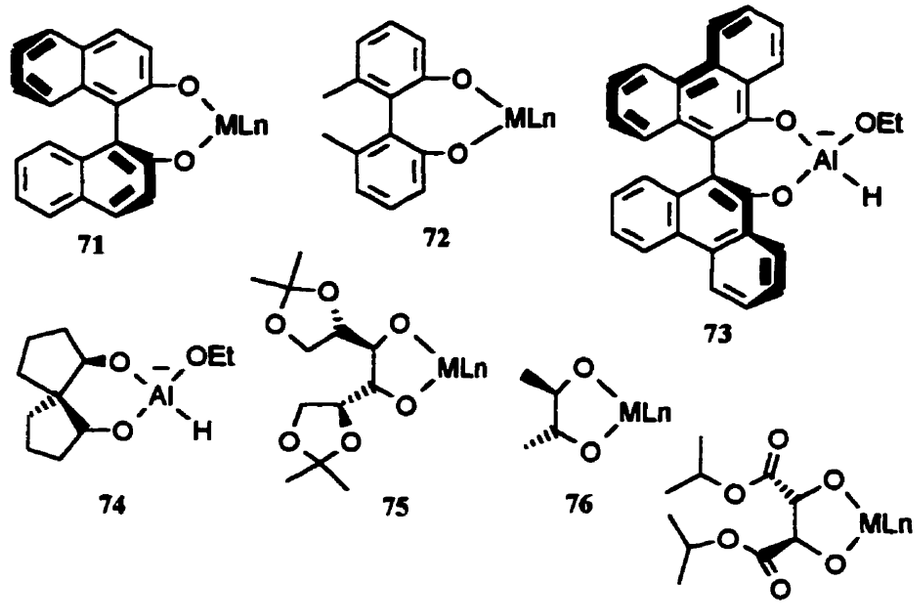
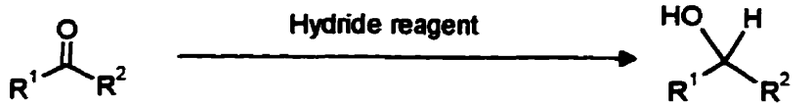


Figure 1.6 Ligands Used for the Asymmetric Reduction of Ketones (Scheme 1.23, Table 1.6) 77



Scheme 1.23

Table 1.6 Results for Hydride Reductions (Scheme 1.23) of Ketones with Auxiliaries Shown in Figure 1.6

Hydride reagent	M	Ln	R^1	R^2	yield (%)	ee (%)	Ref
71	Al	OR,H	conj. unsat.	alkyl	47-92	14-100	84
72	Al	OR,H	Ph	alkyl	12-77	21-98	85
73	-	-	Bn,Ph,iBu	D,Me,Et,Bn	73-78	21-98	86
74	-	-	Ph	alkyl	62-80	70-98	88
72	B	amine,H	Ph	alkyl	39-98	0-84	90
75,76	B	thexyl,H	Ar, alkyl	alkyl	70-98	0-74	91
71,75,77	La,Eu,Er, Yb	OiPr	Pr,Ph,*t*-Bu	Me	<65	3-32	92

A few examples of enantioselective ketone reductions using boron coordinated reducing agents were published in the literature in the 1980's. These results, published separately by Suda[90] and Brown,[91] gave moderate to excellent yields and 0 - 84% ee's.

Huskens *et al.* published examples of asymmetric lanthanide(III) -alkoxide-catalysed Meerwin-Ponndorf-Verley reductions.[92] Although interesting, the poor ee's mean that the technique will be of limited utility.

1.2.14 Summary

Overall, chiral C_2-symmetrical diols have been used successfully to induce asymmetry as Lewis acid bound auxiliaries in a wide range of reaction types. The majority of the work, and typically the better results reported, usually utilise complexes derived from BINOL (**5**), dialkyl tartrate (**2**) and/or TADDOL (**3**). For further information on uses of other chiral auxiliaries, the reader is directed to two recently published books by Seyden-Penne[93], and Santelli and Pons[94] and a review by Whitesell.[95]

1.3 Substrate Bound Auxiliaries

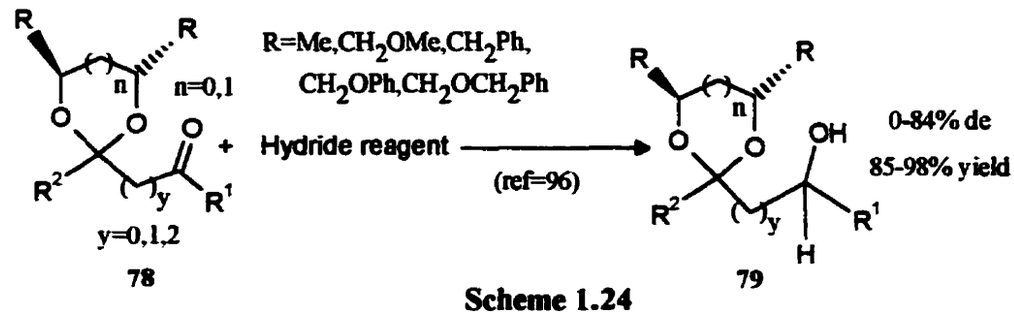
1.3.1 Introduction

The influence of an existing chiral centre(s) in a molecule on the stereochemical outcome of newly forming stereogenic centre(s) is one of the most widely used methods for building up organic molecules. These 'existing chiral centre(s)' can be of a permanent or temporary nature. A centre(s) that is of a permanent nature remains in the various products of a synthetic sequence. A centre(s) that is of a temporary nature either is primarily present for induction of chirality and then removed prior to preparation of the target molecule (substrate bound chiral auxiliary) or initially incorporated, but later the original stereogenic centre is altered or destroyed.

Numerous molecules have been tested as substrate bound chiral auxiliaries,[93] but this section will focus on the utilisation of C_2-symmetric diols. There are two ways that these C_2-symmetric substrate bound diol auxiliaries have been used in the literature. Firstly, to form diastereomers as a tool for determining the ee, *via* the de, of the product after an enantioselective reaction, and second, to transfer chirality by creating diastereomeric

transition states that influence the stereochemical outcome of a reaction. Since this chapter focuses on the induction of chirality, this section will review the transfer or induction of chirality, using C_2-symmetric diol substrate bound auxiliaries. To save space, the C_2-symmetric diol will not be drawn separately, but will be shown already attached to the substrate.

1.3.2 Addition of Hydride to Ketones



Scheme 1.24

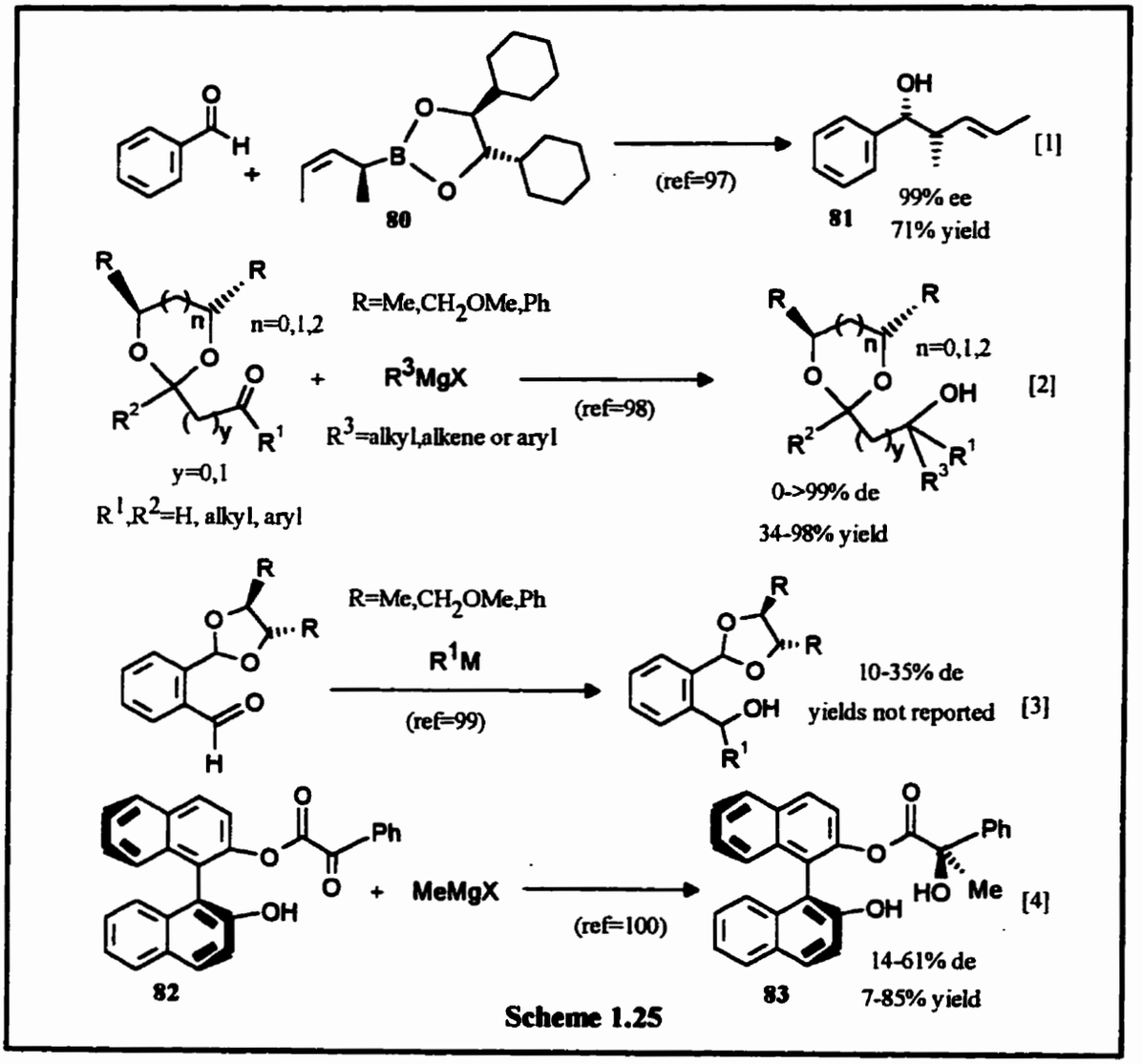
The addition of hydride reagents to carbonyl compounds containing chiral acetals or ketals **78** is a method that has been studied to stereoselectively form a new stereogenic centre. The de's obtained with alcohol **79** ranged from 0 to 84% with excellent yields.[96]

1.3.3 Addition of Organometallics to Aldehydes and Ketones

Hoffmann *et al.* used chiral *Z*-pentenylborates **80** (Scheme 1.25, reaction 1) to form homoallylic alcohol **81** in good yield with an excellent ee.[97] This methodology was then applied to the synthesis of invictolide and a partial structure (C-9 / C-15) of erythronolide A.[97]

Addition of organometallics to ketones or aldehydes containing chiral acetals or ketals (reaction 2 and 3, Scheme 1.25) resulted in alcohols with de's ranging from 0 to greater than 99%.[98,99] One outstanding example in reaction 2 (Scheme 1.25; y, n=0; R=CH_2OMe; R^1=Me; R^2=Ph; R^3=Et; X=Cl) was reported by Tamura *et al.*[98a] where a 98% yield of the product was obtained with greater than 99% de.

Fuji *et al.*[100] found that the addition of methylmagnesium bromide to mono-benzoylformate esters of BINOL **82** produced hydroxy esters **83** with poor to mediocre de's and in varying yields (reaction 4, Scheme 1.25).

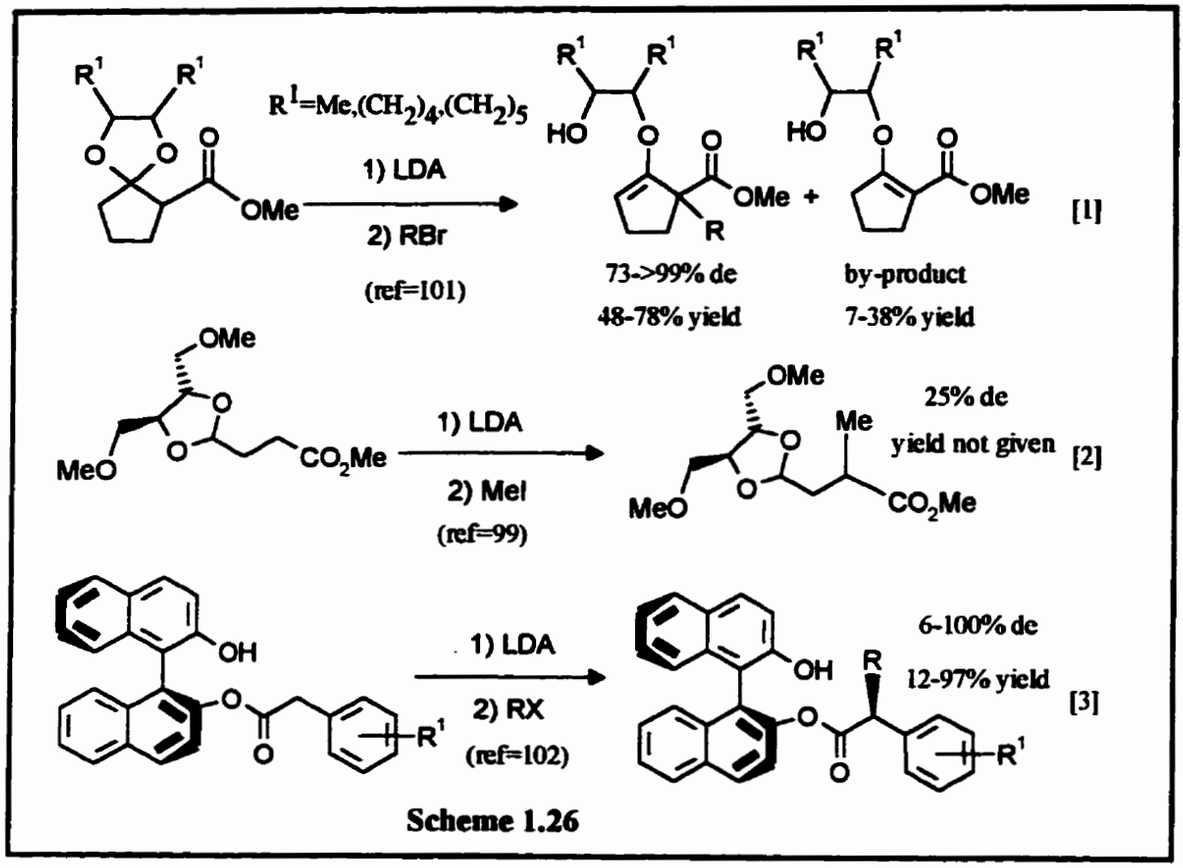


Scheme 1.25

1.3.4 Alkylation of Esters

There are only a few examples where C_2-symmetric diols have been used to induce asymmetry in the alkylation of esters (Scheme 1.26). C_2-symmetric diols were used as chiral auxiliaries by forming a ketal, acetal or being attached to the ester component of a carboxylic acid group (see reactions 1[101], 2[99] and 3[102] respectively, Scheme 1.26). The

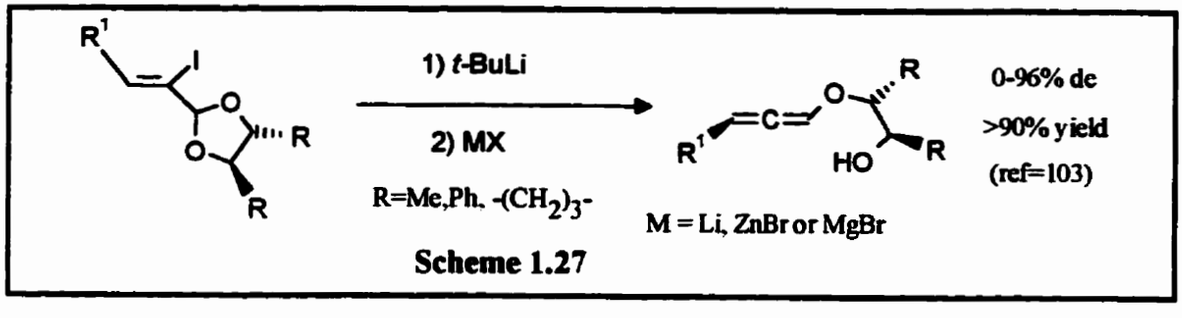
de's were poor to excellent, with one of the best examples for reaction 3 with (X=*p*-OMe,R=iBu) providing an 84% yield of alkylated product with a 100% de.[102]



Scheme 1.26

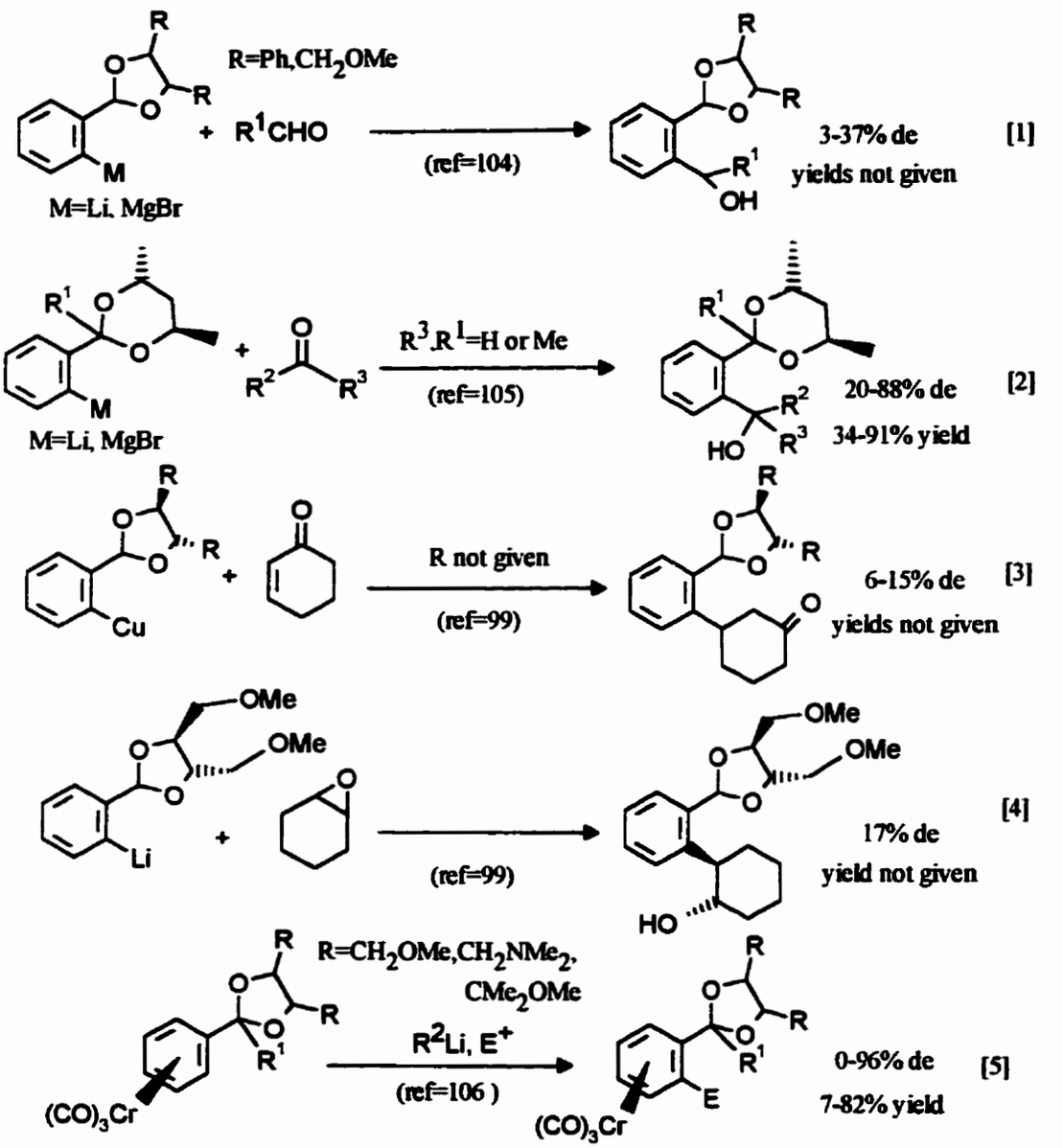
1.3.5 Allene Formation by Acetal Opening

The opening of chiral iodoene-acetals to allenes by the group of Alexakis is shown in Scheme 1.27.[103] The yields for the allene obtained were excellent, but the de ranged from 0 to 96% depending on the metal (M) and the solvent used. The best result (96% de) was obtained with M=Li and ether as the solvent.



Scheme 1.27

1.3.6 Aryl Alkylation

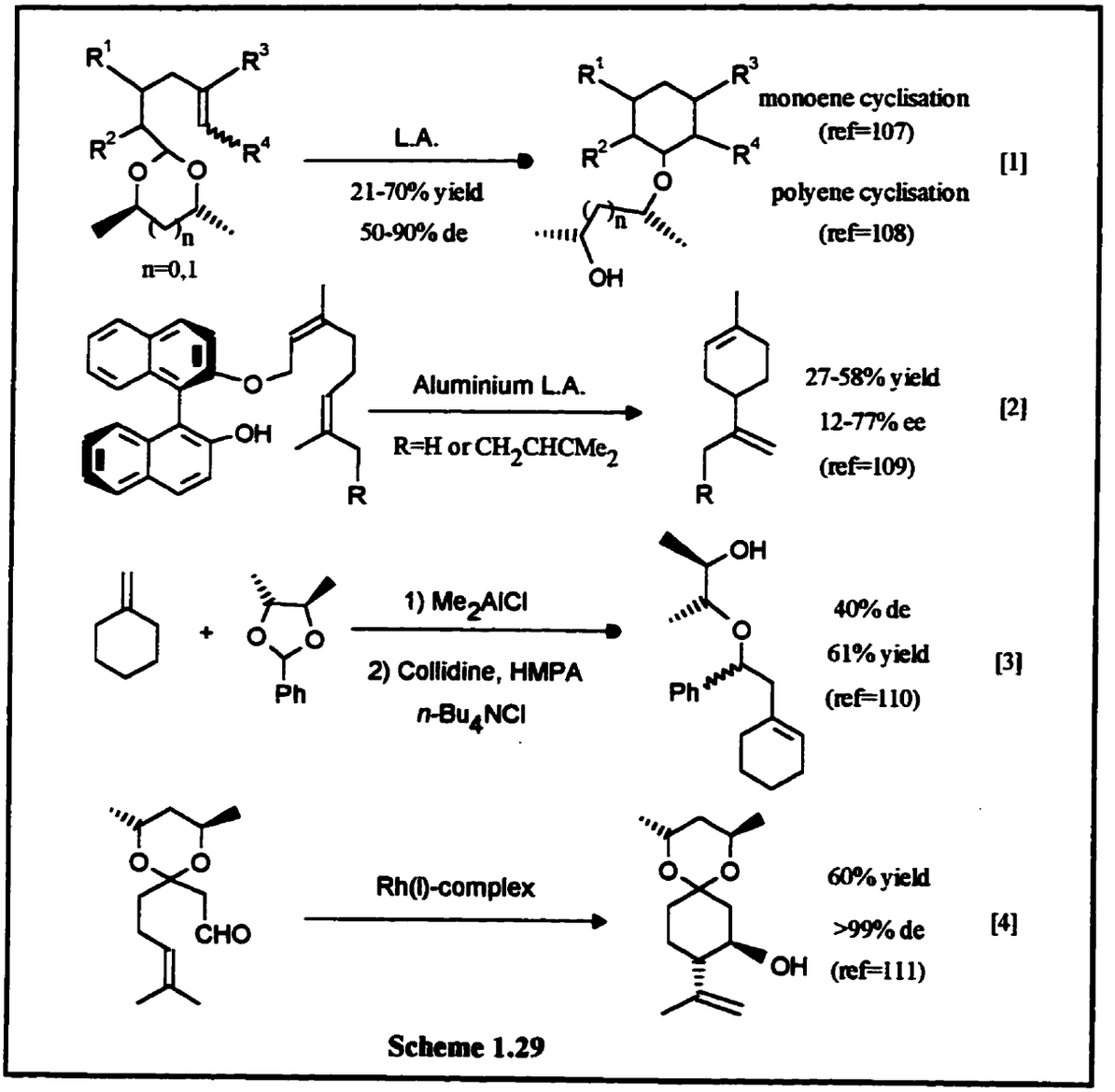


Scheme 1.28

The implementation of chiral acetals or ketals for the alkylation of aryl anions are shown in Scheme 1.28.[99,104-106] The results obtained for reactions 1-4 are reasonable at best.[99,104,105] These reactions also involved the use of aryl bromide starting materials which are expensive, and therefore less desirable.

Better results were obtained by directed metalation of chromium tricarbonyl complexes (reaction 5, in Scheme 1.28).[106] The results (de and yield) obtained when deprotonation was used ranged from poor to excellent depending on the base (R^2Li) and on the electrophile (E^+) used.

1.3.7 Biomimetic Ene, Polyene and Similar Cyclisations



Scheme 1.29

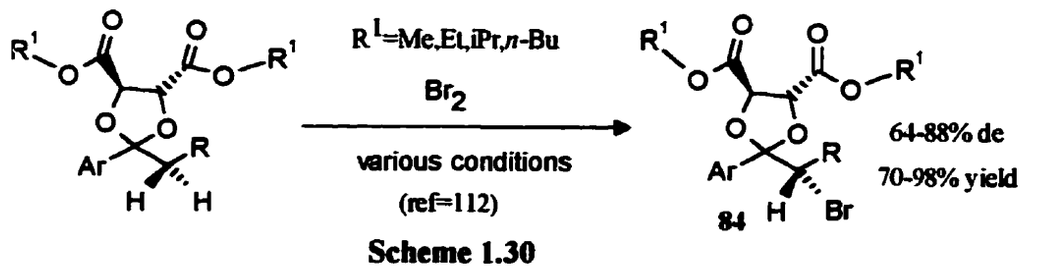
Reaction 1 in Scheme 1.29 shows a biomimetic ene-cyclisation[107] using a chiral acetal in the presence of a Lewis acid. If R^4 is a homoallylic moiety, the substrate is set up

for a polyene-cyclisation.[108] In this way, molecules containing ring systems with frameworks from a decalin to steroid have been synthesised. For the cyclisations in reaction 1, the de's are good to excellent with reasonable yields.

A similar cyclisation, which used BINOL (reaction 2, Scheme 1.29),[109] resulted in a range from mediocre to good for the ee's and the yields for the product. Snider and Burbaum[110] reported an intermolecular variant of the biomimetic ene-reaction (reaction 3). A 61% yield and 40% de was reported for the product.

Reaction 4 in Scheme 1.29 is an example of an carbonyl-ene cyclization. This transformation is similar to the chiral Lewis acid catalysed examples in section 1.2.8, but the chiral source, namely a ketal, is β to the aldehyde. Sakai's group[111] found that the cyclic product was obtain in 60% yield with >99% de.

1.3.8 Bromination and Amination Adjacent to Ketals

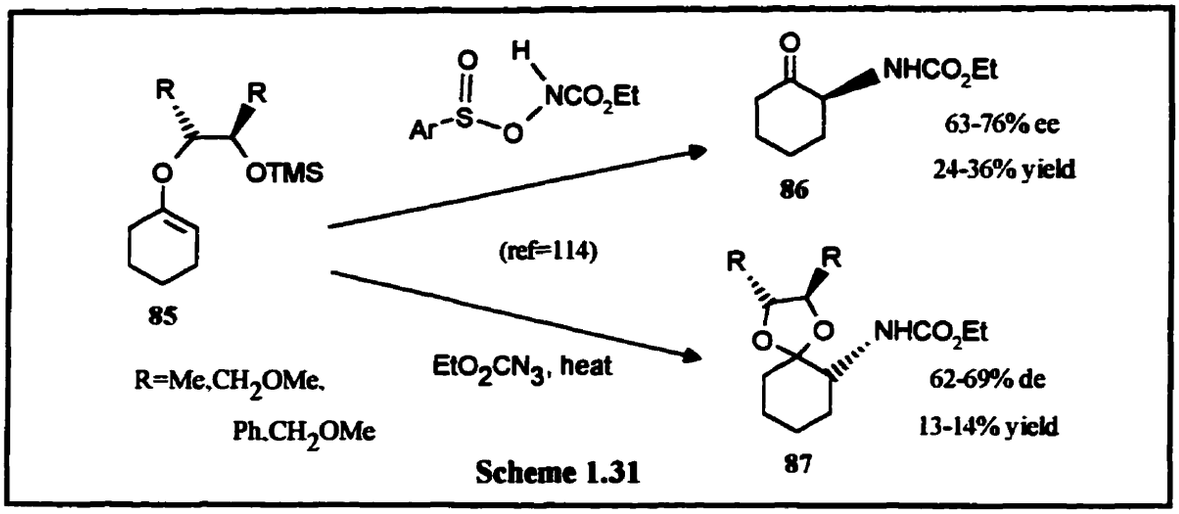


Scheme 1.30

Giordano's group has investigated the influence of chiral aryl ketals on the stereochemical outcome of an α-bromination (Scheme 1.30).[112] This was effectively an asymmetric α-bromination of aryl ketones. Later Giordano[113] reported using the bromoketal **84** (R^1 = H, Scheme 1.30) in a substitution reaction using the carboxyl groups present in the tartrate ester ketal.

Fioravanti *et al.* published an example of the formation of a C-N bond starting from vinyl ether **85** (Scheme 1.31).[114] Depending on the source of (ethoxycarbonyl)nitrene, the vinyl ether either formed chiral ketal **87** or was removed to form ketone **86**. Interestingly, the absolute configuration of the C-N bond was opposite in **86** and **87**. This meant that

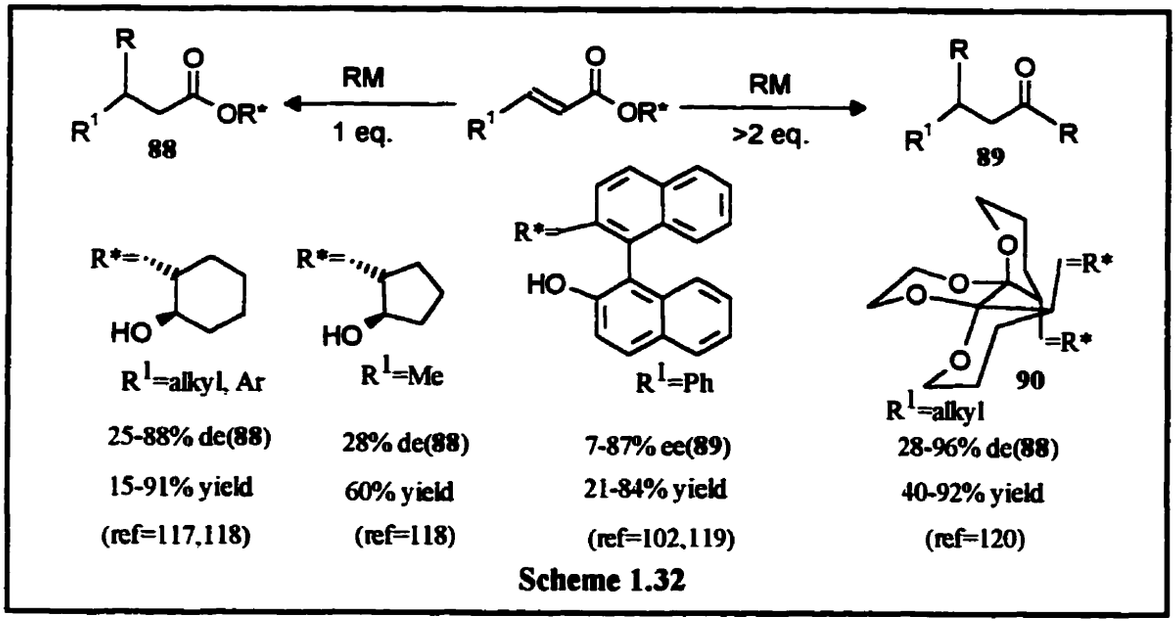
the same chiral auxiliary could be used to form either configuration. Although the de's and ee's were good, the yields were very low.



Scheme 1.31

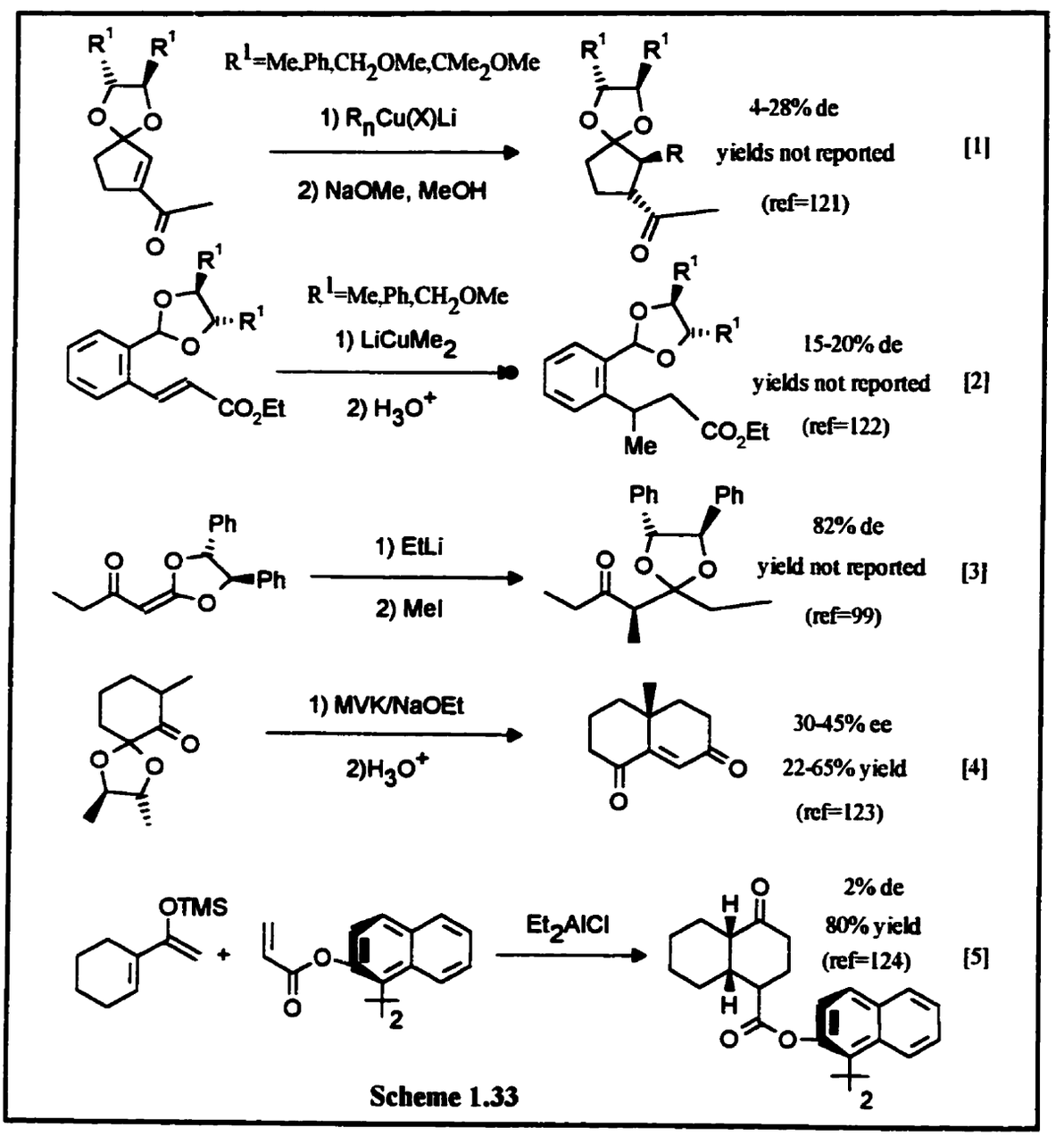
1.3.9 Conjugate Addition Reaction

Conjugate addition typically entails the 1,4-addition of nucleophiles to α,β-unsaturated aldehydes, ketones and esters. However, this section will also cover S_N2' addition of nucleophiles to conjugated acetals and ketals.[99] For more information, the reader is directed to two recent reviews on stereoselective conjugate addition,[21] S_N2' ring openings,[115] and a book by Gawley and Aubé.[116]



Scheme 1.32

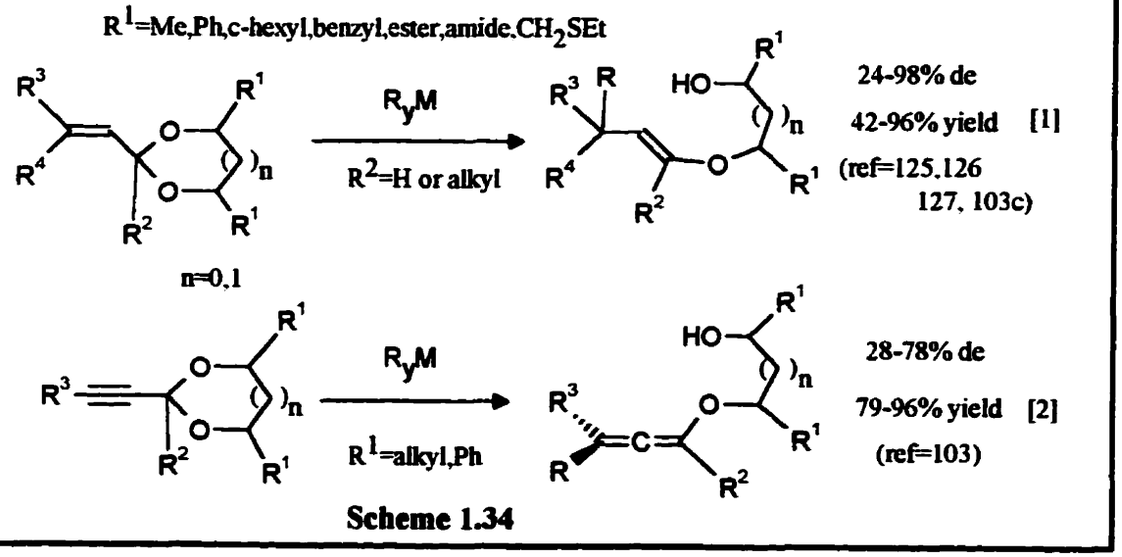
The Michael addition of organometallics to chiral ene-esters are shown in Scheme 1.32. In this reaction two products observed. 1,4-Addition provided ester **88**, but if 1,4-addition occurred followed by a 1,2-addition then ketone **89** was isolated. The diols can have one[102,117-119] or two (in the case of **90**)[120] ene-ester(s) attached during the 1,4-addition reaction. The results for these reactions ranged from poor to excellent. An especially



Scheme 1.33

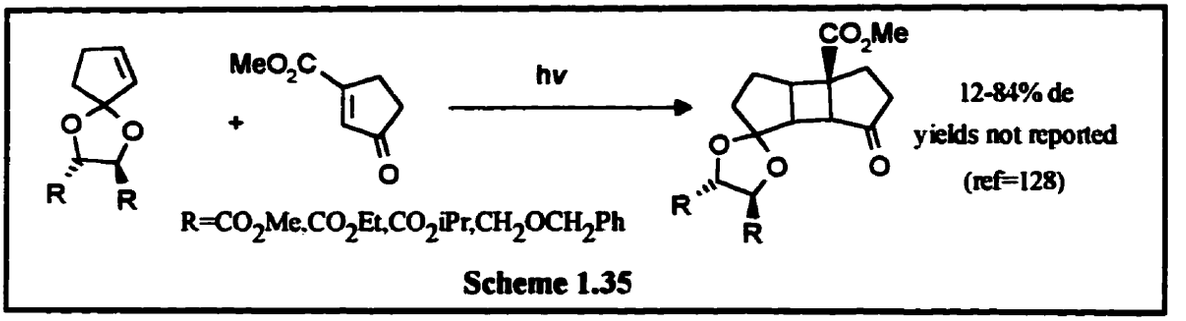
interesting example for this dissertation was spirodiketal **90**. This dispiro compound (published in 1994, Scheme 1.32) produced some products with excellent de's (up to 96%).

Reactions 1-4 in Scheme 1.33 use chiral acetals and ketals, in molecules which undergo an asymmetric conjugate addition, to influence the newly forming stereogenic centre(s). Reaction 5 uses a C_2-symmetric ene-diester BINOL. Reaction 1[121] and 2[122] are Michael additions while reactions 3, 4 and 5 (Scheme 1.33) illustrate a conjugate addition followed by an alkylation (reaction 3)[99], aldol condensation (reaction 4)[123] or second conjugate addition (reaction 5).[124] The examples in Scheme 1.33 (except for reaction 3) produced molecules with low de's or ee's.



Scheme 1.34

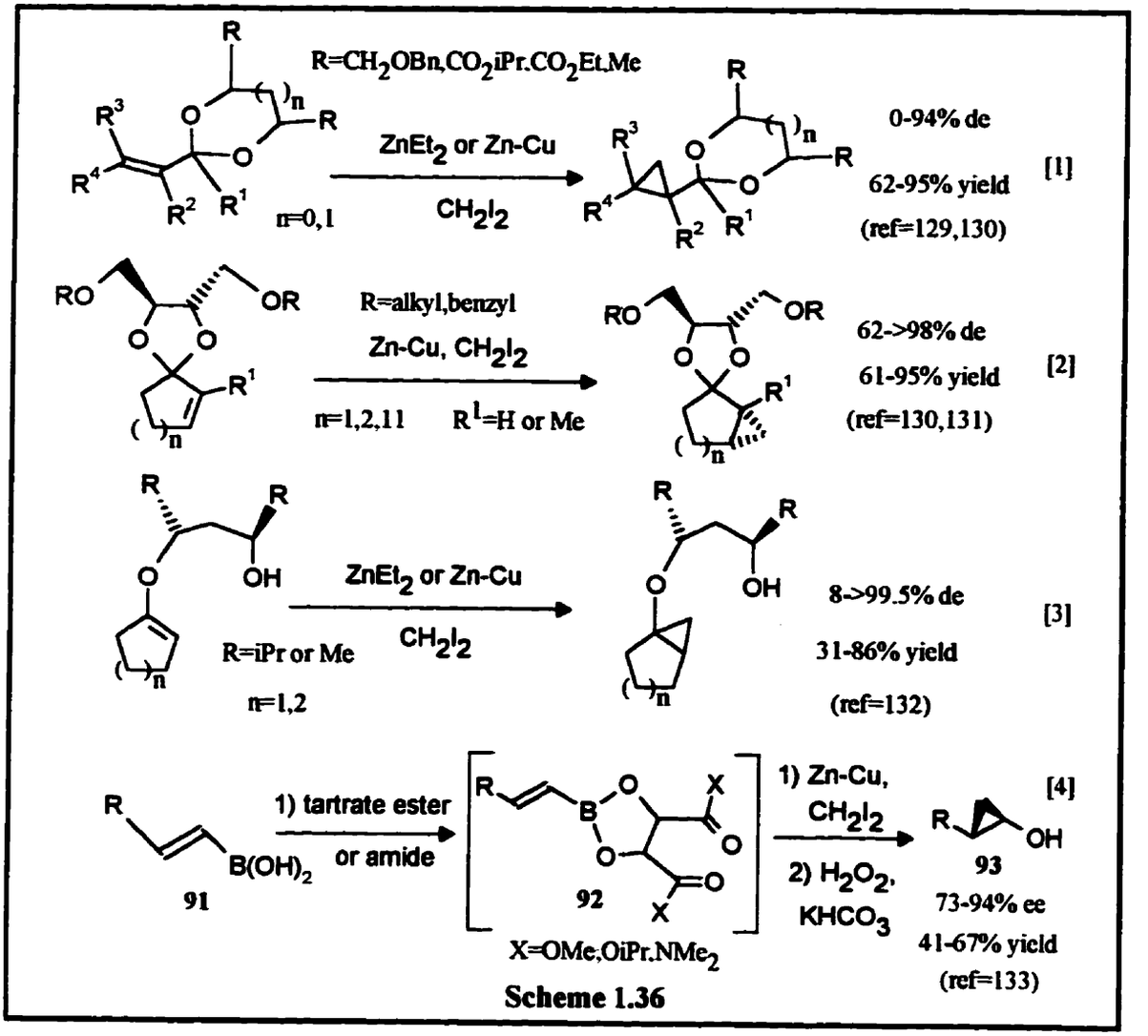
The vast majority of work in the area of S_N2' acetal or ketal ring opening reactions was reported by Alexakis' group.[99] Scheme 1.34 summarises the addition of nucleophiles to conjugated, both ene (reaction 1)[125,126,127,103c] and yne (reaction 2)[103] acetals and ketals. Both reactions 1 and 2 produced molecules with reasonable de's and yields.



Scheme 1.35

1.3.10 Cycloaddition [2+2] Reaction

Lange and Decicco[128] published an example of a cycloaddition reaction (Scheme 1.35) using a variety of chiral 1,2-diols to form ketal auxiliaries. The de of the resulting cyclobutanones ranged from poor to good, but the yields were not reported.

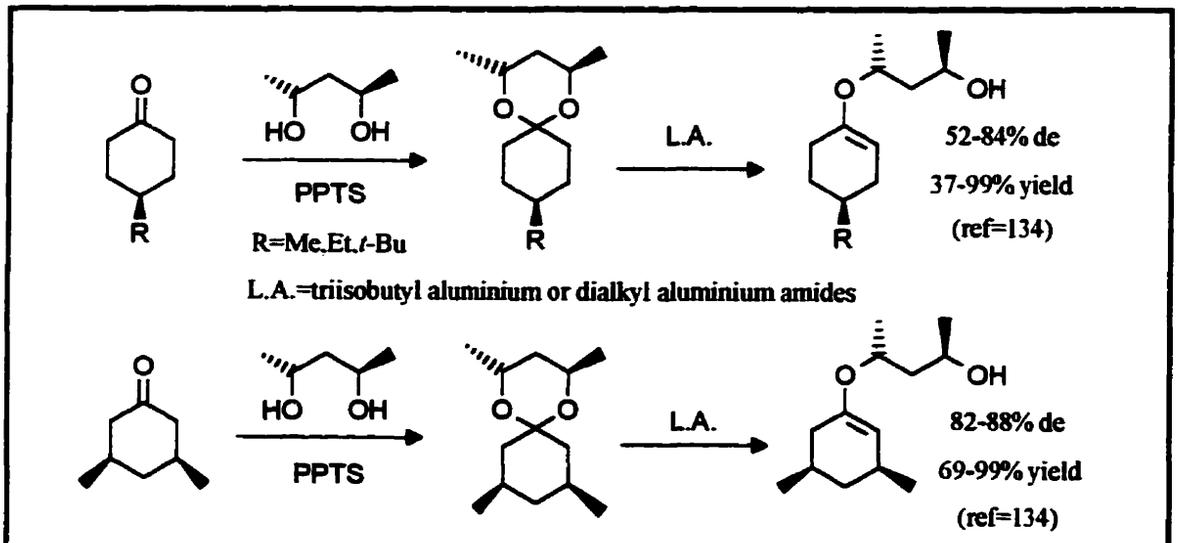


Scheme 1.36

1.3.11 Cyclopropanation Reaction

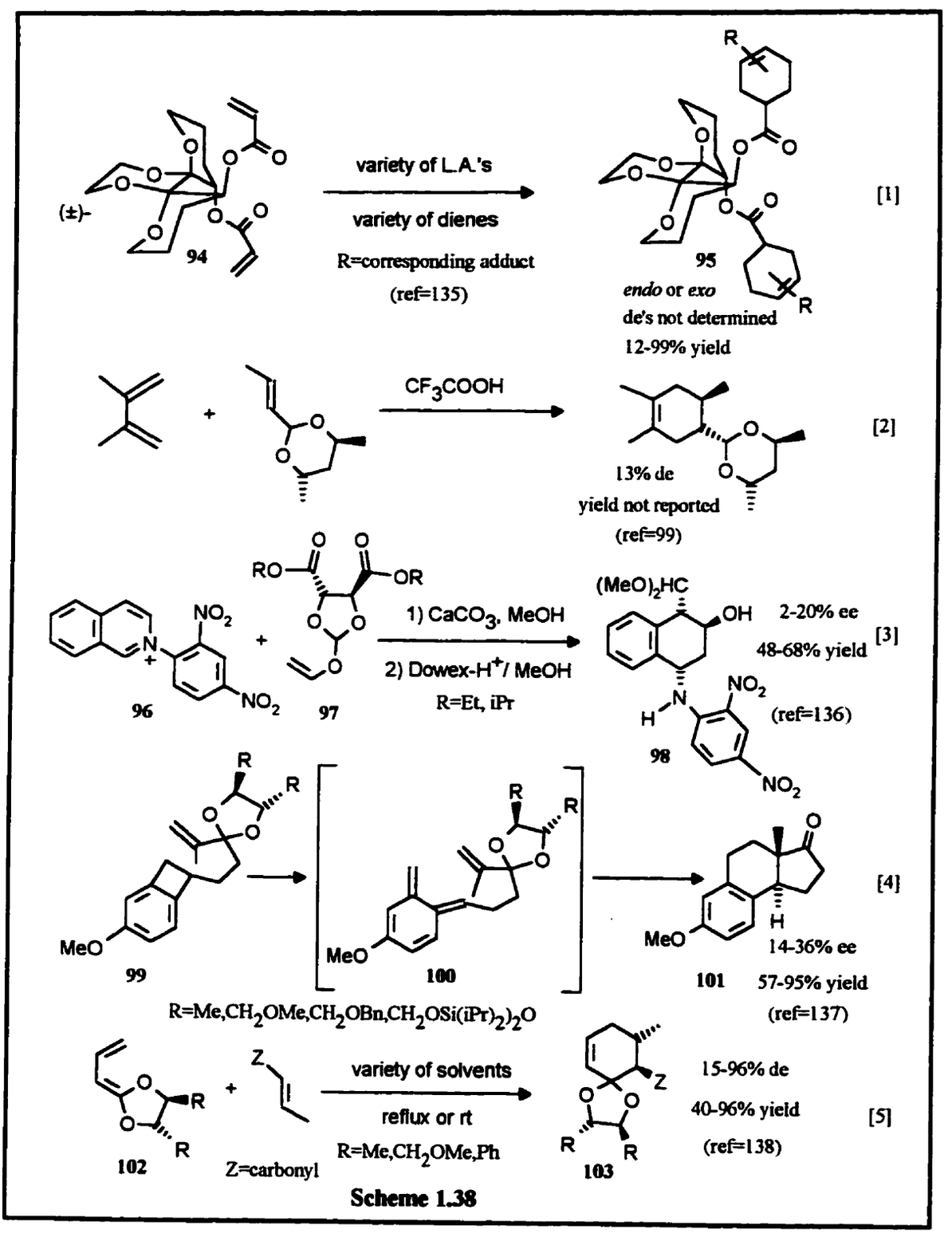
As previously mentioned in Section 1.2.9, asymmetric cyclopropanation is an important technique for synthesis of products containing chiral cyclopropyl moieties. The first two reactions in Scheme 1.36 utilised acetals and ketals to influence the stereochemical outcome of the cyclopropanation reaction.[129-131] Reaction 3 was unique since it used an opened ketal (done by aluminium Lewis acid) for the chiral induction in the cyclopropanation reaction.[132] In reaction 4 in (Scheme 1.36), Imai's group took alkenylboronic acid **91** and converted it into cyclopropyl alcohol **93** in good ee with reasonable yield.[133] Imai *et al.* postulated that boronic ester **92** was responsible for the observed induction.

1.3.12 Desymmetrisation Reaction



Scheme 1.37

Naruse and Yamamoto[134] have used C_2-symmetric diols as a tool for desymmetrisation. They took cyclic ketones and formed the ketals using (2*R*,4*R*)-2,4-pentanediol (Scheme 1.37). A variety of aluminium Lewis acids were tested in the asymmetric opening of the ketal. These openings resulted in good de's with reasonable to high yields.


(±)-
94
variety of L.A.'s
variety of dienes
R=corresponding adduct
(ref=135)
95
endo or exo
de's not determined
12-99% yield
[1]
CF3COOH
13% de
yield not reported
(ref=99)
[2]
96
97
1) CaCO3, MeOH
2) Dowex-H+/ MeOH
R=Et, iPr
(MeO)2HC
OH
2-20% ee
48-68% yield
(ref=136)
[3]
98
99
100
101
MeO
14-36% ee
57-95% yield
(ref=137)
[4]
R=Me,CH2OMe,CH2OBn,CH2OSi(iPr)2)2O
102
Z=carbonyl
variety of solvents
reflux or rt
R=Me,CH2OMe,Ph
103
15-96% de
40-96% yield
(ref=138)
[5]

Scheme 1.38

1.3.13 Diels-Alder Reaction

The first example (reaction 1) in Scheme 1.38 used (±)-spirodiketal **94**. The results published in 1994 by Ley[135] included the yield and *endo* : *exo* ratio, but did not include the de of the *endo* or *exo* isomers. The interesting point about this reaction was that two Diels-Alder reactions occurred on any one molecule of substrate producing diadduct **95**.

Alexakis and Mangeney[99] reported (reaction 2, Scheme 1.38) the addition of 2,3-dimethyl-1,3-butadiene to the acetal of acrolein and (2*S*,4*S*)-2,4-pentanediol in the presence of trifluoroacetic acid resulted in the formation of the corresponding Diels-Alder adduct in 13% de. They did not report the yield for the reaction.

The third reaction also incorporates a chiral diol as a formate ester in dienophile **97**. The reaction of **97** with **96** produced **98**, but the ee obtained was very poor with a only a mediocre yield.[136]

Nemoto *et al.*[137] reported that compound **99** (Scheme 1.38, reaction 4) reacted *via* an electrocyclic ring opening to produce *o*-quinodimethane **100**, which underwent an intramolecular Diels-Alder reaction to produce tricyclic adduct **101**. Although the yields were good to excellent, the ee's were modest.

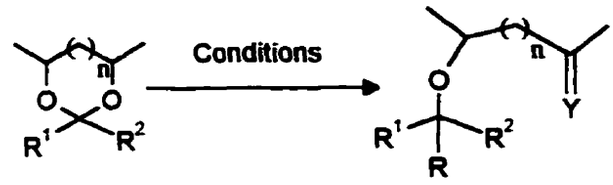
Reaction 4 in Scheme 1.38 was different than the previous three in that the diene **102** had the chiral auxiliary attached. In this case, the reaction with a variety of dienophiles produced adducts **103** in mediocre to excellent yields with poor to excellent de's.[138]

1.3.14 Nucleophilic Opening of Acetals and Ketals

Numerous examples are published in the literature on the opening of ketals or acetals under a variety of conditions (Scheme 1.39).[139-144] A summary of the results are listed in Table 1.7. Although a variety of groups have reported variations of the reaction, the results indicate that both the yields and de's typically range from poor to excellent.

One interesting example reported by Yamamoto's group[142] (Table 1.7) using conditions listed in entry 4 with aluminium Lewis acids resulted in a reduction of the carbon bearing the ketal while the hydroxyl group that results from the opening was

oxidised to a ketone. Yamamoto believed that the mechanism was *via* an intramolecular Meerwein-Pondorf-Verley reduction and Oppenauer oxidation cleavage reaction.



Conditions

1) R_ZCuLi_{1-Z}
2) RMgX, R_2Zn, RLi and L.A.
3) $RSiMe_3$ and L.A.
4) $Me_{3-Z}Al(OC_6F_5)_Z$
5) L.A. and Et_3SiH
6) variety of aluminium hydrides

Scheme 1.39

Table 1.7 Summary of Nucleophilic Substitutions of Acetals and Ketals (Scheme 1.39)

Cond.	R	R^1	R^2	n	Y	% yield	% de	Ref
1	alkyl,Ph	alkyl,Ph	H	0,1	H,OH	48-96	67-100	139
2	alkyl,allyl	Ar,alkyl	H,Me	1	H,OH	15-97	20-96	140
3	variety	alkyl, Ar	H	0,1	H,OH	75-100	39->98	141
4	H	alkyl,Ph	Me,Et	1	O	23->99	46-98	142
5	H	alkyl,Ph	Me	1	H,OH	24-97	30-96	143
6	H,D	alkyl,Ph, yne	Me,*n*-Pr	1	H,OH	58-99	33-99	143, 144

1.3.15 Summary

The results illustrated in this review for substrate bound auxiliaries showed that C_2-symmetric diols provide good chiral induction in many types of reactions. The main way that these diols have been used was either as acetals or ketals; however, they were also tested in other ways (*e.g.* as ester substituents or enol ethers).

Most reactions have involved the use of tartrates, BINOL's and acyclic diols, but very few incorporate spirodiols. The two examples involving spiro systems were used in the Diels-Alder (Section 1.3.13) and conjugate addition (Section 1.3.9) reaction and were

both recently published (1994 and 1995). The next section describes the project goals focusing on the type of the chiral spirodiols we decided to use in synthetic transformations.

1.4 Project Goals

1.4.1 Introduction

In early 1992 we were interested in starting research on the use of chiral auxiliaries in asymmetric syntheses. A search of the literature indicated that one class of C_2-symmetric chiral auxiliaries had not been used in asymmetric transformations; these were spiro C_2-symmetric compounds (*i.e.* spirodiols, spirodiamines and spirodiphoshines). Since chiral amino and phosphino compounds could be generated from hydroxy groups,[9] this dissertation focused on the preparation and utilization of chiral spirodiols. This would allow an evaluation of their use as chiral auxiliaries (both substrate bound and metal or catalyst bound) and would later allow for the preparation of amino and phosphino derivatives. One can imagine numerous spirodiol systems that have C_2-symmetry. The next section focuses on the rationale behind why we chose the system we did.

1.4.2 Determination of an Appropriate Spirodiol System

Three criteria were important for the design of a suitable C_2-symmetric spirodiol: 1) the spiro ring size; 2) the regiomeric positioning of the alcohols on the spiro framework; and 3) the relative orientation of the alcohols to one another.

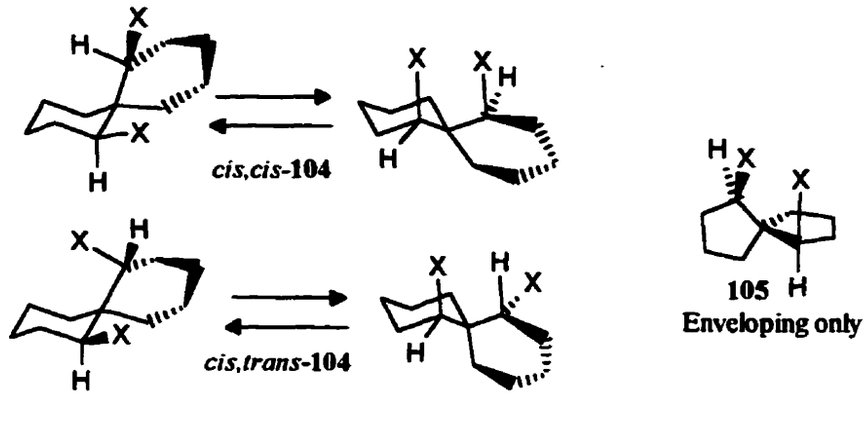
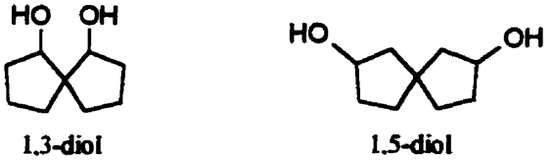


Figure 1.7 Ring Conformational Changes of Two Spiro Systems

The first criterion dealing with the size of the ring system concerns the ease of synthesis of the spirodiol as well as the problems with conformational changes of the ring system that might affect the ability of the diols to simultaneously complex or bond to another atom (e.g. C, Al, Ti). Cyclisation to 5 or 6-membered rings is more readily accomplished than other ring systems; therefore the most logical spiro systems to focus on were the spiro[5.5]undecane systems (**104**, Figure 1.7) and the spiro[4.4]nonane (**105**). Considering the conformational changes possible for these two systems, the spiro[5.5]undecane, which contains two 6-membered rings, can ring flip between chair and other conformations. This could potentially prevent the diols (if X=OH for **104** in Figure 1.7) from always being located close enough for bidentate complexation or bonding to occur. On the other hand, the 5-membered ring is more rigid (although enveloping can occur), and thus maintains a more constant association between the two diols (if X=OH for **105** in Figure 1.7). This means that the logical choice for the target spiro system was the spiro[4.4]nonane system.



1,3-diol 1,5-diol

Figure 1.8 Two Isomers of C_2-Symmetric Spiro[4.4]nonanediol

The second criterion mentioned is the regiomeric positioning of the alcohols on the spiro framework. Since the spiro[4.4]nonane diol system is the framework chosen, there are only two C_2-symmetric regiomeric placements (not including stereochemistry) for the two hydroxyl groups. These are the 1,3 and the 1,5-orientation as displayed in Figure 1.8. However, only the 1,3-diol relationship has the oxygen atoms close enough for bidentate complexation or acetal (ketal) formation to occur, and therefore it was the system selected.

With the selection of the 1,3 diol for the spiro[4.4]nonane system the only criterion remaining was to determine what was the best relative stereochemistry of the two alcohol

groups. Figure 1.9 displays three diastereomers possibilities for the placement of the hydroxyl groups. The *cis,trans*-diol **107** is not C_2-symmetric and the *trans,trans*-diol **108**, as can be seen by the edge on view (Figure 1.9), has the diols oriented in opposite directions. Only *cis,cis*-diol **106** is C_2-symmetric and contains the hydroxyl groups close enough to allow for bidentate complexation or acetal (ketal) formation. Thus, we embarked on the synthesis of *cis,cis*-**106** in order to study its effectiveness in a variety of asymmetric organic transformations.

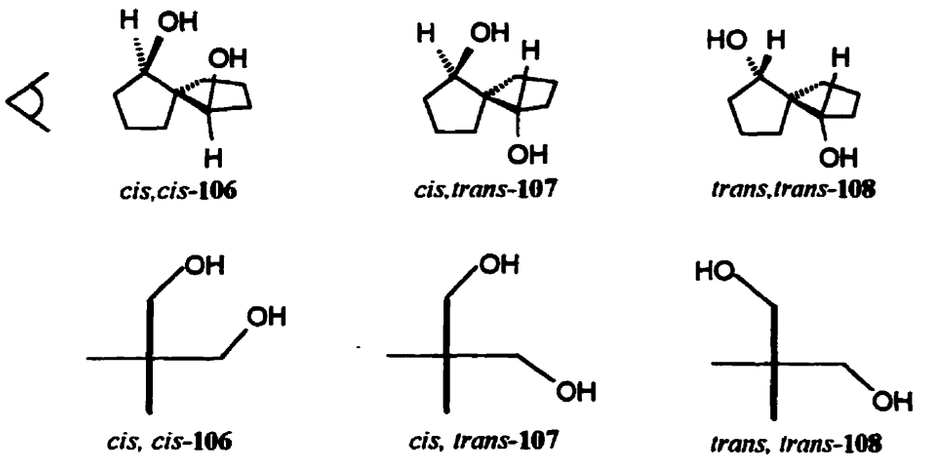


Figure 1.9 Various 1,3-Diol Orientations for Spiro[4.4]nonane-1,6-diols and Edge on View of Their Spatial Arrangements

1.4.3 Conclusion

The target C_2-symmetric spirodiol for synthesis and investigation as a chiral auxiliary, due to its favorable orientation of the hydroxyl groups and relative rigidity of the 5-membered ring system, was *cis,cis*-spiro[4.4]nonane-1,6-diol (**106**, Figure 1.9). The next chapter will illustrate previous syntheses and resolutions of **106**, followed by a better synthesis and new resolution of **106**.

Chapter 2

2 Synthesis and Resolution of (±)-*cis,cis*-Spiro[4.4]nonane-1,6-diol

2.1 Introduction

This chapter outlines the previous syntheses and resolutions of the spiro[4.4]nonane-diols **106-108**, and dione **113** (Section 2.2). Section 2.3 describes in detail an improved synthesis and resolution of (±)-*cis,cis*-spiro[4.4]nonane-1,6-diol (**106**).

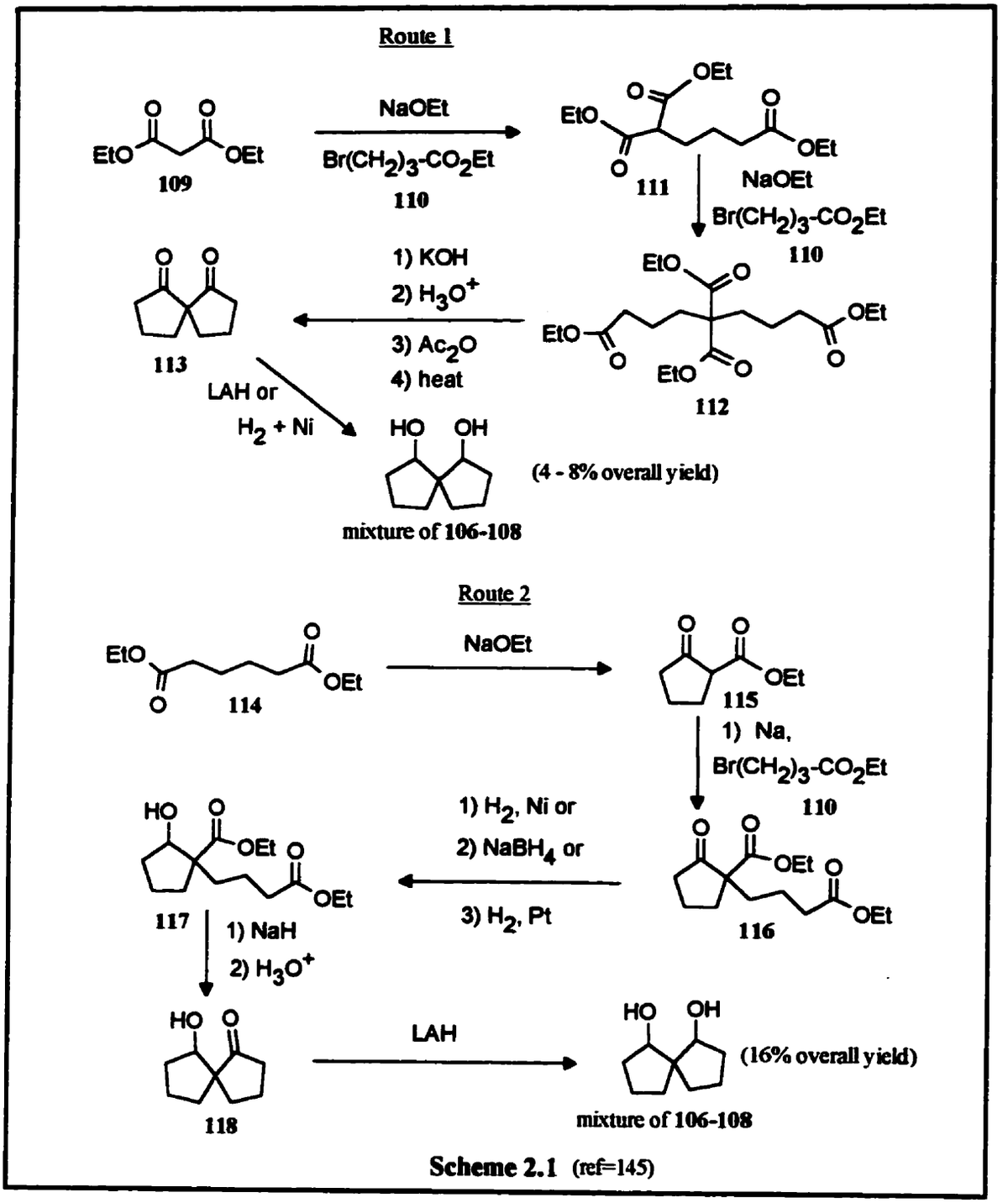
2.2 Previous Syntheses and Resolutions of Spiro[4.4]nonane-1,6-diols (106-108)

2.2.1 Syntheses of Spiro[4.4]nonane-1,6-diols (106-108)

The first reported synthesis of spiro[4.4]nonane-1,6-diols (**106-108**) was in 1954 by Cram and Steinberg.[145] They reported two routes (routes 1 and 2, Scheme 2.1) which both provided mixtures of (±)-spiro[4.4]nonane-1,6-diols **106-108**.

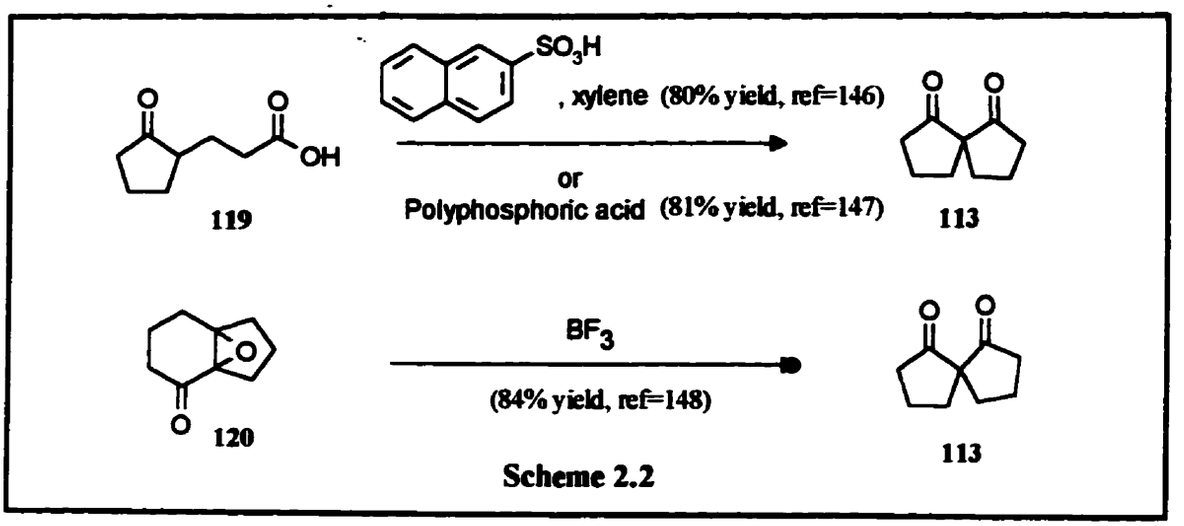
Route 1 started with successive alkylations of β-diester **109** with ethyl 4-bromobutanoate (**110**) producing after the first alkylation **111**, and **112** after the second alkylation. Double Dieckmann cyclisation of **112** produced spiro[4.4]nonan-1,6-dione (**113**). The reduction of dione **113** to a mixture of diols **106-108** was effected with either lithium aluminium hydride or catalytic hydrogenation. The overall yield of the mixture of diols **106-108** was 4 to 8% depending on the reduction method used in the last step. Cram and Steinberg found that these diols were not directly separable, but could be separated *via* their bis-*p*-nitrobenzoate derivatives by chromatographic and fractional crystallisation techniques, followed by the removal of the esters.[145]

Cram and Steinberg's second route started with the Dieckmann cyclisation of diester **114**, which formed β-ketoester **115**. Alkylation of **115** with bromoester **110** produced ketodiester **116**, which was subjected to a variety of reduction conditions, resulting in hydroxy diester **117**. A second Dieckmann cyclisation of **117** produced ketoalcohol **118**. Reduction of the ketone in **118** with lithium aluminium hydride produced a mixture of diols **106-108** in 16% overall yield.



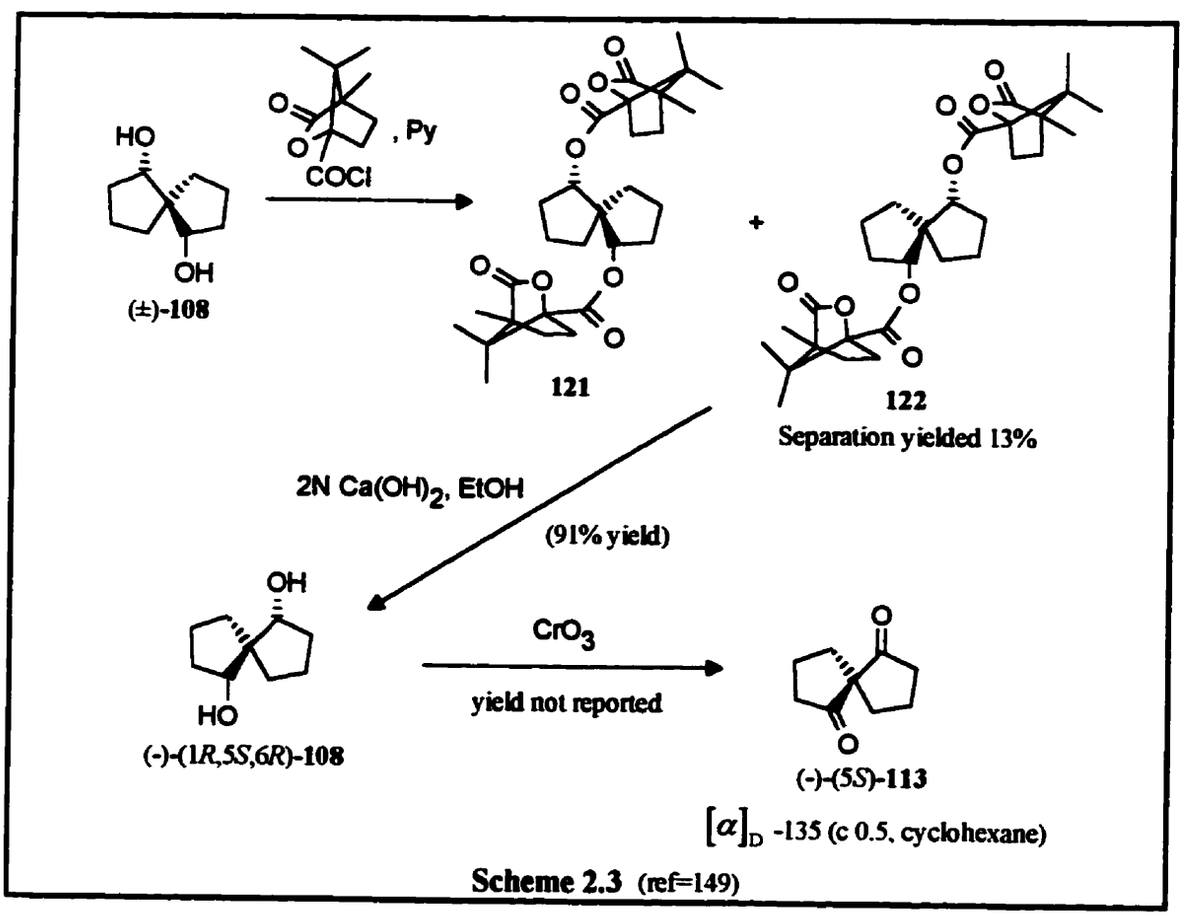
Scheme 2.1 (ref=145)

Other research groups have reported different cyclisation techniques for the production of (±)-spiro[4.4]nonane-1,6-dione (**113**, Scheme 2.2). Cyclisation of **119** by acid catalysis with removal of water (azeotropic distillation[146] or polyphosphoric acid[147])



Scheme 2.2

produced dione **113** in approximately 80% yield. Gerlach reported that the rearrangement of epoxyketone **120** by Lewis acid catalysis (BF_3) produced spirodione **113** in 84% yield.[148]

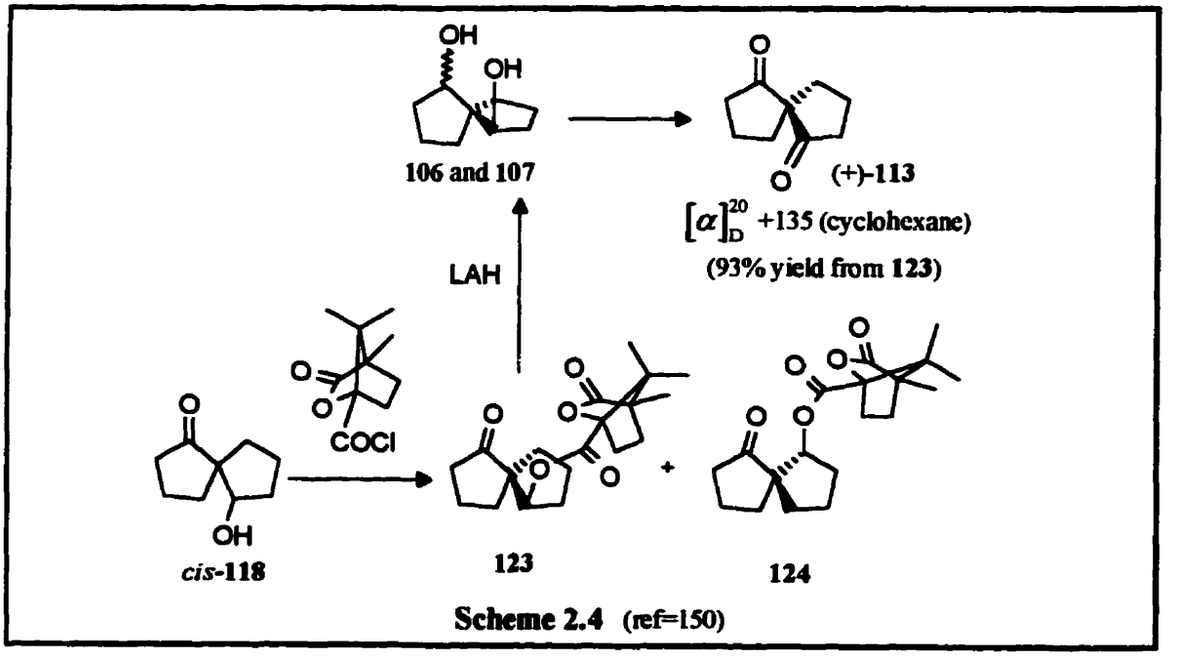


Scheme 2.3 (ref=149)

The above methods summarise the reported syntheses of (±)-spiro[4.4]nonane-1,6-diols **106-108** and dione **113** (Scheme 2.1, route 1). The next section describes the known resolution methods for diols **106-108** and dione **113**.

2.2.2 Resolution of the 1,6-Spiro[4.4]nonane System

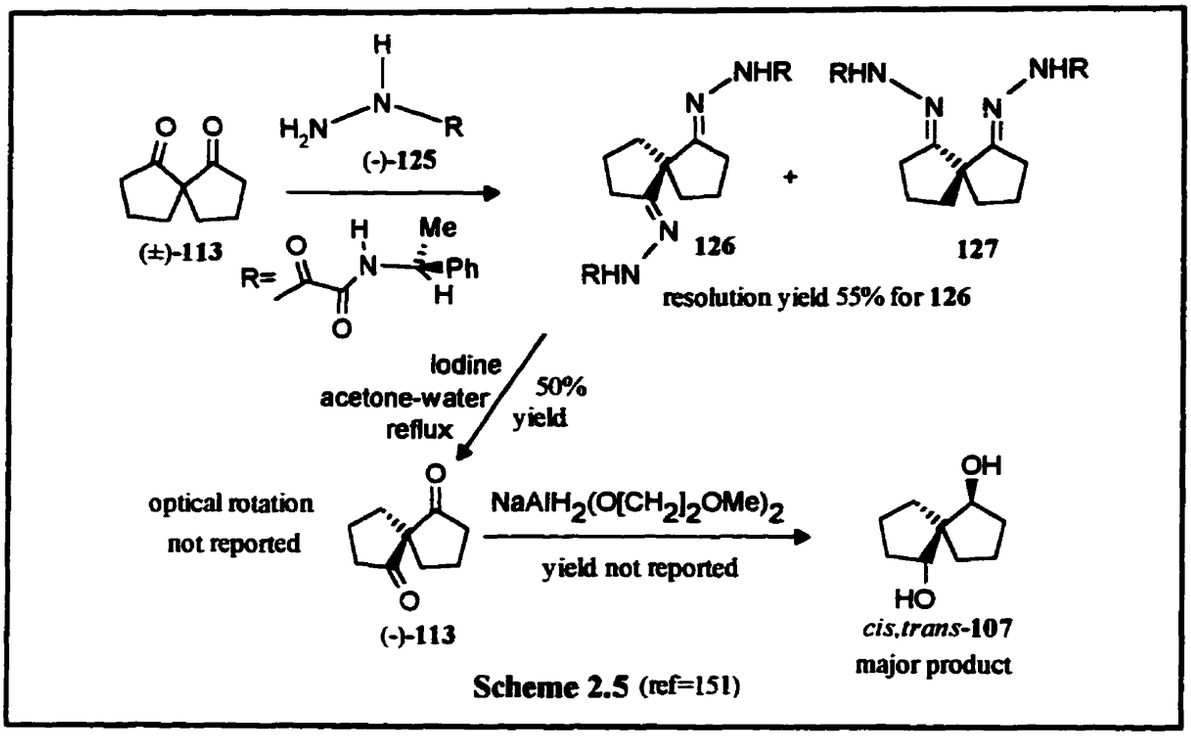
The first reported resolution of these spiro systems was by Gerlach[149] in 1968 (Scheme 2.3). The resolution sequence started with (±)-*trans,trans*-diol **108** which was synthesised according to Cram's method (Scheme 2.1). The formation of the bis-camphanoate ester of (±)-*trans,trans*-diol **108** in pyridine produced a diastereomeric mixture of **121** and **122**. Separation of the diastereomers by column chromatography produced **122** in 13% yield. Hydrolysis of **122** yielded (-)-(1*R*,5*S*,6*R*)-**108** (91% yield) which was oxidised to spirodione (-)-(5*S*)-**113**.



Scheme 2.4 (ref=150)

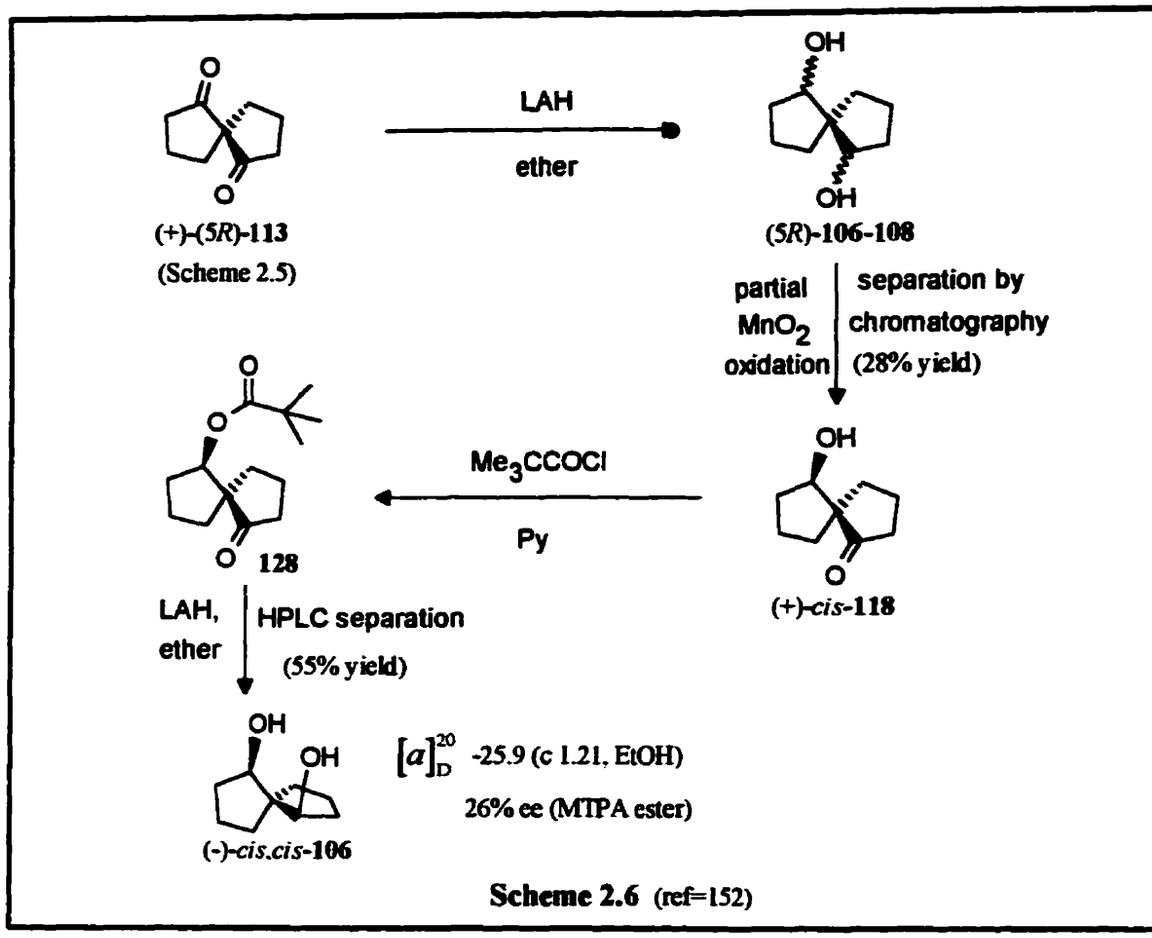
A similar method to that reported by Gerlach (Scheme 2.3), also using diastereomeric camphanoate esters, was reported by Shingu's group (Scheme 2.4).[150] It began with the acylation of keto-alcohol **118** with camphanoyl chloride producing a mixture of diastereomers **123** and **124**. The separation of **123** from diastereomer **124** was

accomplished by column chromatography followed by fractional recrystallisation. Resolved diastereomer **123** was treated with lithium aluminium hydride to remove the camphanoate ester providing a mixture of *cis,cis*-diol **106** and *cis,trans*-diol **107**. The mixture of diols was then oxidised by an unspecified method to (+)-dione **113**.



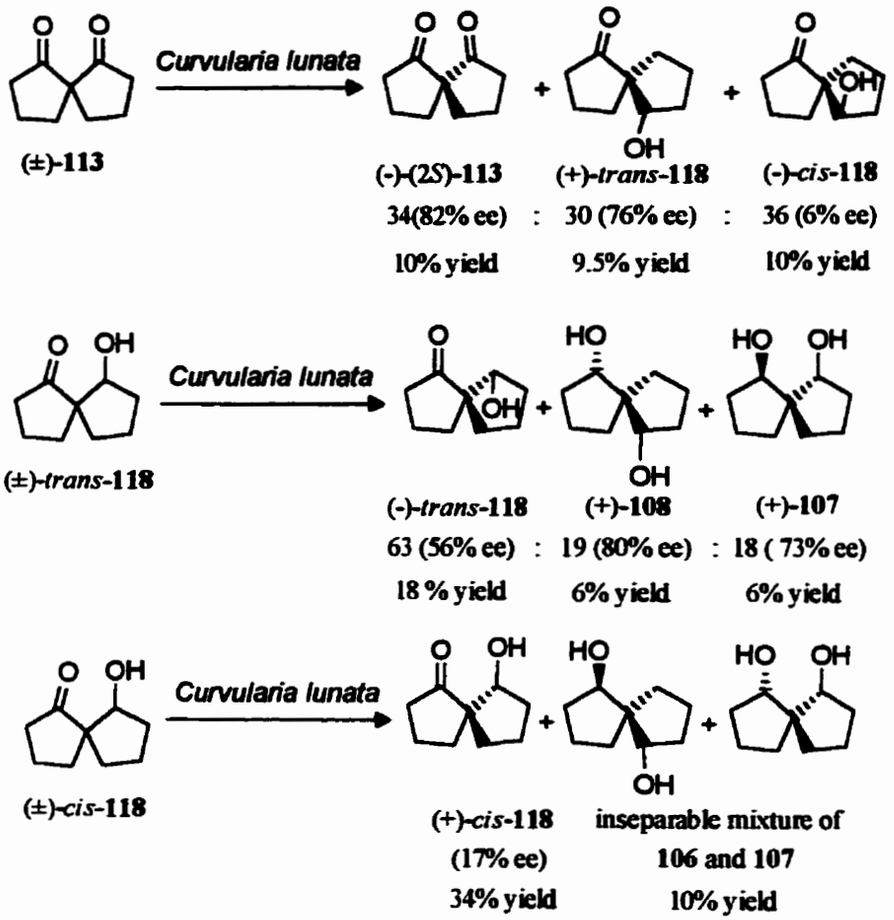
Scheme 2.5 (ref=151)

Harada *et al.* were interested in the preparation of *cis,trans*-diol **107** for circular dichroism studies.[151] They resolved dione **113** by adding oxamohydrazide (-)-**125** to form diastereomeric oxamoylhydrazones **126** and **127** (Scheme 2.5). "Two or three careful recrystallisations"[151] produced (-)-**126** with a yield of 55%. Hydrolysis was accomplished by refluxing **126** in acetone-water in the presence of iodine to give (-)-**113** in 50% yield. The reduction of (-)-**113** with $NaAlH_2(O[CH_2]_2OMe)_2$ (Red-Al®) yielded the *cis,trans*-diol **107** as the major product.

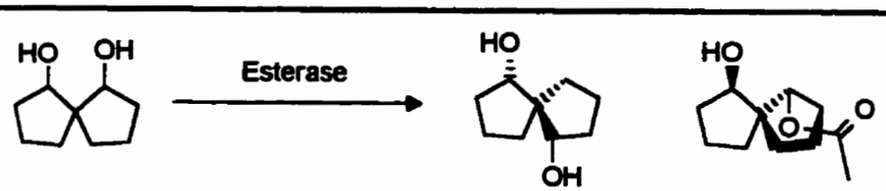


Scheme 2.6 (ref=152)

The group of Yamaguchi used the same method as Harada (Scheme 2.5) to resolve dione **113**, but then applied it to the only reported enantioenriched (scalemic) synthesis of *cis,cis*-diol **106** (Scheme 2.6).[152] This lengthy and inefficient synthesis of *cis,cis*-diol **106** (similar to a racemic one reported by Cram's group)[153] started with the nonselective reduction of (+)-(5*R*)-**113** to a mixture of (5*R*)-**106-108**. Partial oxidation of (5*R*)-**106-108** produced a mixture of (+)-*cis*-**118** and (+)-*trans*-**118**. Separation of the two isomers yielded (+)-*cis*-**118** in 28% yield and (+)-*trans*-**118** in 8% yield. Addition of pivaloyl chloride to (+)-*cis*-**118** in pyridine resulted in formation of ester **128**. Reduction of **128** with LAH resulted in (-)-*cis,cis*-diol **106** (55% yield) in 26% ee (determined by formation of the MTPA ester).



Scheme 2.7 (ref=154)

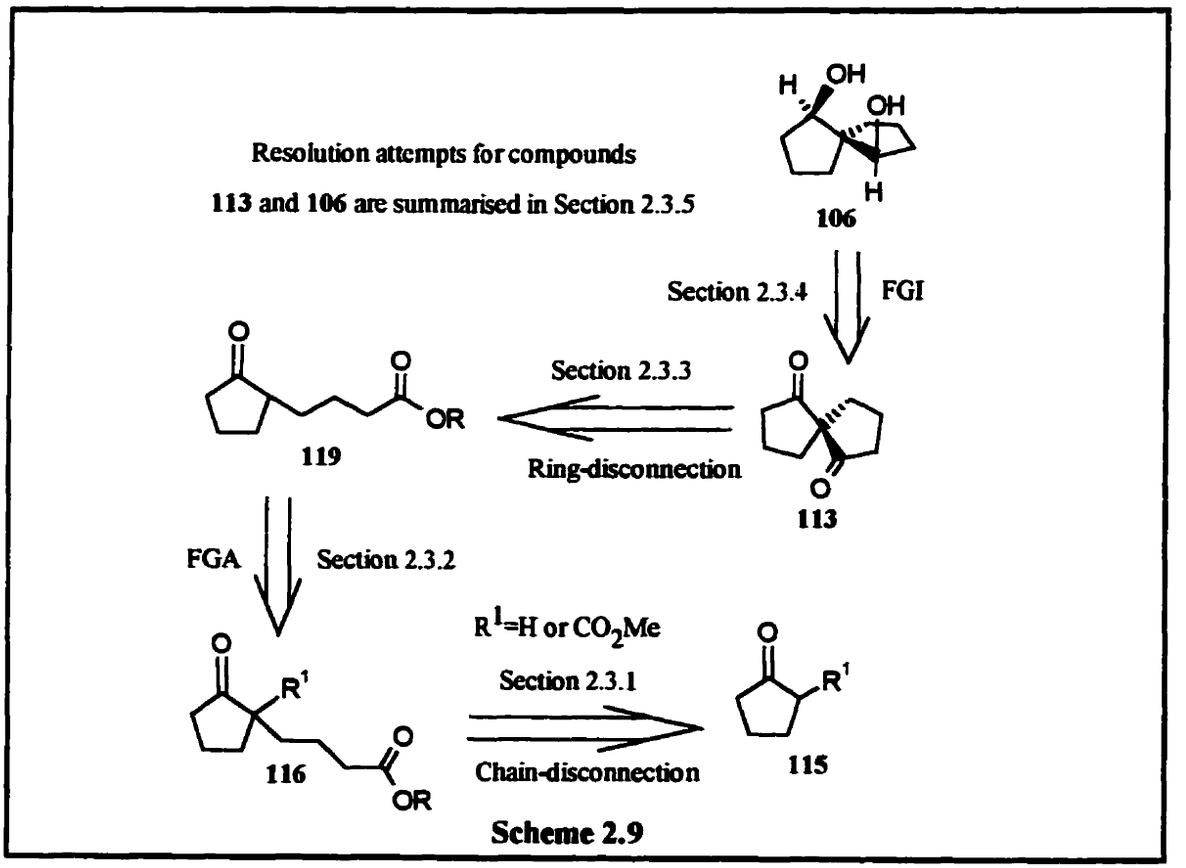


Esterase	(-)-108 Yield(% ee)	(-)-129 Yield(% ee)
Candida cylindracea	58% (31)	29% (38)
Lipase YS	40% (89)	41% (62)
porcine pancreas lipase	56% (70)	37% (83)

Scheme 2.8 (ref=155)

The two other techniques reported in the literature for the resolution of the spiro[4.4]nonane system used a kinetic resolution by microbial reduction and a lipase catalysed esterification. The microbial reduction of (±)-dione **113**, (±)-*trans*-hydroxy **118** and (±)-*cis*-hydroxy **118** by Nakazaki *et al.*[154] produced a mixture of products in low yield with mediocre to excellent ee's (Scheme 2.7). Naemura and Furutani[155] tried a variety of esterases for the kinetic resolution of (±)-*trans,trans*-diol **108** by selective acetylisation. Both unreacted (-)-*trans,trans*-diol **108** and monoacetylated **129** (Scheme 2.8) were produced with low yields and mediocre to good ee's.

2.3 Synthesis and Resolution of (±)-*cis,cis*-Spiro[4.4]nonane-1,6-diol



Scheme 2.9

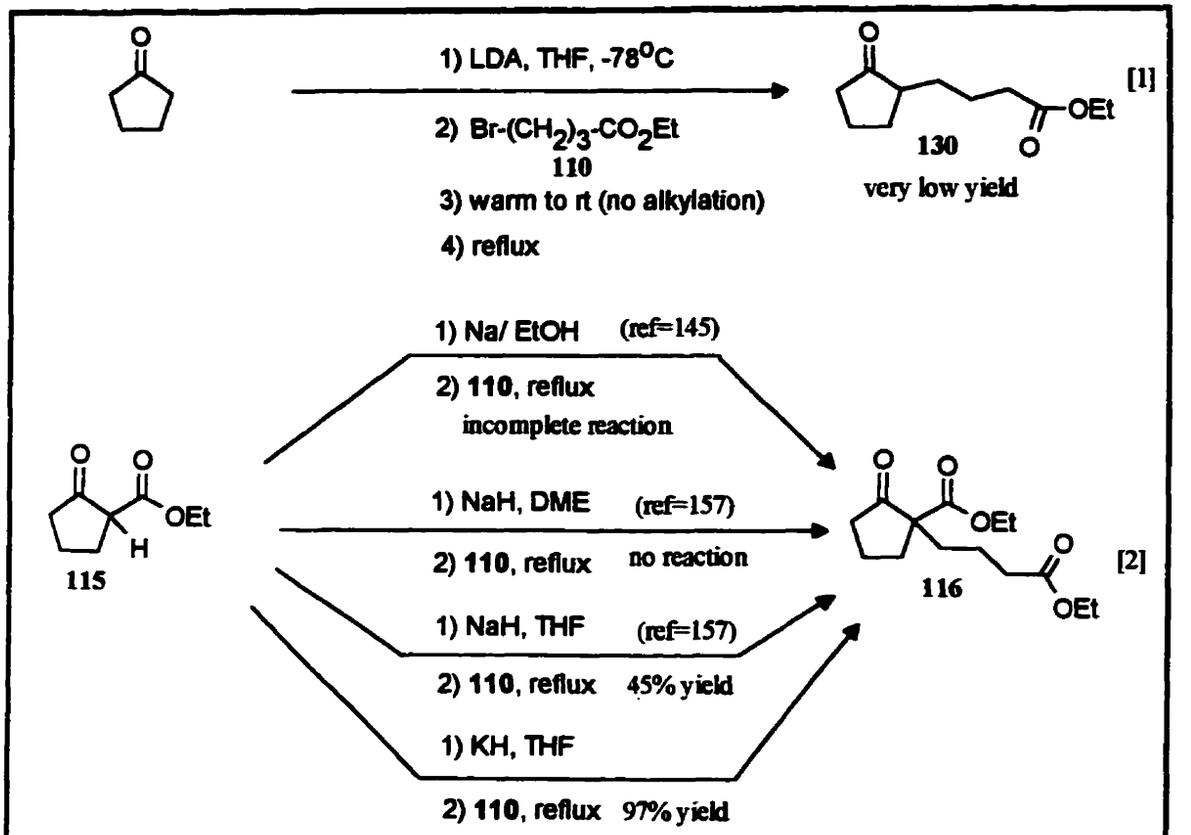
Any versatile chiral auxiliary must be 1) obtainable in large quantities, 2) have both optically pure enantiomers readily available, and 3) be inexpensive to buy or produce. The syntheses shown in Section 2.2.1 were long, low yielding and/or formed inseparable

mixtures of diastereomeric diols **106-108**. Application of resolutions reported in the literature (Section 2.2.2) for the formation of (+)- and (-)-diol **106** would involve many additional steps and fail to produce effectively both enantiomers in highly enantioenriched or enantiopure form. Thus a new and more effective synthesis and resolution of (+)- and (-)-diol **106** was investigated. A retrosynthesis outlining the approach to *cis,cis*-diol **106** is shown in Scheme 2.9. A retrosynthetic functional group interconversion (FGI) of diol **106** would form dione **113** (section 2.3.4) and finally ring-disconnection of dione **113** provide compound **119** (Section 2.3.3). Functional group addition would convert compound **119** to compound **116** (Section 2.3.2); and the last retrosynthetic step involves the alkyl chain disconnection of **116** resulting in **115** (Section 2.3.1). These steps are similar to ones reported previously in the literature (Section 2.2), and hopefully, could be improved upon. The greatest improvement for the formation of (+)- and (-)-**106** was needed in the resolution which should entail the formation of diastereomers at either compound **113** or **106** stage because the stereochemistry of the spirocentre for these compounds is fixed (Section 2.3.5). The stages in the synthetic pathway for the formation of optically pure **106** are presented in separate sections for clarity. In these sections various reagents and conditions are presented followed by a summary (Section 2.3.6) of the best overall synthetic sequence and resolution developed.

2.3.1 Alkylation of 2-Ethoxycarbonyl-1-cyclopentanone (115) with Ethyl 4-bromobutanoate (110)

Initial attempts, using LDA in THF, to directly alkylate cyclopentanone with bromoester **110** failed to produce desired keto ester **130** in a reasonable yield (reaction 1, Scheme 2.10). However, activation of the ketone by the presence of an ester at C-2, allowed for the preparation of **116** by alkylation of the anion of β-ketoester **115** (reaction 2). The loss of the signals for the acidic proton in **115** at δ 3.12 (t, keto form) and approximately δ 10.1 (s, enol form) confirmed the loss of starting material by ^{1}H-NMR spectroscopy. Signals at δ 4.08 (q, 2H), 4.04 (q, 2H) and 1.17 (t, 6H) supported the formation of the two constitutionally heterotopic ethyl esters in compound **116**.

Although this step had previously been reported in the literature[145] (reaction 2, Scheme 2.1) using sodium metal, potassium metal[156] and a similar one by Wheeler *et al.*



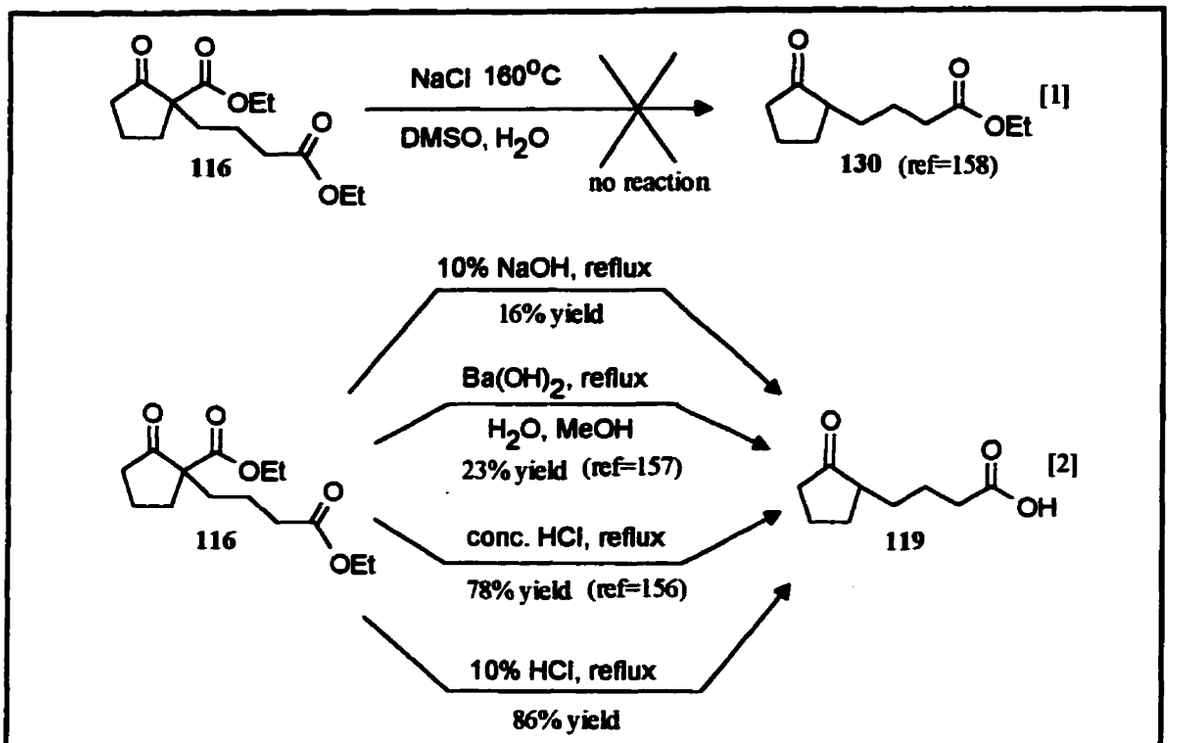
Scheme 2.10

using sodium hydride,[157] far superior results were obtained in the conversion of **115** into **116**, (97% yield) when potassium hydride was used as the base. A possible explanation for the increase in yield from 45 to 97% yield by changing only the counterion for the hydride base from sodium to potassium is the coordination of the cation to the enolate anion. With a sodium ion, the association with the enolate will be tighter than with a potassium ion. This weaker ion contact pair for the potassium enolate could have resulted in alkylation proceeding more readily than with the sodium enolate.

With the diester **116** in hand, the next step was the removal of the ethyl ester at C-2 which is reported in the next section.

2.3.2 Ester Saponification and Decarboxylation of 116

Endeavors to remove the α-ester group[158] in **116** with NaCl in DMSO at elevated temperature (reaction 1, Scheme 2.11) failed to produce the desired product **130**. These conditions were reported by Krapcho and co-worker to cleave both methyl and ethyl esters.[158]



Scheme 2.11

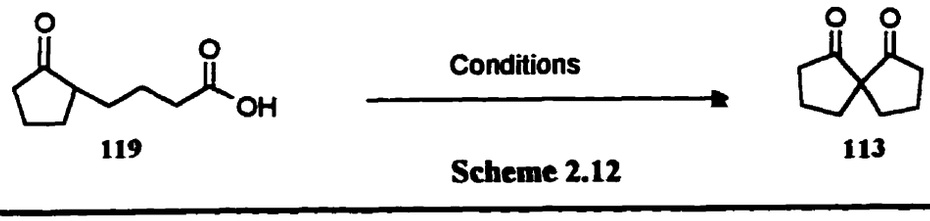
Reaction conditions to combine the saponification and decarboxylation reactions of **116** were investigated. Both basic and acidic conditions were tried and the results are reported in Scheme 2.11 (reaction 2). Loss of the ethyl ester signals, two quartets at δ 4.08 and 4.04 (4H, number of H's for both CH_2 of the ethyl group) and the signal at 1.17 ppm (t, 6H), in the ^{1}H-NMR spectrum of the product confirmed the removal of the ethyl functionalities. Decarboxylation was substantiated by ^{13}C-NMR spectroscopy which showed only two carbonyl functionalities in compound **119** at δ 221.4 and 179.2 where three were present in starting material **116** (δ 214.3, 172.6 and 170.4).

Refluxing **116** in sodium hydroxide or barium hydroxide[157] resulted in poor yields of **119**; however, utilising a procedure reported by Bachmann and Struve[156] by placing **116** in refluxing concentrated hydrochloric acid produced a 78% yield of **119**. Since refluxing a compound in concentrated hydrochloric acid was quite severe, the reaction was repeated using 10% aqueous hydrochloric acid which gave an 86% yield of **119**. These latter conditions represent the best conditions reported to date for this type of reaction.

Step 1 (**115** → **116**, Section 2.3.1) and step 2 (**116** → **119**, this section) could be combined into a single pot reaction, which precluded the need for isolation and purification of compound **116** and produced **119** in an 80% yield from **115**. After the reaction to form **116** was complete, the THF was removed *in vacuo* and 10% HCl was added and the mixture was refluxed to provide **119**.

2.3.3 Cyclisation of Keto Acid 119

Although the cyclisation of **119** into spiro dione **113** (Scheme 2.12) has previously been reported by Gerlach[148] and Carruthers,[146] attempts to repeat these results were unsuccessful (entries 1 and 3, Table 2.1). Therefore, an investigation into finding superior conditions to produce **113** was undertaken. After a variety of conditions were tried (Table 2.1) the best yield of 72% yield (92% based on recovered starting material) was obtained by treatment of acid **119** with 0.5 equivalents of *p*-toluenesulfonic acid in toluene with azeotropic removal of water (entry 13). The main differences by NMR spectroscopy between starting material **119** and product **113** were observed by comparing their ^{13}C-NMR spectra. For acid **119** the ^{13}C-NMR contained 9 resonances (δ 221.4, 179.2, 46.7, 37.9, 33.8, 29.4, 28.9, 22.5, and 20.6) while C_2-symmetric dione **113** contained only 5 signals (δ 217.3, 65.0, 39.1, 34.9, and 20.4).



119 113

Scheme 2.12

Table 2.1 Conditions Tried for the Cyclisation of Keto Acid **119** into Dione **113** (Scheme 2.12)

Entry	Conditions (acid/solvent)	% Yield of 113	Ref
1	0.15 eq. naphthalene-2-sulfonic acid/ xylene with azeotropic removal of water	33 (80[a])	146
2	0.5 eq. naphthalene-2-sulfonic acid/ toluene with azeotropic removal of water	61	
3	polyphosphoric acid/ glacial acetic acid	51 (81[a])	148
4	70% sulfuric acid and heat from 50 to 130°C	0 (dec.)	
5	$FeCl_3$ doped montomorillonite k_{10} clay[159,160] / chlorobenzene	0 (s.m.)	
6	$AlCl_3$ doped montomorillonite k_{13} clay[160,161]	30	
7	cat. TsOH/ xylene with azeotropic removal of water	38	
8	0.15 eq. TsOH/ xylene with azeotropic removal of water	24	
9	3.0 eq. TsOH/ xylene with azeotropic removal of water	37	
10	cat. TsOH/ benzene with azeotropic removal of water	26	
11	0.3 eq. TsOH/ toluene with azeotropic removal of water	52	
12	0.4 eq. TsOH/ toluene with azeotropic removal of water	36	
13	0.5 eq. TsOH/ toluene with azeotropic removal of water	72 (92[b])	
14	0.6 eq. TsOH/ toluene with azeotropic removal of water	58	
15	1 eq. TsOH/ toluene with azeotropic removal of water	64	

a) reported in the literature. b) based on recovered starting material

2.3.4 Diastereoselective Reduction of Spiro[4.4]nonane-1,6-dione (113)

Only twice in the literature has the reduction of spirodione **113** been reported[145,151] and both times a mixture of diols **106-108** were produced. Figure 2.1 shows the stepwise addition of hydride to dione **113** resulting in the formation of diols **106-108**. Statistically the *cis,trans*-diol **107** should be produced twice as often as diols **106** or **108** since the *cis,trans*-diol **107** can be produced from both *cis*- and *trans*-**118** while both *cis,cis*-diol **106** and *trans,trans*-diol **108** are only produced by one route. As previously mentioned (section 1.4), only *cis,cis*-diol **106** was desired, therefore, conditions for the selective reduction of dione **113** were investigated.

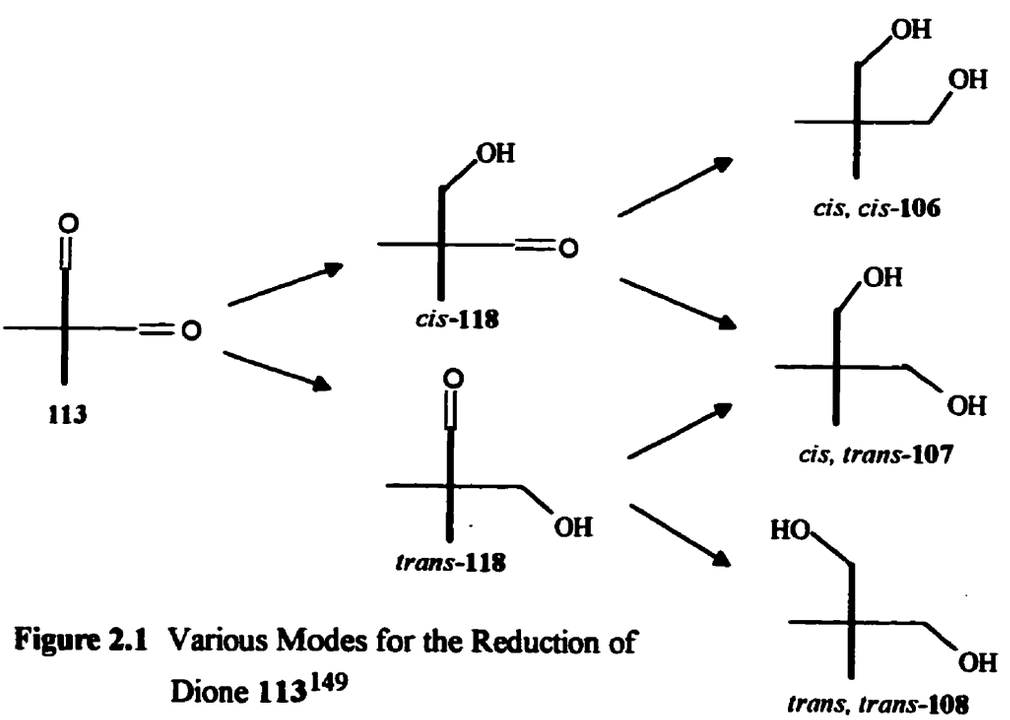
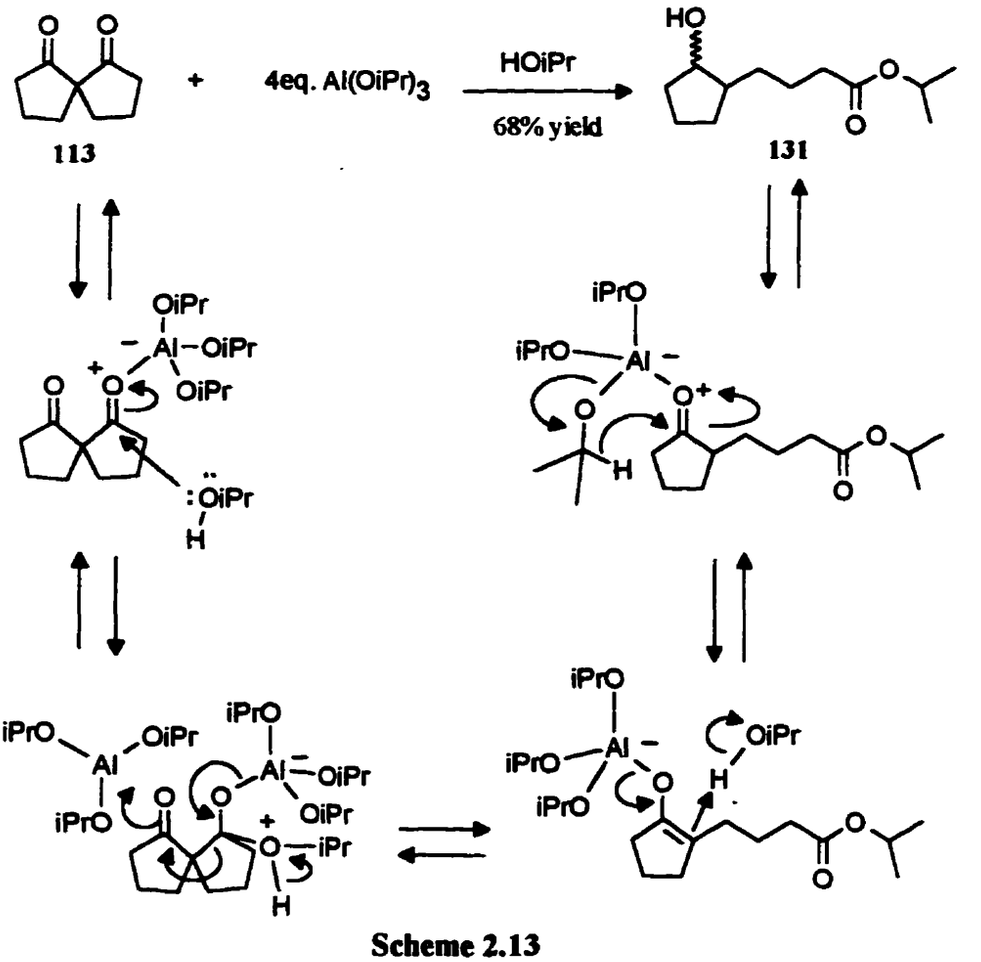


Figure 2.1 Various Modes for the Reduction of Dione **113**[149]

Unfortunately, reduction attempts using DIP-Cl™,[162] $NaBH_4$/MeOH, and Meerwin-Pondorf-Verley (MPV)[163] reduction did not produce any of the required diols **106-108**. The choice of DIP-Cl™ was two fold: 1) to produce **106** selectively and 2) to determine if one enantiomer of dione **113** would be selectively reduced (kinetic resolution), but the use

of 0.5, 1.0, and 3.0 equivalents (eq.) failed to react with **113**. Reduction with $NaBH_4$ in methanol produced a complex mixture of products, but diols **106-108** were not detected in the ^{1}H-NMR spectrum of the crude mixture.[164] The MPV reduction produced isopropyl ester **131** (Scheme 2.13). The isopropyl ester was evident from the ^{1}H-NMR spectrum which showed resonances at approximately δ 5.01 (septet, 1H) and 1.23 (d, 6H). The alcohol functionality in compound **131** was assigned based on two resonances in the ^{1}H-NMR spectrum at δ 3.82 (q) and 4.19 (t) which likely correspond to the *cis-* and *trans-* orientation for the hydrogen on the carbon containing the hydroxyl group.

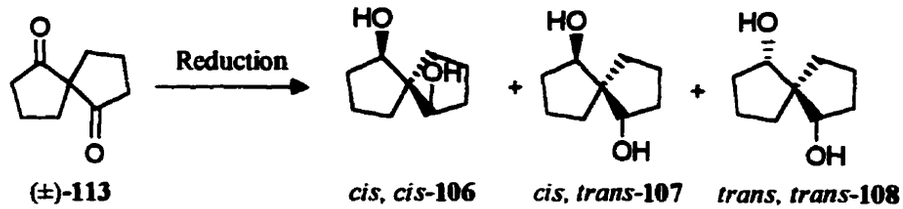
A mechanism is proposed to explain this unexpected product (Scheme 2.13). The key steps in this mechanism consist of the addition of an isopropoxy group to one of the



Scheme 2.13

homotopic diones followed by a retro-"aldol-like" reaction and an MPV reduction of the remaining ketone to produce ester **131**.

The results of the investigation of other hydride sources that produced diol products **106-108** are summarised in Table 2.2 (Scheme 2.14). Both LAH and DIBAL-H produced close to statistical mixtures (*i.e.* 1:2:1). Harada's group[151] previously reported that Red-Al® yielded the *cis,trans*-diol **107** as the "major product"; however, when it was used *cis,trans*-diol **107** constituted only 82% of the mixture. The application of Super-Hydride® produced a 91% composition of the desired *cis,cis*-diol **106**, but the best result was obtained with lithium *tert*-butyldiisobutylaluminium hydride,[165] which reduced dione **113** to the desired diol **106** with 100% diastereoselectivity (by ^{1}H-NMR spectroscopy) in an isolated yield of 91%.

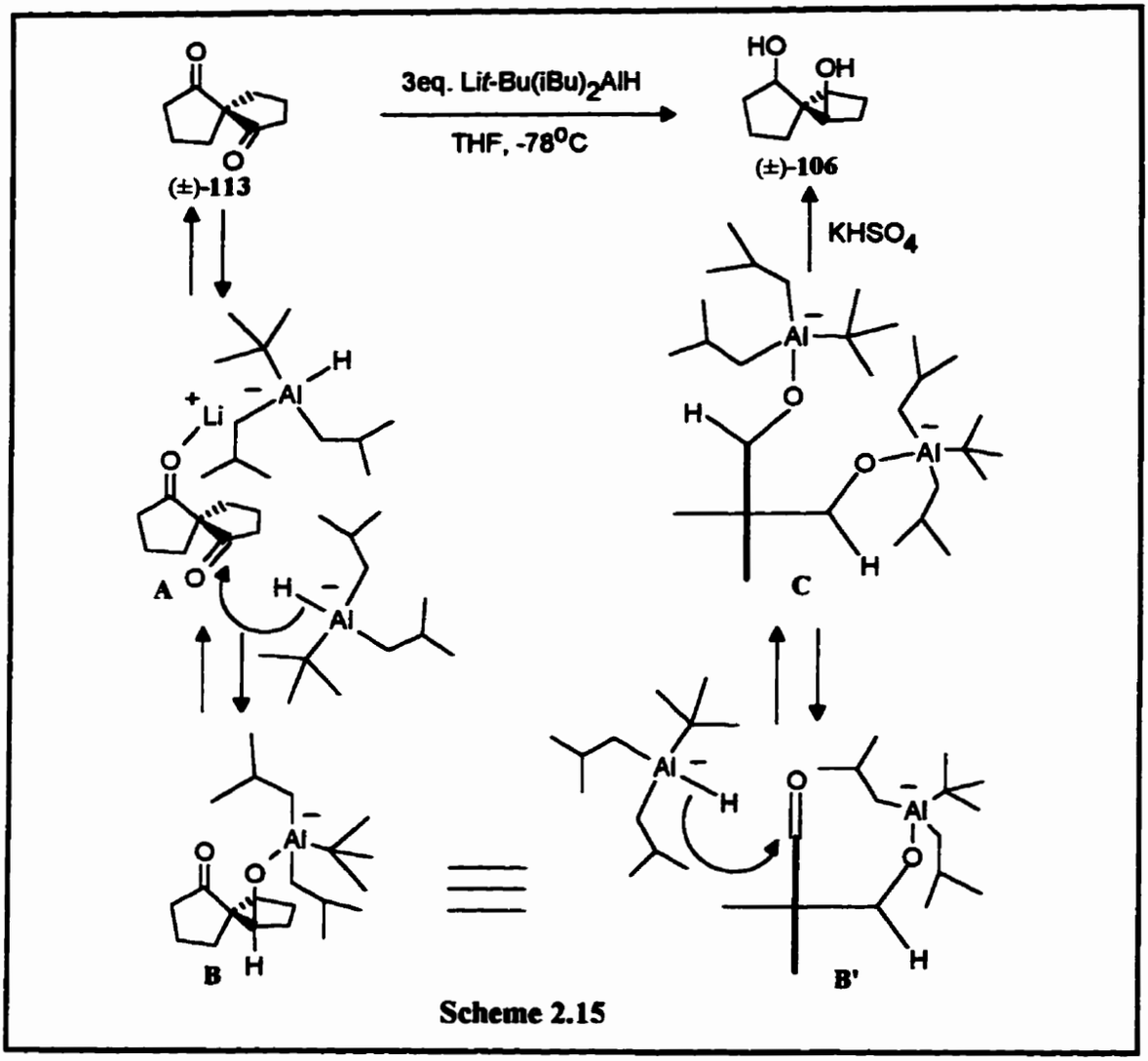


Scheme 2.14

Table 2.2 The Ratio of Stereoisomers **106-108** Produced by Reduction of **113** by Various Reducing Agents (Scheme 2.14)

Reducing Agent	Conditions	Diol 106[a]	Diol 107[a]	Diol 108[a]	Isolated Yield(%)
LAH[145]	Et_2O, 0°C	22	59	19	82
DIBAL-H	THF, -78°C	27	57	16	96[b]
Red-Al®[151]	THF, -78°C	4	82	14	78
$LiEt_3BH$	THF, -78°C	91	9	0	96[b]
Li *t*-Bu(iBu)$_2$AlH	THF, -78°C	100	0	0	91

a) ratio by ^{1}H-NMR spectroscopy. b) crude yield.



Scheme 2.15

A possible explanation for the diastereoselective formation of *cis,cis*-diol **106** by lithium *tert*-butyldiisobutylaluminium hydride is shown in Scheme 2.15. Coordination of the lithium *tert*-butyldiisobutylaluminium hydride to one of the homotopic ketones produces **A** in Scheme 2.15. This results in a large steric discrepancy in the two faces of the uncomplexed ketone which forces the hydride reduction to occur from the opposite side, producing structure **B**. The resulting alkoxyaluminate in intermediate **B'** (same intermediate as **B** but viewed from an edge-on angle) then acts as the steric influence causing the hydride to react with the remaining ketone from the opposite side producing dialkoxydialuminate **C**. Work up of **C** by pouring the contents of the reaction flask into a

mixture of aqueous potassium bisulfate and chloroform produces the observed *cis,cis*-diol **106** exclusively.

Figure 2.2 shows the ^{1}H-NMR resonances of the hydrogen (bolded on the structure shown) on the same carbon as the hydroxyl moiety in the three diols **106-108**. The first ^{1}H-NMR (Figure 2.2a) shows a mixture of three diols obtained from the LAH reduction of

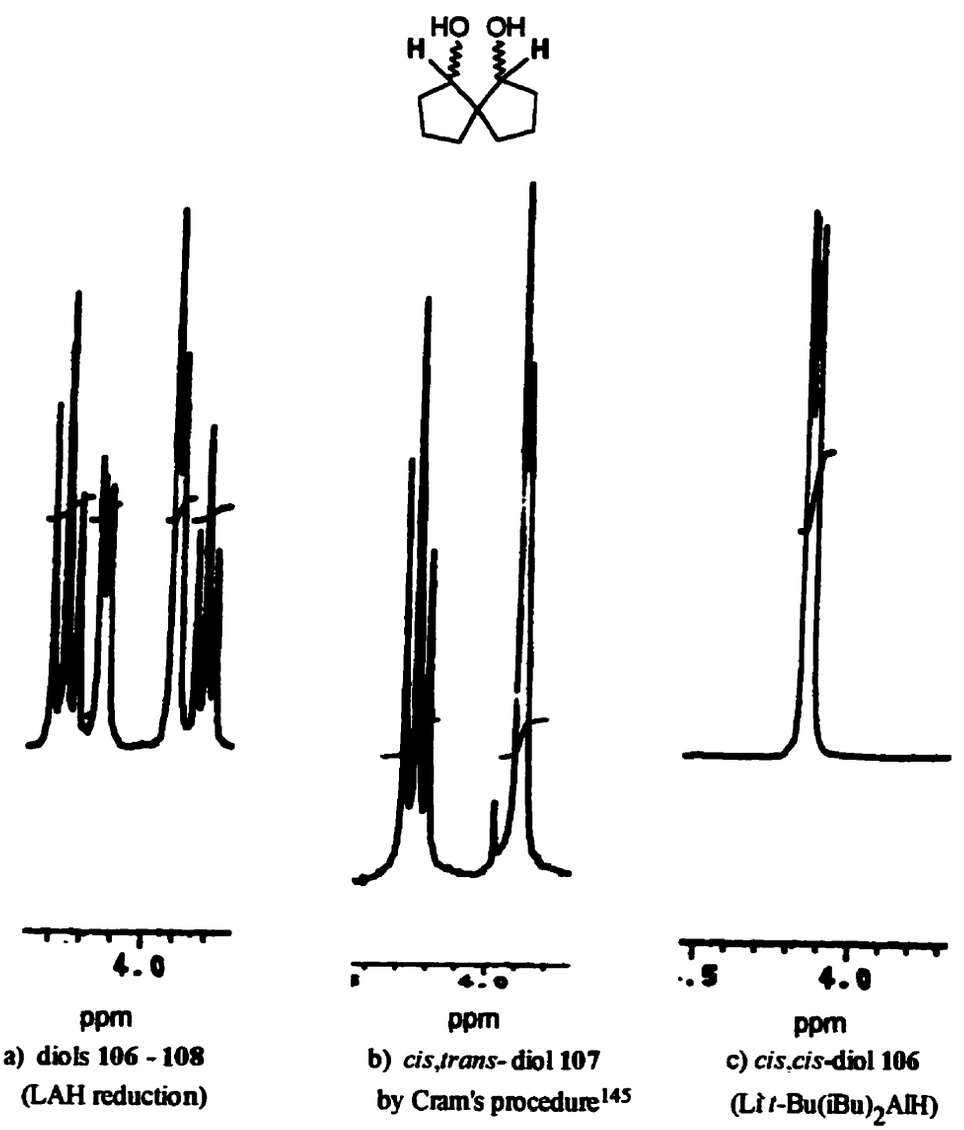
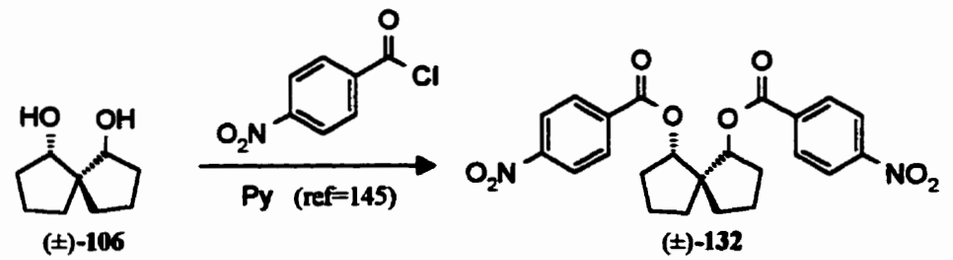


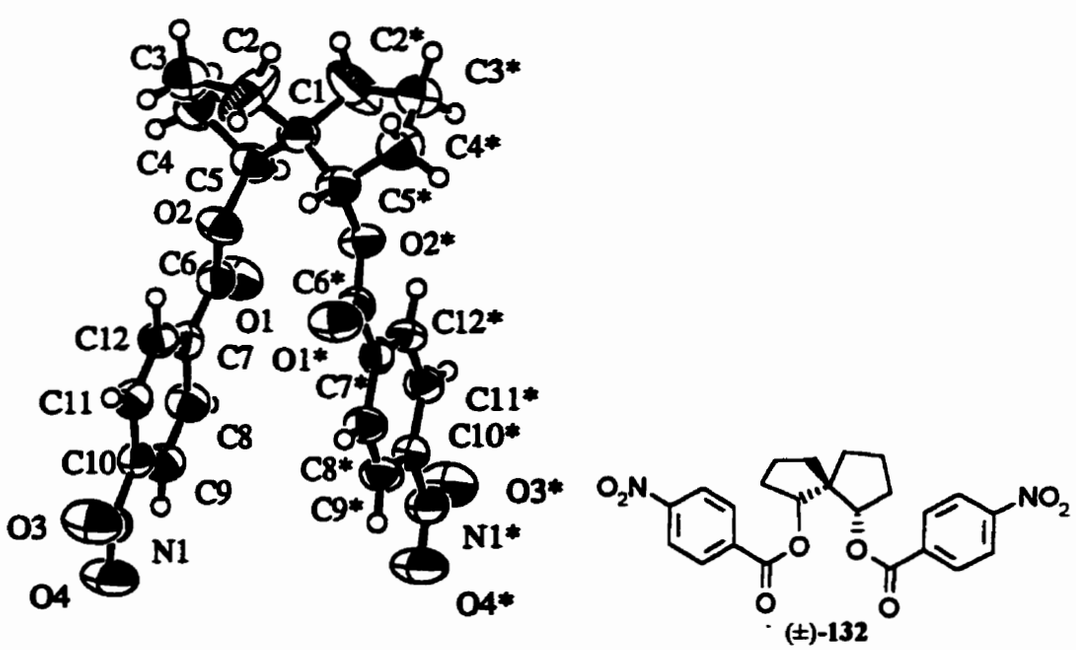
Figure 2.2 The ^{1}H-NMR Spectra of the Methine Hydrogen Atoms for: a) Mixture of Diols **106 -108**, b) *cis,trans*-Diol **107**, and c) *cis,cis*-Diol **106**



(±)-106 (±)-132

Scheme 2.16

dione **113**. The second ^{1}H-NMR spectrum (b) is *cis,trans*-diol **107**, which was isolated by hydrolysis of the bis-(*p*-nitrobenzoate) derivative after chromatographic separation from the esters of the two other diols (*i.e.* **106** and **108**) according to the procedure reported by Cram and Steinberg.[145] The last ^{1}H-NMR spectrum (Figure 2.2c) is the *cis,cis*-diol **106** obtained after reduction using lithium *tert*-butyldiisobutylaluminium hydride.



(±)-132

Figure 2.3 X-ray Crystal Structure of Bis-(*p*-nitrobenzoate) Derivative **132**

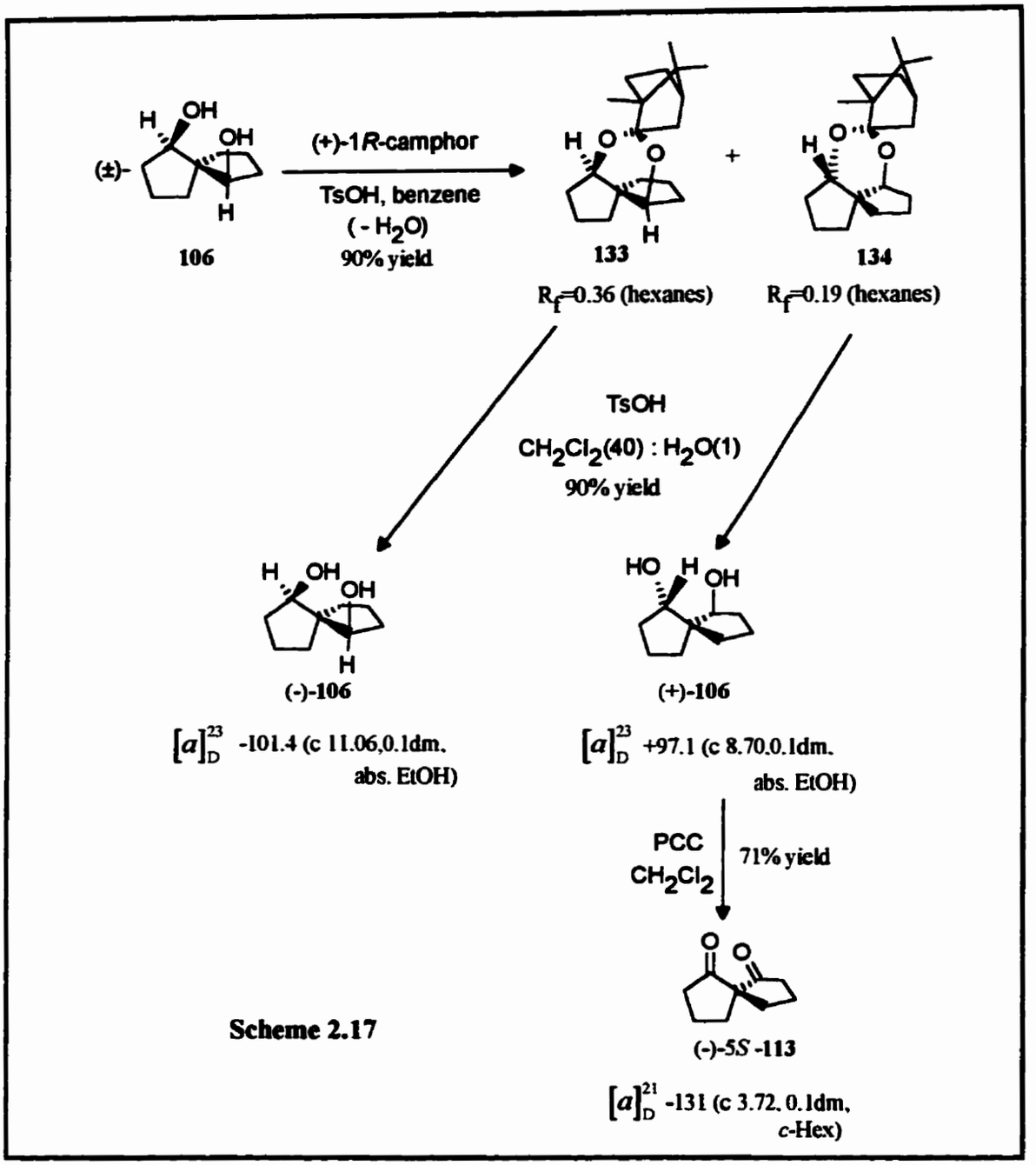
In the early literature published by Cram and Steinberg, there was an uncertainty as to the proper assignment of structure to diols **106-108**.[145] In a later publication, Cram's group claimed to have cleared up the controversy;[153] however, before using spirodiol **106** as a chiral auxiliary, it was decided to ensure at this stage that the product from the reduction had indeed the *cis,cis*-orientation. To obtain proof of the relative stereochemistry an X-ray crystal structure of the bis-(*p*-nitrobenzoate) derivative of diol **106** was obtained. The procedure for the formation of this derivative (Scheme 2.16) had previously been reported by Cram and Steinberg.[145] Suitable crystals were obtained by slow evaporation of an acetone solution of **132**. The X-ray crystal structure of compound **132** is displayed in Figure 2.3 which clearly shows that the two hydroxyl groups are in a *cis,cis*-relationship.[166]

2.3.5 Resolution of (±)-*cis,cis*-Spiro[4.4]nonane-1,6-diol

With the development of a highly stereoselective synthesis of (±)-*cis,cis*-diol **106** in hand, the production of diol **106** in enantiomerically pure form was investigated next. Since attempts to form diol **106** using an enantioselective reduction with DIP-Cl™ failed,[167] a resolution of (±)-**106** was investigated.

Repeating the method reported by Harada *et al.*[151] for the separation of spirodione **113** by the formation of diastereomeric oxamoylhydrazones **126** and **127** (Scheme 2.5) failed to produce acceptable quantities of both the *R*- and *S*-spirocentres. Attempts to react dione **113** with dimethyl (L)-tartrate to form diastereomeric ketals resulted in a complex mixture. Since the (±)-dione **113** could not be resolved satisfactorily, attention was turned towards the resolution of (±)-diol **106**.

Cram's group[153] reported the formation of an acetonide ketal of (±)-*cis,cis*-diol **106**. Thus reacting (±)-*cis,cis*-diol **106** with an inexpensive chiral ketone (from the chiral pool) to produce diastereomers could be an effective resolution method. This route would only involve two additional reactions, ketal formation, separation of diastereomers, followed by removal of the chiral ketone. Three relatively inexpensive ketones were selected from the chiral pool: (-)-*R*-carvone, (+)-*R*-pulegone and (+)-1*R*-camphor. Formation of the



Scheme 2.17

(±)-*cis*,*cis*-diol **106** ketal of both (-)-*R*-carvone and (+)-*R*-pulegone produced complex mixtures possibly due to double bond isomerisation (in the case of (-)-*R*-carvone) and epimerisation of an adjacent centre (for (+)-*R*-pulegone). Diastereomeric ketals **133** and **134** (Scheme 2.17) produced from the two enantiomers of *cis*,*cis*-diol **106** and (+)-1*R*-camphor proved to be readily separable by column chromatography (90% combined

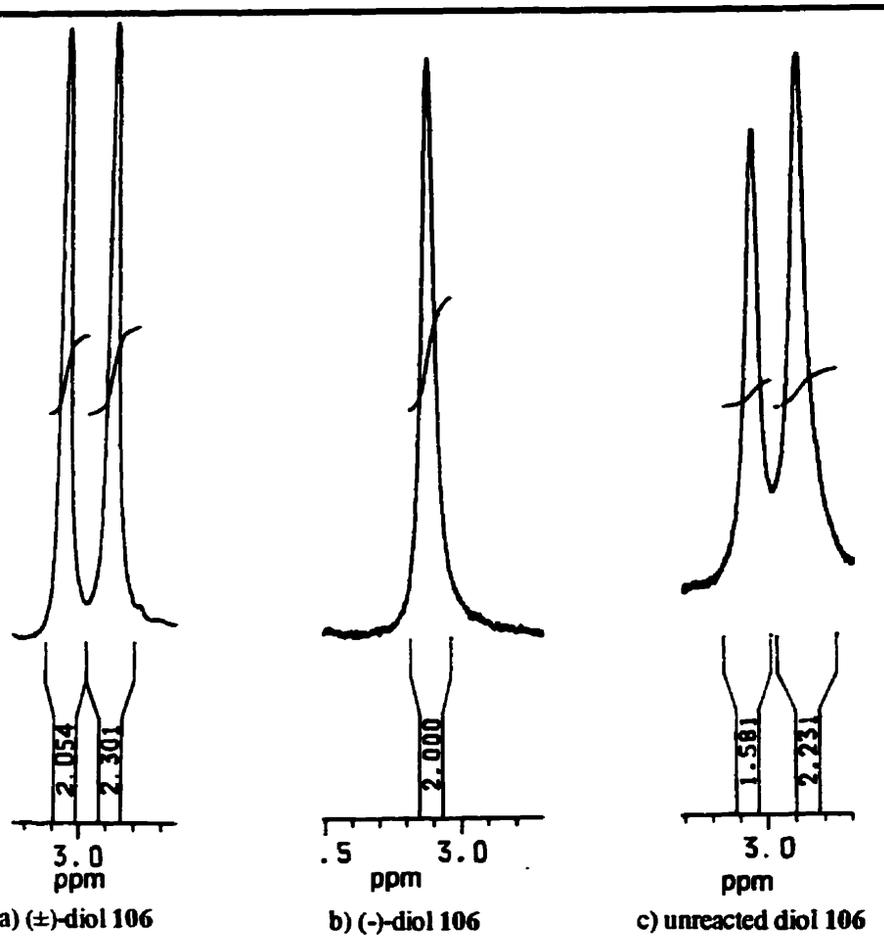
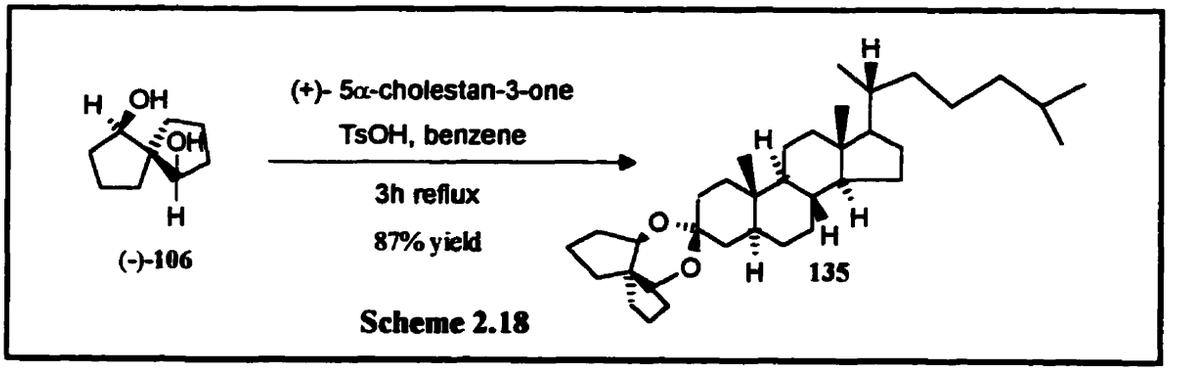


Figure 2.4 Part of the ^{1}H-NMR Spectra of Diol 106 with Pra-Opt®

yield, hexanes, R_f = 0.19 and 0.36). Removal of the ketal from **133** and **134** yielded the corresponding diols (-)-**106** and (+)-**106** in an average yield of 90%. Both (-)- and (+)-**106** had identical NMR (both ^{1}H and ^{13}C) spectra to (±)-diol **106**. Comparison of the optical rotation obtained for (-)- and (+)-diol **106** (-101.4 and +97.1) to the specific rotation predicted by Kabuto *et al.*[152] of -99.6 (α_D^{20} -25.9, 26% ee, Scheme 2.6) indicated that the resolution technique produced both (-)- and (+)-diol **106** in extremely high enantiomeric purity. Confirmation of the high optical purity was obtained by comparing the ^{1}H-NMR spectra obtained in the presence of a chiral shift reagent Pra-Opt® with (±)-diol **106** (Figure 4.2a) to that with (-)-diol **106** (Figure 2.4b). A reaction to form the (+)-

1*R*-camphor ketal was prematurely stopped, and the ^{1}H-NMR spectrum of the unreacted diol **106** was obtained in the presence of Pra-Opt® (Figure 2.4c). The spectrum showed that the two diols react to almost the same extent with the (+)-1*R*-camphor and therefore separation by kinetic resolution could not be accomplished.

Oxidation of (+)-diol **106** with PCC in methylene chloride formed (-)-dione **113** in 71% yield (Scheme 2.17). The optical rotation observed for this dione was -131°, which was very close to the specific rotation of -135° reported whose absolute stereochemistry was predicted to be 5*S*.[149,150,168] The absolute stereochemistry of dione **113** and diols **106-108** was empirically determined by Horeau's method,[148,149] MTPA esters with achiral lanthanide shift reagents,[152] and chemical correlations.[169] These assignments were later supported by using the exciton chirality method in conjunction with theoretical calculations.[150,151,170] These determinations of absolute stereochemistry provided strong evidence that the absolute configuration of the (+)-diol **106** is 1*S*,5*S*,6*S* (and thus the (-)-diol **106** is 1*R*,5*R*,6*R*.). To unequivocally prove the absolute stereochemistry an X-ray crystal structure of the ketal of one of the enantiomers bound to a ketone of known absolute stereochemistry was obtained.



Scheme 2.18

The first logical choice for a suitable ketal was **133**, which was previously synthesised (Scheme 2.17). However, every recrystallisation solvent system tried with **133** failed to form suitable crystals for X-ray analysis. Therefore, the synthesis of a larger sized ketal that might produce suitable crystals was undertaken. The reaction of (-)-diol **106** and (+)-5α-cholestan-3-one produced ketal **135** (Scheme 2.18), which formed suitable crystals when acetonitrile (top layer) was allowed to slowly dissolve into a THF

solution of **135** (bottom layer) in an NMR tube. The ORTEP diagram (Figure 2.5) solved for the structure (additional crystal data in the Experimental section) proved that the (-)-diol **106** has the 1*R*,5*R*,6*R* configuration, and thus, the (+)-diol **106** must have the 1*S*,5*S*,6*S* configuration.

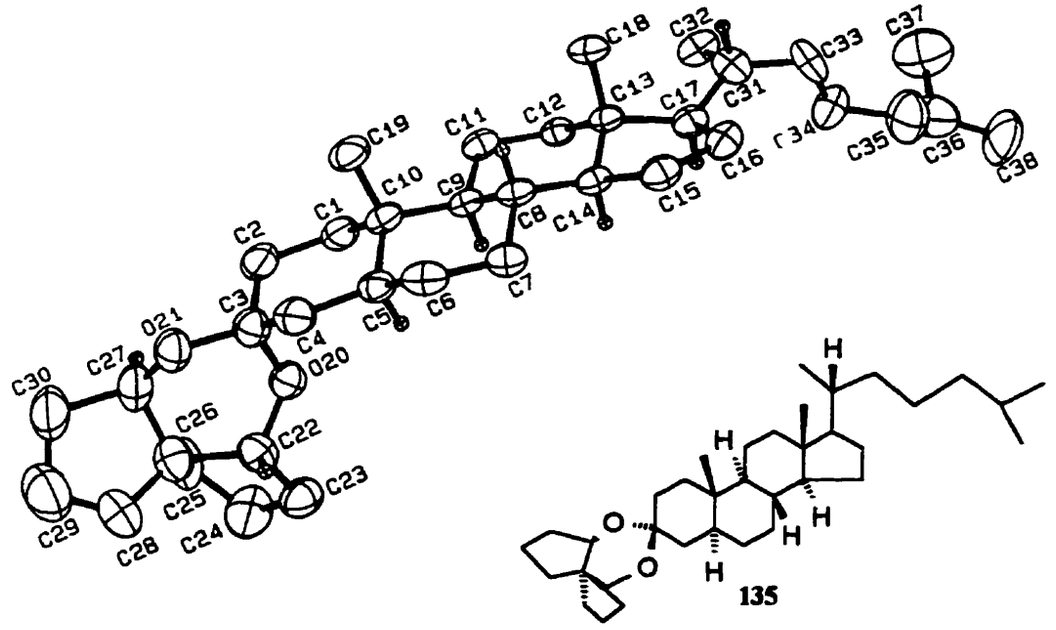
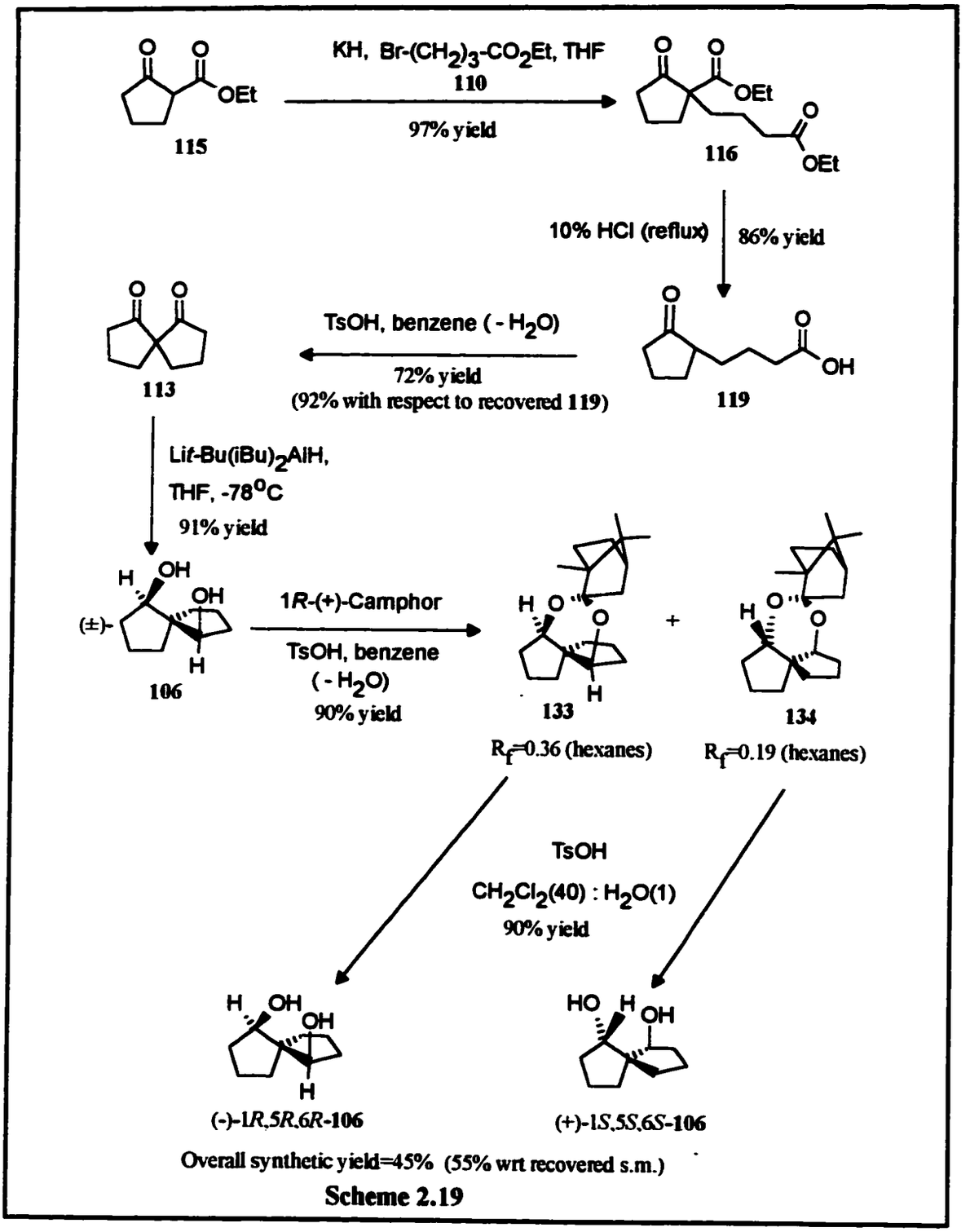


Figure 2.5 X-ray Crystal Structure of Compound **135**

2.3.6 Summary

This short 100% stereoselective synthesis produced a yield of 55% of (±)-diol **106**, and an overall yield of 45% for resolved 1*R*,5*R*,6*R*-(-)-diol **106** and 1*S*,5*S*,6*S*-(+)-diol **106** (Scheme 2.19).[171] These yields are considerably higher than those reported using previous synthetic approaches and resolutions, which makes this approach far superior to those reported previously in the literature. The next chapter describes attempts to convert diol **106** into other functional groups for use as chiral auxiliaries.


KH, Br-(CH2)3-CO2Et, THF
110
97% yield
115
116
10% HCl (reflux)
86% yield
TsOH, benzene (- H2O)
72% yield
(92% with respect to recovered 119)
113
119
Lit-Bu(iBu)2AlH,
THF, -78°C
91% yield
(±)-
106
1R-(+)-Camphor
TsOH, benzene
(- H2O)
90% yield
133
134
Rf=0.36 (hexanes)
Rf=0.19 (hexanes)
TsOH
CH2Cl2(40) : H2O(1)
90% yield
(-)-1R,5R,6R-106
(+)-1S,5S,6S-106
Overall synthetic yield=45% (55% wrt recovered s.m.)

Scheme 2.19

Chapter 3

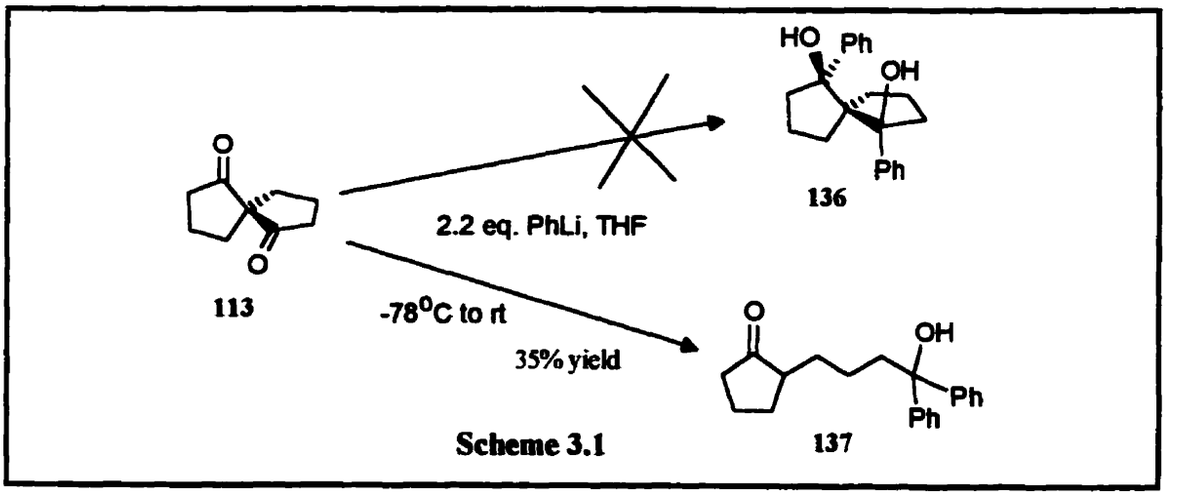
3 Attempted Preparation of Analogues of Dione 113 and Diol 106

3.1 Introduction

As mentioned in Section 1.1.3 alcohols can be converted into phosphorus and nitrogen containing moieties. With the completion of the synthesis and resolution of *cis,cis*-diol **106** and dione **113**, transformations of the hydroxyl group(s) or ketone(s) should allow access to essentially optically pure diamines, diphosphines, or amino alcohols for use as auxiliaries in asymmetric transformations. This chapter will outline the interesting chemistry discovered in the pursuit of these and other functional groups with the spiro[4.4]nonane system.

3.2 Reaction of Dione 113 with Phenyllithium

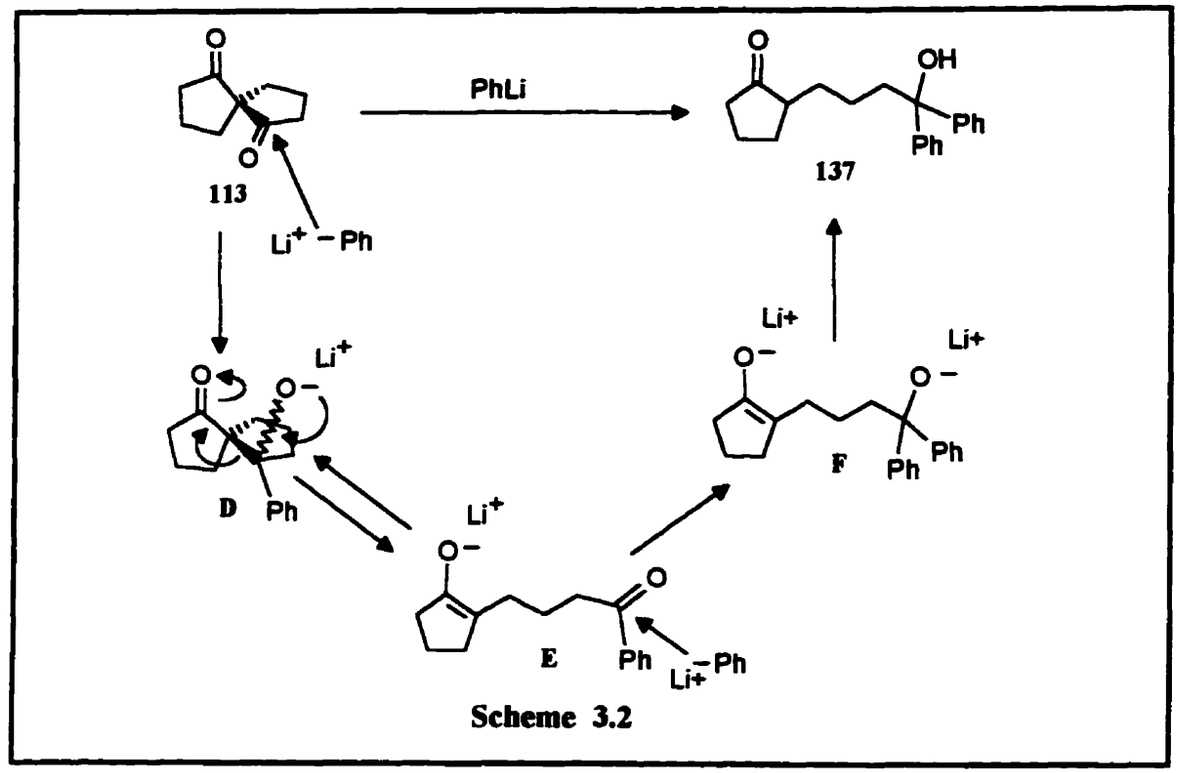
Although this first section does not involve the attempted conversion of dione **113** into a diamine, diphosphine, or amino alcohol some intriguing chemistry was observed. Addition of phenyllithium (PhLi) to dione **113** was expected to readily form compound **136**, which was to be used in conjunction with diol **106** for comparison purposes in various asymmetric transformations.



Scheme 3.1

The reaction was performed by the dropwise addition of a THF solution of dione **113** dropwise to a THF solution of phenyllithium (2.2 eq.) at -78°C and the reaction mixture was slowly warmed to room temperature. However, as is shown in Scheme 3.1,

the desired reaction did not occur, but instead a mixture of products was obtained. The major compound obtained after column chromatography was keto alcohol **137** which did not contain a spirocentre.

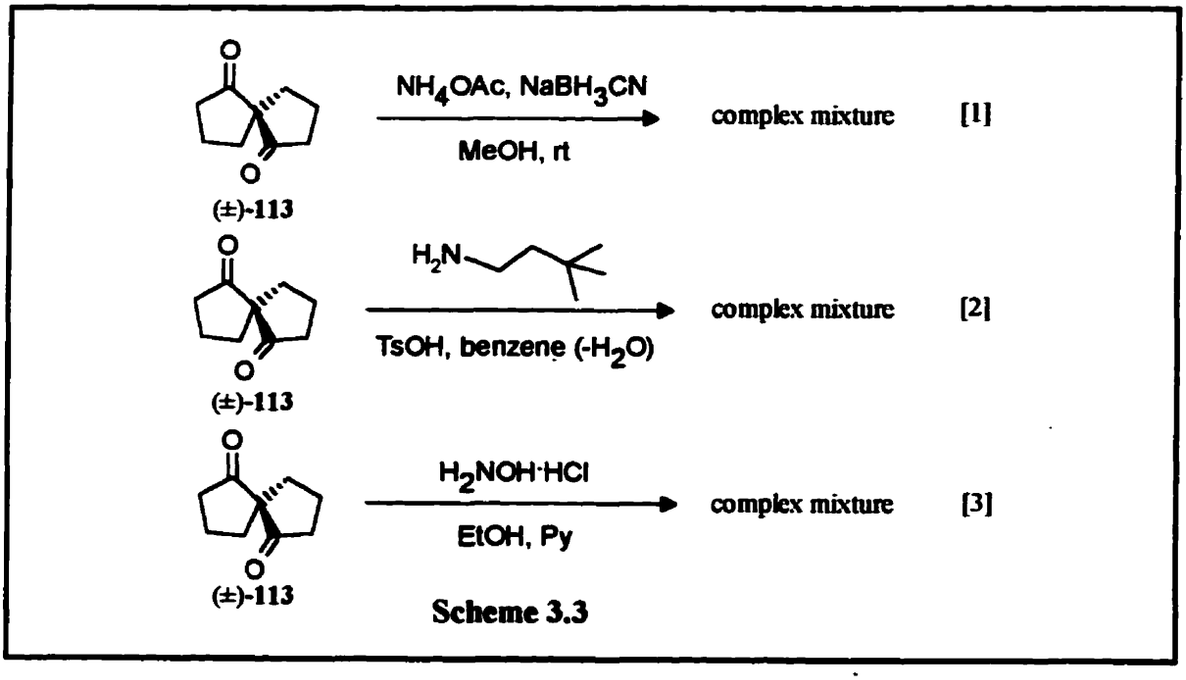


Scheme 3.2

A probable mechanism for the conversion of **113** into **137** is shown in Scheme 3.2. The addition of phenyllithium to one of the ketones in **113** produces intermediate lithium alkoxide **D**, which undergoes a retroaldol reaction to form keto enolate **E**. Intermediate **E** contains a ketone and an enolate, of which the former undergoes attack by phenyllithium forming **F**. Finally, the addition of ammonium chloride protonates both the enolate and alkoxide producing **137**. A similar reaction that resulted in the opening of the spirocentre was also observed with the MPV reduction of **113** in Scheme 2.13. The fascinating feature about this reaction, however, is the opening of the spirocentre (to produce **E** in Scheme 3.2) which occurred faster in excess phenyllithium at low temperature (-78°C) than the addition of the second equivalent of phenyllithium to the ketone in **D**.

3.3 Attempted Conversion of Dione 113 to Imines or Amines

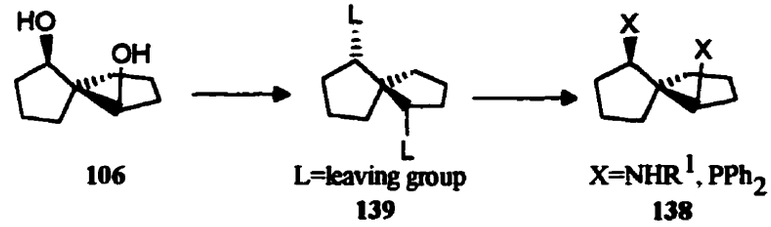
In an effort to convert dione **113** directly into a diamine by reductive amination[172] (reaction 1, Scheme 3.3), freshly distilled dione **113** was treated with ammonium acetate and sodium cyanoborohydride in MeOH at room temperature.[173] The reaction provided a complex mixture, by both ^{1}H-NMR and GC/MS analysis. The attempted reductive amination was comprised of two steps: the first was the formation of the imine and the second step was its reduction to an amine. In an attempt to clarify what was occurring in reaction 1 with dione **113**, attempts to prepare the diimine (or dioxime) were tried (Scheme 3.3), which if successful, would be reduced in a later step. The various reactions attempted to form the imine and oxime[145] failed to proceed as desired and instead gave mixtures of unidentified products, by ^{1}H-NMR spectroscopy and GC/MS. The identity of these products were still undetermined even after LAH reduction of the crude products from reaction 2 and 3.



Scheme 3.3

3.4 Attempted Conversion of (±)-*cis,cis*-Diol 106 into (±)-*trans,trans*-Disubstituted Spiro[4.4]nonanes

After the failure of the reductive amination reported in Section 3.3, the next route attempted was the formation of a spiro[4.4]nonane system with good leaving groups in a *trans,trans* relationship (**139**, Scheme 3.4), which hopefully could be displaced with sodium azide, amines or phosphines to form *cis,cis*-**138**. Attempts to convert **106** into **139** are described in this section.

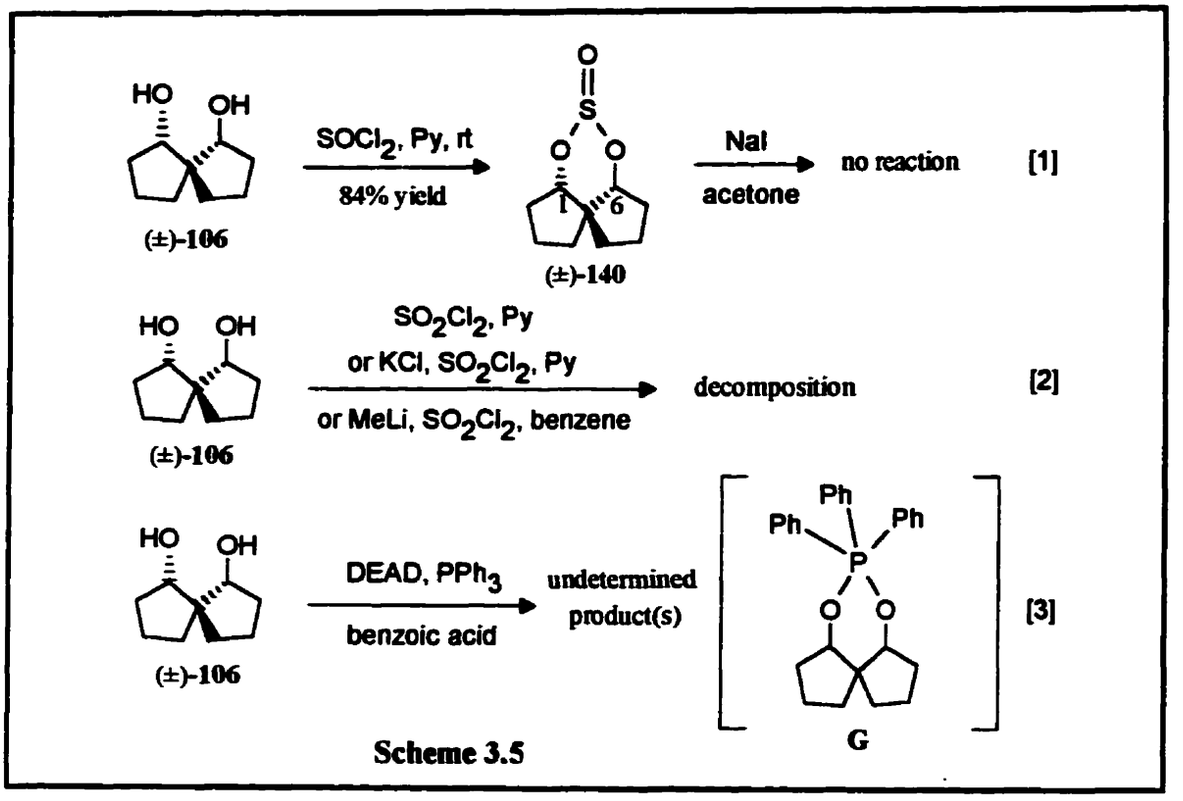


106 L=leaving group **139** X=NHR^1, PPh_2 **138**

Scheme 3.4

The method of most interest to us was one that would directly convert diol **106** into a molecule **139** having a *trans,trans*-orientation. Thionyl chloride in pyridine is one reaction commonly used to convert an alcohol into a chloride with inversion of configuration.[174] However, reaction of diol **106** with thionyl chloride in pyridine (reaction 1, Scheme 3.5) failed to produce the *trans,trans*-orientation of the corresponding dichloride, but instead an 84% yield of sulfite **140** was obtained, after column chromatography. The ^{1}H-NMR spectrum of **140** was interesting because the sulfite group breaks the C_2-symmetry which explains why two signals in the ^{1}H-NMR spectrum were observed for the hydrogens on carbons 1 and 6 at δ 4.74 (dd, 1H) and 4.18 (dd,1H). Compound **140** was formed by the reaction of both alcohols with one molecule of thionyl chloride. Further attempts to displace the sulfite in **140** with, for example, sodium iodide in refluxing acetone yielded only recovered starting material. The use of sulfuryl chloride (reaction 2, Scheme 3.5), in an attempt to form an alkyl sulfate intermediate that could subsequently be displaced by chloride ion, produced a black tar under all reaction

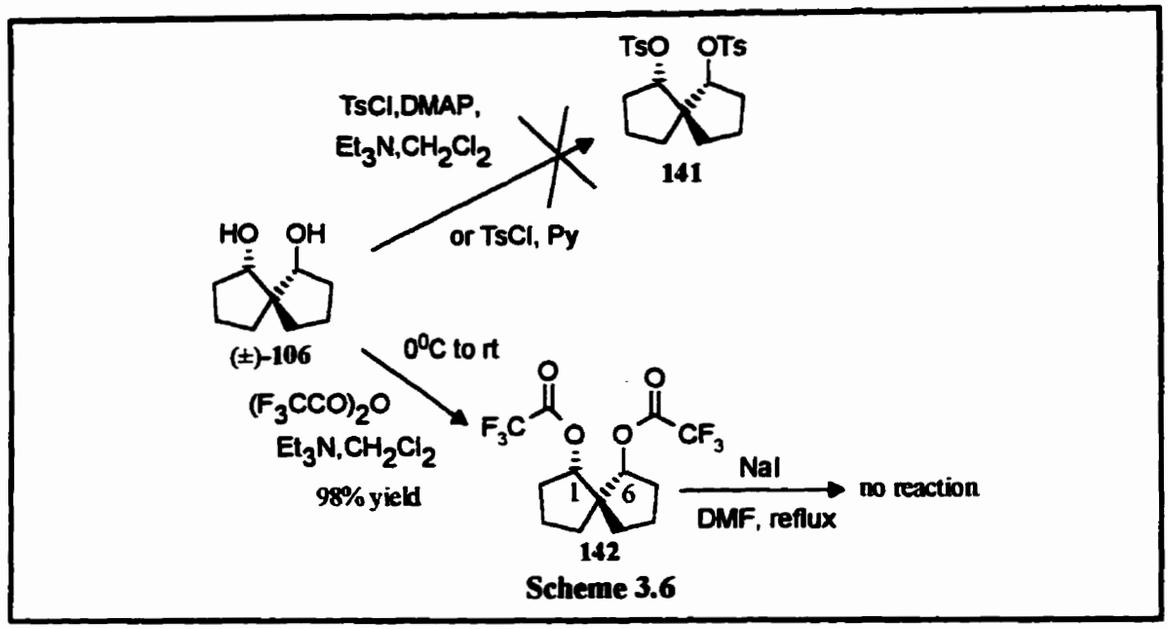
conditions tried. The sulfate, or potentially dichloride, was not detected by ^{1}H-NMR spectroscopy.



Scheme 3.5

A Mitsunobu inversion,[175] with **106** also failed to generate the desired *trans,trans*-orientation of the expected benzoate esters; only a small quantity of unidentified compound(s) was obtained after workup of the reaction mixture. Examination of the review by Mitsunobu furnished a potential explanation.[175] Diol compounds, with similar orientations to diol **106**, were observed (by NMR only) to form cyclic intermediates like phosphorane **G**. Mitsunobu found these diols produced poor yields of the desired inverted product since intermediates like **G** are unreactive and thus, are not displaced by the benzoate anion. Therefore, diol **106** was not suitable for inversion under the conditions reported by Mitsunobu.

The next step taken was the attempt to convert the hydroxyl groups in diol **106** into better leaving groups with the hope that they could be displaced (S_N2) by iodide (Scheme 3.6). By ^{1}H-NMR spectroscopy of the crude product mixture, addition of the first



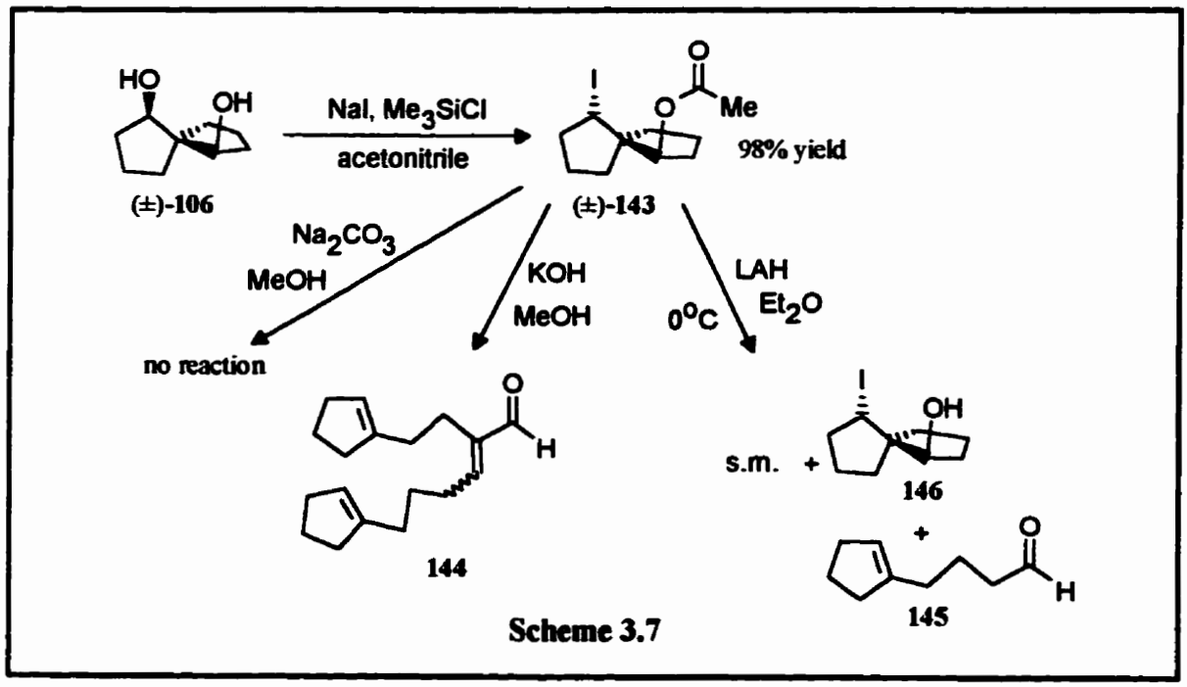
Scheme 3.6

tosylate proceeded, but ditosylate **141** would not form even at elevated temperatures when decomposition and polymerisation occurred. Replacement of tosyl chloride with mesyl chloride also failed to yield the desired product. One possible reason that the formation of ditosylate **141** (or the mesylate analog) failed to proceed was that the steric bulk of the sulfonate group (the sulfur is tetrahedral) of the first tosylate was large enough to prevent the attachment of the second sulfonate group to the remaining alcohol. The fact that ester functionalities are planar would explain why diester **132** (Scheme 2.16) and **142** formation occurred readily. The formation of **142** was observed by ^{1}H-NMR spectroscopy which showed the resonances for the hydrogens on C-1 and C-6 (Scheme 3.6) shifted to δ 5.23 (d, see Figure 3.1) from δ 4.14 in diol **106**. However, endeavors to displace the trifluoroacetate group with iodide failed.

Iodotrimethylsilane chemistry[176] (Scheme 3.7 and Scheme 3.10) was attempted next in an effort to form **139** (Scheme 3.4, L=I). The addition of NaI to Me_3SiCl in acetonitrile was reported to result in the formation of Me_3SiI, which has been used to react with an alcohol followed by a displacement with iodide.[177] Under these conditions, however, diol **106** (Scheme 3.7) formed product **143** in 98% yield.

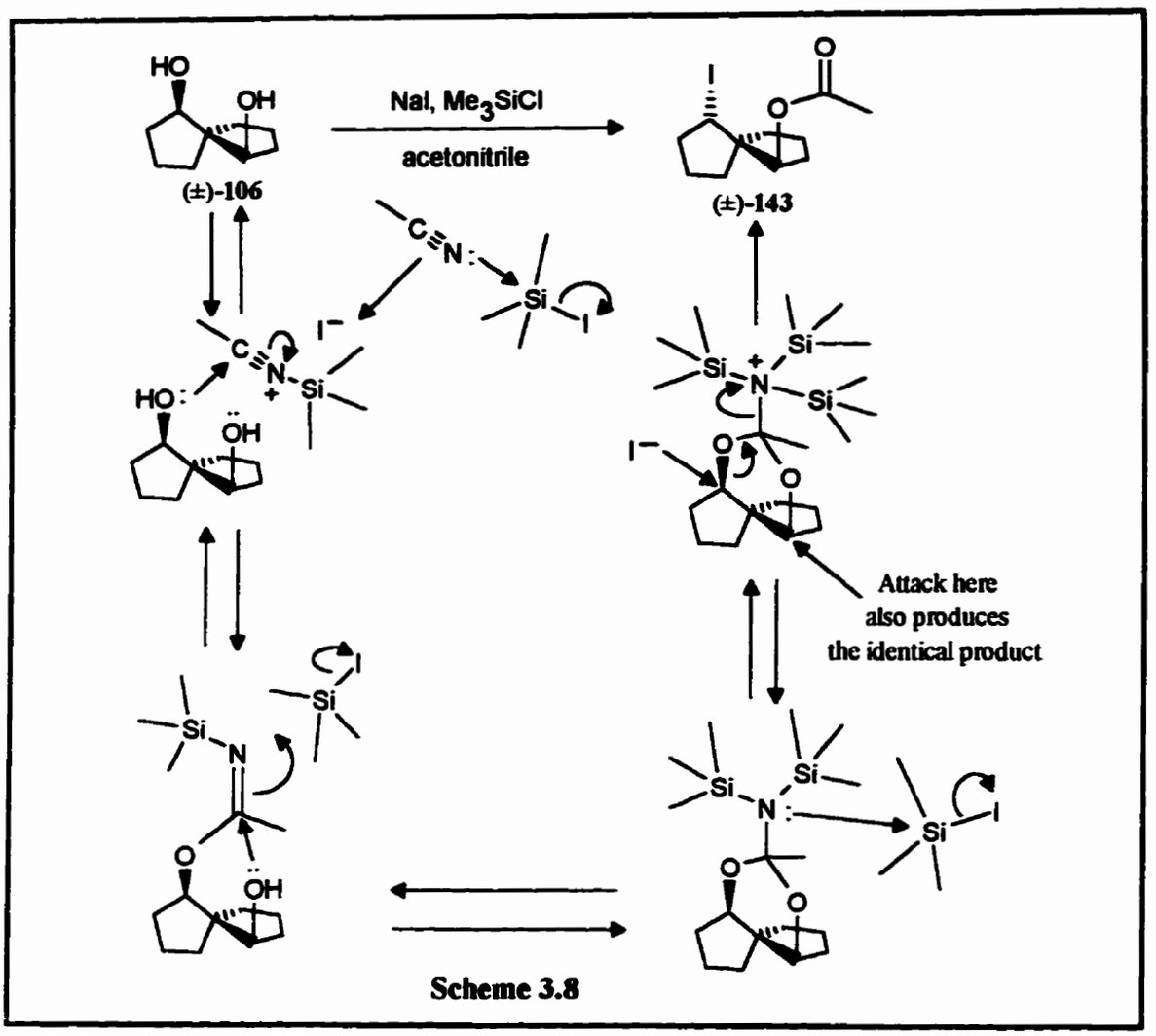
A possible mechanism for the formation of **143** is shown in Scheme 3.8. The interesting incorporation of an acetate into product **143** is explained by the reaction of the hydroxyl groups with an acetonitrile molecule.

The assignment of the *trans*-orientation of the iodine is based on the observed triplet pattern at δ 4.51 (Figure 3.1) in the ^{1}H-NMR spectrum which is the same pattern (triplet) previously observed for the geminal proton on a *trans*-orientated alcohol (Figure 2.2). The acetate group is identifiable by the characteristic methyl singlet at δ 2.06 and the significant downfield shift of the geminal proton from δ 4.14 in diol **106** to δ 4.87 in product **143** (Figure 3.1). The *cis*-orientation of the acetate in (±)-**143** is postulated on the basis of the narrow doublet pattern observed in the ^{1}H-NMR spectrum which is typical for esters attached to the *cis*-hydroxyl groups for diol **106** (*e.g.* compound **142**, Figure 3.1).



Scheme 3.7

Removal of the acetate in **143** (Scheme 3.7) failed to occur when it was treated with sodium carbonate in methanol. Only starting material was present based on TLC. The addition of a small amount of 10% potassium hydroxide, however, provided a mixture which by ^{1}H-NMR and ^{13}C-NMR spectroscopy appeared to consist mainly of aldehyde



Scheme 3.8

144 (Scheme 3.7). Endeavors to remove the acetate group with LAH in Et_2O at 0°C produced a mixture, by ^{1}H-NMR spectroscopy, which was comprised of unreacted starting material **143**, aldehyde **145**, and iodoalcohol **146**.

A mechanistic rationalisation for the formation of aldehyde product **145** is shown in Scheme 3.9. A similar mechanism is observed in a Grob fragmentation (γ-hydroxy halides or tosylates) in which the reacting groups prefer an anti-periplanar arrangement.[178] The predicted *trans*-orientation would likely allow the best overlap for the observed fragmentation because it would be able to adopt the preferred anti-periplanar (Newman projection **H** in Scheme 3.9) orientation. Newman projection **I** is the conformation

expected if the iodine had the *cis*-orientation. The syn-periplanar arrangement would also be able to fragment, but for the *cis*-orientation the iodine and the hydroxide group (or hydroxyl group depending on the exact mechanism) would repel one another which would minimise this *syn*-periplanar overlap. Therefore, based on the two possible arrangements (H and I) for the fragmentation, the anti-periplanarity should be the one most likely to react, this also supports the assignment of the *trans*-orientation of the iodine in **143**.

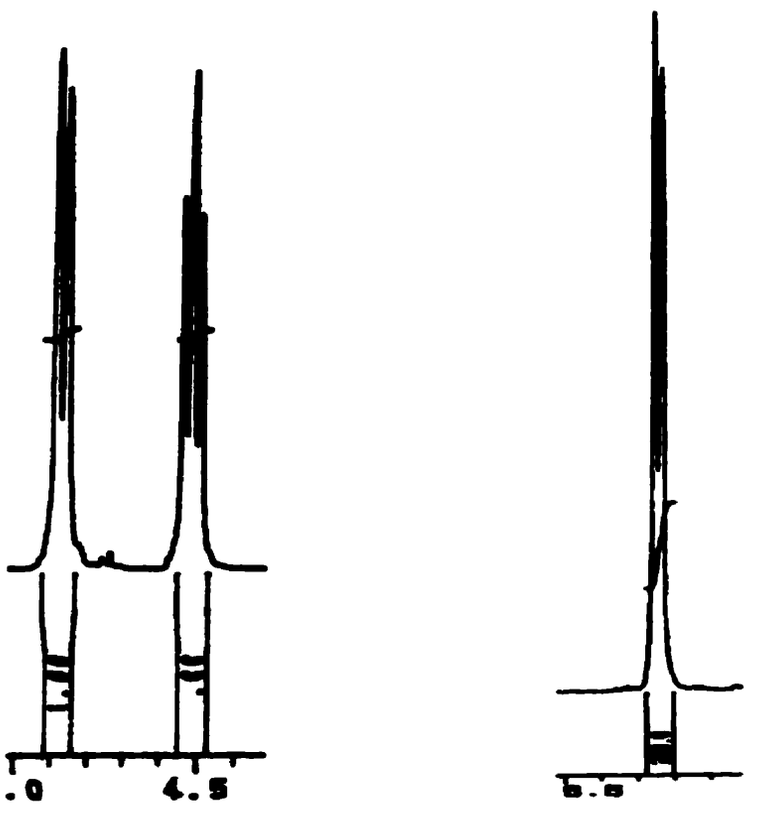
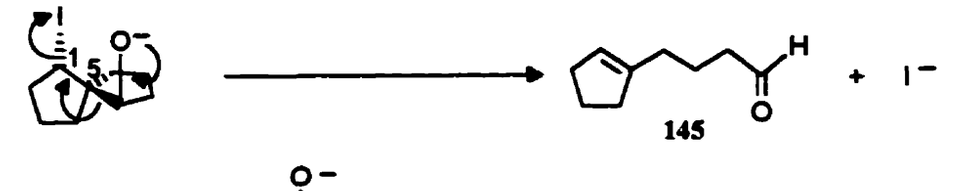
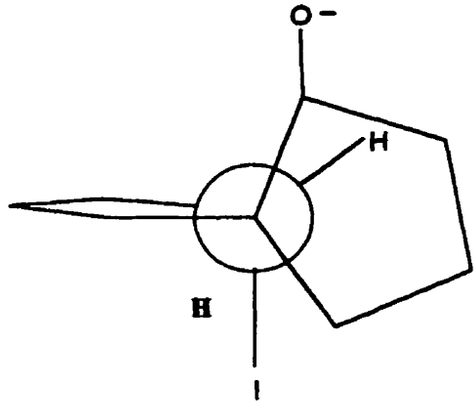


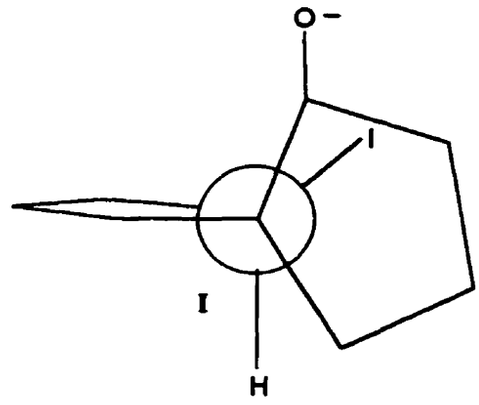
Figure 3.1 The Methine Proton in the ^{1}H-NMR Spectrum for a) Compound **143** and b) Diester **142**



145



Newman projection down the 5 to 1 bond showing close to the anti-periplanar overlap need for the concerted mechanism. Enveloping of 5-membered rings can also increase this overlap.



Newman projection down the 5 to 1 bond showing close to syn-periplanar overlap. However, the repulsion between oxygen and the large iodine will minumize this overlap.

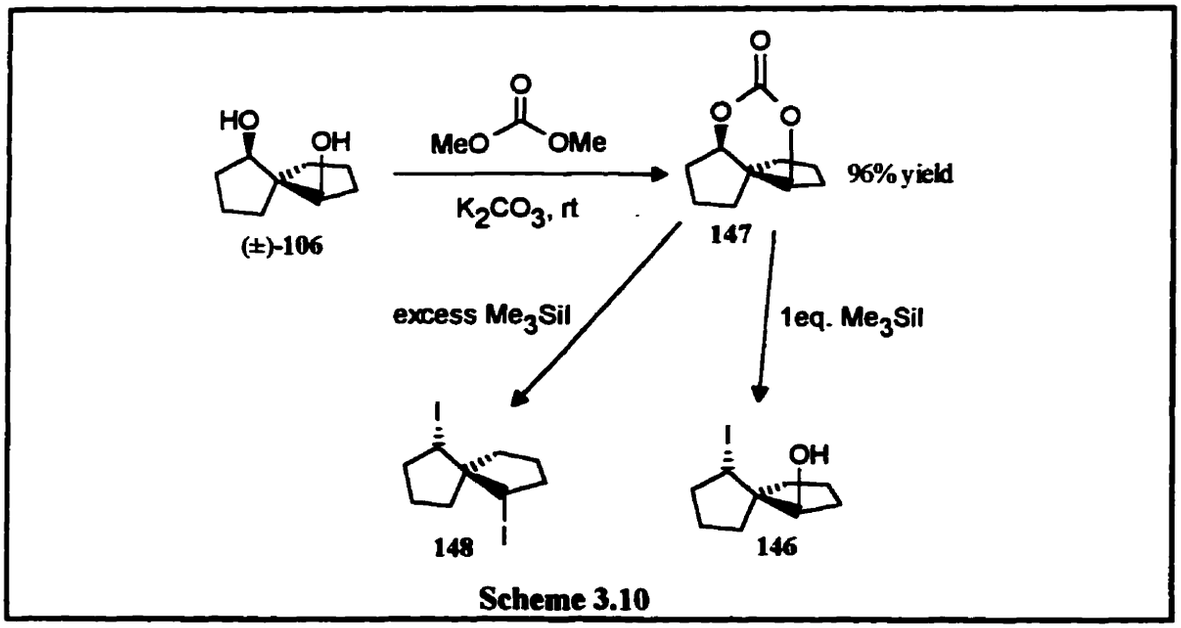
Scheme 3.9

Aldehyde **145** (Scheme 3.7) was isolated from the LAH reaction, which means that workup of the reaction was where the fragmentation occurred. Otherwise a by-product from the reduction of the aldehyde should have also been observed. Formation of **144** from **145** was simply *via* an aldol condensation between two molecules of **145**, which can occur readily under basic (potassium hydroxide) conditions (Scheme 3.7).

Decomposition, formation of inseparable mixtures, and formation of undesired products prevented the detailed charaterisation of compounds **144**, **145**, and **146**. With

the formation of only a small amount of unstable iodo product **146** after multiple steps it seemed a better idea to attempt a different route towards the preparation of **139**.

Displacement of carbonates with iodide using different quantities of iodotrimethylsilane was reported by Kricheldorf.[179] With the facile formation of sulfite **140** (Scheme 3.5) the formation of carbonate **147** should also occur readily (Scheme 3.10). Treatment of (±)-**106** with potassium carbonate and excess dimethyl carbonate produced the desired cyclic alkyl carbonate **147** in 96% yield. Reaction of carbonate **147** with 1 eq. of iodotrimethylsilane apparently produced iodo alcohol **146** as similar ^{1}H-NMR resonances were observed as the product from the LAH reduction of (±)-**143** (Scheme 3.7). Treatment of **147** with excess iodotrimethylsilane produced what appeared to be diodide **148** (by ^{1}H-NMR).



Scheme 3.10

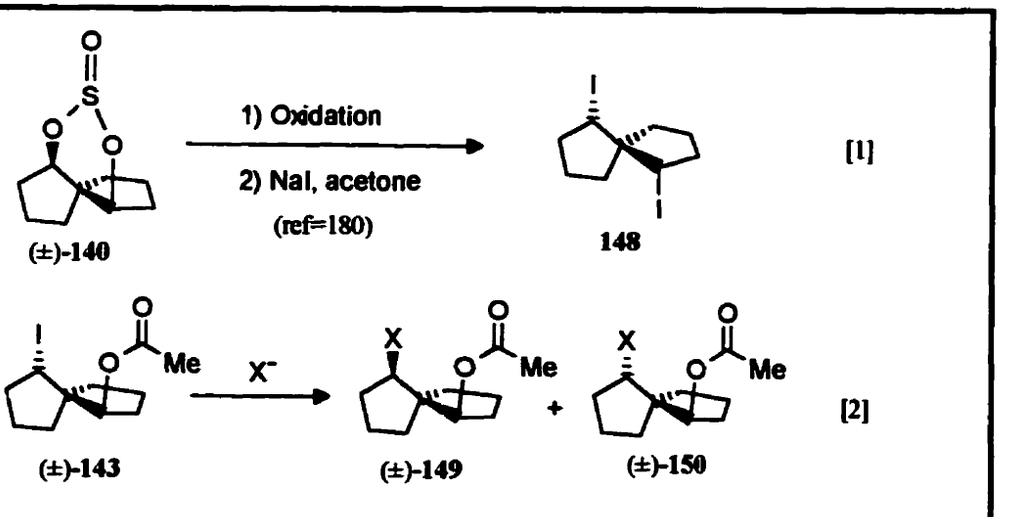
Unfortunately, the products from these reactions readily decomposed and attempts to repeat these results (formation of **146** and **148** from carbonate **147**) with a new ampule of iodotrimethylsilane failed. Thus these products could not be characterised.

3.5 Conclusions and Future Work

This chapter does not represent an exhaustive search for conditions or reagents that would result in the conversion of diol **106** into amino alcohols, diamines, and/ or

diphosphines; however it was all that time permitted. It should be viewed as a starting point towards the synthesis of systems like **139** (Scheme 3.3) and has been included in the thesis because it is not only an important stepping stone for future work, but also these results were important for understanding coordination and reactions typical for the *cis,cis*-spiro[4.4]nonane-1,6-diol (**106**) and spiro[4.4]nonane-1,6-dione (**113**) systems. From the chemistry in this chapter, three conclusions can be draw for the spirononane system: 1) the nucleophilic addition to dione **113** is prone to a retroaldol ring opening of the spirocentre; 2) the conversion of **106** to **139** proved difficult due to both hydroxyl groups complexing or reacting with the reagent(s); and 3) the fact that the functional groups (hydroxyl groups or ketones) of diol **106** and dione **113** are located at a neopentyl site makes it difficult for them to undergo various transformations.

In all the sections reported in this chapter further study with different reagents and conditions might produce the desired product. This section, however, will focus on some other ideas that stemmed from the new methodology reported in this chapter, and due to time restraints were not attempted. These ideas are shown in Scheme 3.11 as possible experiments for future work.



Scheme 3.11

Reaction 1 (Scheme 3.11) is an idea that was obtained while reading a paper by Burk.[180] Burk displaced a diol by forming the sulfite, oxidised it to the sulfate and then displaced the sulfate with an alkylphosphine. For the spiro[4.4]nonane system a similar sequence could be employed with the readily formed sulfite **140** which could be oxidised to the sulfate and then displaced to form, for example, diiodide **148**.

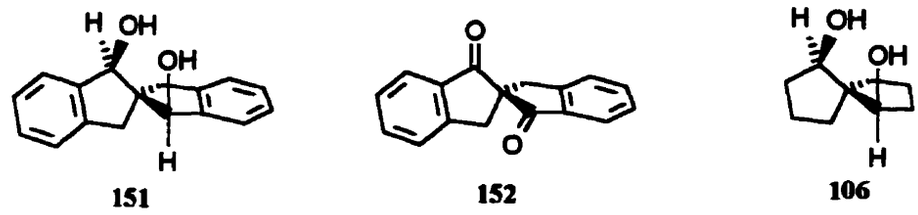
Reaction 2 in Scheme 3.11 is an interesting idea for potentially forming amino alcohols. If $X=N_3^-$, then after the formation of **149**, the reduction with lithium aluminium hydride could produce an amino alcohol. However, there are some possible problems with this idea. First of all, the azide could cleave the ester faster than it displaces the iodide which would probably result in fragmentation to form aldehyde **145** (Scheme 3.9). Another possible problem is the acetate can anchimerically assist with the leaving of the iodide which could result in the formation of the wrong stereochemistry of the azide (compound **150**). The next chapter describes the synthesis and resolution of *cis,cis*-2,2′-spirobiindane-1,1′-diol.

Chapter 4

4 Synthesis and Resolution of (±)-*cis*,*cis*-2,2′-Spirobiindane-1,1′-diol

4.1 Introduction

The interest in 2,2′-spirobiindane-1,1′-diol (**151**, Figure 4.1) arose after the initial investigation of spiro[4.4]nonane-1,6-diol (**106**) as a chiral auxiliary bound to a Lewis acid



151 **152** **106**

Figure 4.1 Structure of *cis*,*cis*-1,1'-Spirobiindane-2,2'-diol (**151**), 1,1'-Spirobiindane -2,2'-dione (**152**), and *cis*,*cis*-Spiro[4.4]nonane-1,6-diol (**106**)

in enantioselective transformations (Chapter 5) failed to produce higher ee's than those reported in the literature with (*S*)-BINOL. A molecular modeling investigation of the aluminium complex of spiro[4.4]nonane-1,6-diol showed that a possible reason for the poorer results could be that the *cis*-hydrogens on C-3 and C-8 (Figure 4.2) might be preventing complete overlap of the oxygen lone pairs in the substrate and the empty orbital on the Lewis acid.

Investigation of other types of spiro compounds that do not have interfering *cis*-hydrogens at the C-3 and C-8 (Figure 4.2) positions resulted in the design of diol **151** (Figure 4.1) as a typical example. Diol **151**, with the two benzene rings, might also sterically hinder the Lewis acid compared to diol **106**, but not block the Lewis acidic site in the same manner as the *cis*-hydrogens (C-3 and C-8) are doing in Figure 4.2. The hindrance created by the aromatic rings could also assist in increasing the percent ee observed for products when compared to those obtained with diol **106**.

In order to compare the effectiveness of diols **106** and **151** as auxiliaries in enantioselective transformations, the synthesis of both enantiomers of *cis*,*cis*-2,2′-

spirobiindan-1,1′-diol (**151**) was required. Section 4.2 reports the previous syntheses and resolutions of 2,2′-spirobiindane-1,1′-dione (**152**, Figure 4.1) and *cis,cis*-2,2′-spirobiindane-1,1′-diol (**151**), while Section 4.3 describes, in detail, an improved synthesis and resolution of (±)-*cis,cis*-2,2′-spirobiindan-1,1′-diol (**151**).

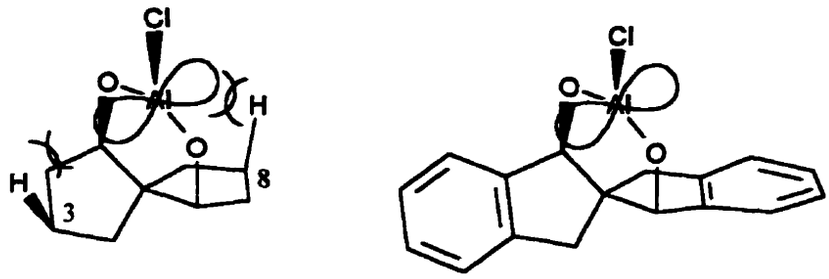
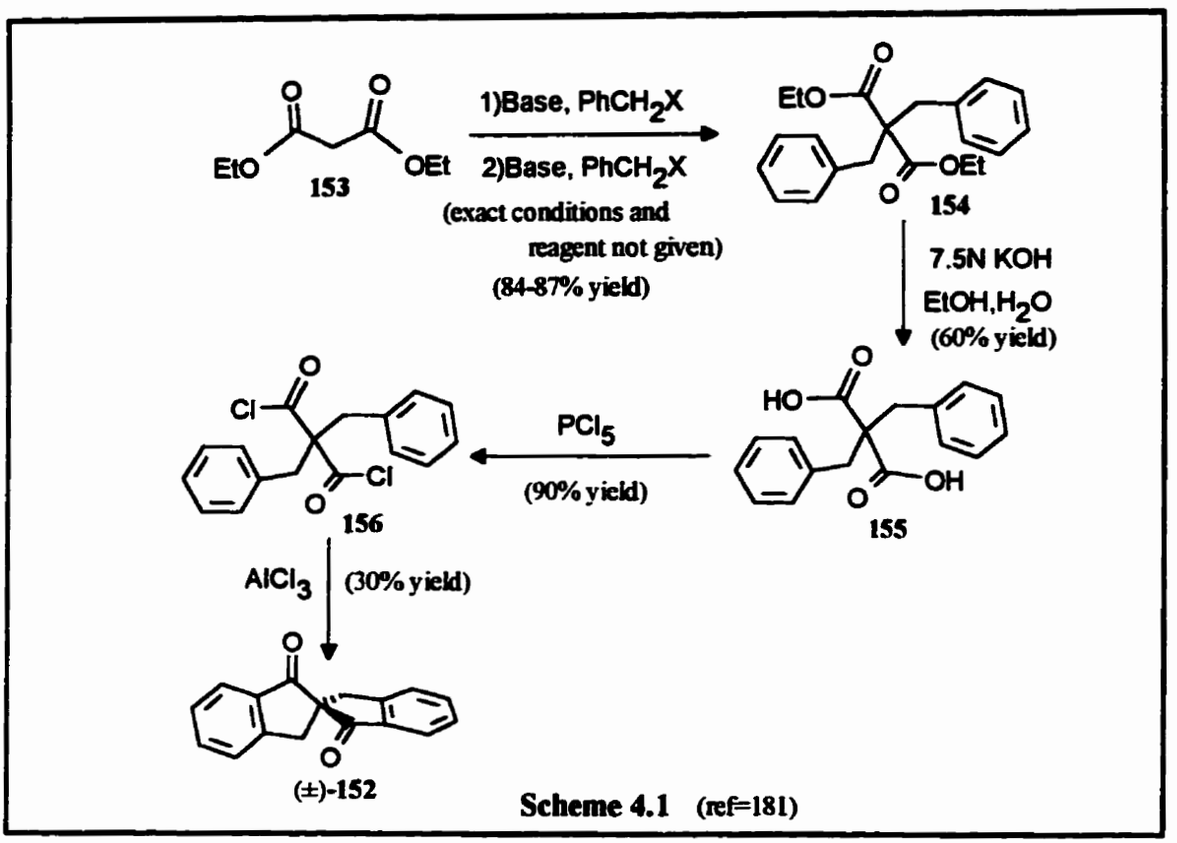


Figure 4.2 The Lewis Acidic Site on Two Aluminium Spirodiol Complexes

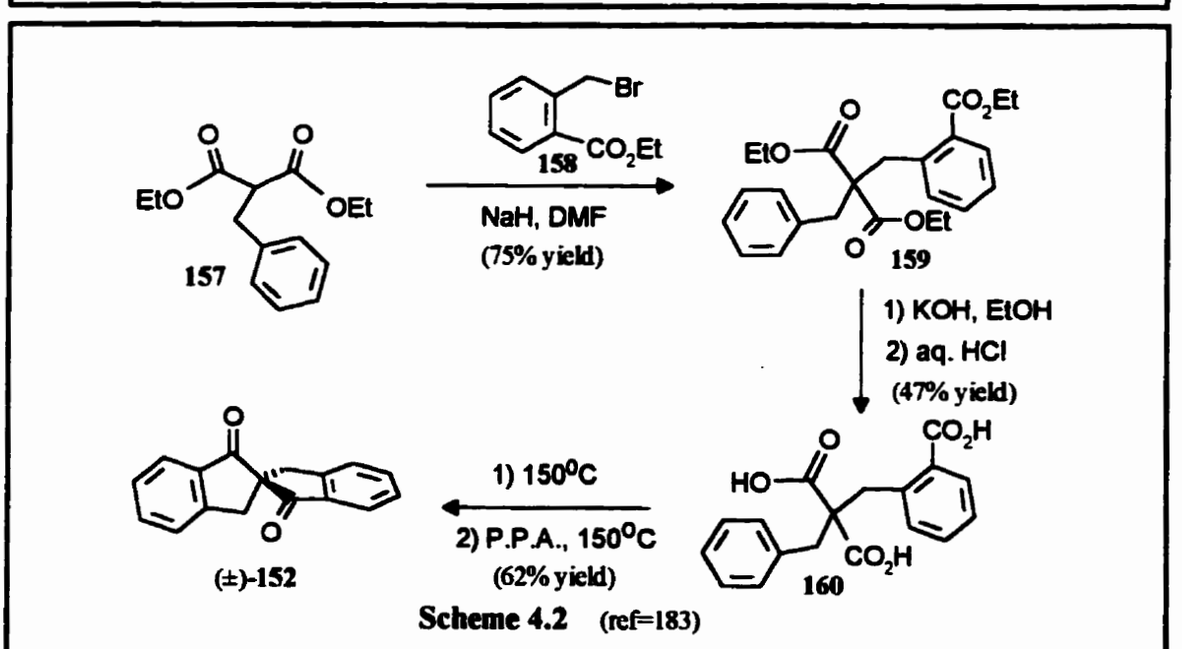
4.2 Previous Syntheses and Resolutions of 2,2′-Spirobiindane-1,1′-dione (152) and *cis,cis*-2,2′-Spirobiindane-1,1′-diol (151)

4.2.1 Syntheses of (±)-2,2′-Spirobiindane-1,1′-dione (152)

The first synthesis of dione **152** was reported in 1912 by Leuchs and Radulescu (Scheme 4.1).[181] The synthesis began with diethyl malonate (**153**), which was converted to diethyl dibenzylmalonate (**154**) in 84-87% yield although the conditions and reagents were not given. Saponification of the esters in **154** was accomplished with 7.5 N potassium hydroxide in ethanol which produced diacid **155** in 60% yield with some loss of product due to decarboxylation. Reaction of diacid **155** with phosphorus pentachloride resulted in the formation of the diacid chloride **156** in 90% yield. Treatment of **156** with 1-2% aluminium chloride followed by distillation of (±)-dione **152** from the reaction mixture provided **152** in 30% yield. An overall yield of 14% of (±)-dione **152** was obtained by this procedure. In a later publication, Ingold and Wilson[182] found the last two steps (Scheme 4.1) did not proceed as reported and they altered the procedure slightly by using phosphorus pentachloride in chloroform for the penultimate step, and in the last step changed the Lewis acid from aluminium chloride to ferric chloride ($FeCl_3$).



Scheme 4.1 (ref=181)



Scheme 4.2 (ref=183)

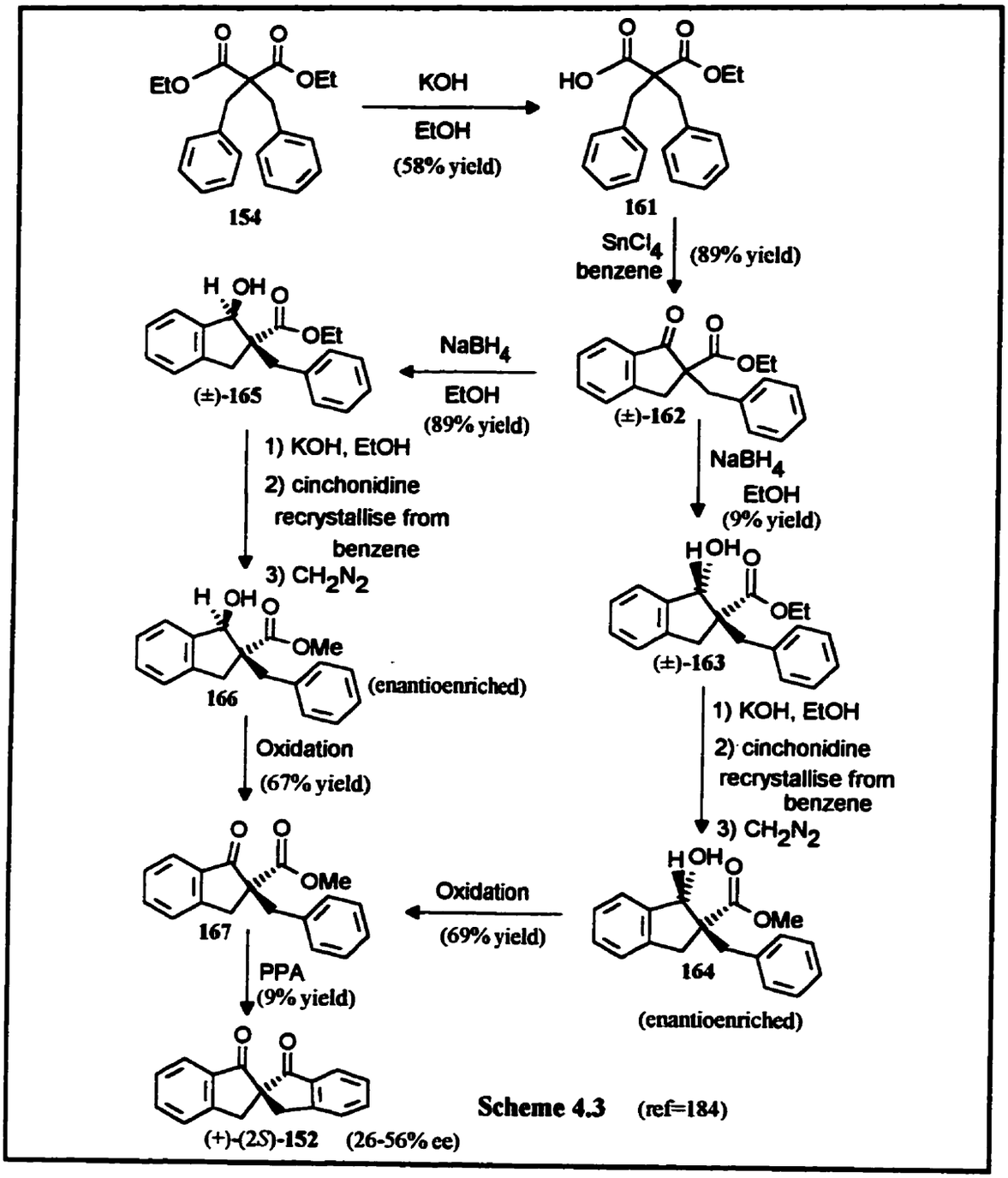
Another synthesis was reported in 1972 by Dynesen (Scheme 4.2)[183] and started with the deprotonation of diethyl benzylmalonate (157) with NaH in DMF followed by the

addition of ethyl α-bromo-*o*-toluate (**158**). Triester **159** was obtained in 75% yield. Saponification of the three esters in **159** resulted in triacid **160**. Decarboxylation of **160** at 150°C followed by the addition of polyphosphoric acid and heating to 150°C produced (±)-dione **152** in 62% yield. The overall yield of the synthesis was 22%.

4.2.2 Synthesis of Enantioenriched 2,2′-Spirobiindane-1,1′-dione (152) and *cis,cis*-2,2′-Spirobiindane-1,1′-diol (151) by Resolution Techniques

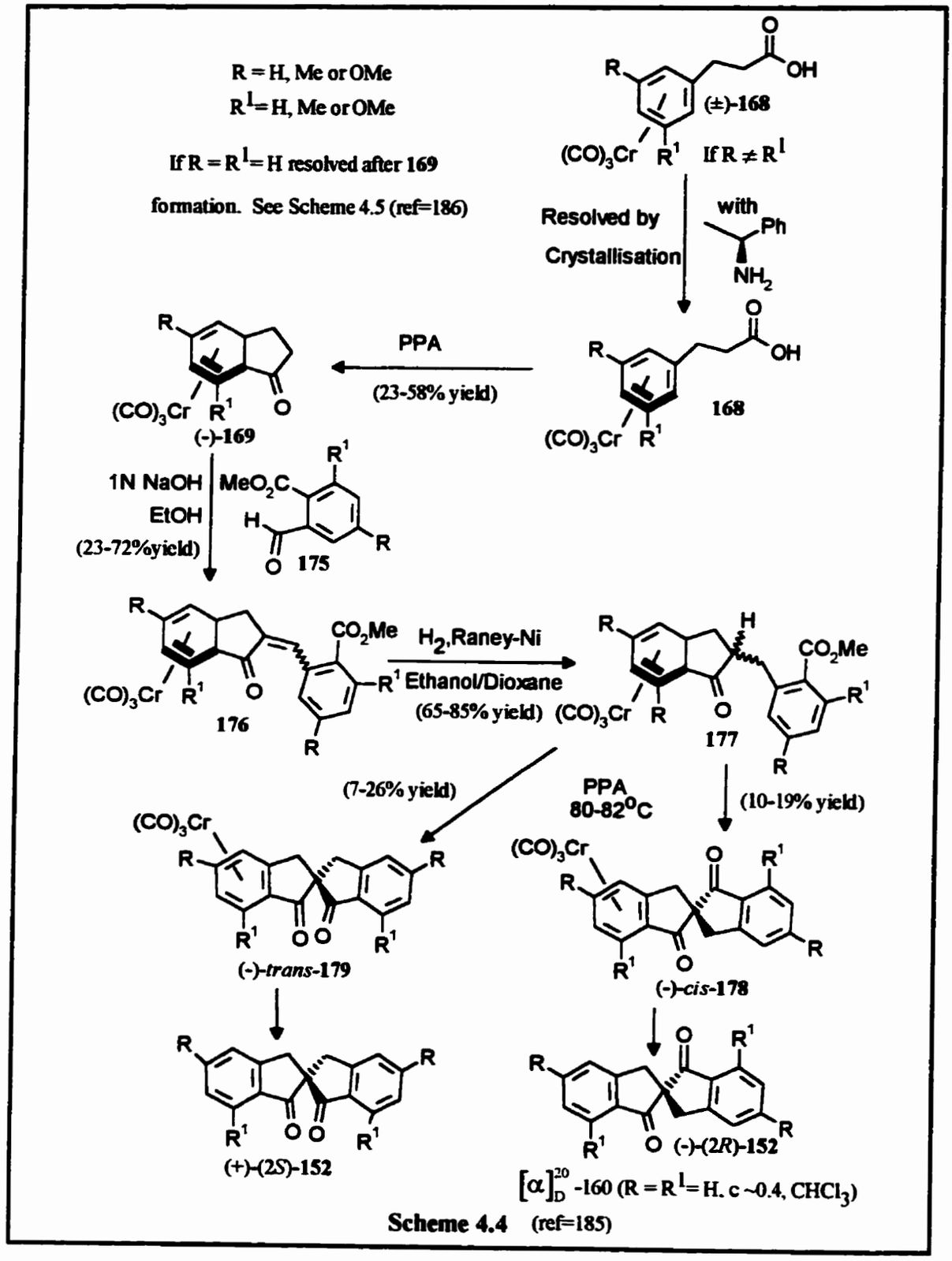
Most of the work in this area has come from the Schlögl laboratory. The first synthesis and resolution was reported in 1974 (Scheme 4.3).[184] The synthesis started with diethyl dibenzylmalonate (**154**) which was previously reported in Scheme 4.1. Monoacid-monoester **161** was formed in 58% yield by selective saponification of one ester in **154** with potassium hydroxide in ethanol. Cyclisation of monoacid **161** was accomplished with tin(IV) chloride in benzene producing **162** in 89% yield. Reduction of the ketone with sodium borohydride produced a mixture of *cis*-**163** and *trans*-**165**, which were subsequently separated. Individually, the ester groups in *cis*-**163** and *trans*-**165** were then saponified producing acids, which were crystallised from benzene in the presence of cinchonidine resulting in enantioenrichment. Treatment of these acids with diazomethane produced *cis*-**164** and *trans*-**166**. Oxidation of either *cis*-**164** or *trans*-**166** produced ketone **167** in approximately 68% yields. The final step was the cyclization to spirodione **152** which was produced in 9% yield. The measured optical rotation showed that the enantioenrichment was between 26 and 56% ee.

Another route published by Schlögl for the synthesis and resolution of (±)-spirodione **152** used a resolution method involving a chromium tricarbonyl complex (Scheme 4.4).[185] This method was also applied to similar systems with different substitution patterns on the aromatic ring system (where $R \neq R^1$; R, R^1 = H, Me, or OMe); however, for R = H and R^1 = H, the system of interest in this dissertation, the resolution procedure could not be employed because compound **168** was not chiral. A different resolution procedure had to be applied when R = R^1, which when R = R^1 = H the resolution method turned out to be very lengthy (Scheme 4.5). The resolution method



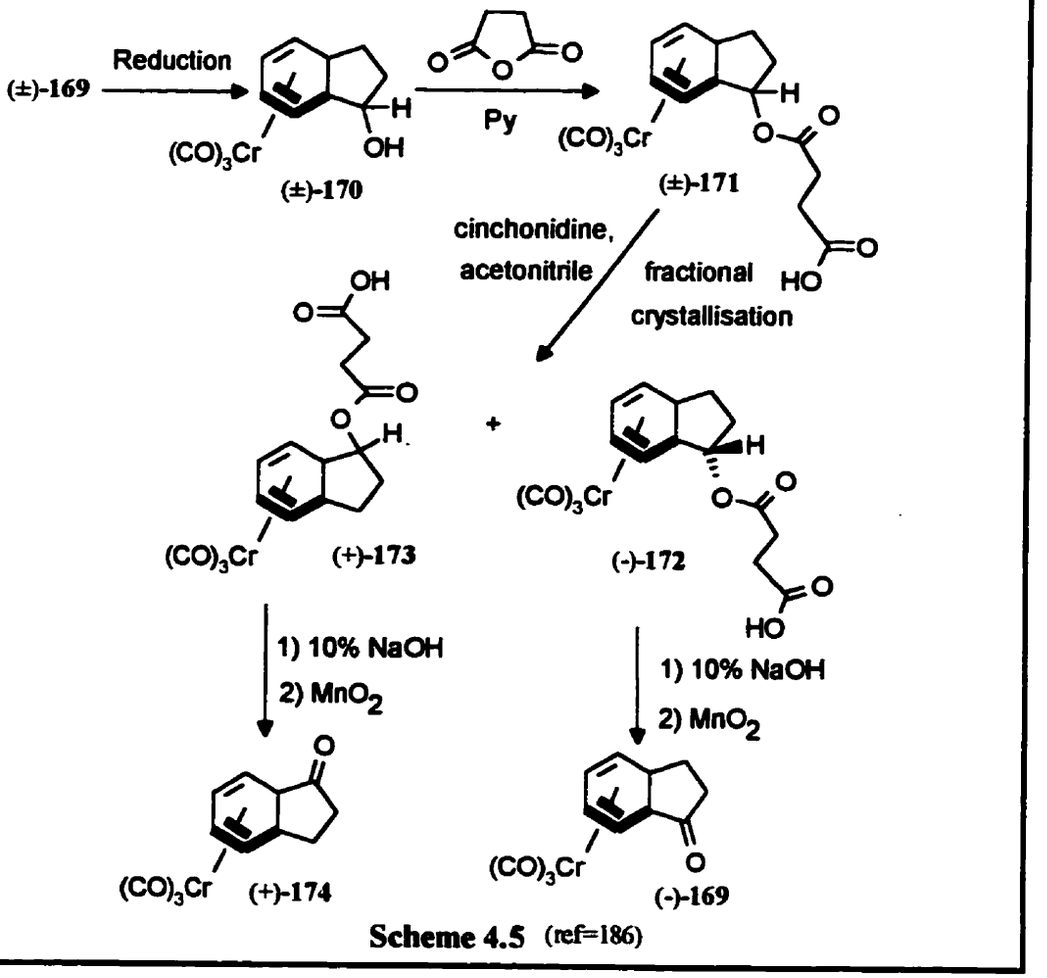
Scheme 4.3 (ref=184)

that was adopted (Scheme 4.5) started with (±)-indanonechromiumtricarbonyl (**169**), which was formed in an undisclosed yield by the cyclisation of **168** with polyphosphoric acid (Scheme 4.4).



Scheme 4.4 (ref=185)

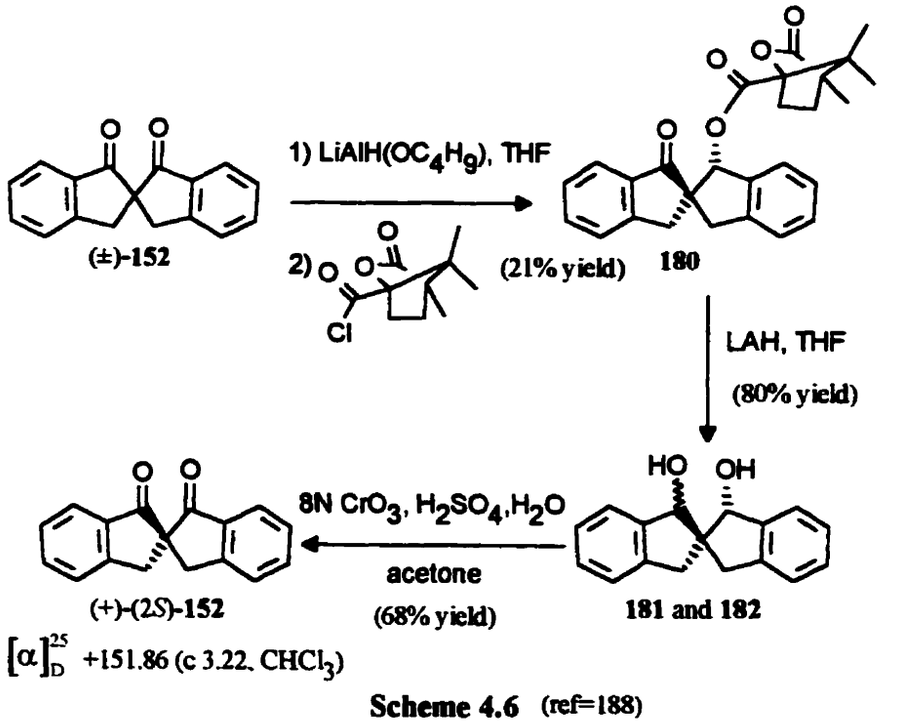
Meyer, Neudeck and Schlögl used the published procedure by Jaouen and Meyer[186] (Scheme 4.5) to resolve the racemates for 1-indanolchromiumtricarbonyl (**170**) which was formed from **169** in an undisclosed reduction method. The resolution reported by Jaouen and Meyer (Scheme 4.5) involved conversion of (±)-*cis*-1-indanolchromiumtricarbonyl **170** to its succinate derivative **171**. The salt formation of the succinate half esters **171** with cinchonidine and fractional crystallisation allowed separation of the two succinate-cinchonidine diastereomers which upon removal of the cinchonidine produced resolved **172** and **173**. Cleavage of the succinate and oxidation with MnO_2 provided enantioenriched dione **169**. The only yield reported by Jaouen and Meyer (Scheme 4.5) was for the last oxidation step (70%); therefore the overall utility of this procedure was not apparent.



Scheme 4.5 (ref=186)

With enantioenriched **169** in hand, Schlögl continued with the synthesis of dione **152** reported in Scheme 4.4. The next step was an aldol condensation of ketone **169** with aldehyde **175**. The resulting α,β-unsaturated ketone **176** was obtained in 72% yield as a mixture of double bond isomers. Hydrogenation of the double bond was reported to proceed with hydrogen and Raney nickel, forming **177** in 70% yield. Cyclisation with polyphosphoric acid produced both *cis*-**178** and *trans*-**179**. Separation of these diastereomers (*cis*-**178** and *trans*-**179**) and removal of the chromiumtricarbonyl moiety produce both (+)-(2*S*)- and (-)-(2*R*)-spirodione **152** with high enantiomeric purities.

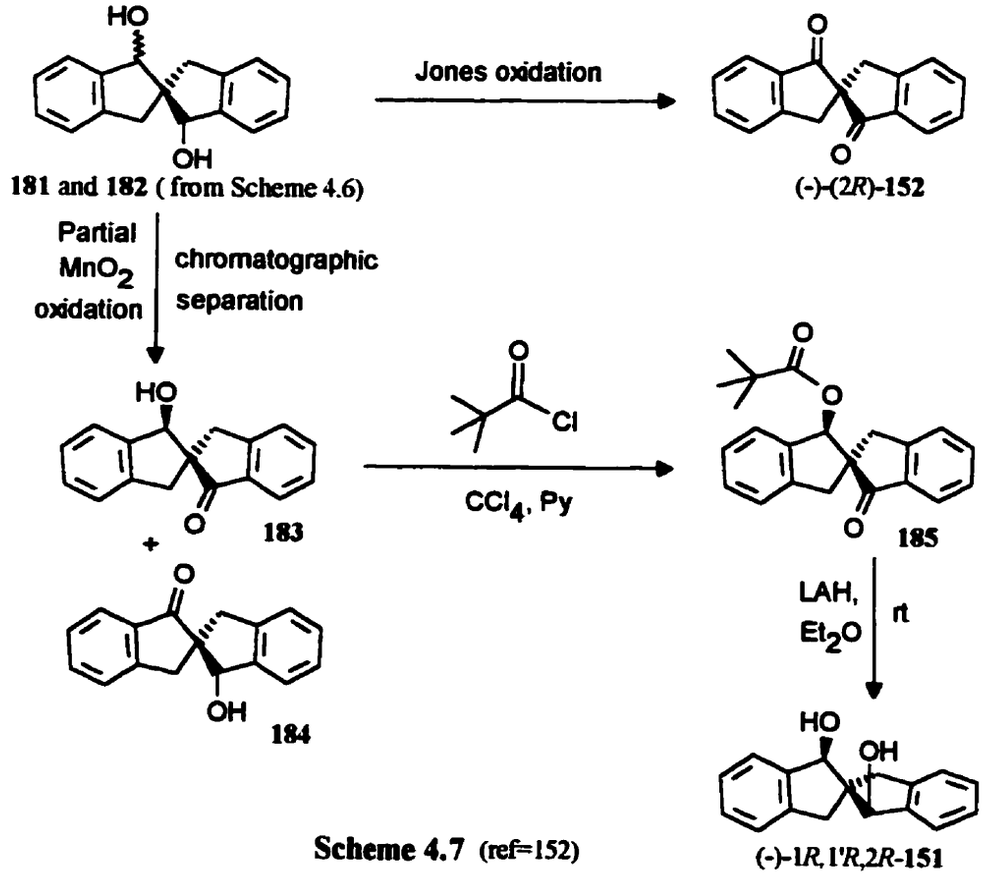
The last method reported by Schlögl to resolve dione **152** was by "medium pressure chromatography on a triacetylcellulose column in ethanol or ether".[187] Schlögl and Widhalm were able to get baseline separation on this "specially prepared column". The reasons this method was not used by us was due to: 1) the lengthy preparation of this "special column", and 2) only 5-50 mg could be separated at once. Since larger quantities of spirodione **152** were necessary for chiral auxiliary evaluation, this procedure was not



Scheme 4.6 (ref=188)

practical.

Dynesen reported a different procedure for resolving dione **152** (Scheme 4.6).[188] He used the same procedure for the formation of (±)-dione **152** as shown in Scheme 4.2. The reduction of (±)-dione **152** with one equivalent of hydride followed by the formation of the camphanoate ester of the resulting alcohol, produced a mixture of diastereomeric ketoesters. Compound **180** was separated from the diastereomeric ketoester mixture by recrystallisation from acetone (21% yield from (±)-**152**). Lithium aluminium hydride reduction of ketoester **180** produced a mixture of alcohols **181** and **182** in 80% yield. Oxidation of both alcohols with chromium trioxide provided (-)-(2*S*)-dione **152** in 68% yield. Harada's group also used this procedure to resolve dione **152**, but they also showed that the mixture of diols obtained after removal of the camphanoate ester (**181** and **182**)



Scheme 4.7 (ref=152)

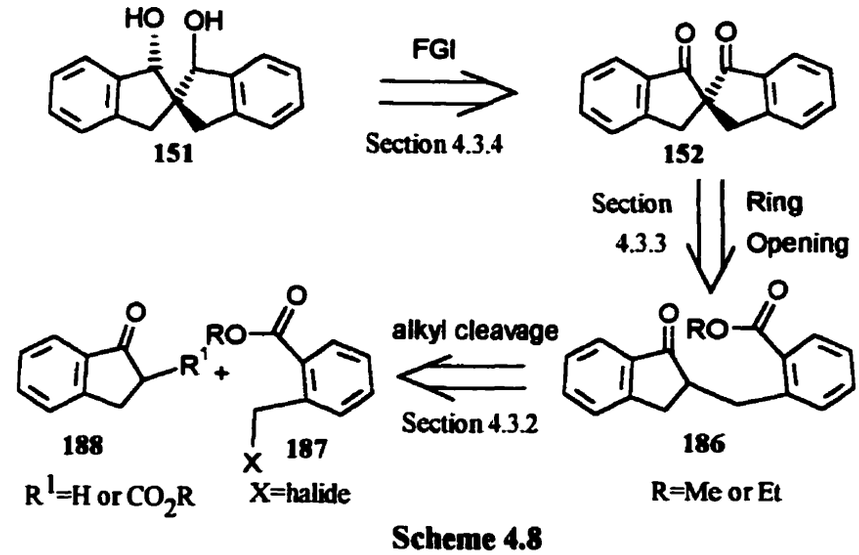
had the *cis,trans*- (**181**) and *trans,trans*-orientations (**182**).[189] Overall, this is a good resolution but adds four steps to the synthesis, and both antipodes are not readily available.

Kabuto *et al.*, using the resolution reported by Dynesen[188] in Scheme 4.6 and the modifications by Harada,[189] synthesised enantioenriched *cis,cis*-diol **151** (Scheme 4.7).[152] The sequence started with compounds **181** and **182** (from Scheme 4.6) which were only partially resolved. Jones oxidation of these diols (**181** and **182**) produced (-)-2*R*-dione **152** which demonstrated that **181** and **182** were enantiomerically enriched and confirmed the absolute stereochemistry of the spirocentre. Partial oxidation of diols **181** and **182** resulted in a mixture of *cis*-**183** and *trans*-**184** that was separated by column chromatography. Esterification of *cis*-**183** with pivaloyl chloride resulted in ketoester **185**. Treatment of ketoester with LAH provided enantioenriched (-)-diol **151**. The entire procedure, by Kabuto *et al.*,[152] in Scheme 4.7 was analogous to the one reported for the stereoselective formation of the *cis,cis*-spiro[4.4]nonane system (Scheme 2.6).

4.3 Improved Synthesis and Resolution of (±)-2,2'-Spirobiindane-1,1'-diol

4.3.1 Introduction

Previous syntheses of (±)-dione **152** were accomplished with low overall yields

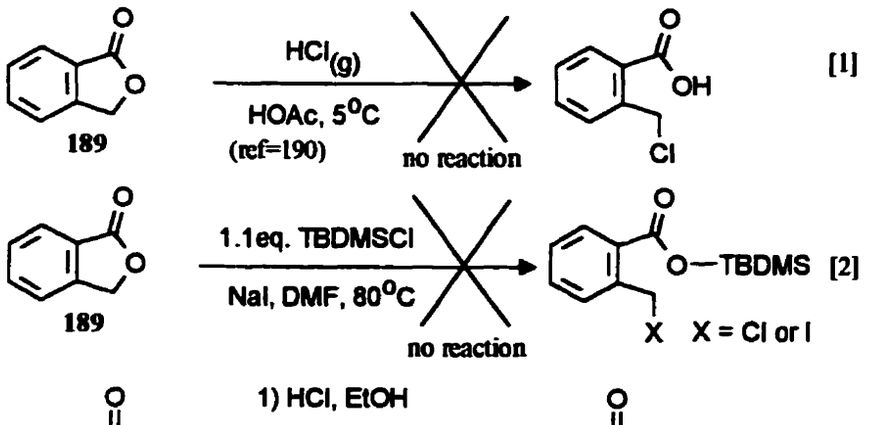


Scheme 4.8

(14% and 22%). The resolution sequences were also more than 2 steps in length and yielded only one enantiomer. Therefore an improved synthesis and resolution of *cis,cis*-diol **151** was needed and investigated (retrosynthesis in Scheme 4.8). The first step in the retrosynthesis was the functional group interconversion to dione **152** (Section 4.3.4). Ring cleavage of either of the two homotopic ketones produced keto ester **186** (Section 4.3.3). Alkyl cleavage produced compounds **187** and **188** (Section 4.3.2).

This retrosynthesis is efficient and would allow for a resolution after the formation of the spirocentre at the diol **151** and dione **152** stage. A thorough examination of the synthesis of **151** is reported in the following sections and each step in the synthesis is covered in a separate section for clarity. A new resolution of (±)-**151** is presented in Section 4.3.5.

4.3.2 Alkylation of the 1-Indanone with Ethyl α-bromo-*o*-toluate (158)



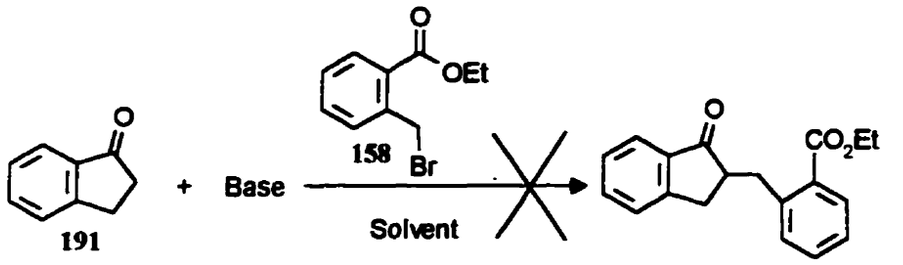
Scheme 4.9

Before investigating the alkylation of 1-indanone, a synthesis of haloester **158** had to be developed. The approaches taken towards the formation of **158** are summarised in Scheme 4.9. The first two reactions were attempts to open phthalide (**189**) to provide a

chloroacid[190] or chlorosilylester respectively, but both reactions failed to proceed as desired (Scheme 4.9).

Reaction 3 involved esterification of *o*-toluic acid (**190**) to ethyl *o*-toluate (quantitative) followed by an NBS bromination (in refluxing carbon tetrachloride) in the presence of benzoyl peroxide as the initiator (93% yield with 7% starting material).[191] This produced bromoester **158**, which was purified by distillation (86% yield) and immediately used in the alkylation of 1-indanone (**191**) or the β-ketoester of 1-indanone (**192**).

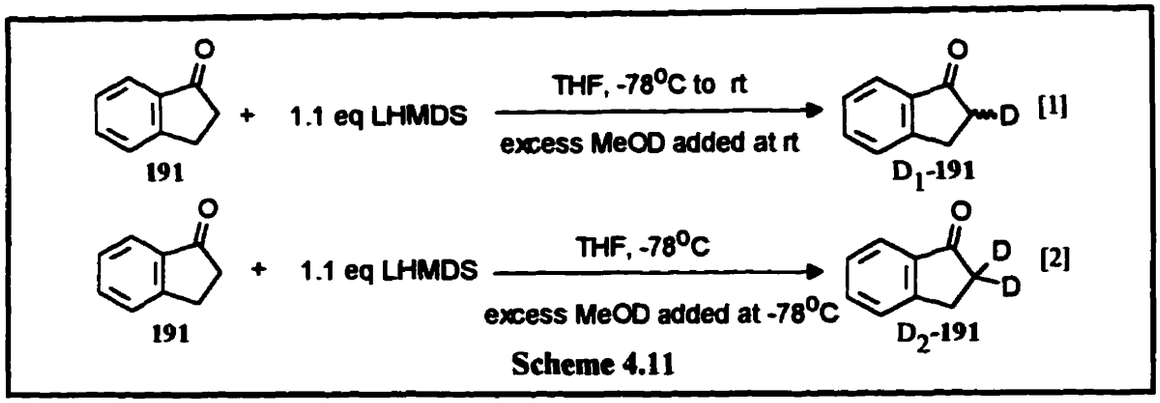
A variety of conditions for the alkylation of 1-indanone with bromoester **158** (Scheme 4.10) were attempted and are shown in Table 4.1. In all cases tried, either unreacted 1-indanone or a mixture of products was obtained.



Scheme 4.10

Table 4.1 Conditions Used for the Reaction Between 1-Indanone and Bromoester **158** (Scheme 4.10)

Reaction	Base (eq.)	Solvent/ T(°C)	Product
1	LDA (1)	THF/ -78 to rt	no reaction
2	LHMDS (1.05)	THF/ -78 to rt	no reaction
3	LHMDS (2.1)	THF/ -78 to rt	no reaction
4	KH (2.1)	THF/ -78 to rt	mixture
5	KH (2)	HO*t*-Bu/ rt	mixture
6	NaH (1)[186]	benzene-DMF/ rt	mixture



Scheme 4.11

In order to determine if the lithium enolate was forming deuteration studies for the deprotonation with LHMDS were undertaken (Scheme 4.11). Under both conditions reported in Scheme 4.11 deuterium incorporation had occurred, which leads to the conclusion that the enolate was indeed forming. This conclusion was based on the decrease in the intensity of the signal at δ 2.7 (Figure 4.3b) when the starting material (Figure 4.3a) was compared to the product obtained from reaction 1 (t, 1H) and reaction 2 (Figure 4.3c; signal almost nonexistent). In parallel, a change in the coupling of the adjacent protons (resonance at δ 3.15) was also observed between the starting material (t, 2H), reaction 1 (d, 2H), and reaction 2 (s, 2H). Based on these observations, reaction 1 was monodeuterating as expected, but reaction 2, which occurred at a lower temperature, resulted in dideuteration. These two reactions were run in parallel with similar quantities and times, with the only main difference being the temperature of the reaction when the MeOD was added. This dideuteration was unexpected, especially because the reaction at lower temperature was the one that resulted in double deuteration. If incorporation of a second deuterium was to occur due to the presence of LiOMe (formed by quenching the Li enolate with MeOD), one would suspect it would occur more readily at higher temperature. Although an exact explanation for this observation was not known, the LiOMe may remain associated with the ketone at lower temperature which results in removal of the remaining α-H with MeOLi, which results in the formation of the dideuterated product.

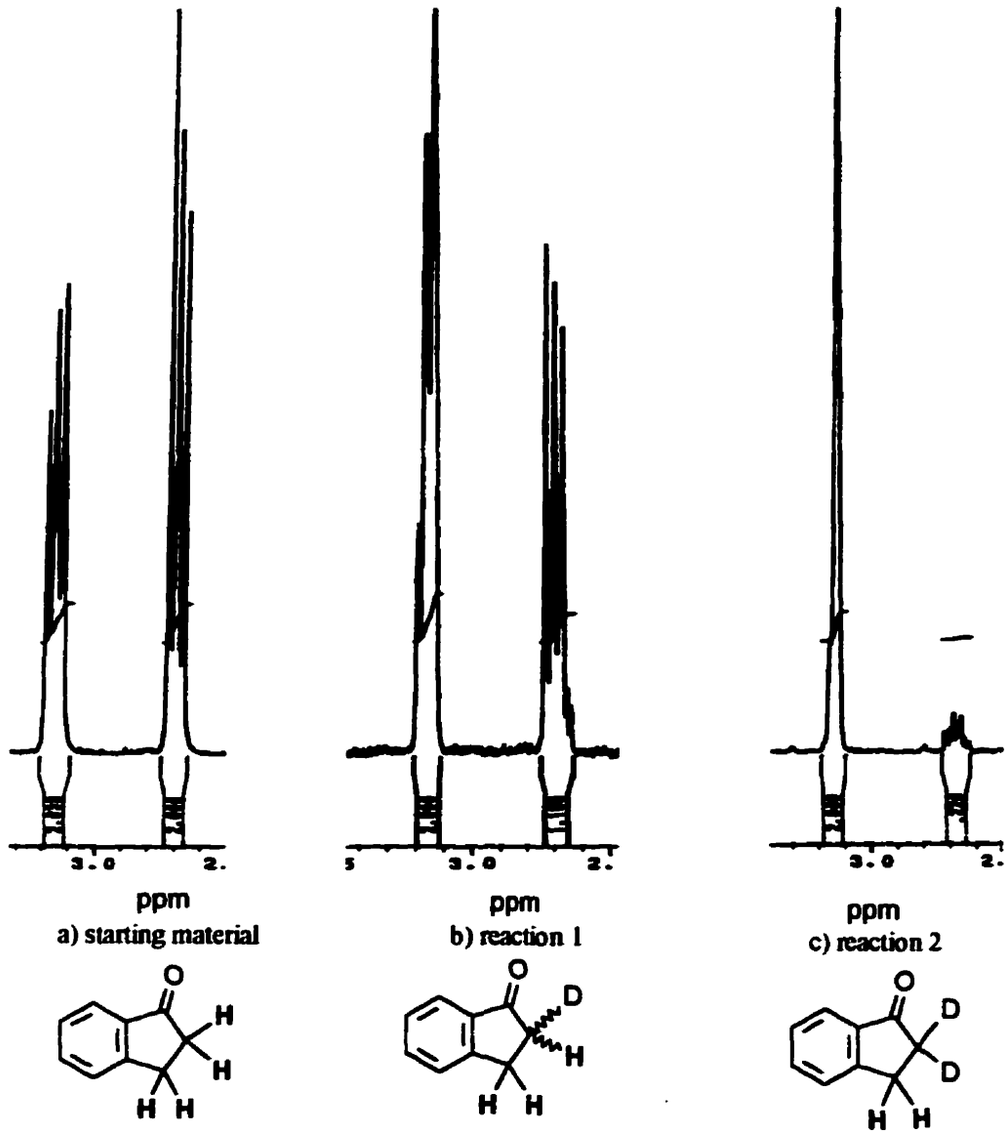
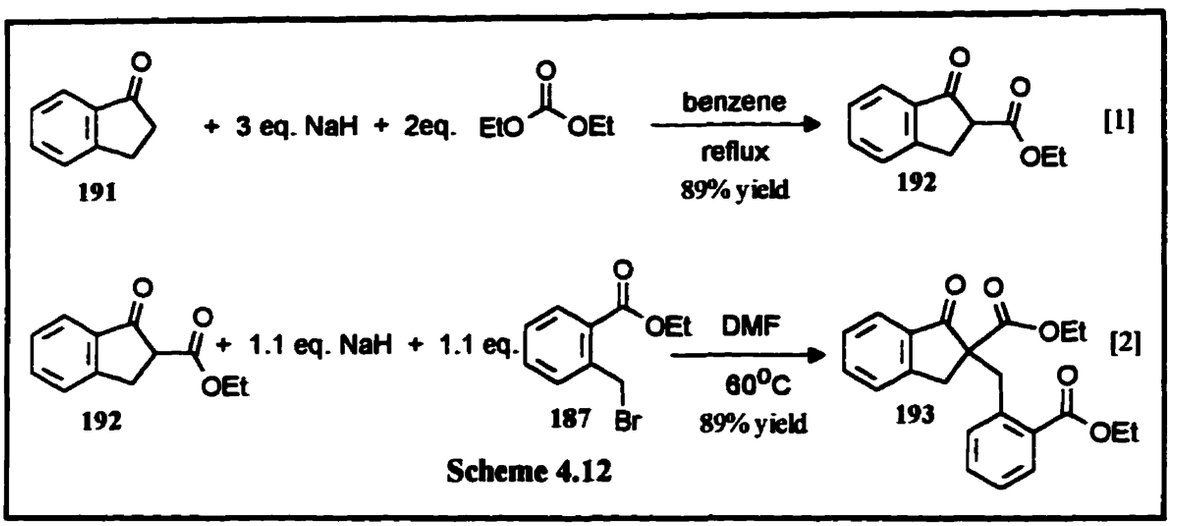


Figure 4.3 The Partial ^{1}H-NMR Spectra of the Bolded Hydrogens for a) Starting Material, b) Reaction 1, and c) Reaction 2 from Scheme 4.11

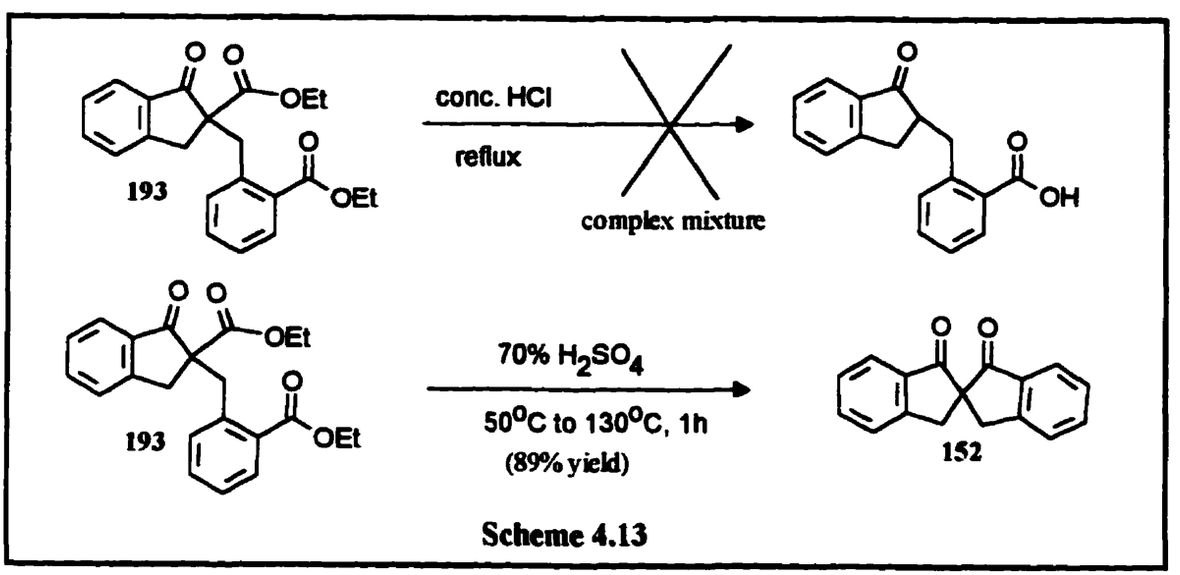
The failure to alkylate 1-indanone directly suggested that activation of the α-site might be necessary. Investigation into methods to produce β-ketoesters from ketones yielded a procedure by Krapcho *et al.*,[192] which upon application to 1-indanone (**191**) produced β-ketoester **192** in 89% isolated yield (Scheme 4.12). Deprotonation of **192** with NaH in DMF followed by addition of bromoester **158** and heating to 60°C for 87



Scheme 4.12

hours produced a compound in 89% yield which exhibited three carbonyl signals in the ^{13}C-NMR spectrum (δ 202.6 (ketone), 170.8 (ester), 167.7 (ester)), two of which were determined to be ethyl esters by examination of the ^{1}H-NMR spectrum (δ 4.30 (q, 2H, J=7.1Hz), 4.15 (q, 2H, J=7.1Hz), 1.32 (t, 3H, J=7.1Hz), 1.17 (t, 3H, J=7.1Hz)).[183] These spectral signals along with others listed in the Experimental section supported the assignment of structure **193** (Scheme 4.12).

4.3.3 Saponification, Decarboxylation and Cyclisation of Keto Diester 193 to 2,2'-Spirobiindane-1,1'-dione (152)



Scheme 4.13

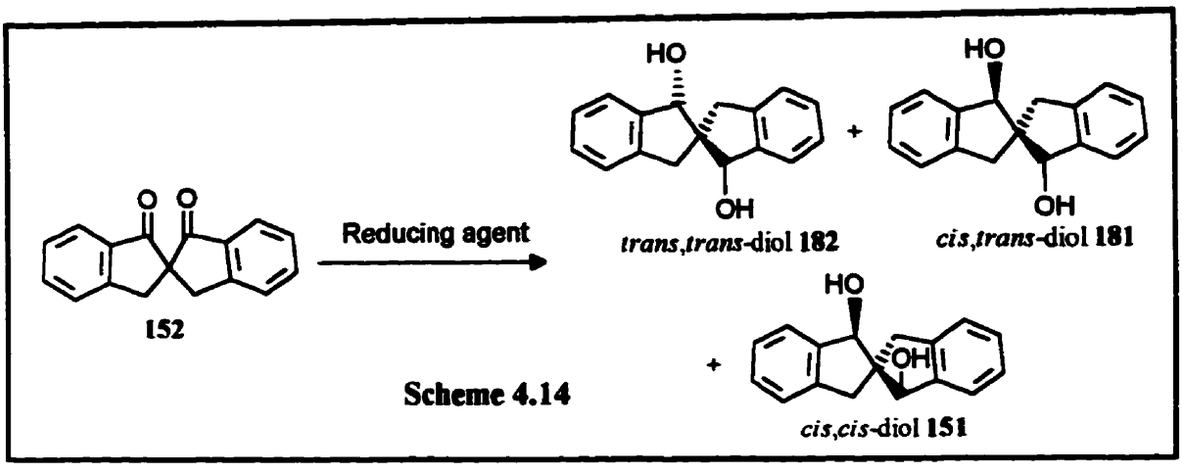
Applying the conditions previously identified in Section 2.3.2 to hydrolyse and decarboxylate ester **116**, to compound **193** resulted in a complex mixture (Scheme 4.13). While investigating other possibilities for the conversion of **193** into **152**, an interesting reaction was found in the literature which used 70% H_2SO_4 to cyclise a cyano group onto an aromatic ring resulting in a cyclic ketone.[193]

Using these reaction conditions with ketodiester **193** provided **152** in 89% yield. This reaction sequence thus involved hydrolysis of the esters to acids, a decarboxylation and "aldol-like" cyclisation to **152**. The mass spectrum indicated a molecular ion of 248 and only nine carbon resonances were observed in the ^{13}C-NMR spectrum (δ 202.6, 153.8, 135.3, 135.2, 127.7, 126.3, 124.7, 65.2, 39.9) thus confirming that the product was indeed compound **152**.

4.3.4 Stereoselective Reduction of (±)-2,2′-Spirobiindane-1,1′-dione (152) to (±)-*cis*,*cis*-2,2′-Spirobiindane-1,1′-diol (151)

A stereoselective reduction of spiro[4.4]nonane-1,6-dione (**113**) with lithium *tert*-butyldiisobutylaluminium hydride was reported in Section 2.3.4. Since the 2,2′-spirobiindane-1,1′-dione (**152**) has a similar orientation of the carbonyl groups as **113**, the reaction with lithium *tert*-butyldiisobutylaluminium hydride under the same conditions was expected to provide only *cis*,*cis*-2,2′-spirobiindane-1,1′-diol (**151**). While the reduction with LAH and DIBAL-H provided a mixture of diols in excellent yield, lithium *tert*-butyldiisobutylaluminium hydride provided only the *cis*,*cis*-diol **151** in 97% yield (Figure 4.4, Table 4.2, Scheme 4.14).

The *cis*,*cis*-orientation of **151** has never been unequivocally proven. It has, however, in a roundabout way been proven by combining the results from four papers. First of all Iversen *et al.*[194] proved the absolute stereochemistry of camphonoate **180** (Scheme 4.6) by getting an X-ray crystal structure. This meant that the ^{1}H-NMR signals obtained for the compound Dynesen[188] and Harada *et al.*[189] isolated from the hydrolysis of



Scheme 4.14

Table 4.2 Reduction of (±)-2,2′-Spirobiindane-1,1′-dione with Different Reducing Agents

Reducing Agent	Conditions	*trans,trans*-diol 182 (%)[a]	*cis,trans*-diol 181 (%)[a]	*cis,cis*-diol 151 (%)[a]	Yield (%)
LAH	Et_2O, 0°C	16	75	9	94
Dibal-H	THF, -78°C	19	46	35	97
Li*t*-Bu(iBu)$_2$AlH	THF, -78°C	0	0	100	97

a) determined by ^{1}H-NMR spectroscopy.

compound **180** could be positively identified to the structure **184** (Scheme 4.7). When Kabuto *et al.*[152] separated compound **184** and **183** they knew which had the *trans*-orientation (**184**) by the ^{1}H-NMR spectrum and therefore they knew which one had the *cis*-orientation (**183**). Kabuto *et al.* then formed compound **185**, which must have the *cis*-stereochemistry (Scheme 4.7). Reduction of **185** can only produce two possibilities for the configuration of the reduced diol (*cis,trans* (**181**) and *cis,cis* (**151**)) because one of them must be *cis* due to the orientation of the ester. The ^{1}H-NMR signal observed by Kabuto *et al.*[152] for the hydrogens on the carbon geminal to the hydroxy groups consisted of a single resonance (δ 4.94 (2H)). The fact that only one resonance was observed at δ

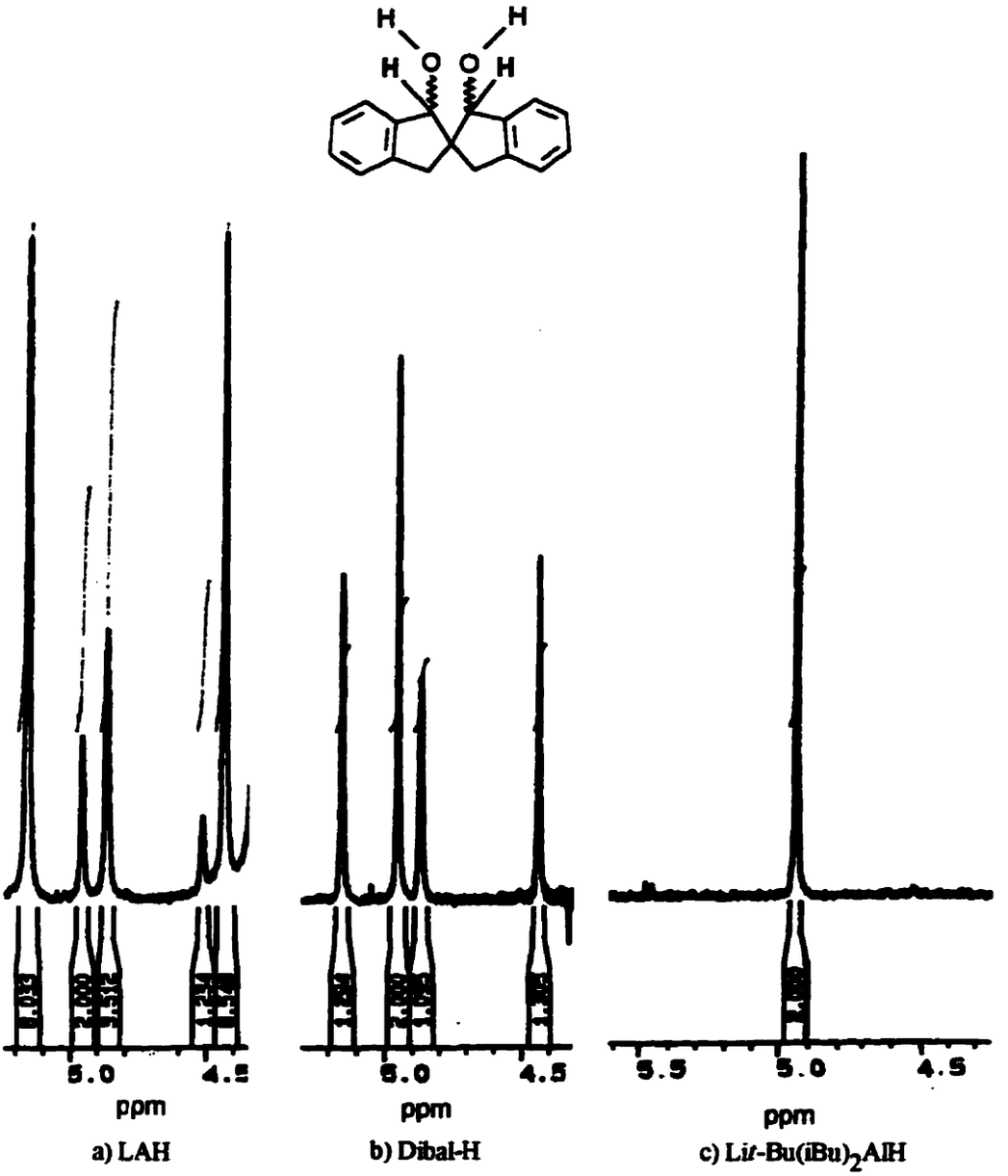


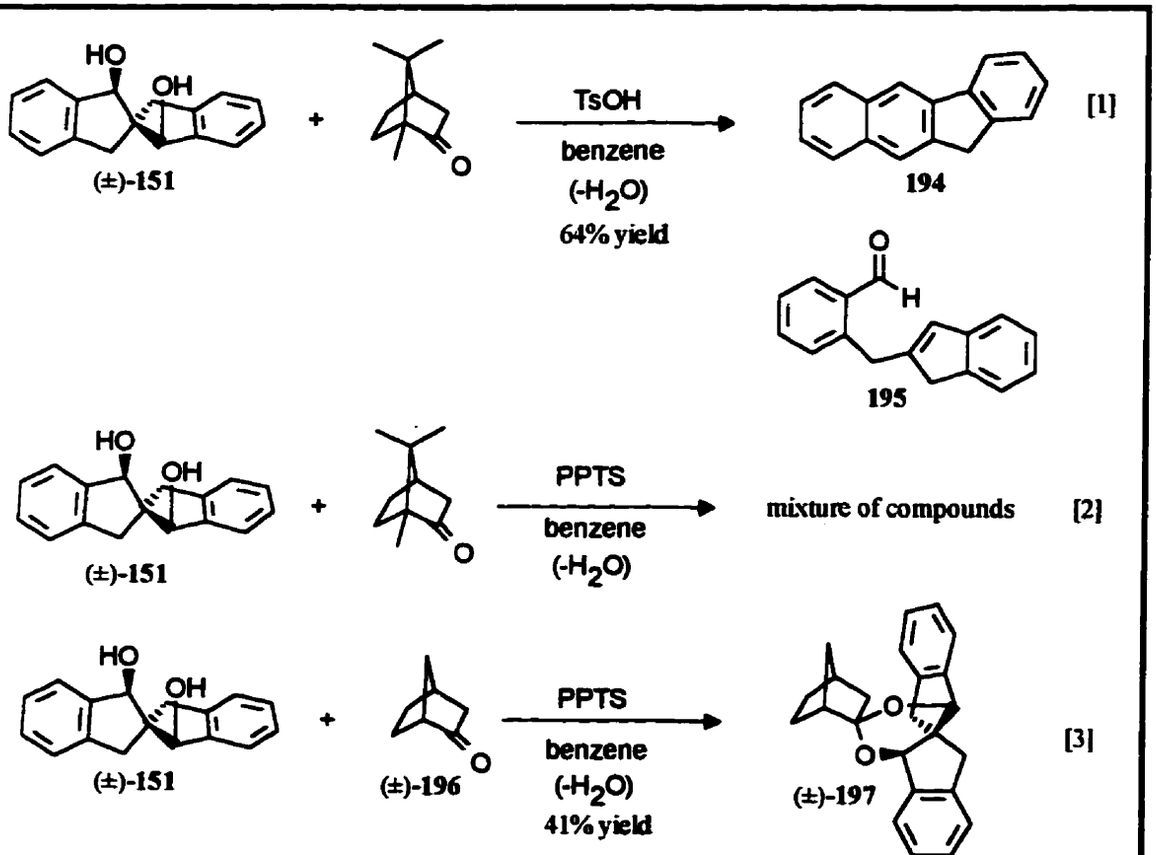
Figure 4.4 A Portion of the ^{1}H-NMR Spectra (for the Bolded Hydrogens) of the Mixture of Diols Produced from Three Aluminium Hydride Reducing Agents (D_6-DMSO (reference = 2.49 ppm) with a few drops of D_2O)

4.94 indicated that the product (**151**, Scheme 4.7) had C_2-symmetry and since one alcohol must have the *cis*-orientation so must the other. This proved that indeed Kabuto *et al.*[152]

did in fact isolate *cis,cis*-diol **151**, and because this was the identical resonance observed by reduction with lithium *tert*-butyldiisobutylaluminium hydride (Figure 4.4) the product was exclusively the *cis,cis*-diol **151**.

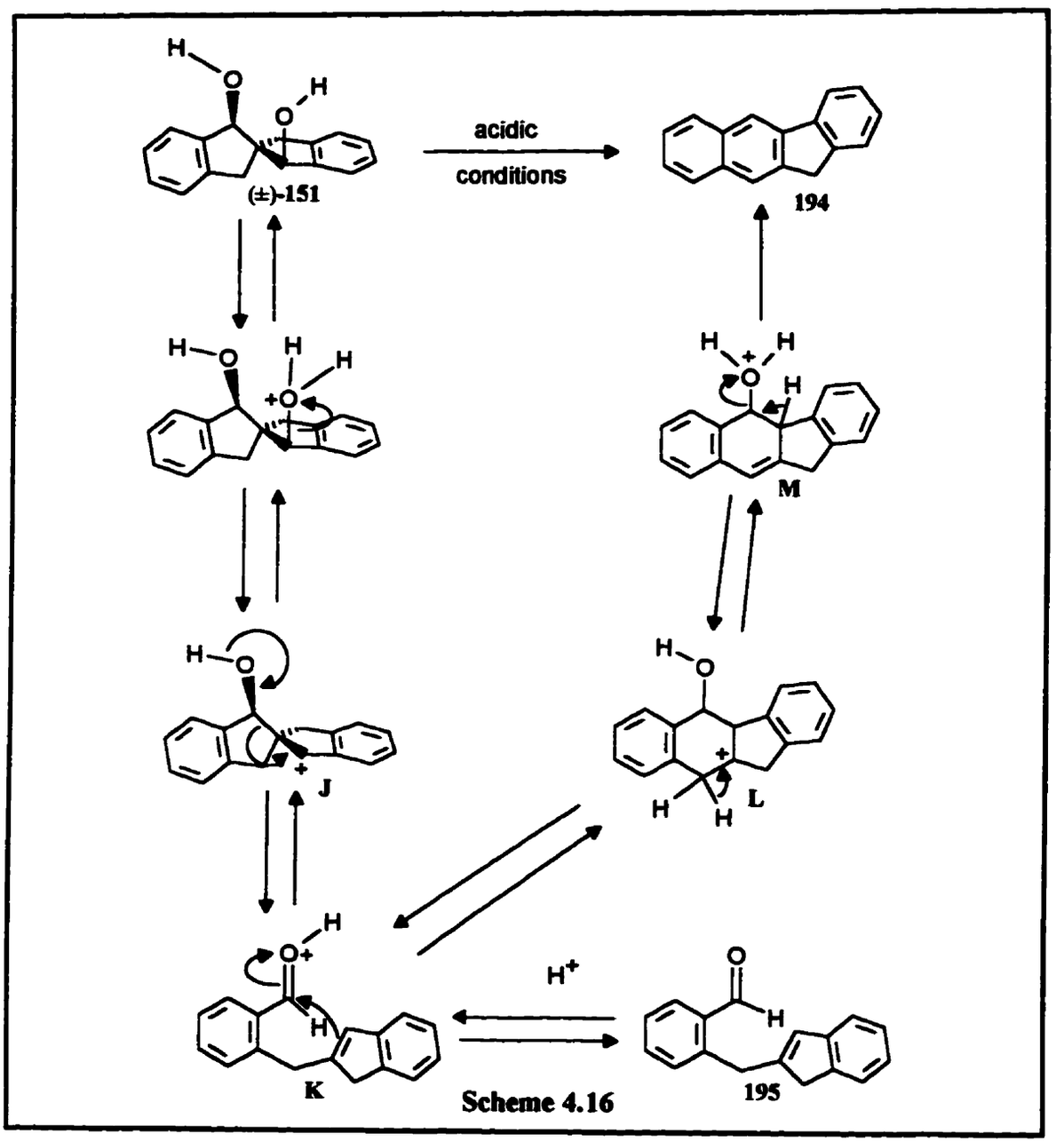
4.2.5 Resolution of (±)-*cis,cis*-2,2′-Spirobiindane-1,1′-diol

Spirodiol **151** has a similar 3-dimensional orientation and configuration as diol **106**, which was readily resolved (Section 2.3.5) by making diastereomeric ketals with (+)-(1*R*)-



Scheme 4.15

camphor. The first logical resolution attempt was therefore to use (±)-diol **151** to make a ketal of (+)-(1*R*)-camphor (reaction 1, Scheme 4.15). Unfortunately, none of the expected diastereomers were obtained. Instead (±)-diol **151** rearranged under acidic conditions to 2,3-benzofluorene (**194**, also called benzo[*b*]fluorene) in 64% yield. It was later found that the presence of (1*R*)-camphor was not needed for the conversion of (±)-**151** into **194** and **195**.[195] Switching from TsOH to the weaker acid PPTS resulted

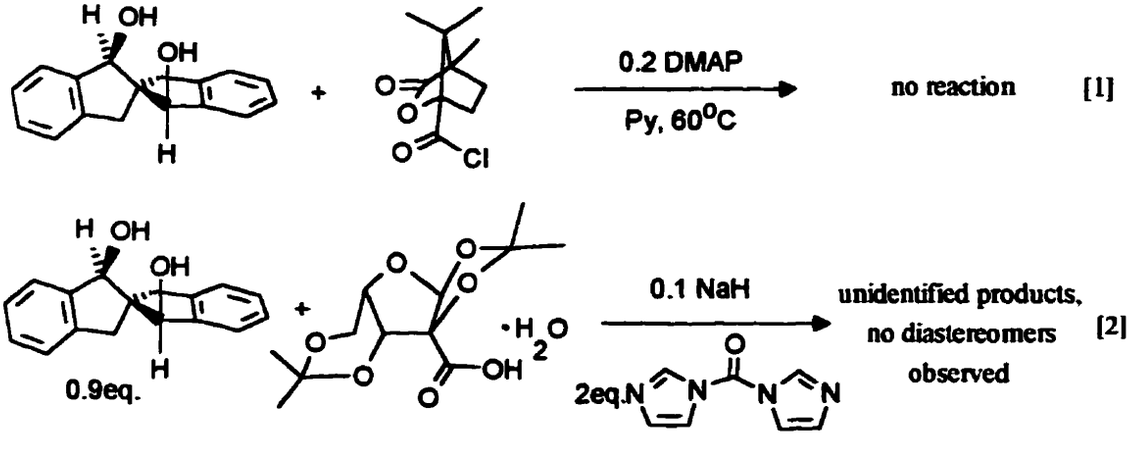


Scheme 4.16

in the formation of a mixture of compounds, one of which appeared to be **195**. The assignment of aldehyde **195** was based solely on the ^{1}H-NMR spectrum of a very small quantity isolated after column chromatography (9:1, hexanes : ethyl acetate). The ^{1}H-NMR spectrum consisted of: a conjugated aldehyde at δ 10.29 (s, 1H); 8 aromatic hydrogens at δ 7.9 (d, 1H), 7.56 (t, 1H), 7.48 (d, 1H), 7.37 (d, 2H), and 7.25 - 7.15 (m,

3H); a conjugated olefinic hydrogen at δ 6.35 (s, 1H); and 2 singlets each integrating to two hydrogens at δ 4.28 (s, 2H) and 3.36 (s, 2H). These observations were consistent with the proposed structure **195**.

Similar rearrangements to **194** have been previously reported with diols **151**, **181**, and **182** in hydrochloric acid (although only 20% yield was obtained).[196] The mechanism for this rearrangement was postulated by Schönberg and Sidky (Scheme 4.16).[196] Protonation of one of the alcohols results in the formation of carbocation **J**, which then undergoes a fragmentation to protonated aldehyde **K**. A Prins-type reaction[59] of **K** produces the tetracyclo carbocation **L**, which loses a proton to form **M**. Loss of water then results in the formation of 2,3-benzofluorene (**194**). The fact that aldehyde **195** was



Scheme 4.17

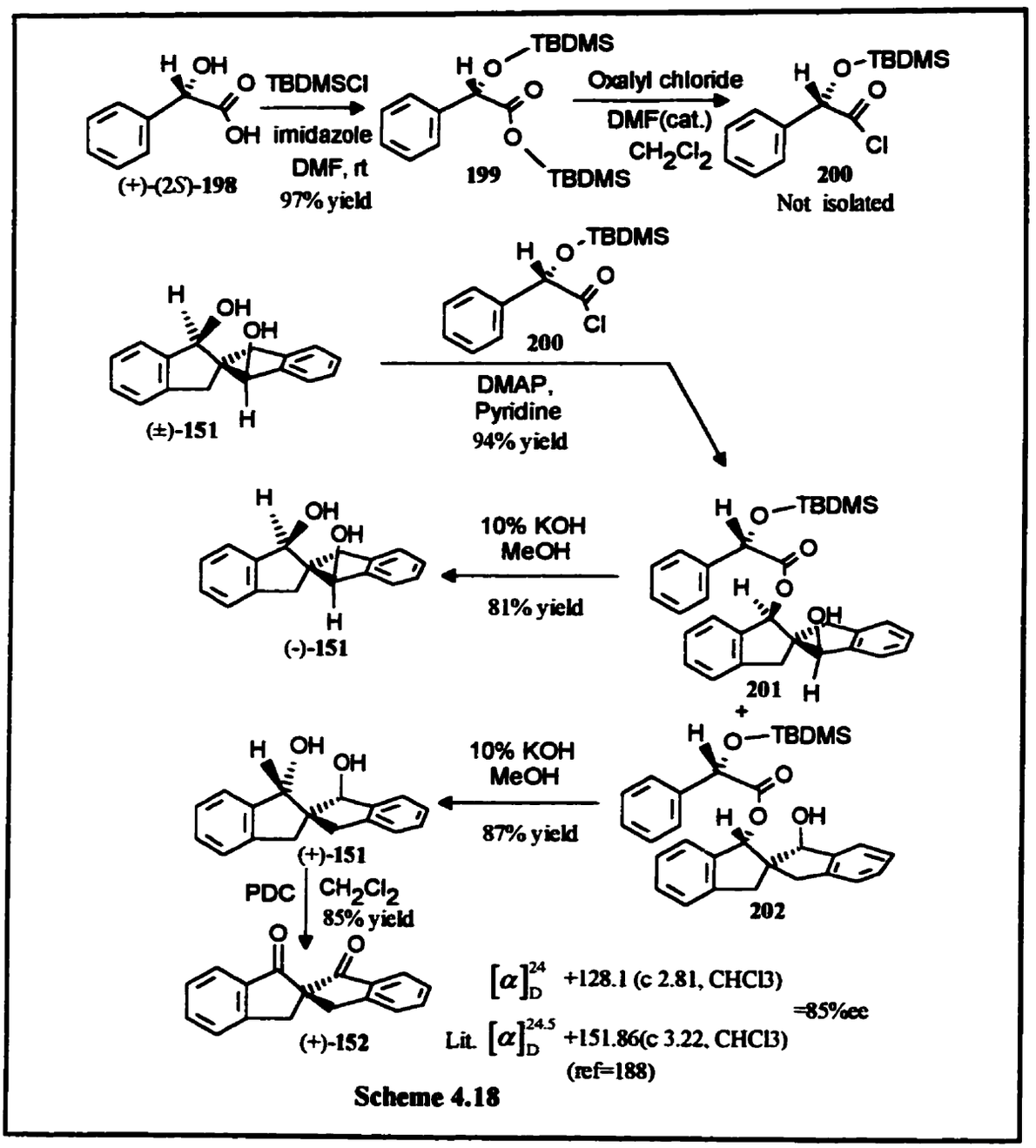
observed by ^{1}H-NMR spectroscopy (small amounts were observed in reactions 1, 2 and 3. (Scheme 4.15)), supports this proposed mechanism for the formation of **194** from (±)-**151** (Scheme 4.16).

Formation of a ketal between diol **151** and bicycloketone **196** was possible (reaction 3, Scheme 4.15), which demonstrated that diol **151** was capable of forming ketals (**197**). The steric bulk of the camphor moiety must be hindering the formation of a similar ketal and thus the rearrangement of **151** to **194** competes. Since compound **196** was only available in racemic form[197] another chiral auxiliary was needed for the resolution of diol

151. Other failed attempts to form separable diastereomers of diol **151** are summarised in Scheme 4.17. Reaction 1 was an attempt to form similar diastereomeric compounds to **180** (Scheme 4.6); however, no formation of products was observed, possibly because camphanoyl chloride was sterically too bulky. Reaction 2 represented an endeavor to couple a readily available chiral carbohydrate to (±)-**151** but this unfortunately formed a mixture of products.

Whitesell and Reynolds used mandelic esters with various racemic alcohols as a method for resolution.[198] The formation of the necessary esters involved using either acidic conditions or DCC. For diol **151**, the acidic conditions might rearrange the diol to compound **194** or **195**, while DCC might be too bulky to couple diol **151** with mandelic acid. Therefore, a new method was needed which used nonacidic conditions. If both the alcohol and the carboxylic acid of mandelic acid (**198**, Scheme 4.18) were silylated, then the silyl ester can be converted directly to an acid chloride **200** by the procedure reported by Wissner and Grudzinskas.[199] The attachment (once or twice) of acid chloride **200** to diol **151** (forming diastereomers) could allow for separation. An added benefit of this system was if the silylated diastereomers **201** and **202** could not be directly separated then removal of the silanes would form alcohols which are more polar and could prove more readily separable by chromatography.

Disilylation of mandelic acid produced a 94% isolated yield of compound **199**, which by ^{1}H-NMR spectroscopy indicated the presence of two silyl groups (δ 0.92 (s, 9H), 0.83 (s, 9H), 0.2 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.02 (s, 3H)), the α-proton (δ 5.15 (s, 1H)), and the aromatic hydrogens (δ 7.49-7.28 (m, 5H)). The reaction of disilyl compound **199** with oxalyl chloride in methylene chloride with a catalytic amount of DMF produced acid chloride **200** which was immediately used in the esterification reaction with (±)-diol **151**. The monoesterification of (±)-diol **151** was accomplished by mixing acid chloride **200** and DMAP in pyridine at room temperature. The products were obtained as a mixture in 94% yield, which was separable by column chromatography

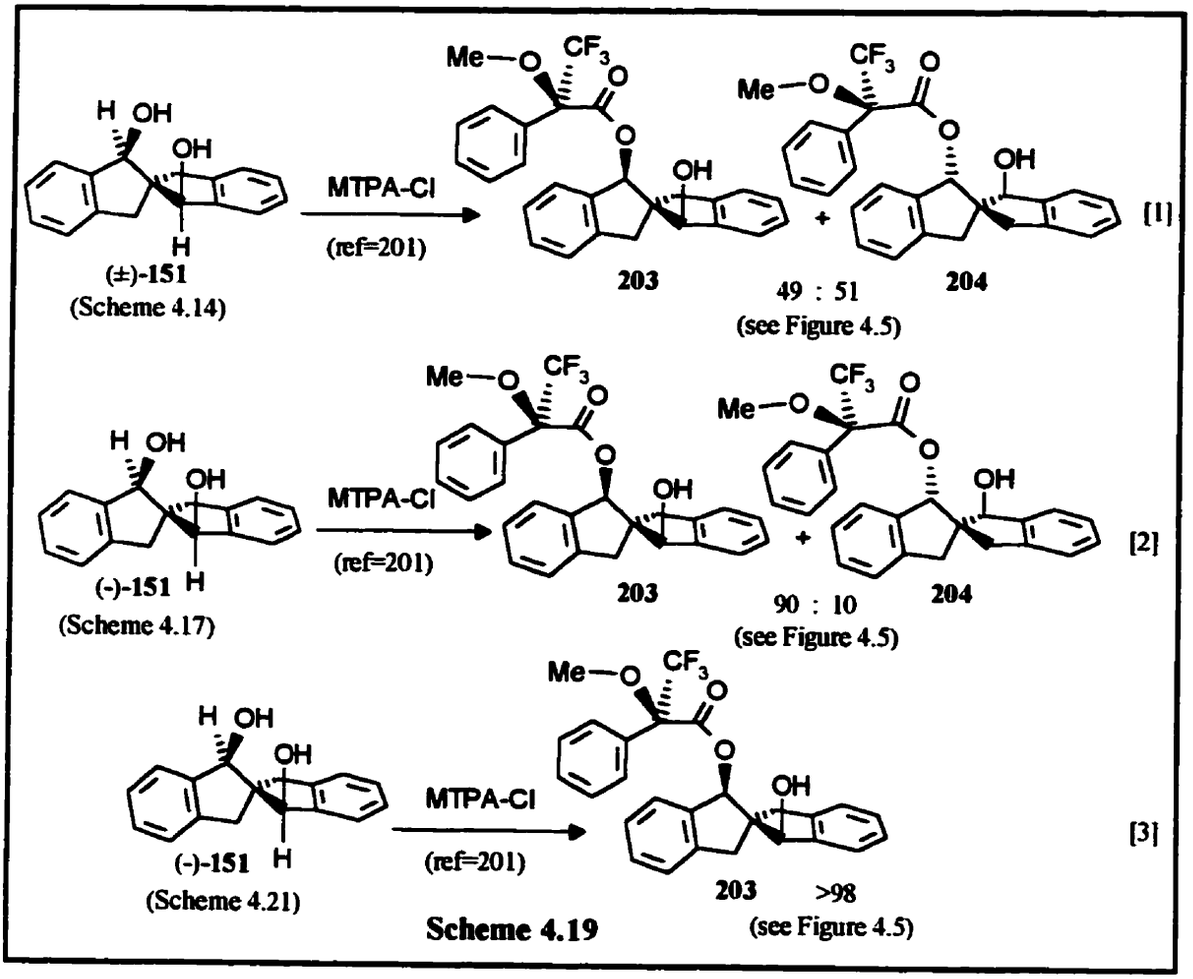


Scheme 4.18

(chloroform, R_f = 0.24 (**201**) and 0.14 (**202**)). The monoesterification was confirmed by the characteristic downfield shift (by ^{1}H-NMR, $CDCl_3$) of one of the hydrogen atoms on the carbon bearing the hydroxyl group in **151** at δ 5.21 to δ 6.13 in **201** and δ 6.12 in **202**. Desilylation of **201** and **202** with TBAF or HF/Py resulted in a mixture of products from both a desilylation and ester hydrolysis. This mixture proved more difficult to separate

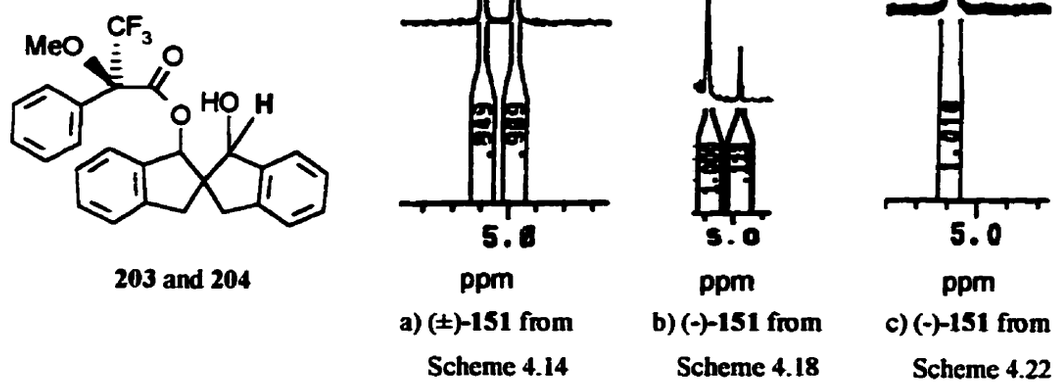
than **201** and **202**. Diastereomers **201** and **202** were separated on a column of silica gel using chloroform as the mobile phase. The saponification of ester **201** was accomplished using 10% KOH in methanol at room temperature and produced an 81% yield of (-)-diol **151**. Subjection of ester **202** to the same saponification conditions yielded (+)-diol **151** in 87% yield.

Oxidation of (+)-diol **151** using PDC provided (+)-dione **152** in 85% yield (Scheme 4.18).[200] Comparison of the literature value for the optical rotation of (+)-dione **152** to the optical rotation obtained for synthetic (+)-dione **152** (Scheme 4.18), showed that (+)-dione **152** was formed in only 85% ee. This method was checked by preparing the MTPA[201] ester of (±)-diol **151** and (-)-diol **151** (reaction 1 and 2 in Scheme 4.19, and



Scheme 4.19

Figure 4.5). Analysis of the ^{1}H-NMR spectra of the products from the above reaction unfortunately supported the 85% ee (82% ee by MTPA ester) assigned for (+)-dione **152** (compare Figures 4.5a and 4.5b). This result was unexpected, because the starting (2*S*)-



203 and 204

a) (±)-**151** from Scheme 4.14

b) (-)-**151** from Scheme 4.18

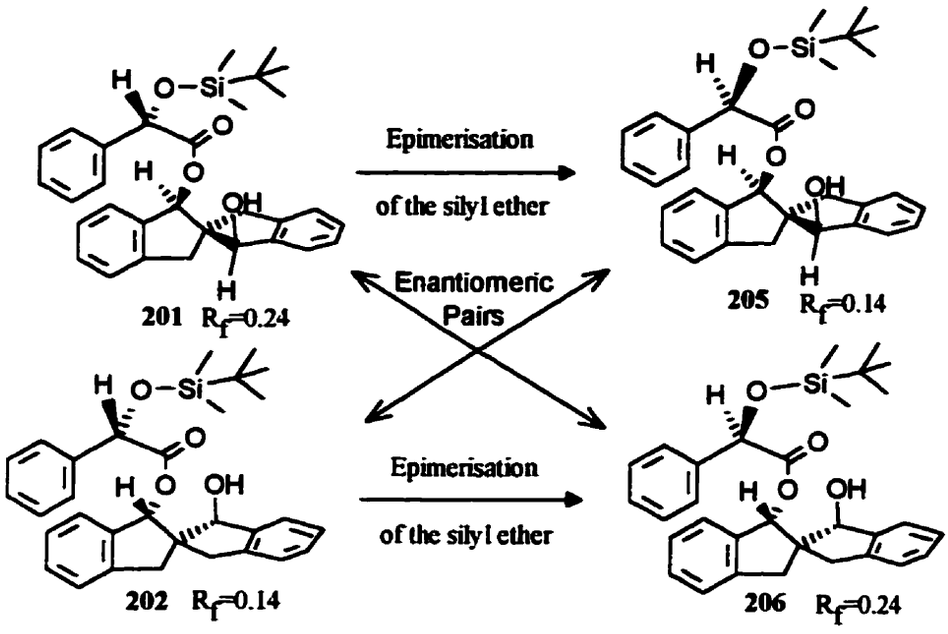
c) (-)-**151** from Scheme 4.22

Figure 4.5 A Portion of the ^{1}H-NMR Spectra for the Bolded Hydrogen Atom in Compound **203** and **204** from Scheme 4.19

mandelic acid (**198**) was optically pure and the diastereomeric esters (**201** and **202**) were separated to the limit of detection by ^{1}H-NMR spectroscopy (≥99% de[202]). Therefore, the only other reasonable explanation was that the mandelate group was partially epimerising somewhere along the synthetic pathway.

Epimerisation (Scheme 4.20) would convert compound **201** into compound **205**. Since, **202** and **205** are enantiomers, they would not be separable on silica gel. The result would be the isolation of a mixture of esters **202** and **205** which upon hydrolysis would form a scalemic mixture of (-)- and (+)-diol **151** (of lower percent ee). Similarly,

epimerisation of **201** would provide **206**. The main question was where exactly was this partial epimerisation (or racemisation) occurring? If partial racemisation was occurring prior to or during the formation of acid chloride **200** then this resolution procedure



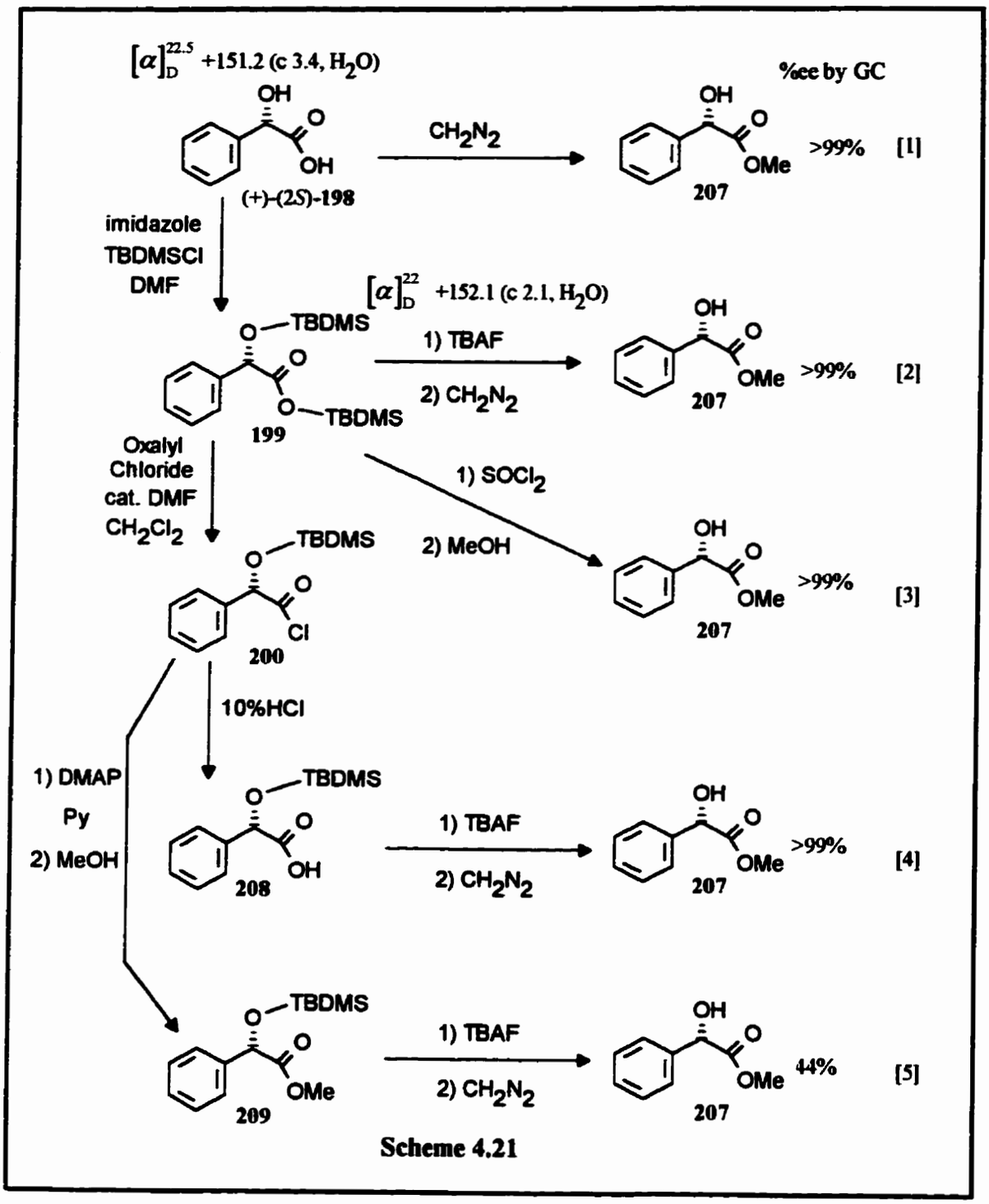
Hydrolysis of a mixture of ester **201** and **206** would result in a mixture of (-)- and (+)-diols **151** in a ratio that is dependent on the extent of epimerisation.

Scheme 4.20

would be ineffective. Another way of explaining this is if racemisation of the mandelate (**198**, **199** or **200**, Scheme 4.18) was occurring, then alternative reagents and procedures might prevent racemisation, but if epimerisation of esters **201** and **202** was transpiring then this resolution procedure might prove ineffective. Therefore, it was necessary to determine at what step partial epimerisation or racemisation was occurring.

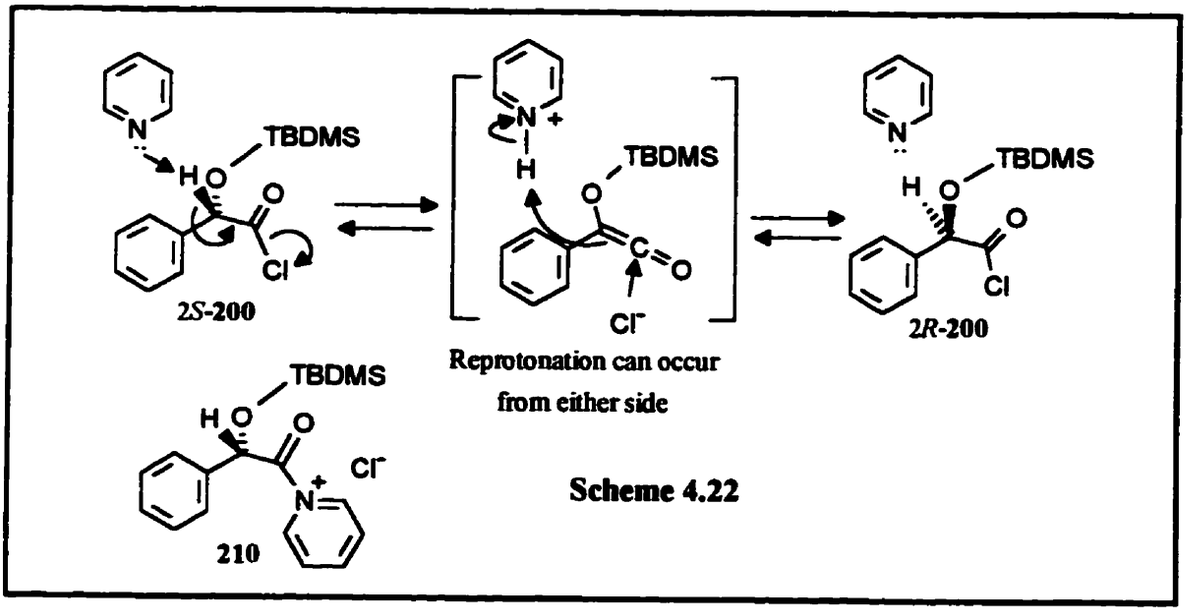
The method developed to determine at what stage epimerisation or racemisation was occurring hinged on the observation that (±)-methyl mandelate (**207**) could be separated (baseline) using a chiral GC cyclodextrin column (Scheme 4.21). First, the percent ee of (+)-2*S*-mandelic acid was confirmed by converting it into the methyl ester **207**.[203] Chiral GC analysis indicated an ee of 99% indicating **198** was essentially optically

pure. Second, it was necessary to determined if partial racemisation was occurring during the formation of disilyl compound **199**. Disilyl compound **199** was treated with TBAF in THF to afford



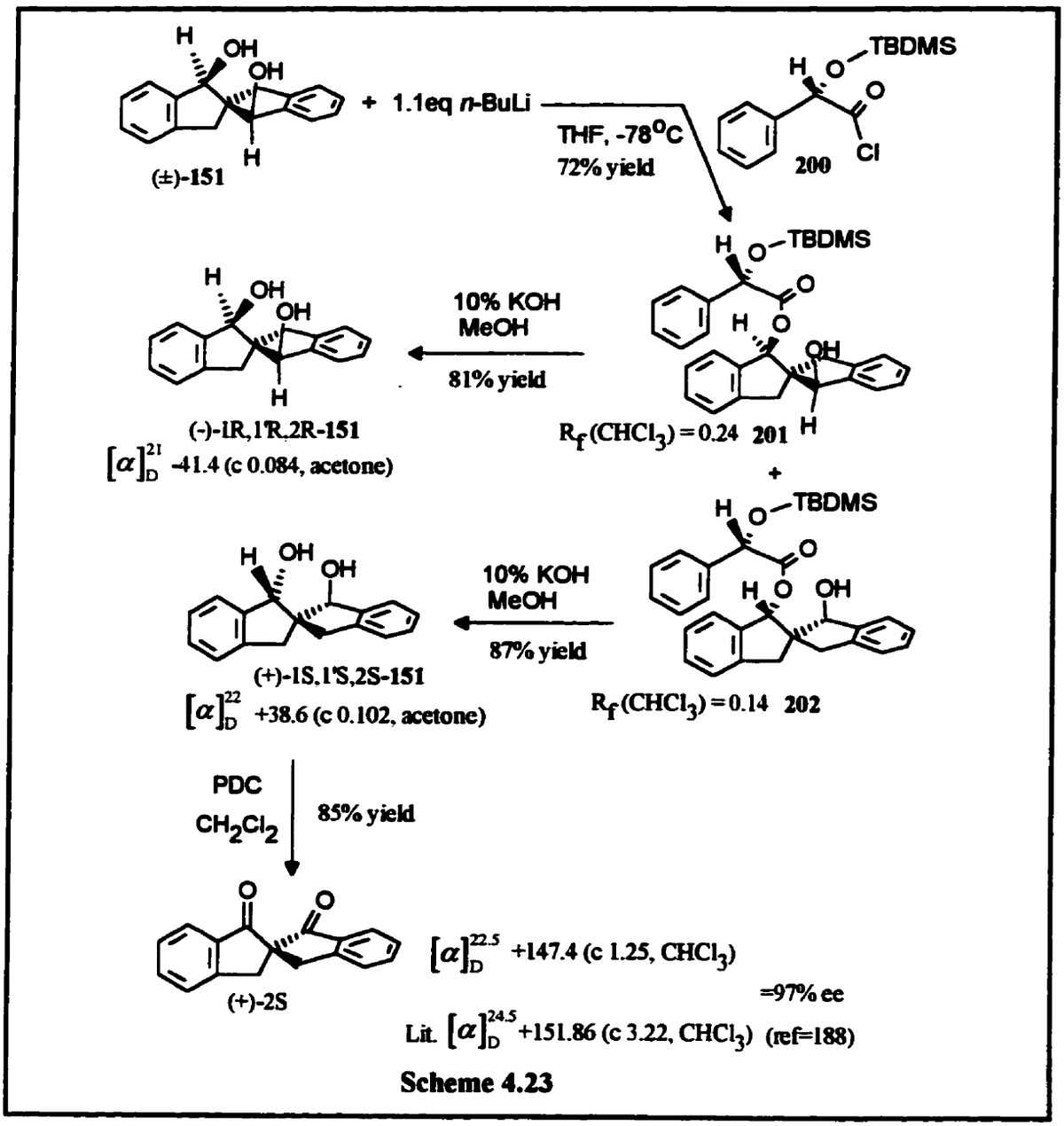
Scheme 4.21

mandelic acid (**198**). The optical rotation of mandelic acid showed that the ee was >99%.[203] This was confirmed by conversion of mandelic acid from reaction 3 into **207** with diazomethane; GC analysis indicated an ee >99% (reaction 2). To determine if the reaction of **199** to form acid chloride **200** resulted in racemisation, **200** was treated with 10% HCl (resulting in **208**), followed by TBAF and esterified to form **207** (reaction 4). Analysis by chiral GC indicated a >99% ee. To double check that epimerisation was not occurring during the formation of **200**, **199** was treated with thionyl chloride followed by methanol workup. This provided methyl mandelate (**207**) with a >99% ee by GC (step 3, Scheme 4.21). The final step where racemisation was possible was during the formation of esters **201** and **202**. Esterification of **200** (step 5, Scheme 4.21) under similar conditions reported in Scheme 4.18, but with the addition of MeOH instead of (±)-diol **151** resulted in methyl ester **209** (by ^{1}H-NMR). The silyl group and ester were removed with TBAF and reesterification of the resulting mandelic acid with diazomethane resulted in methyl mandelate (**207**). Chiral GC analysis of ester **207** indicated the ee was only 44%. Therefore, the esterification step in Scheme 4.18 was where the partial racemisation of the α-chiral centre of the mandelate portion was occurring.



Scheme 4.22

Similar occurrences of racemisation of stereogenic centres with hydrogens atoms α to acid chlorides in the presence of pyridine have been observed.[204] A possible intermediate to explain this would be the formation of a ketene (Scheme 4.22). The ketene could form from 2*S*-**200** by base-induced elimination of HCl. The addition of HCl to the ketene intermediate can occur from either side which would result in reformation of 2*S*-**200** or its enantiomer 2*R*-**200**. The formation of 2*R*-**200** causes the racemisation and



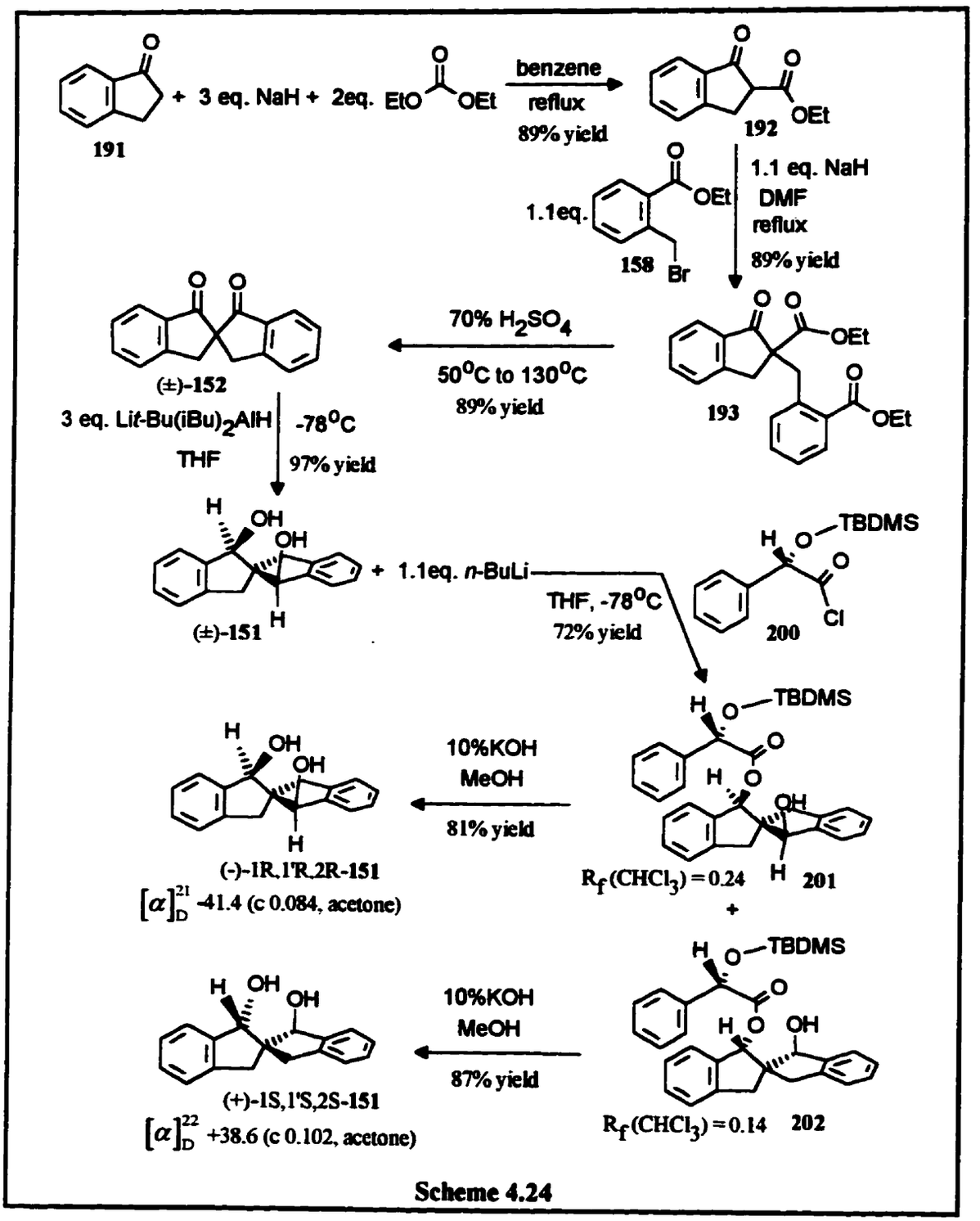
Scheme 4.23

therefore the lower de of resolved diol **151**. The ketene formation could also proceed for the acyl pyridinium salt **210** instead of the acid chloride (Scheme 4.22), but either way the same ketene intermediate would be responsible for the racemisation of **200**. No by-products were observed to support the formation of the ketene intermediate so the mechanism is purely speculative, although a ketene intermediate was also postulated for the racemisation of other hydrogens α to acid chlorides.[204]

Thus, a new set of conditions were needed for the formation of esters **201** and **202**, which would not result in a racemisation of acid chloride **200**. If the pyridine and DMAP were responsible for the racemisation, then a possible procedure to alleviate racemisation was to form the monolithium alkoxide of (±)-**151** with *n*-BuLi (1 eq.) followed by addition of this alkoxide to acid chloride **200** in THF at -78°C (Scheme 4.23). This procedure would not result in the formation of HCl (which may result in a rearrangement of diol **151**) and would not require the presence of base to neutralise the acid (which caused the racemisation); only LiCl would be formed. Treatment of **151** with *n*-BuLi followed by the addition of **200** provided esters **201** and **202** in 72% yield (Scheme 4.23). These esters were separated and the mandelate portion of the molecules were removed with 10% KOH in MeOH at room temperature, resulting in the formation of (-)- and (+)-**151** (84% yield after column chromatography). (+)-Dione **152** was obtained in 97% ee (by optical rotation comparison) and 85% yield after oxidation of (+)-**151** with PDC in methylene chloride. The MTPA ester of the resolved (-)-diol **151** also failed to show signs of the MTPA ester of (+)-diol **151** (reaction 3 in Scheme 4.19 and Figure 4.5). Therefore, the resolution of (-)-1*R*,1′*R*,2*R*- and (+)-1*S*,1′*S*,2*S*-diols **151** was successful. The absolute stereochemistry of (-)- and (+)-diols **151** was unequivocally assigned based on the X-ray crystal structure of **180** (Scheme 4.6) published by Iversen *et al.*[194]

4.2.6 Summary

A four step stereoselective synthesis of (±)-*cis*,*cis*-2,2′-spirobiindane-1,1′-diol (**151**) was developed (68% yield, Scheme 4.24). The resolution of (±)-*cis*,*cis*-diol **151** using (2*S*)-2-(*tert*-butyldimethylsilyl)mandeloyl chloride (**200**) as a chiral auxiliary was also



Scheme 4.24

accomplished after partial racemisation problems were solved.[205] This was the first time **200** was used as a chiral auxiliary for resolutions.

Chapter 5

5 Application of *cis,cis*-Spiro[4.4]nonane-1,6-diol (106) and *cis,cis*-2,2'-Spirobiindane-1,1'-diol (151) as Chiral Auxiliaries in Enantio- and Diastereoselective Reactions

5.1 Introduction

After completion of the synthesis and resolution of *cis,cis*-spiro[4.4]nonane-1,6-diol (**106**) and *cis,cis*-2,2'-spirobiindane-1,1'-diol (**151**), the next step was the application of these spirodiols as chiral auxiliaries. Diol **106** was synthesised a year prior to diol **151**, and therefore diol **106** was tested in more reactions than diol **151**. The results obtained for these diols as Lewis acid bound chiral auxiliaries are reported in Section 5.2 and the application of these diols as substrate bound chiral auxiliaries are covered in Section 5.3.

5.2 Investigation of *cis,cis*-Spiro[4.4]nonane-1,6-diol (106) and *cis,cis*-2,2'-Spirobiindane-1,1'-diol (151) as Lewis acid Bound Chiral Auxiliaries

5.2.1 Introduction

The logical first step for diols **106** and **151**, prior to attempting any Lewis acid catalysed reactions, was to determine if they would survive typical Lewis acid conditions experienced in stereoselective reactions (Section 1.2).

To diol **106** (1 eq.) in CH_2Cl_2 (or $CDCl_3$ or toluene) at -78°C was added a Lewis acid (1 eq. of Me_2AlCl or $TiCl_2(OiPr)_2$ or $Ti(OiPr)_4$) and the solution was allowed to warm to room temperature. The solution was poured into saturated ammonium chloride and was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed *in vacuo* producing a good to excellent yield of diol **106** (based on the ^{1}H-NMR spectrum of the crude material).

This investigation of what Lewis acidic conditions the diols could survive, was especially important for *cis,cis*-2,2'-spirobiindane-1,1'-diol (**151**) after the discovery that it rearranges in Bronsted-Lowry acidic media to 2,3-benzofluorene **194** (Scheme 4.15). Subjecting diol **151** to the same conditions as reported for diol **106** (Me_2AlCl, $TiCl_2(OiPr)_2$, and $Ti(OiPr)_4$) allowed recovery of diol **151** in good yield (based on the ^{1}H-

NMR spectrum of the crude material). If, however, $TiCl_4$ was added to a solution ($CDCl_3$) of diol **151** at -78°C and allowed to warm to room temperature decomposition of diol **151** occurred (based on the ^{1}H-NMR spectrum of the crude material). Therefore, diol **151** was stable only in weaker Lewis acidic media, which meant that if diol **151** was to be employed as a Lewis acid bound chiral auxiliary in stereoselective reactions then the Lewis acid could not be too strong or decomposition of the auxiliary would occur.

After determining the stability of diols **106** and **151** in the presence of various Lewis acids, the next step was to determine how effective Lewis acid complexes of diols **106** and **151** would be in various stereoselective reactions.

5.2.2 Diels-Alder Reaction

The first reaction investigated after the resolution of *cis,cis*-spiro[4.4]nonane-1,6-diol (**106**) was the Diels-Alder reaction reported in 1986 by Reetz *et al.*[42] (Section 1.2.6). Reetz *et al.* found that the reaction of methacrolein with cyclopentadiene catalysed by a titanium dichloride BINOL (*S*)-**5** complex produced a 56% yield of mainly the *exo* (90%) Diels-Alder adduct **211** in 16% ee (entry 1, Table 5.1). Application of diol **106** to the same reaction conditions produced mainly the *exo* (92%) Diels-Alder adduct **211** with a 13% ee (Entry 2).

The reaction conditions[42] used consisted of the addition of *n*-BuLi (2 eq.) to diol **106** (1 eq.) in ether at -78°C, followed by warming to room temperature, and after stirring for 15 min. at room temperature, the reaction was cooled back down to -78°C. To the mixture was added $TiCl_4$ (1 eq.) and the resulting solution warmed to room temperature and the ether removed *in vacuo*. Toluene was added and the solution was cooled to -78°C. Cyclopentadiene (5 eq.) was added followed by methacrolein (5 eq.) and the reaction was allowed to warm to room temperature overnight. Work-up conditions were not reported by Reetz *et al.*, but consisted of the addition of water, filtering through Celite®, and extraction with hexanes and ether. The enantiomeric excess was determined by a ^{1}H-NMR study of product **211** with $Eu(hfc)_3$, as previously reported by Wulff's group.[44] The ratio of the two enantiomers were determined by integration of the

separated signals for the two enantiomeric aldehyde protons (diastereotopic in the presence of $Eu(hfc)_3$).

The slightly lower ee obtained for adduct **211** prompted development of the synthesis and resolution of *cis,cis*-2,2′-spirobiindane-1,1′-diol (**151**, Chapter 4). The investigation of diol **151** under identical conditions (Table 5.1) resulted in not only a lower *exo* ratio (86%), but also a poor ee (only 9%, entry 3). This suggested that diol **151** was no better as a chiral auxiliary than diol **106** for enantioselective induction in this Diels-Alder reaction (Scheme 5.1). The assumptions, therefore, made in Section 4.1, based on semi-empirical calculations, on the possible reason that diol **106** (interference of substrate complexation by the *cis*-hydrogens on C-3 and C-8) produced a lower ee's obtained than BINOL ((*S*)-**5**) were not substantiated by the similar ee's obtained for diols **106** and **151** (the latter of which does not contain hydrogens on C-3 and C-8).

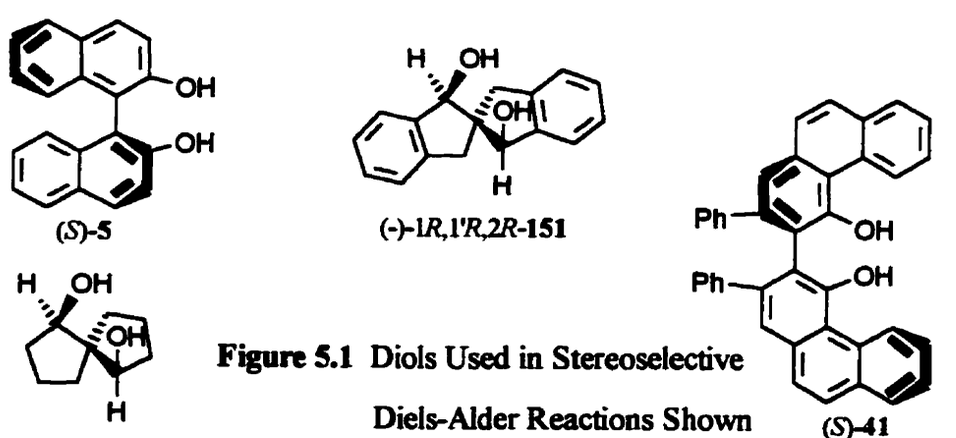
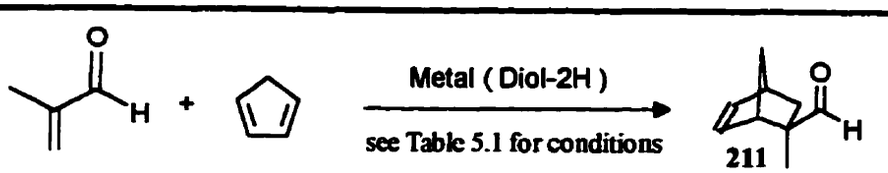


Figure 5.1 Diols Used in Stereoselective Diels-Alder Reactions Shown in Scheme 5.1 and Table 5.1



Scheme 5.1

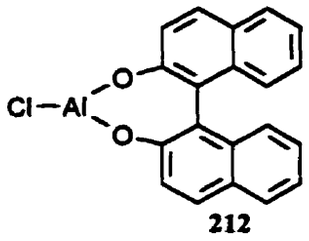
Table 5.1 Results for Diels-Alder Reaction in Scheme 5.1 with Titanium and Aluminium Lewis Acids

Entry	Diol (Figure 5.1)	Metal Used	Solvent	Ratio (*exo*:*endo*)[a]	ee[a] (%)	Yield[a] (%)
1	(-)-(S)-**5**[42]	$TiCl_4$[b]	Toluene	90:10	16[c]	56[d]
2	(-)-1*R*,5*R*,6*R*-**106**	$TiCl_4$[b]	Toluene	92:8	13	42
3	(-)-1*R*,1'*R*,2*R*-**151**	$TiCl_4$[b]	Toluene	86:14	9	68
4	(-)-(*S*)-**5**[44]	Et_2AlCl[e]	CH_2Cl_2	97:3	23	99
5	(+)-(*S*)-**41**[44]	Et_2AlCl[e]	CH_2Cl_2	98:2	98	100
6	(-)-1*R*,5*R*,6*R*-**106**	Me_2AlCl[e]	CH_2Cl_2	-	-	no rxn

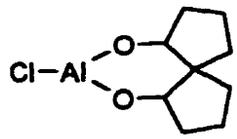
a) yield determined by integration of the ^{1}H-NMR spectrum of the crude mixture unless otherwise indicated. b) reaction warmed from -78°C to rt overnight. c) determined by optical rotation. d) isolated yield. e) reaction at -78°C for 24h.

During the investigation of diol **106** as a titanium bound auxiliary for the enantioselective synthesis of **211** (Scheme 5.1), Bao *et al.* reported using aluminium complexed with chiral biaryl complexes **5** and **41** (entry 4 and 5, Figure 5.1). This system, with complexes of **41**, gave superior results for the formation of enantioenriched **211**.[44] For example, treatment of methacrolein with cyclopentadiene in the presence of catalytic quantities of the aluminium complex (*S*)-**41** produced compound **211** in quantitative yield with a 98% ee of the *exo* adduct. When compound **41** was replaced with diol **106** and subjected to similar conditions no reaction occurred. This was unexpected since the reaction of BINOL (**5**) or diol **106** with Et_2AlCl or Me_2AlCl in CH_2Cl_2 at room temperature for 30 min. should have resulted in the formation of complex **212** or **213** (Figure 5.2). Since **212** promotes the Diels-Alder reaction, it was surprising that **213** did not. In an attempt to explain the lack of reaction with complex **213** (derived from diol **106**), semi-empirical calculations (PM3) were performed on complexes **212** and **213**. The only significant difference that the orbital calculations showed was the energy of the

LUMO's were different by 2.34 KJ/mol (0.56 Kcal/mol). The energy of the LUMO of compound **212** was lower and thus would be expected to be more reactive than **213**, which was observed.



212



213

LUMO (KJ/mol)	-2.34	0

Figure 5.2 Relative LUMO Energies of **212** and **213** from PM3 Semi-Empirical Calculations

Semi-empirical calculations are not completely reliable since they are gas phase calculations, but the relative reactivity between **212** and **213** is also supported by applying Orbital Interaction theory (OIT).[206] OIT predicts that the oxygen lone pairs of BINOL (**5**) are less Lewis basic than the oxygen lone pairs in diol **106** (oxygen lone pairs in BINOL interact with the aromatic system, decreasing their energy and coefficient size and hence decreasing their Lewis basicity), therefore the interaction between the oxygen lone pairs for complexes of diol **106** with the empty orbital on the aluminium atom would be stronger than for complexes of BINOL (**5**). This stronger interaction would result in a higher energy LUMO and would also result in a lower coefficient on the aluminium atom in the LUMO molecular orbital of **213**, both of which would make it less reactive. The semi-empirical calculations only support the lower energy LUMO of **212**, because the coefficients calculated for the aluminium atom in the LUMO orbital in **212** and **213** were almost identical.

The lack of reaction using catalyst **213** (Figure 5.2) in Scheme 5.1 and semi-empirical calculations suggested that complexes of aluminium with diol **106** would be less reactive than aluminium complexes with BINOL (**5**). Other metals, however, may have a

poorer overlap (interaction) with the oxygen atom lone pairs in complexes similar to **212** and **213** and thus be less influenced by the higher basicity (relative to BINOL) of the lone pairs on the oxygen atom of diol **106**. This meant that the investigation of reactions with Lewis acid complexes of diol **106** should be: 1) with Lewis acids other than aluminium (*e.g.* Ti or Zn) for comparison with other reactions involving BINOL (**5**) or 2) focus on reactions that give higher ee's with diols having similar oxygen lone pair Lewis basicities to that of diol **106** (*e.g.* **2** (Scheme 5.2) or **3** (Scheme 5.3)).

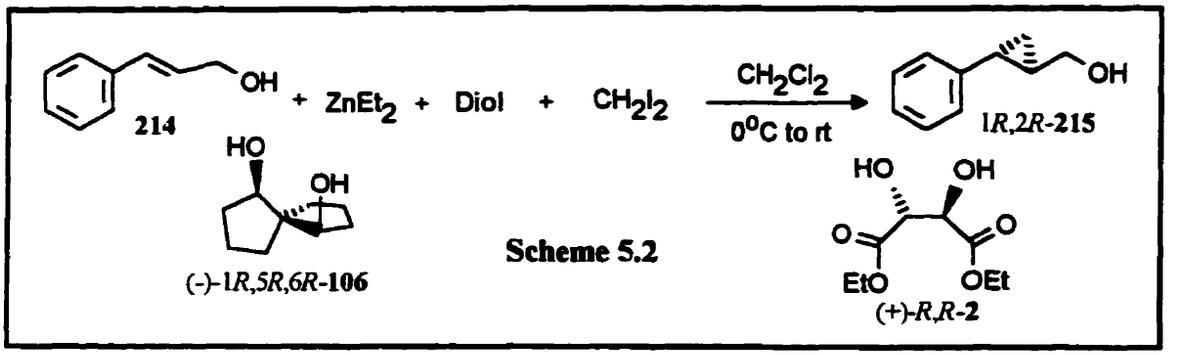
5.2.3 Cyclopropanation Reaction

Section 1.2.5 reviewed the application of C_2-symmetric diol auxiliaries in the enantioselective cyclopropanation reaction. Application of diol **106** to the cyclopropanation methodology developed by Ukaji *et al.*[32a] with (+)-**2** (Scheme 5.2, Table 5.2) are reported in this section.

The reaction involved addition of $ZnEt_2$ (1 eq.) to a solution of freshly distilled alcohol **214** in CH_2Cl_2 at 0°C (Scheme 5.2). The reaction was stirred for 15 min. and freshly distilled diol (0.9 eq. of diol **106** or **2**) was added and stirred for 1 h. After the reaction was cooled to -20°C more $ZnEt_2$ (1.8 eq.) was added followed by, after 10 min., CH_2I_2 (3.6 eq.). The reaction mixture was stirred at -20°C for 10 min., put in an ice bath and allowed to warm to rt overnight. The reaction was quenched (no starting material by TLC (1:1, hexanes : ethyl acetate)) with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic phases were dried, filtered and the solvent was removed *in vacuo*. The formation of product **215** was evident in the ^{1}H-NMR spectrum by the loss of resonances for the hydrogens attached to the double bond in starting material **214** at δ 6.64 (dt,1H) and 6.38 (dt, 1H), and the formation of signals due to the cyclopropane moiety in **215** at δ 1.90 - 1.78 (m, 1H), 1.56 - 1.40 (m, 1H) and 1.04 - 0.90 (m, 2H).

Compound **215** was formed in 58% yield with an 18% ee (by optical rotation), and (-)-1*R*,5*R*,6*R*-diol **106** was recovered in 92% yield. Although a higher yield of cyclopropane **215** was obtained with **106** when compared to that obtained by Ukaji *et*

al.[32a] with (+)-*R,R*-diol **2** (58% compared to 22%, Table 5.2), a lower ee resulted (only 18% compared to 50%). Both **106** and **2** containing exclusively *R* stereogenic centres produced the 1*R*,2*R*-cyclopropane derivative. The absolute stereochemistry was determined by comparison of the sign of rotation of **215** with the known levorotory enantiomer of **215**.[32a]



Scheme 5.2

Table 5.2 Comparison of Enantioselective Cyclopropanation Reactions of Diol **106** with Diol **2** (Scheme 5.2)

Diol	Percent ee[a] ($[\alpha]_D$ (EtOH))	Isolated Yield (%)
(-)-1R,5R,6R-**106**	18 (-16.2, c 2.45)	58
(+)-*R,R*-**2**[32a]	50 (-46, c 0.4-2.1)	22

a) determined by comparison of the optical rotation of purified cyclopropane **215** to the rotation for optically pure cyclopropanol **215**.

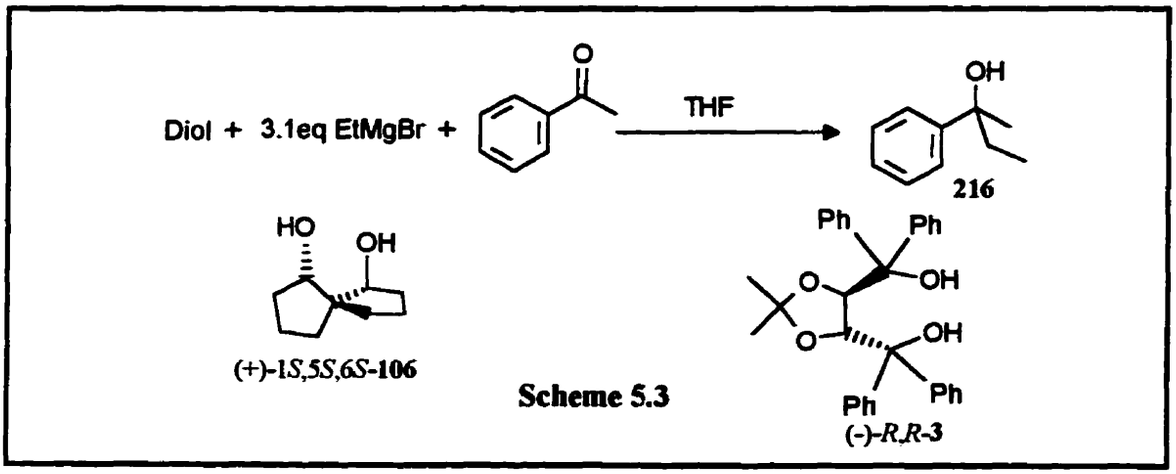
There could be many reasons why (-)-1*R*,5*R*,6*R*-diol **106** produced lower enantiomeric excesses than with (+)-*R,R*-diethyl tartrate (**2**). These include: an influence (steric or electronic) of the diesters; solvation effects; and a result of (+)-*R,R*-diethyl tartrate (**2**) being an open chained 1,2-diol while diol **106** was a rigid 1,3-diol.

Optimisation of the enantioselective cyclopropanation conditions for diol **106** may have demonstrated that better ee's could be obtained than with diol **106** than the literature values for diol **2**; however, it was decided to test diol **106** in other enantioselective reactions.

5.2.4 Grignard Addition

In 1992 Weber and Seebach[12] reported the enantioselective addition of EtMgBr to acetophenone in the presence of TADDOL **3**. The addition of 3.1 eq. of ethyl magnesium bromide to TADDOL **3** at -70°C in THF, cooling the mixture to -105°C (temperature in Table 5.3) followed by the addition of acetophenone (or other aromatic aldehyde or ketone) provided, after 9 h at -105°C, alcohol **216** with an ee of 98%. The ee was determined by GC using a cyclodextrin capillary column.[12]

Application of this same procedure (at -85°C and -105°C) with (+)-1*S*,5*S*,6*S*-diol **106** produced the disappointing ee's reported in Table 5.3. These poor ee's (9% and 11%) were determined by GC analysis of the crude product using a cyclodextrin column.



Scheme 5.3

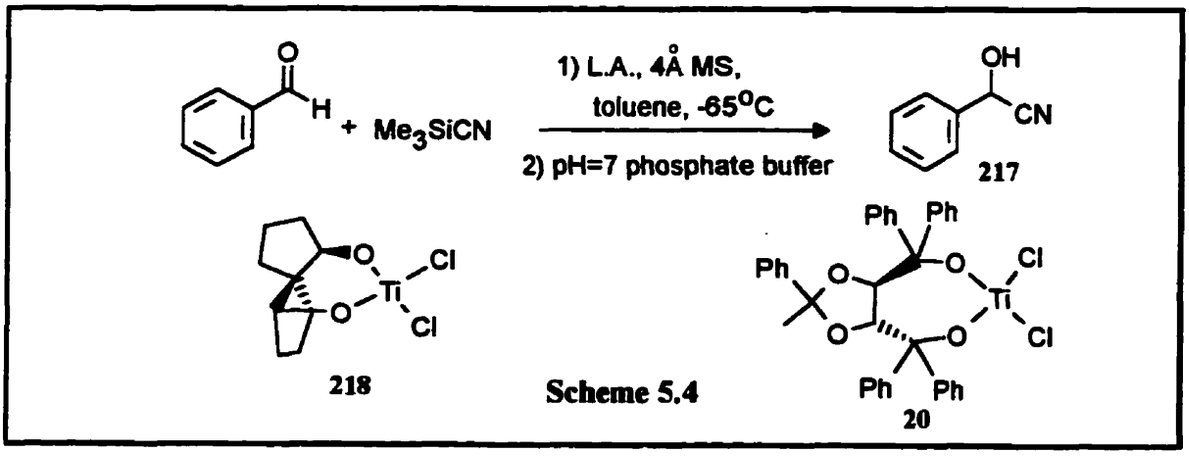
Table 5.3 Results for the Addition of Ethylmagnesium Bromide to Acetophenone in the Presence of Chiral Diols (Scheme 5.3)

Diol	Temperature (°C)	
	-105	-85
(+)-1*S*,5*S*,6*S*-**106**	11% ee[a]	9% ee[a]
(-)-*R*,*R*-**3**[12]	98% ee[a]	-

a) determined by GC analysis on a cyclodextrin capillary column

Two possible reasons why (+)-diol **106** produced inferior ee's compared to (-)-**3** are listed below. First the alcohol groups in TADDOL (**3**) are sterically more congested (3° in TADDOL versus 2° in diol **106**) than the alcohol groups in diol **106**, which would greatly influence the approach of the substrate to the Lewis acid site (proposed by Weber and Seebach[12] to be a magnesium dialkoxide complex). The second reason for the superior results with TADDOL (**3**) was that it underwent a heterogenous reaction while diol **106** underwent a homogenous reaction. Weber and Seebach[12] observed that TADDOL (**3**) and EtMgBr formed a "colourless precipitate" at low temperature and thus a heterogenous reaction occurred; however with the reaction of (+)-diol **106** with EtMgBr no apparent precipitation occurred at low temperature which meant that the reaction was homogeneous. Acetophenone could complex to a heterogenous catalyst in a selective orientation while in a homogenous reaction mixture might have greater degrees of freedom which results in unselective complexation with the Lewis acid thereby resulting in lower selectivity. Both reasons are speculative and no supporting experimental data was obtained to support one over the other.

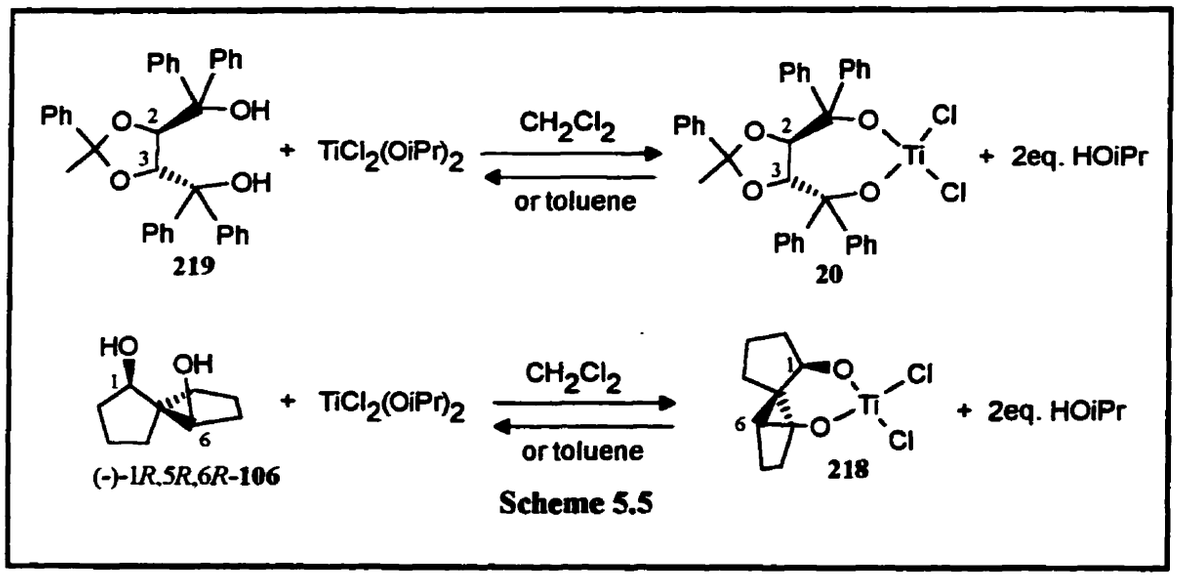
5.2.5 Hydrocyanation Reaction



Scheme 5.4

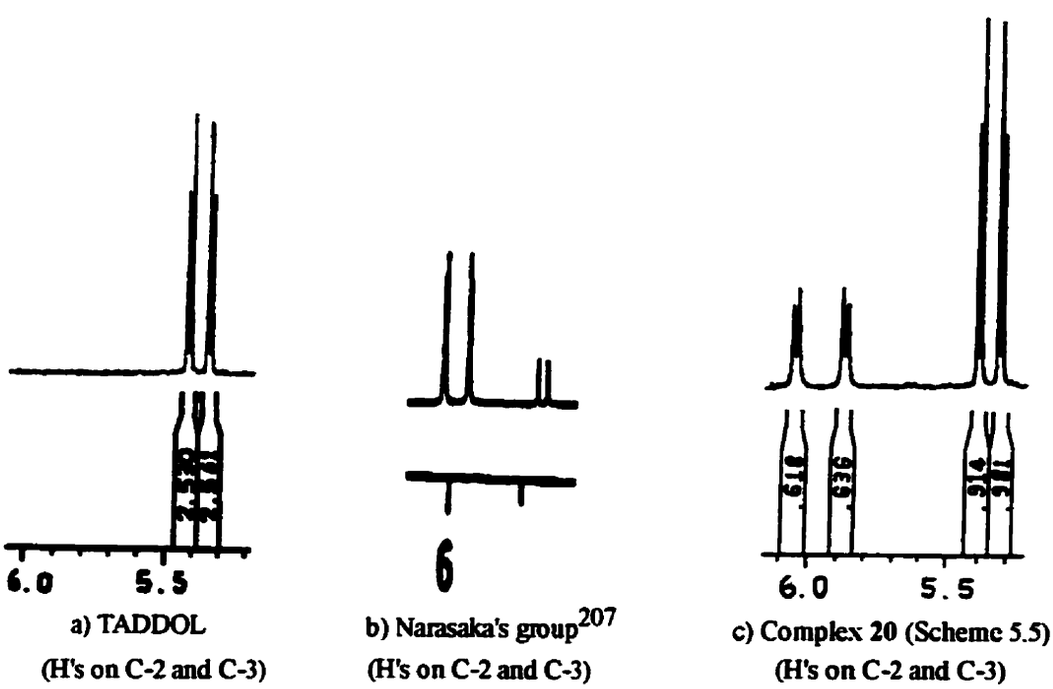
The hydrocyanation reaction with C_2-symmetric diols was reviewed in Section 1.2.11. In 1987, Narasaka's group reported the use of TADDOL complex **20** in the enantioselective hydrocyanation reaction (Scheme 5.4).[79] The reaction of benzaldehyde with TMSCN produced cyanohydrin **217** in 79% isolated yield with an optical purity of

96%. Under similar conditions, titanium complex **218** failed to promote the formation of cyanohydrin **217**. Repeated attempts at higher temperature also failed to yield any cyanohydrin product **217**. The next logical step was to repeat the reaction reported by Narasaka[79] to determine not only whether **20** would promote the reaction, but also if their ee's were reproducible. Repeating the procedure of Narasaka with **20** also failed to produce any of product **217**. The formation of **217** (Scheme 5.4) did proceed when $TiCl_2(OiPr)_2$ was used; therefore, the failure to promote the reaction under enantioselective conditions was most likely due to a problem with the formation of chiral Lewis acids **20** or **218**.



Scheme 5.5

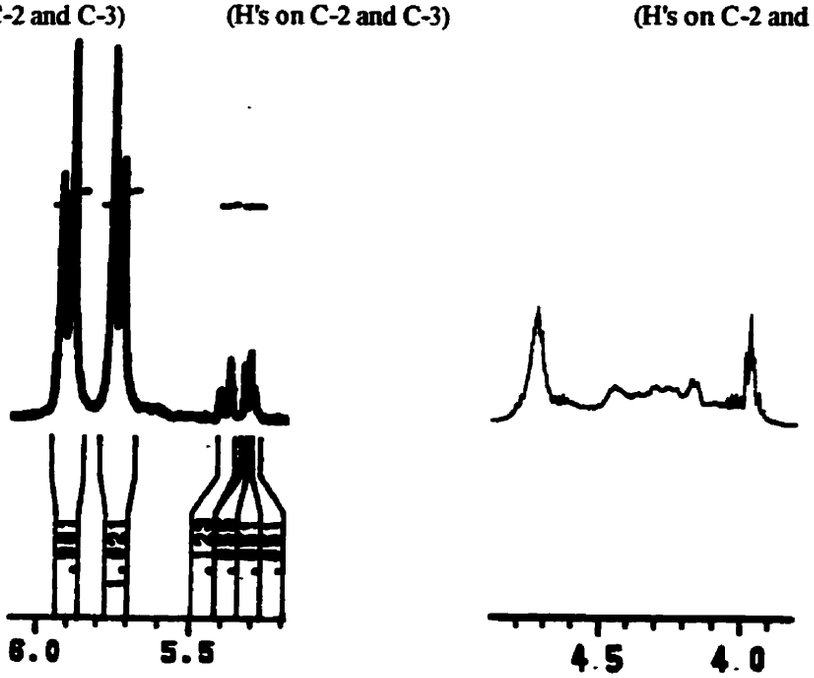
An investigation to determine a reason(s) why no cyanohydrin was obtained with either **218** or **20** was undertaken. The formation of chiral Lewis acids **20** and **218** involved the exchange of isopropyl alcohols with the alcohol groups of the auxiliaries (Scheme 5.5). Addition of freshly dried 4Å MS to the reactions illustrated in Scheme 5.5 was supposed to absorb the isopropyl alcohol, thereby shifting the equilibrium towards complex **20** and **218**. In 1989, Narasaka[207] published an ^{1}H-NMR study (in toluene-d_8) of the formation of complex **20** (Figure 5.3). Attempts to repeat these results using the conditions reported by Narasaka (Figure 5.3b) produced only a small amount of complex **20** (Figure 5.3c). A literature search revealed that other groups also found difficulty forming catalyst **20** using



a) TADDOL (H's on C-2 and C-3)

b) Narasaka's group[207] (H's on C-2 and C-3)

c) Complex **20** (Scheme 5.5) (H's on C-2 and C-3)



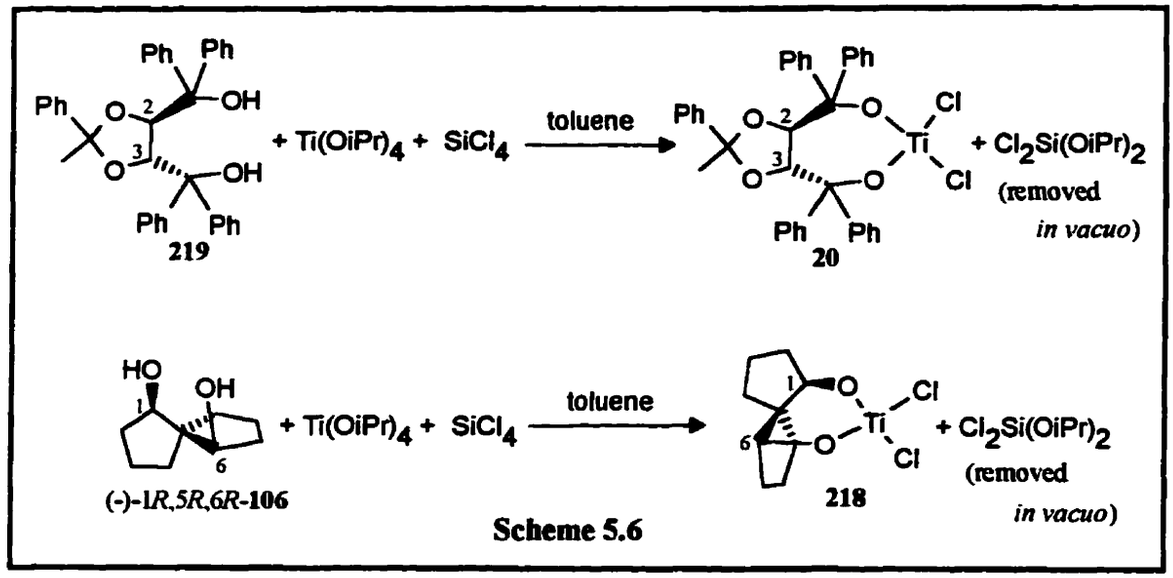
d) Complex **20** (Scheme 5.6) using Corey's method (H's on C-2 and C-3)

e) Complex **218** (Scheme 5.6) using Corey's method (H's on C-1 and C-6)

Figure 5.3 Part of the ^{1}H-NMR Spectra (in ppm) of TADDOL (**219**), Complex **20** and Complex **218**

Narasaka's conditions.[38,208]

A different procedure was developed in Corey's lab[38] to form **20** (Scheme 5.6), which involved addition of $Ti(OiPr)_4$ to **219** in toluene at rt followed by addition of $SiCl_4$ and subsequent removal of the solvent and $Cl_2Si(OiPr)_2$ *in vacuo*. Formation of the TADDOL complex **20** using Corey's method was successful by comparison of Figure 5.3 b and d.[207]



Scheme 5.6

Application of Corey's method for the formation of titanium complex **218** (Scheme 5.6) failed to produce signals in the ^{1}H-NMR spectrum that could be attributed to complex **218** (Figure 5.3e) in analogy to those observed for TADDOL complex **20** (Figure 5.3d). The signals indicated that an equilibrium process between various titanium-diol species was occurring. This meant that diol **106** was not completely forming the desired complex **218**, which suggested that diol **106** would not likely produce high ee's as was previously observed for the titanium TADDOL complex **20**.

The observation that TADDOL more readily formed a stable complex than diol **106** was also supported by literature studies which show that for cyclic titanium complexes a 7-membered ring was optimal.[209] This means that cyclic titanates of chiral auxiliaries with "1,4-diols are preferred over 1,2- and 1,3-diols, which commonly form complex polymeric

or highly clustered titanium complexes."[209] This literature precedent and the equilibrium processes observed (Figure 5.3e) prompted the abandonment of diol **106** as a Lewis acid bound chiral auxiliary.

5.2.6 Conclusions

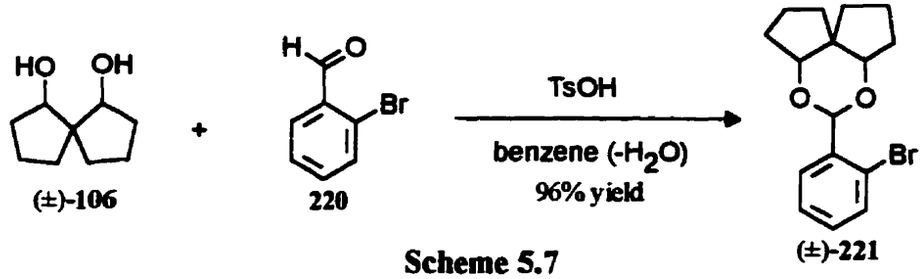
Diol **106** (and in one case **151**) provided inferior results as a Lewis acid bound chiral auxiliary than was previously reported using BINOL, diethyl tartrate or TADDOL. The discovery of: 1) unfavourable equilibrium processes (by ^{1}H-NMR spectroscopy) towards a titanium complex with diol **106** and 2) no reaction due to lower Lewis acidity of an aluminium complex with diol **106** prompted the investigation of diol **106** (and to a lesser extent **151**) as a substrate bound chiral auxiliary. The results for these investigations are reported in the next section.

5.3 Investigation of *cis,cis*-Spiro[4.4]nonane-1,6-diol (106) and *cis,cis*-2,2'-Spirobiindane-1,1'-diol (151) as Substrate Bound Chiral Auxiliaries

5.3.1 Introduction

There are two ways that C_2-symmetric diols have been used as substrate bound chiral auxiliaries (Section 1.3). The first was using diols to make chiral acetals or ketals (Section 5.3.2 and Section 5.3.3) and performing subsequent reactions. The second method was by attachment of different groups (or 2 similar groups) to the two alcohols (*e.g.* formation of a diester, Section 5.3.4) and performing various reactions on one group (or possible both). The following sections describe the results in these areas.

5.3.2 Aryl Alkylation and Aryl Coupling Reactions

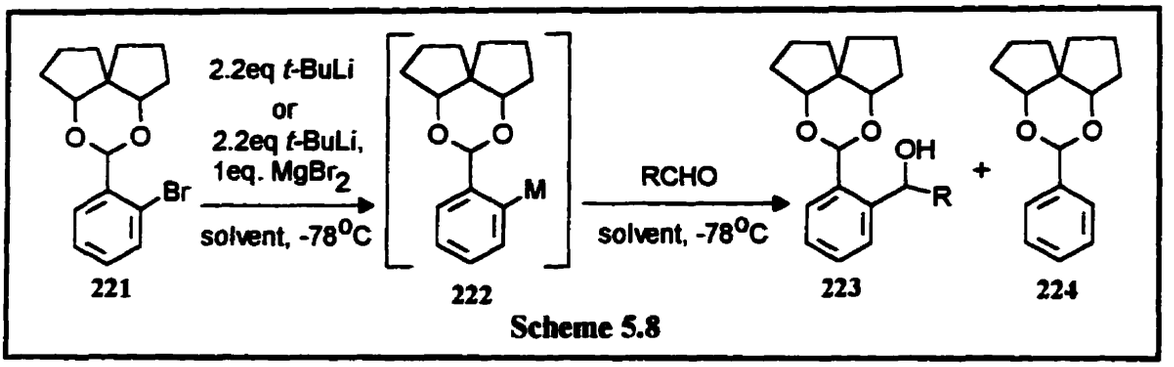


Scheme 5.7

Reaction of (±)-**106** with bromoaldehyde **220** in the presence of catalytic amounts of *p*-toluenesulfonic acid in benzene (azeotropic removal of water) produced acetal **221** in 96% yield, after column chromatography (20:1 hexanes:ethyl acetate). Acetal **221** was identified by examination of the ^{1}H-NMR spectrum (*o*-disubstituted aromatic δ 7.72 (dd, 1H, J = 7.6 and 1.8 Hz), 7.54 (dd, 1H, J = 7.8 and 1.2 Hz) 7.35 (dt, 1H, J = 7.6 and 1.2 Hz), 7.19 (dt, 1H, J = 7.8 and 1.8 Hz); acetal δ 5.97 (s, 1H); and the spirosystem δ 4.31 (t, 1H, J = 7.9 Hz), 4.02 (d, 1H, J = 5.0 Hz), 2.40 - 1.35 (m, 12H)) and the mass spectrum (CI), the latter which showed the presence of a bromine atom (two equally intense peaks at M+H (323) and [M+2]+H (325)). Racemic **221** was initially used in the investigation of each reaction, and if a high de (relative to literature values) was obtained the reaction would be repeated using chiral diol **106**. This would then form enantiopure **221** and allow for the determination of the absolute stereochemistry of the product(s). This section summarises the results obtained with (±)-**221** in a variety of reactions.

Lithium bromine exchange of **221** with *t*-BuLi should produce an organometallic intermediate **222** which could react with aldehydes to produce a new stereogenic centre (2° alcohol carbon) in compound **223** (Scheme 5.8, Table 5.4). Section 1.3.6 reported previous literature examples of this type of reaction. Examples in the literature (similar to Scheme 5.8) showed that aliphatic aldehydes provided products with poor de's (3-38%).[104] Treatment of acetal **221** under a variety of conditions produced (by ^{1}H-NMR analysis of the crude product) mixtures consisting of compounds **223** and **224**. The acetal of **224** was easily identified in the ^{1}H-NMR spectrum by aromatic peaks at δ 7.55 - 7.3 (m), the acetal hydrogen at δ 5.7 (s) and the spiro[4.4]nonane portion at δ 4.26 (t), 3.97 (d), 2.2-1.0 (m). Compound **223** (R = Me) was identified by the change in the aromatic signal to a multiplet and incorporation of the resonances at δ 5.46 (q) for the benzylic proton and the doublet at 1.58 for the methyl group. The de of **223** was determined by integration of the two acetal hydrogen resonances at δ 5.94 and 5.96. Halogen metal exchange with 2.2 eq. of *t*-BuLi followed at -78°C in THF the addition of ethanal provided a 1.24:1 ratio of **223**:**224**. Nuclear magnetic resonance analysis indicated a de of 12%

(entry 1, Table 5.4). Changing the reaction solvent to ether or using propanal instead of ethanal produced only debrominated compound **224** (entries 2 and 3). An explanation of these results is that the aryllithium could be abstracting a proton adjacent to the aldehyde.



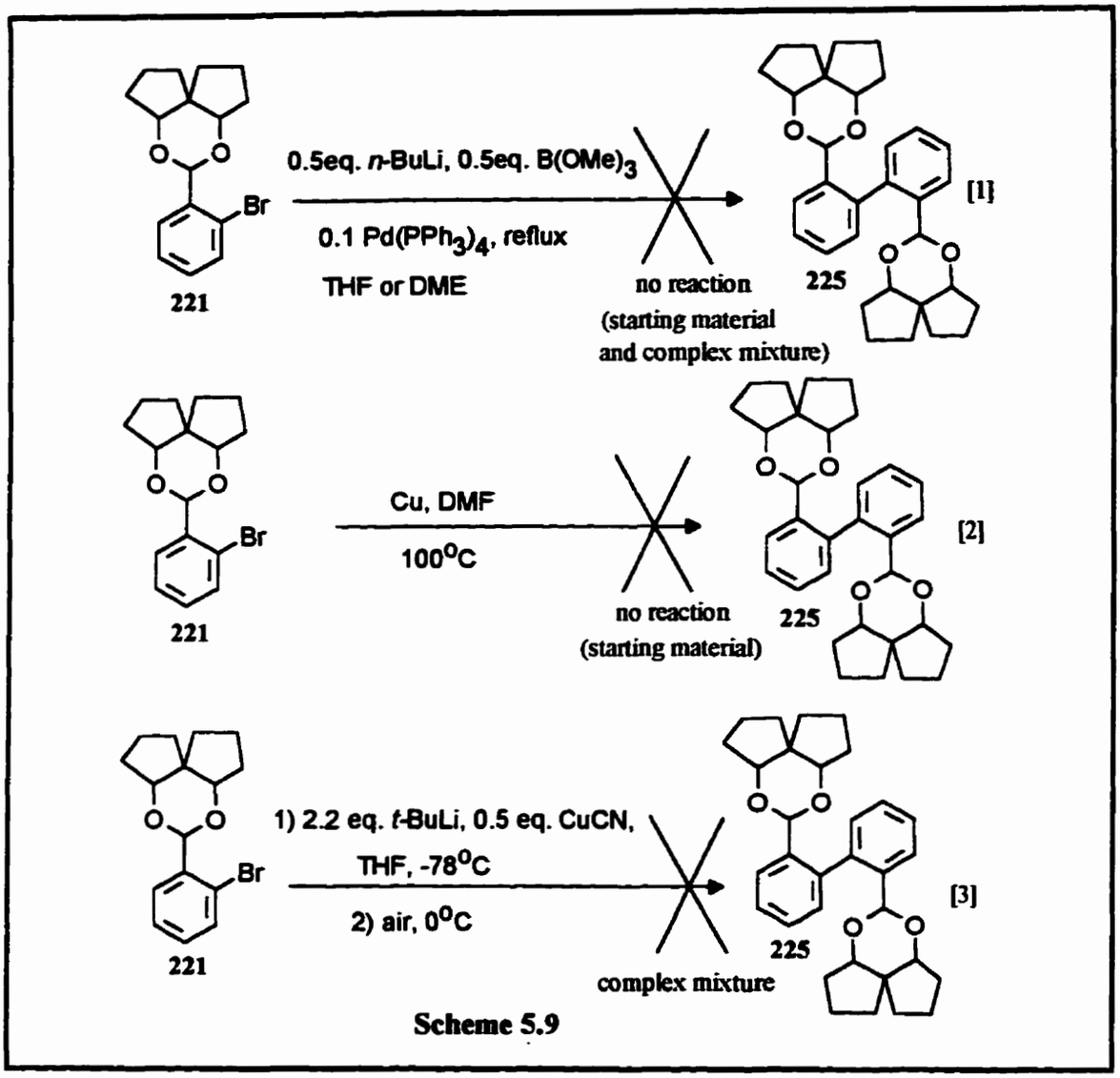
Scheme 5.8

Table 5.4 Diastereoselectivity of the Reaction of Various Aldehydes with Organometallic Intermediate **222** (Scheme 5.8)

R	M	Solvent	Ratio (223 : 224)[a]	Percent de (223)[a]	Literature
Me	Li	THF	1.24 : 1	12	3 - 38%[104]
Me	Li	Et_2O	0 : 1	-	3 - 38%[104]
Et	Li	THF	0 : 1	-	-
Me	MgBr	Et_2O	0.37 : 1	0	3 - 38%[104]
Ph	MgBr	Et_2O	0.62 : 1	11	88%[105]

a) based on integration of the ^{1}H-NMR spectrum of the crude mixture.

Formation of the magnesium salt **222** also produced inferior results to entry 1 in Table 5.4. Reaction of **222** (M = MgBr) with benzaldehyde produced a 0.62:1 mixture of products **223** and **224**. Integration of the acetal hydrogens at δ 5.9 (s) and 5.85 (s) indicated a de of 11% for **223** (R=Ph). The de's obtained for acetal **223** are considerable lower than those observed in the literature for analogous reactions (obtained with other chiral diol acetals, see Section 1.3.6); this prompted the investigation of other reactions.



Scheme 5.9

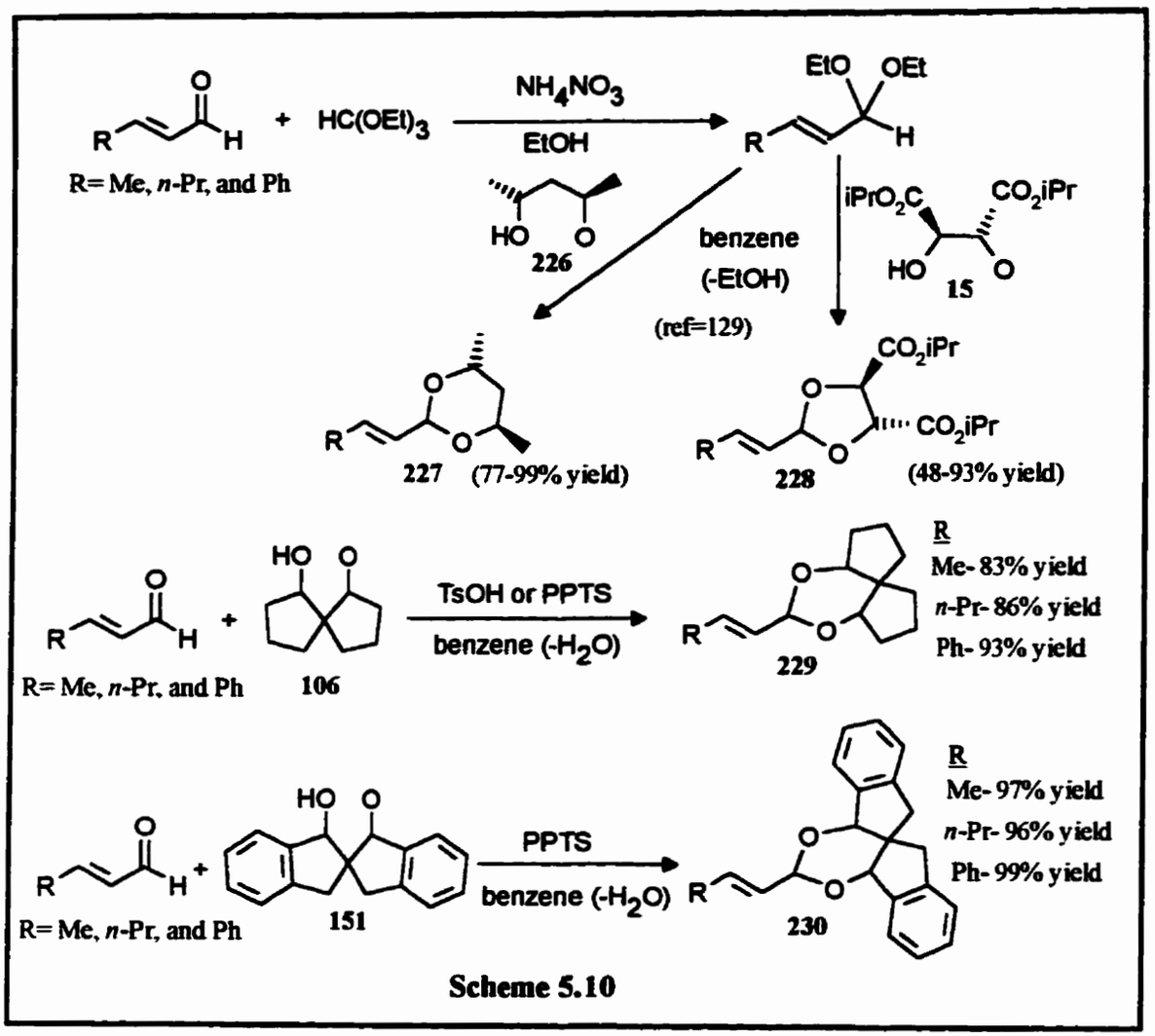
One of the interests in Dr. Keay's laboratory has been the coupling of two aromatic rings to form a biaryl.[210] The premise of using chiral compound **221** in a biaryl coupling reaction would be to influence the formation of the aryl-aryl bond by producing a chiral axis. The chiral acetals could then be removed forming an enantioenriched biaryl compound (*e.g.* biphenyl or binaphthyl).

The first coupling reaction explored with bromo compound **221** was the *in situ* Suzuki coupling methodology developed in Dr. Keay's lab (reaction 1, Scheme 5.9).[210,211] The reaction involves conversion of half the bromine atoms into borate esters by treatment

of 1 eq. of compound **221** with 0.5 eq. of *n*-BuLi at -78°C followed by addition of 0.5 eq. trimethylborate and warming to rt. The Suzuki coupling of the resulting 0.5 eq. of the borate ester with 0.5 eq. of unreacted **221** in the presence of palladium at reflux should produce biaryl compound **225**. When the reaction was attempted a complex mixture containing mainly starting material was produced. The failure of **221**, which contains a large acetal group in the *ortho* position, to cleanly couple was consistent with other hindered systems investigated in Dr. Keay's laboratory. In an attempt to alleviate the problem due to steric congestion during the coupling reaction of the aryl bromides, other reactions were investigated (reaction 2 and 3, Scheme 5.9). Ullmann coupling[212] conditions (Cu, DMF, 100°C) resulted in recovery of starting material (reaction 2) and was not explored further. Finally a recent procedure reported by Lipshutz,[213] which involved the reaction of higher order aryl cuprates with oxygen was tried. Application of the Lipshutz method to the coupling of bromoaryl compound **221** produced a mixture of compounds, but **225** was not detected by ^{1}H-NMR spectroscopy. Unfortunately, time did not permit further investigation of this reaction.

5.3.3 Cyclopropanation Reaction

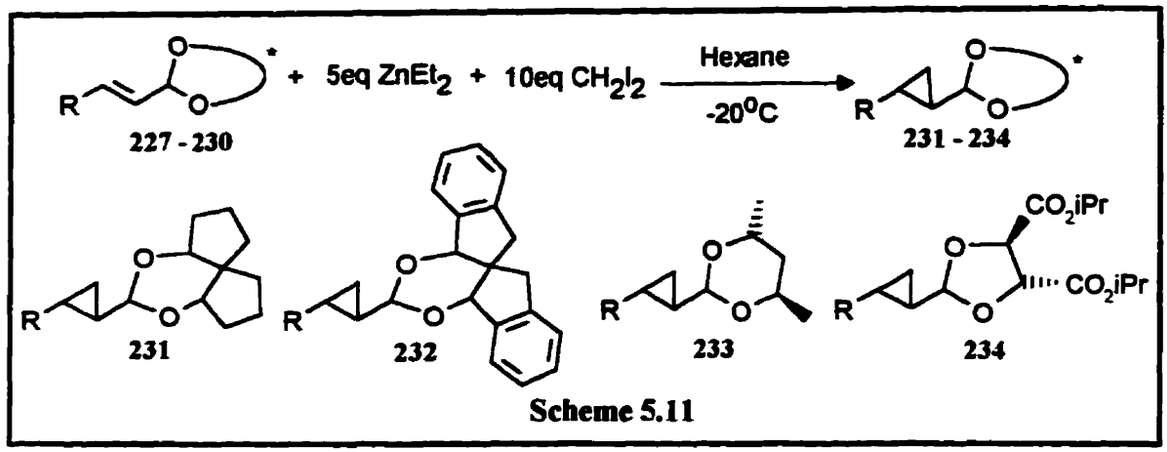
Literature examples using C_2-symmetric diols as chiral bound substrates in diastereoselective cyclopropanation reactions were summarised in Section 1.3.11. Yamamoto[129] published two papers that examined diols **15** and **226** as chiral acetal auxiliaries in the cyclopropanation reaction. The syntheses of corresponding acetals **227** and **228** was accomplished by Yamamoto's group over two steps (Scheme 5.10) in mediocre to excellent yield (48-99% yield). Thus, refluxing a diethyl acetal with **226** or **15** in benzene produced **227** and **228** respectively. The syntheses of acetals with diols **106** and **151** were performed by refluxing the mixture in benzene using PPTS or TsOH with azeotropic removal of water. Acetals **229** and **230** were formed in high yield (83-99% yield, Scheme 5.10). The formation of the acetal was confirmed by the appearance of a doublet, which corresponded to the acetal hydrogen resonance, at δ 5.10 (d, 1H, J ≈ 5.5



Scheme 5.10

Hz) in the H-NMR spectrum of **229** and **230** (R = Me or *n*-Pr). When R = Ph, the signal for the acetal hydrogen appeared at δ 5.35 (d, 1H, J = 5.0 Hz).

The cyclopropanation results using acetals **229** and **230** are reported in Table 5.5 using Yamamoto procedures.[129] The successful formation of cyclopropane acetals **231** and **232** were obvious by examination of ^{1}H-NMR spectra for three main reasons: 1) loss of the signals for olefinic hydrogens in the starting material; 2) upfield shift of acetal hydrogen doublet; and 3) appearance of resonances due to the hydrogens on the cyclopropane moiety below δ 1.0 (or around δ 1.0 for R = Ph).



Scheme 5.11

Table 5.5 Results for the Cyclopropanation of **227 - 230** (Scheme 5.11)

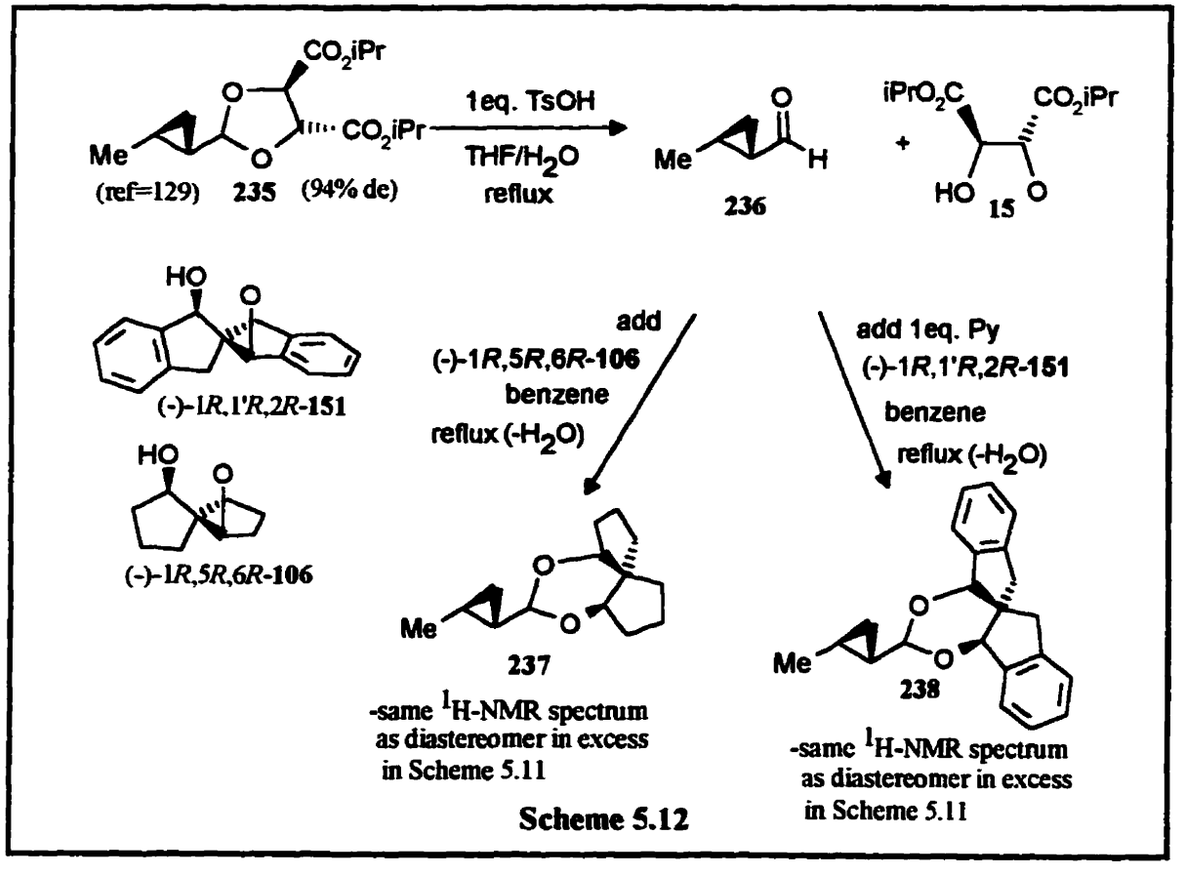
R	Ene-acetal Product			
	231 %de[a] (% yield)	**232 %de[a] (% yield)**	**233 %de[a] (% yield)[129]**	**234 %de[a] (% yield)[129]**
Me	53 (99)[b]	53 (86)[b]	69 (74)[b]	94 (90)[b]
Ph	67 (36)[c]	65 (75)	68 (85)	91 (92)
n-Pr	36 (85)	54 (74)	71 (95)	91 (80)

a) percent de determined by integration of the acetal hydrogen. b) the all *R* chiral auxiliary produced the *R,R*-configuration for the two chiral centres of the cyclopropane moiety. c) hydroxy ester **239** (Scheme 5.13) was isolated in 29% yield.

The ratio of diastereomers for cyclopropane product **231** and **232** were determined by integration of the two diastereomeric acetal hydrogens. The de obtained for the cyclopropanation with ene-acetal **229** ranged from 36 to 67% with a yield variance between 32 and 99% (the low yield when R = Ph will be explained later in this section). The results for the cyclopropanation reaction of acetal **230** proved more consistent; the de ranged from 53 to 65% with the yield between 74 to 86%. The percent de for the diastereoselective cyclopropanation of **229** and **230** proved comparable to that reported for **227**, but were inferior to the percent de's reported by Yamamoto for **228** (Table 5.5). The reason(s) for the superior results with **228** was not clear. The reason may result from

the fact that acetals generated with diisopropyl tartrate **15** form a five-membered ring while diols **106**, **151** and **227** produce six-membered acetal rings. The five-membered ring may result in greater steric interactions due to: 1) the increased rigidity of the ring (over the six-member ring in **106**, **151**, and **227**) and 2) the shorter distance the substituents are from the double bond. Also, the higher diastereoselectivity of the diisopropyl tartrate acetal **228** might have been a result of the ester functionalities complexing with the diethylzinc increasing their steric influence. The exact reason that diisopropyl tartrate (**15**) produced higher de's than **227**, **229** and **230** was not determined, but the reasons listed above are likely the cause.

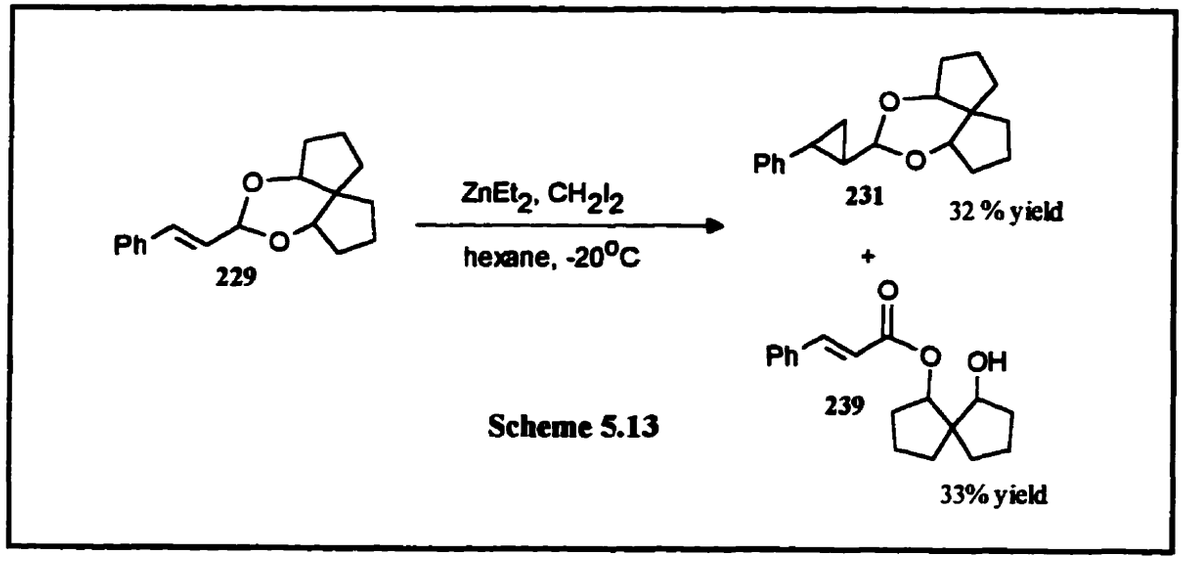
The relative configurations of **231** and **232** (for R = Me) were determined in an indirect way. Yamamoto determined the absolute configuration of **234** (R = Me) by conversion to *trans*-3-methylcyclopropanecarboxylic acid for which the absolute



Scheme 5.12

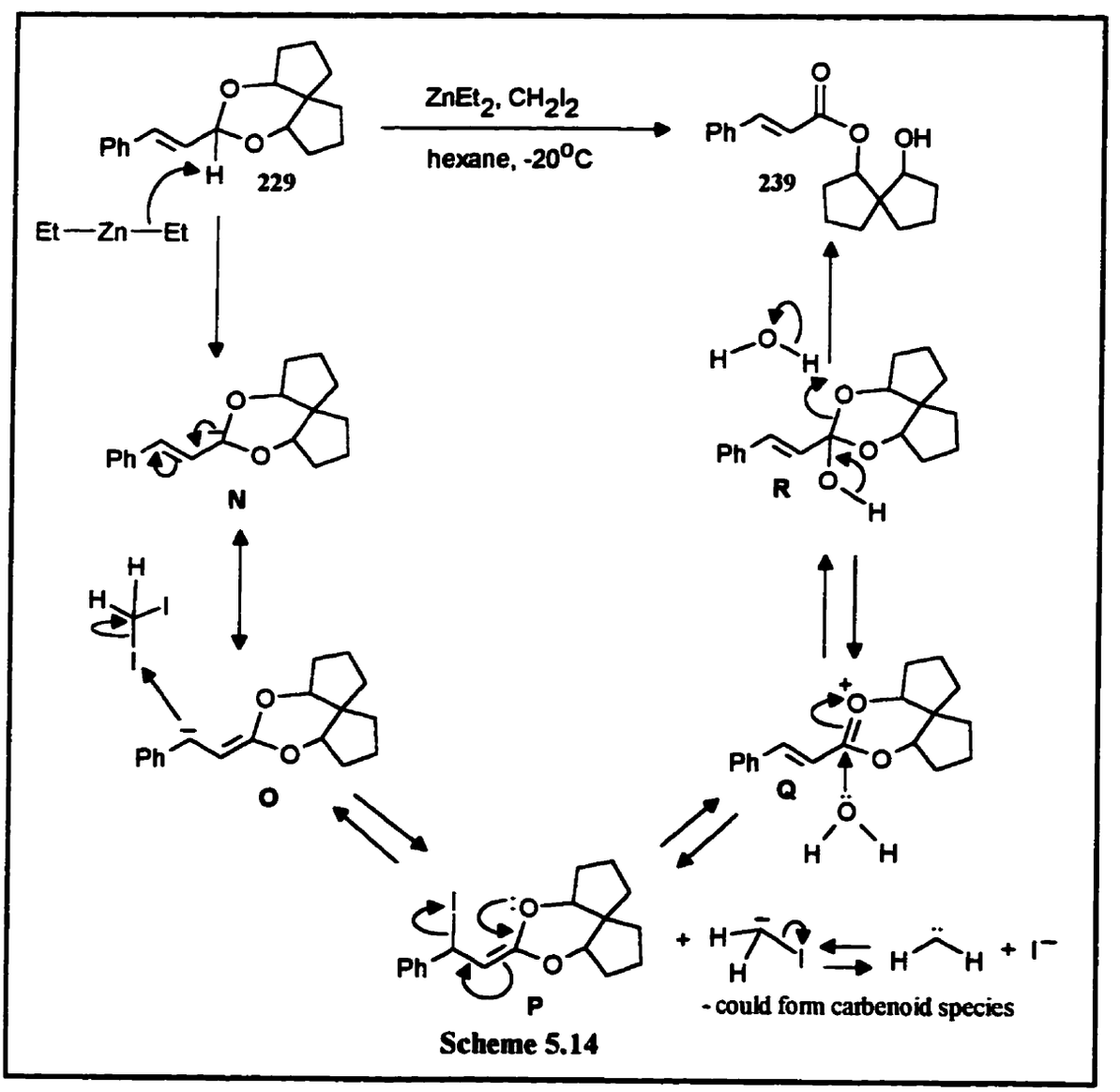
stereochemistry for each optical isomer is known.[129] Yamamoto reported that when L-(+)-diisopropyl tartrate was used, the cyclopropane formed had the 1*R*,2*R*-configuration.[119] Repeating Yamamoto's reported cyclopropanation procedure with **228** (R = Me) formed **235** (Scheme 5.12). The tartrate acetal was removed to provide a mixture of **236** and **15** which was used immediately in the next reaction. Reaction of (-)-1*R*,5*R*,6*R*-**106** with the mixture of **236** and **15** formed a mixture of tartrate **15** and **237**. Comparison of the ^{1}H-NMR spectrum of the crude mixture for the formation of **237** to that obtained for (±)-**231** (R = Me, Scheme 5.11) illustrated that the 1*R*,5*R*,6*R*-configuration of the spiro system resulted in formation of cyclopropane **231** with a 1*R*,2*R*-configuration, while 1*S*,5*S*,6*S*-diol **106** produced greater amounts of **231** the 1*S*,2*S*-configuration of the cyclopropane. Likewise following the same method above, it was shown by comparison of the ^{1}H-NMR spectra of **238** (Scheme 5.12) and (±)-**232** (Scheme 5.11) that the 1*R*,1′*R*,2*R* acetal of **229** produced **232** with a 1*R*,2*R* configuration. Use of the 1*S*,1′*S*,2*S*-configuration of the spiro system **232** produced the 1*S*,2*S* cyclopropane in excess.

The most interesting feature observed in this diastereoselective reaction was with the cyclopropanation of **229** (R = Ph, Table 5.5). Only a 36% yield was produced of the desired cyclopropane **231** (R = Ph, Table 5.5); however, an unexpected compound was



Scheme 5.13

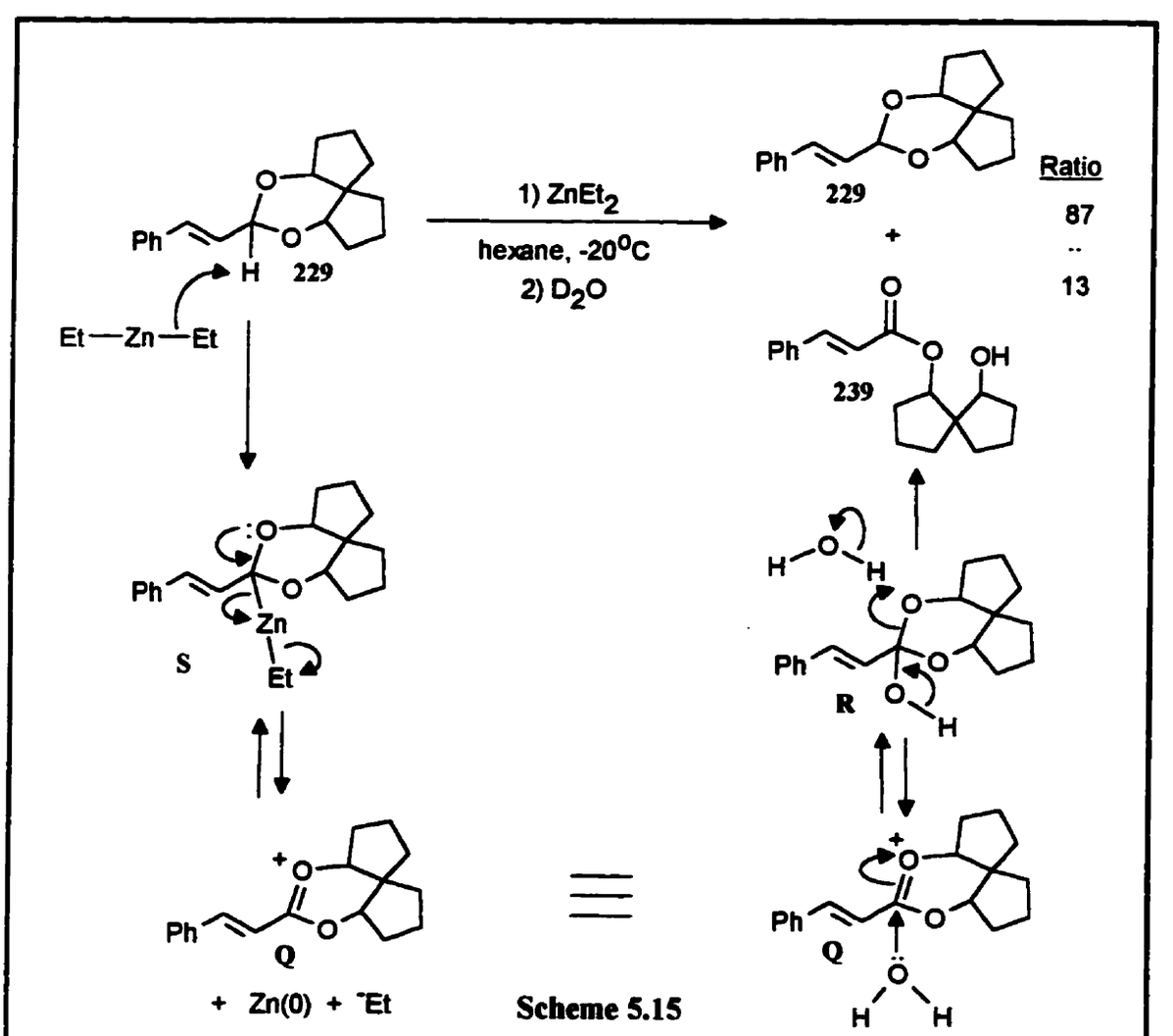
also formed (Scheme 5.13). This unexpected compound was isolated by column chromatography (5:1, hexanes : ethyl acetate) in 29% yield ($M^{+\cdot}$ = 286). The functional groups in this unexpected product were: 1) a *trans*-conjugated double bond (^{1}H-NMR δ 7.71 and 6.46 signals a with coupling constant J= 16.0 Hz); 2) a monosubstituted benzene (^{1}H-NMR δ 7.57 - 7.52 (m, 2H) and 7.43 - 7.37 (m, 3H)); 3) a conjugated ester (^{13}C-NMR δ 167.7); and 4) an alcohol (broad peak at 3587 cm^{-1} in the IR). With these data, structure **239** was assigned for this unexpected product.



Scheme 5.14

The mechanism proposed for the formation of **239** involves diethylzinc acting as a base to deprotonate the acetal hydrogen forming stabilised anion **N** (Scheme 5.14). An alternative resonance structure of **N** is **O**, which can attack an iodine atom of diiodomethane to produce **P** and a carbene (or carbenoid). Loss of the iodine atom produces **Q**, which upon workup with water forms **R**. Ring opening of **R** leads to **239**.

To test this mechanism (Figure 5.14), the addition of diethylzinc to compound **229** should result in some anion formation (**N** or **O**, Scheme 5.14) that upon quenching with D_2O should reform **229** (or a double bond isomer) with some deuterium incorporation. Treatment of **229** with diethylzinc (in the absence of CH_2I_2) followed by the addition of



Scheme 5.15

D_2O surprisingly formed a mixture of **229** and **239** with no deuterium incorporation (Scheme 5.15). This meant that CH_2I_2 was not involved in the mechanism. The mechanism, therefore, must involve the diethylzinc acting as an oxidant.

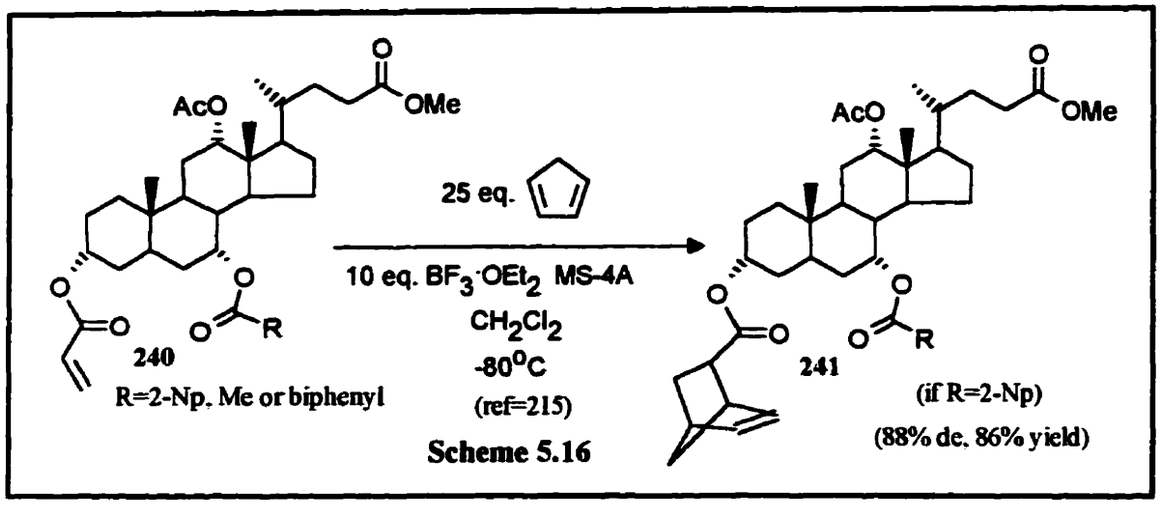
A mechanism that explains why CH_2I_2 is not required is shown in Scheme 5.15. Again the diethylzinc is acting as a base, but instead of the resulting anion attacking the iodine atom of CH_2I_2, as in Scheme 5.14, the alkyl zinc **S** forms **Q**, metallic Zn and Et. Oxonium intermediate **Q** could produce compound **239** upon addition of water, as in Scheme 5.14. The most troublesome step of the mechanism in Scheme 5.15 is the transformation of **S** into **Q**, metallic Zn and Et. The ethyl carbanion may be aided in leaving by interacting with a second molecule of diethylzinc or simultaneously acting as a base. Either way, carbanions are extremely poor leaving groups and that is why this mechanism is unlikely; however, it is the only one that supports the observed results.

It was interesting that this oxidation reaction was only observed with acetal **229** when R = Ph (Table 5.5); both **230** and **228** (R = Ph, Table 5.5) did not show evidence that this oxidation reaction took place. A search of the literature failed to uncover precedent for this type of reaction and due to time constraints, further investigation into the exact mechanism was not undertaken.

Although the formation of the ene-acetals of diols **106** and **151** were more efficient than those for diols **15** and **227**, their application as chiral acetals in the diastereoselective cyclopropanation reaction produced lower de's. Unfortunately, time did not permit the investigation of the diastereoselective cyclopropanation of ene-ketals or cyclopropanation with different reagents (e.g. Zn/Cu and CH_2I_2).

5.3.4 Diels-Alder Reaction

The last and the most successful application of the *cis,cis*-spiro[4.4]nonane-1,6-diol (**106**) as a substrate bound chiral auxiliary was in the Diels-Alder reaction.[214] The idea for this reaction came from reading an article published in 1995 by Mathivanan and Maitra.[215] In that article Mathivanan and Maitra report the use of a new steroid-based chiral dienophile **240**, derived from cholic acid, in the Diels-Alder reaction between acrylate and



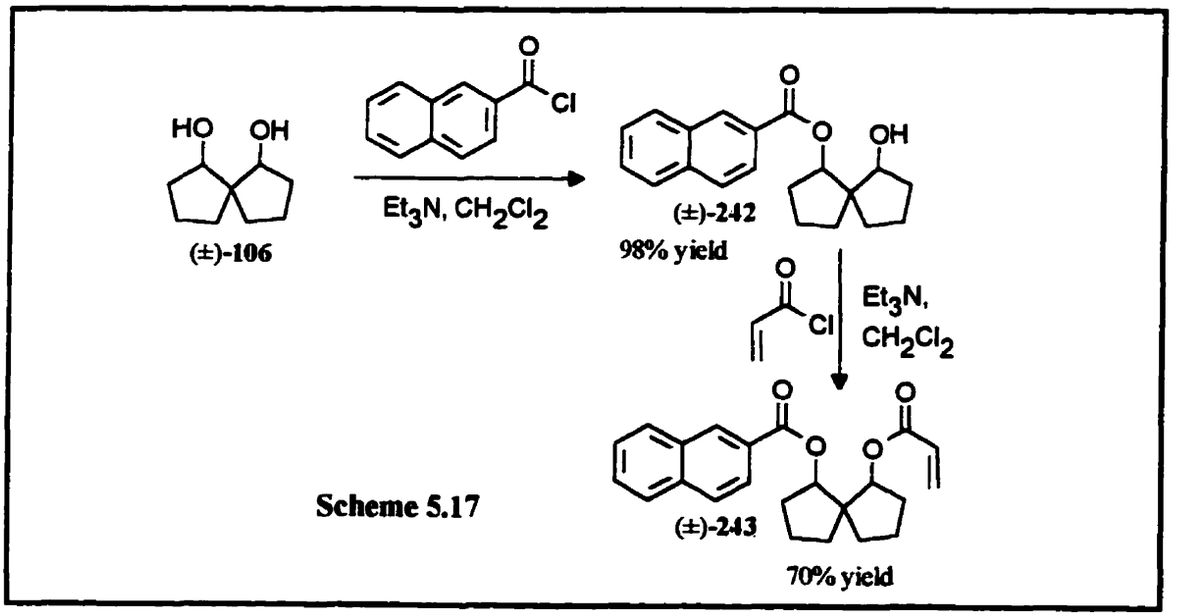
Scheme 5.16

cyclopentadiene (Scheme 5.16). The best results reported for **240** were when 2-naphthoate was employed as the "blocking group" (R = 2-Np) which produced an 88% de and 86% yield of the Diels-Alder adduct **241**. This prompted an investigation using diol **106** as a chiral auxiliary in an analogous reaction. The advantage that diol **106** could have over Mathivanan and Maitra's cholic acid auxiliary would be that only two ester functionalities are present (instead of four), thus less Lewis acid should be required and, unlike cholic acid, both antipodes of diol **106** are available (Section 2.3.5) which would allow either enantiomer of the Diels-Alder adduct to be formed.

Diol **151** was not examined in this section because of the strong probability of rearrangement, in the presence of strong Lewis acids, to aldehyde **195** or polycyclic aromatic **194** (Scheme 4.15).

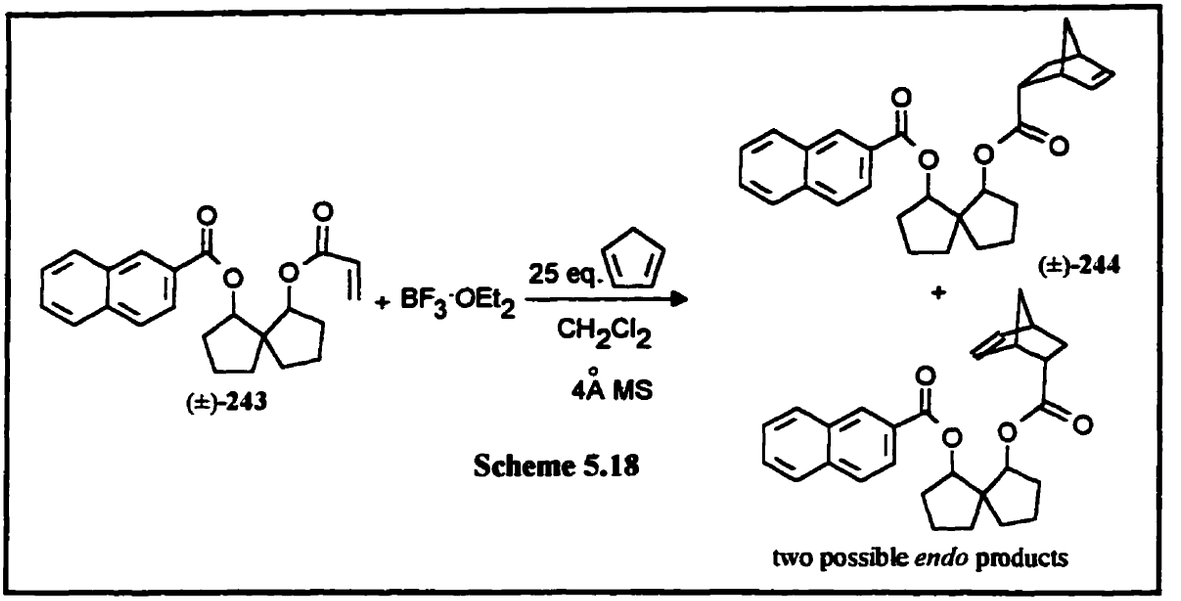
The strategy for the investigation reported in this section was the transformation of one of the hydroxyl groups in diol **106** into a "blocking group" and placement of the dienophile (*e.g.* acrylate) on the other hydroxyl group. If the "blocking group" was oriented correctly and was sterically encumbering then approach of the diene to the dienophile would occur in a very selective manner producing product with high diastereoselectivity. The report by Mathivanan and Maitra[215] found that the best "blocking group" was a 2-naphthoate group; therefore, the first logical group to investigate as a "blocking group" for diol **106** was the 2-naphthoate. The synthesis of the mono-2-

naphthoate hydroxyspiro (±)-**242** and the subsequent acrylate ester (±)-**243** (Scheme 5.17) proceeded as expected in 69% overall yield. The formation of diester (±)-**243** was substantiated by the presence of the resonances in the ^{1}H-NMR spectrum due to the aromatic protons of 2-naphthoate and the alkene protons from the acrylate ester. The main change in the ^{1}H-NMR spectrum of the spiro[4.4]nonane portion upon going from diol **106** to diester **243** was the loss of the alcohol proton resonance (ranged from δ 3.5 to 2.3 (br. s, 2H)) and the downfield shift of the methine hydrogen of the carbinol group from δ 4.14 in **106** to δ 5.41 and 5.36. These shifts are indicative of the alcohol in **106** now being an ester oxygen atom.[216] High resolution mass spectrometry found the molecular ion had a mass of 364.1654, which agreed with the molecular formula of $C_{23}H_{24}O_4$ assigned to compound **243**.



Scheme 5.17

With the synthesis of (±)-**243** complete, the next step was to determine the optimal conditions for the Diels-Alder reaction. Since Mathivanan and Maitra[215] reported that $BF_3{\cdot}OEt_2$ worked the best (Scheme 5.16), it was tried first. The temperature and time of the reaction and the number of equivalents of $BF_3{\cdot}OEt_2$ were varied and are illustrated in Table 5.6.



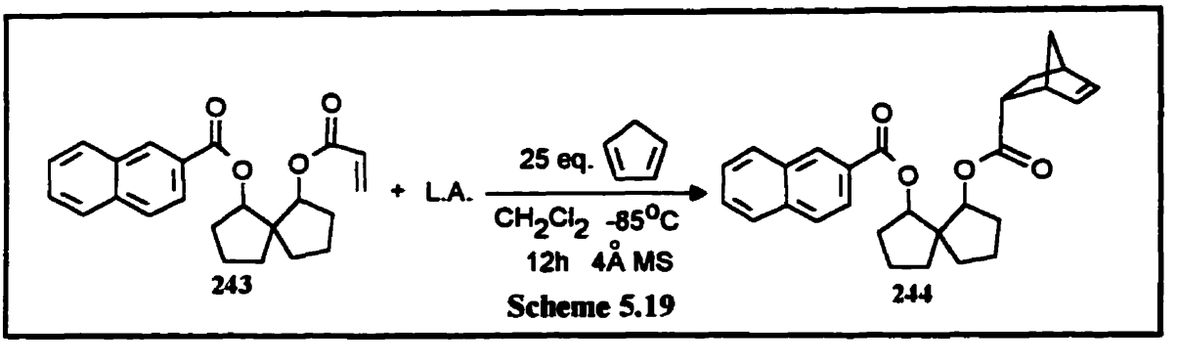
Scheme 5.18

Table 5.6 Results for Diels-Alder Reactions of 2-Naphthoate **243** with Cyclopentandiene (Scheme 5.18) in the Presence of Various Amounts of $BF_3 \cdot OEt_2$ at Different Temperatures

Entry	Eq. of $BF_3 \cdot OEt_2$	Temp. (°C)	Time (h)	*endo*[a] (%)	*endo* de[a] (%)	Conversion[a] (%)
1	0	8	-	84	7	100[b]
2	2	-85	0.5	-	71	2
3	1	-85	12	98	75	21
4	2	-85	12	98	73	25
5	8	-85	12	98	72	63
6	2[c]	-85	12	98	72	27
7	2	-70	12	97	76	63
8	4	-70	12	98	76	94
9	2	0	12	92	67	58

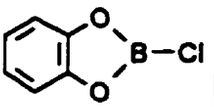
a) determined by HPLC using an ODS column with methanol/water (90:10). b) cyclopentadiene added until the reaction was complete. c) $BF_3 \cdot OEt_2$ and dienophile stirred at rt first for 0.5 h.

The total percent of products with the *endo*-stereochemistry in the total adduct (*endo* and *exo* are possible),[217] the percent de of one *endo*-isomer adduct over the other, and percent conversion to product **244** were determined by HPLC and confirmed by analysis of the ^{1}H-NMR spectrum of the crude mixture. In the absence of $BF_3{\cdot}OEt_2$ an *endo* : *exo* ratio of 84:16 was obtained with only a 7% de for the *endo* isomers. This reaction was performed so that HPLC retention times and ^{1}H-NMR resonances of the *endo* (both diastereomers) and *exo* (only minor amounts) adducts of **244** could be obtained for future comparisons.[218] Entry 2 demonstrated that the reaction was not complete after 0.5 h, and needed longer reaction times. Since slow polymerisation of cyclopentadiene competes with the Diels-Alder reaction then no further reaction with **243** would occur after approximately 12 h (overnight). Thus, the rest of the reactions in Table 5.4 were run for 12 h. Entries 3, 4 and 5 demonstrated that the de of the *endo* adduct remained essentially constant when the amount of $BF_3{\cdot}OEt_2$ was increased, but the percent conversion increased as the amount of Lewis acid increased. To determine if the equilibrium of diester **243** and $BF_3{\cdot}OEt_2$ had enough time to be reached, they were stirred at rt for 0.5 h prior to the addition of cyclopentadiene. The results were almost identical to entry 4, which confirmed that stirring **243** and $BF_3{\cdot}OEt_2$ for 5 minutes at -85°C, before adding cyclopentadiene was sufficient time for the system to reach equilibrium. When the Diels-Alder reaction was performed at -70°C (entry 7 and 8) similar de's, but higher yields (than entries 4) were obtained. If the reaction temperature was increased to 0°C (entry 9) a lower percent de and yield was obtained compared to entry 4. The lower yield potentially might be a result of more polymerisation of cyclopentadiene by $BF_3{\cdot}OEt_2$. The results in Table 5.6 were encouraging, but other Lewis acids (Table 5.7) might improve the percent conversion and percent de of Diels-Alder adduct **244**.



Scheme 5.19

Table 5.7 Influence of Various Lewis Acids on the Diels-Alder Reaction of Diester **243** with Cyclopentadiene (Scheme 5.19)

Entry	Eq. of L.A.	L.A.	*endo*[a] (%)	*endo* de[a] (%)	Conversion[a] (%)
1	2	$BF_3{\cdot}OEt_2$	98	73	25
2	1.1	$TiCl_4$	97	54	6
3	3	$TiCl_4$	96	40	5
4	2	$SiCl_4$	-	54	8
5	1.1	$SnCl_4$	95	80	15
6	3	$SnCl_4$	-	-20[b]	14
7	2.1	$SbCl_5$	94	53	74
8	1.1	$AlCl_3$	98	40	100
9	1.1	$AlMeCl_2$	96	51	100
10	3	$AlMeCl_2$	97	59	100
11	2		98	69	100
12	1	BCl_3	98	74	100
13	2	BCl_3	96	75	100

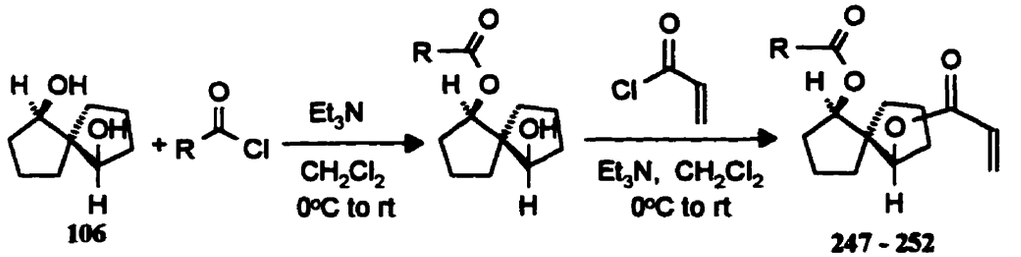
a) determined by HPLC using an ODS column with methanol/water (90:10). b) indicates that the opposite stereochemistry of the *endo* adduct was formed.

The reaction of **243** with cyclopentadiene was performed in the presence of various Lewis acids and in various amounts (Table 5.7) and the results were compared to the results from the use of 2 eq. of $BF_3{\cdot}OEt_2$ (entry 1). Titanium tetrachloride (entry 2 and 3) resulted in a lower percent conversion and de. Silicon tetrachloride (entry 4) also produced a lower de and conversion than $BF_3{\cdot}OEt_2$. Tin(IV) chloride (entry 5 and 6) formed Diels-Alder adduct **244** with a lower percent conversion (than entry 1), but interestingly the minor *endo* diastereomer that formed with 1.1 eq. of $SnCl_4$ became the major isomer when 3 eq. of $SnCl_4$ was increased. A possible reason for this change may be a change in the preferred conformation of the acrylate ester when the number of equivalents of $SnCl_4$ that can bind to the two esters in **243** was increased. This is purely speculative and no further work was done to substantiate this idea.

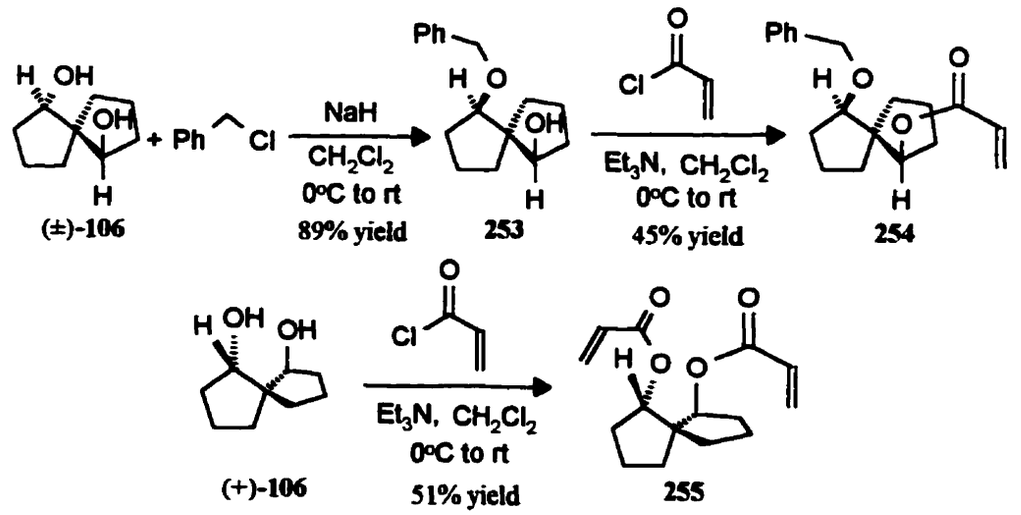
Improved conversion to **244** was observed when antimony pentachloride (entry 7, Table 5.7) was used; however a lower *endo* de was produced when compared to entry 1 ($BF_3{\cdot}OEt_2$). The use of aluminium containing Lewis acids (entries 8, 9 and 10) yielded a 100% conversion to products, but the lower *endo* percent de's obtained for these aluminium based Lewis acids were disappointing. The use of chlorocatecholborane (entry 11) as the Lewis acid not only produced the product with 100% conversion, but also provided a percent de close to that with $BF_3{\cdot}OEt_2$ (69% versus 73%). One or two equivalents of BCl_3 (1.0 M in heptane) not only provided similar *endo* percent de results of entry 1, but also furnished the products with 100% conversion (entries 12 and 13). Since BCl_3 gave the best results for the conversion of **243** to **244**, the next step was to find a "blocking group" that would result in even greater *endo* diastereoselectivity under these optimised reaction conditions.

Various diesters were synthesised using a similar approach to that reported in Scheme 5.17 for compound **243**, and the results are summarised in Scheme 5.20.

Next, the use of these dienophiles (**247** - **252**) in the Diels-Alder reaction with cyclopentadiene was investigated (Scheme 5.21, Table 5.8). The first two entries indicated that benzoate **247** reacted to a greater extent with a slightly higher *endo* de with



R	Optical isomer of 106	% Yield	% Yield
Ph-	(±)-, (-)-	93 (245)	84 (247)
Ph_2HC-	(±)-	77	80 (248)
p-MeO-Ph-	(±)-	76	52 (249)
p-O_2N-Ph-	(±)-	99	86 (250)
Me_3C-	(±)-, (+)-	92 (246)	76 (251)
1-Np	(-)-	91	75 (252)



Scheme 5.20

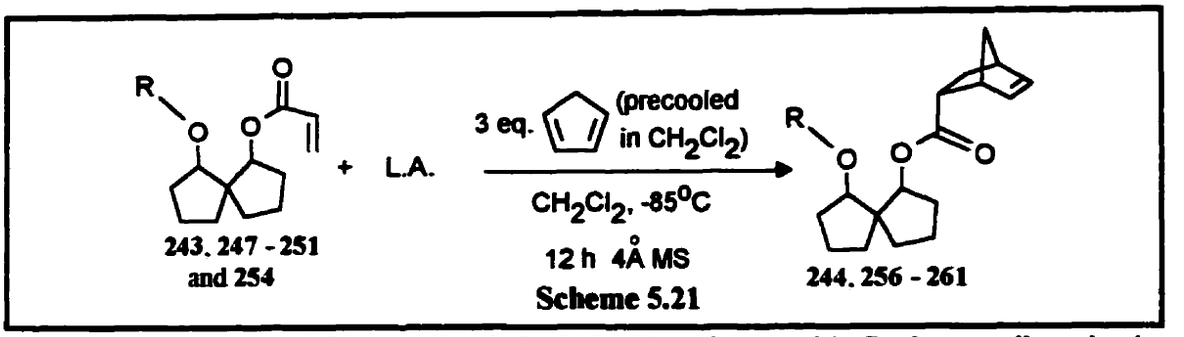
$BF_3{\cdot}OEt_2$ than 2-naphthoate. The Diels-Alder reaction of benzoate **247** in the presence of BCl_3 proceeded in an 85% de of the *endo* enantiomer (entry 4) which was higher than the de (75%) obtained from the more sterically encumbering 2-naphthoate (entry 3). Since

work-up was difficult due to the polymerisation of cyclopentadiene a new procedure was developed.

This new modified procedure proved to provide the best results. It involved the addition of CH_2Cl_2 to the dienophile and 4Å molecular sieves and cooling to -85°C prior to the addition of 2 eq. of BCl_3. After stirring for 5 min, a precooled (-85°C) solution of freshly cracked cyclopentadiene (3 to 5 eq.) in CH_2Cl_2 was added *via* a cannula. The reaction was stirred at -85°C for 12 hours (overnight) and was filtered through silica gel. The solvent was removed *in vacuo* resulting in crude product. Purification was achieved by separation on a column of silica gel or by using a Chromatotron with hexanes : ethyl acetate (9:1).

Entries 5 and 6 (Table 5.8) used the improved procedure and showed slight improvement in the *endo* percent de's, when compared to entries 3 and 4 which used the previous procedure (addition of cyclopentadiene (25 eq.) neat at rt). The promising results obtained with BCl_3 prompted an examination of the Diels-Alder reaction with BBr_3; however, no reaction occurred when the Diels-Alder reaction of **247** and cyclopentadiene was attempted in the presence of BBr_3 (entry 7).

The functionality joining the "blocking group" was altered (entries 8 and 9) from an ester to a benzyl ether to: 1) allow for more chemoselective removal of the ester connecting the Diels-Alder adduct; 2) alter the electron density of the aromatic ring in the "blocking group", which might produce a higher de by such means as π-stacking; and 3) alter the configurations possible from the more rigid ester to a more rotationally free ether, which might also increase the de. Entries 8 and 9 summarise the results obtained with benzyl ether **254**. The percent *endo* de with 1 eq. of BCl_3 (entry 8) was 75%, but with 2 eq. of BCl_3 it dropped to 45% de (entry 9). The extra equivalent of BCl_3 might be causing the benzyl ether to adopt a slightly different preferred conformation resulting in a drop of the *endo* diastereoselectivity. The reaction with the *p*-nitro (**250**, entry 10) or the *p*-methoxy (**249**, entry 11) benzoate derivative did not noticeably increase (or decrease)



243, 247 - 251 and 254

Scheme 5.21

244, 256 - 261

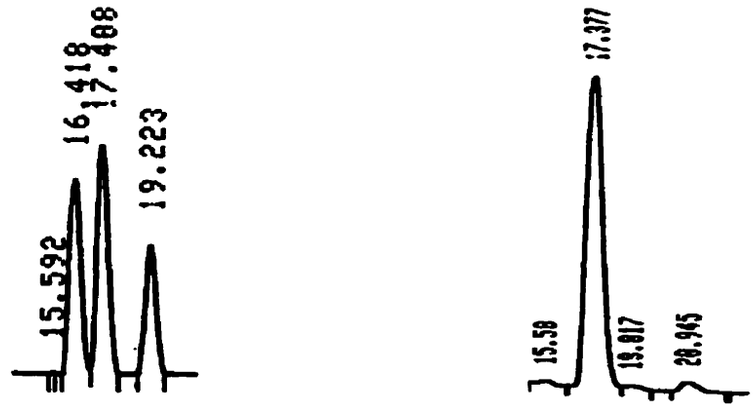
Table 5.8 Reaction of Dienophiles **243**, **247-251** and **254** with Cyclopentadiene in the Presence of Different Lewis Acids (Scheme 5.21)

Entry	R on (±)-243, 247 - 251 and 254	L.A. (eq.)	L.A.	*endo*[a] (%)	*endo* de[a] (%)	Percent Conversion[a] (% yield[b])	Adduct
1[c]	2-NpCO	2	$BF_3{\cdot}OEt_2$	98	73	25	**244**
2[c]	Bz	2	$BF_3{\cdot}OEt_2$	99	77	68	**256**
3[c]	2-NpCO	2	BCl_3	96	75	100	**244**
4[c]	Bz	2	BCl_3	99	85	100	**256**
5	2-NpCO	2	BCl_3	96	79	100 (79)	**244**
6	Bz	2	BCl_3	99	88	100 (72)	**256**
7[c]	Bz	2	BBr_3	-	-	0	-
8	Bn	1	BCl_3	-	75[c]	100[d] (99)	**257**
9	Bn	2	BCl_3	-	45[c]	100[c]	**257**
10	*p*-NO_2Ph	2	BCl_3	98	84	100 (98)	**258**
11	*p*-MeOPh	2	BCl_3	98	88	100 (83)	**259**
12	Ph_2CHCO	2	BCl_3	≥97[d]	90[d]	100[d] (99)	**260**
13	Me_3CCO	2	BCl_3	≥97[e]	≥97[e]	100[e] (80)	**261**

a) determined by HPLC using an ODS column with methanol/water (90:10). b) isolated yield. c) procedure involved addition of 25 eq. of cyclopentadiene at rt. d) determined by ^{1}H-NMR spectroscopy. e) determined by both HPLC and ^{1}H-NMR spectroscopy.

the de (compared to benzoate, entry 6) indicating that electronic interactions, such as π-stacking, may not be responsible for the high de's. Increasing the steric bulk to diphenyl acetate **248** (entry 12) resulted in an increase in diastereoselectivity of the *endo* isomer in the Diels-Alder reaction to 90%. Since steric size appears to increase the percent *endo* de, a pivaloate was prepared (**251**) and used in the Diels-Alder reaction (Scheme 5.21). Only one adduct was obtained; the other *endo* and *exo* diastereomers were not observed by ^{1}H-NMR spectroscopy or HPLC (Figure 5.4). Thus the percent de was modestly assigned to be ≥97%.[219]

With the best blocking group now determined and the experimental conditions needed for outstanding selectivity complete, attention was turned to the use of enantiopure diol **106** with the goal of determining the absolute configuration of the Diels-Alder adduct(s) obtained. The blocking groups used in the enantiopure Diels-Alder



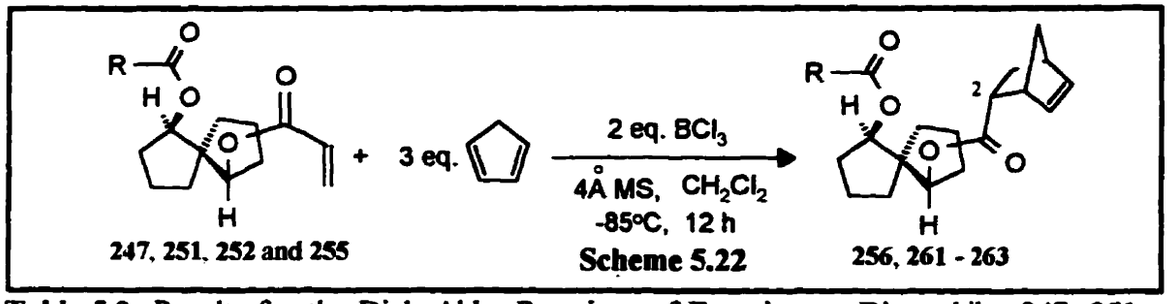
a) mixture of two *endo* (16.4 and 17.4 min) and two *exo* (19.2 min) adducts for compound **261**

b) exclusively one *endo* (17.4 min) adduct of compound **261**

Figure 5.4 A Portion of the HPLC Trace (85:15, MeOH : H_2O, UV detector at 220 nm) of Diels-Alder Product **261** Formed by the Reaction of Cyclopentadiene and Dienophile **251** at a) 8°C with no Lewis Acid, and b) -85°C in the Presence of BCl_3 (entry 13, Table 5.8)

reactions were the: 1-Np, Ph, H_2C=CH, and Me_3C (Table 5.9). Enantiopure 1-naphthoate **252** (entry 1, Table 5.9) provided a slightly lower diastereoselectivity of adduct **262** than (±)-2-naphthoate did of **244** (Table 5.8, entry 5), while enantiopure benzoate **247** (entry 2, Table 5.9) produced the same percent de reported previously (entry 6, Table 5.8).

The percent de for enantiopure **263** from the reaction with bis-acrylate **255** appeared by ^{1}H-NMR spectroscopy to be approximately 75%, but unlike the other examples in Table 5.9 did not reflect the percent ee of the bicycloadducts after removal from the diol. This will be explained later. The enantiopure pivalate **251** (entry 4, Table 5.9) provided **261** with the expected percent de of ≥97% (as was previously observed in Table 5.8, entry 13).

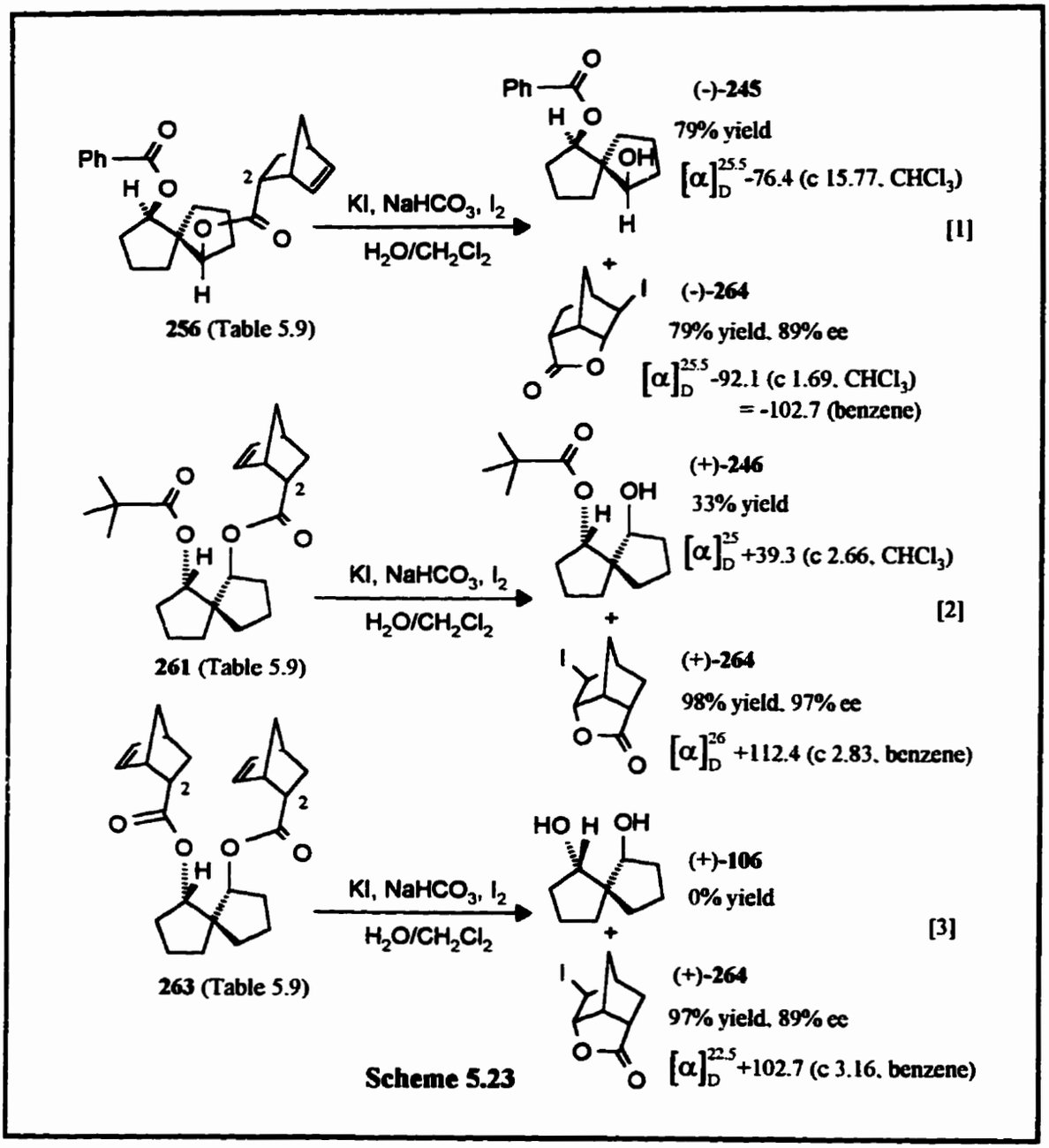


Scheme 5.22

Table 5.9 Results for the Diels-Alder Reactions of Enantiopure Dienophiles **247**, **251**, **252** and **255** (Scheme 5.22)

Entry	R	Configuration used for 106	Percent Endo[a]	Percent de[a] (% ee[b])	Percent yield[c]	Adduct
1	1-Np	(-)-1*R*,5*R*,6*R*-	98	75	89	**262**
2	Ph	(-)-1*R*,5*R*,6*R*-	99	88 (89)	72	**256**
3	H_2C=CH[d]	(+)-1*S*,5*S*,6*S*-	-[e]	75[f] (89)	84	**263**
4	Me_3C	(+)-1*S*,5*S*,6*S*-	≥97[g]	≥97[g] (97)	80	**261**

a) refers to endo diastereomers, determined by HPLC using an ODS column with MeOH/H_2O (90:10), unless otherwise indicated. b) determined by optical rotation of iodolactone (Scheme 5.23). c) refers to the isolated yield. d) both acrylates undergo the Diels-Alder reaction. e) could not be determined. f) ratio could only be estimated by ^{1}H-NMR spectroscopy due to a mixture of diastereomers. g) determined by both HPLC and ^{1}H-NMR spectroscopy.



Scheme 5.23

A literature search to find the best method for determining the absolute configuration for the Diels-Alder adduct revealed that iodolactonisation of bicycloadducts like **256**, **261** - **263** would produce iodo lactone **264** (Scheme 5.23). The optical rotation of **264** has previously been correlated to the absolute stereochemistry.[215] The enantiomer of **264** that provides the levorotatory ($[\alpha]_D^{22}$ -116 (c 2.2, benzene))[220] rotation was shown

to be the (1*R*,4*R*,6*R*,8*S*,9*R*)-**264** enantiomer.[215,221] Subjection of compounds **256**, **261**, and **263** to the iodolactonisation conditions (Scheme 5.23) produced iodolactone **264** in 79, 98, and 97% yield, respectively. Unfortunately, the chiral auxiliary **245** could only be isolated in 79% yield. This recovery of the chiral auxiliary has not been optimised and may increase with further studies.

Measurement of the optical rotation of iodo lactone **264** obtained from **256** indicated **264** was obtained in 89% ee as the (-)-enantiomer which meant that the 1*R*,4*R*,6*R*,8*S*,9*R*-iodolactone **264** was produced. This value (89% ee) agreed nicely with the de obtained for adduct **256** (Table 5.23). Thus the use of the 1*R*,5*R*,6*R*-diol produced the *R* configuration at C-2 in compound **256**.

The second reaction in Scheme 5.23 resulted in the isolation of iodo lactone **264** as the (+)-enantiomer with a 97% ee which meant that the 1*S*,4*S*,6*S*,8*R*,9*S*-iodolactone **264** was produced. This value (97% ee) agreed nicely with the de obtained for adduct **261** (Table 5.9). Thus the use of 1*S*,5*S*,6*S*-diol **106** produced the *S* stereochemistry at C-2 in compound **261**.

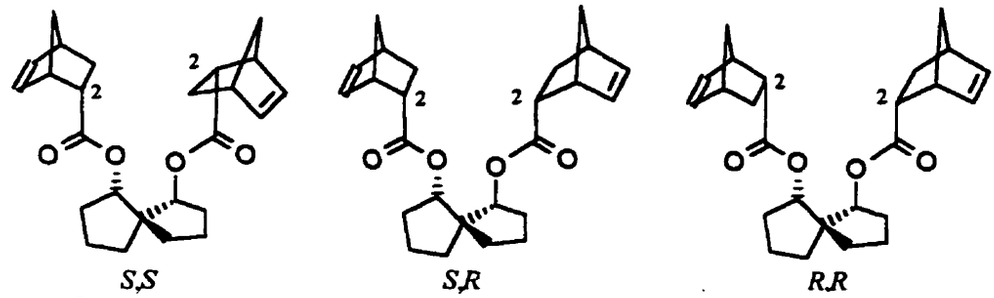


Figure 5.5 The Three Possible Bis-*endo* Orientations (at C-2) for Diadduct **263** Derived from 1*S*,5*S*,6*S*-**106**

Iodolactonisation of compound **263** (reaction 3, Scheme 5.23) resulted in the production of (+)-**264** with an 89% ee, which meant that 1*S*,4*S*,6*S*,8*R*,9*S*-iodolactone **264** was produced. Thus, the use of 1*S*,5*S*,6*S*-diol **106** produced mainly the *endo S* stereochemistry at both C-2 centres in compound **263**. This was an interesting example

because this meant that one of the homotopic acrylates acted as a blocking group while the other one underwent Diels-Alder reaction and then the adduct from the reacted acrylate acted as the blocking group as the other acrylate reacted with cyclopentadiene. The independent reaction of the two acrylates could have resulted in "same" or "different" absolute stereochemistry of the adducts. The preference for the "same" stereochemistry was determined by iodolactonisation of **263** (Scheme 5.23) which produced an 89% ee of iodolactone **264**. The 89% ee can be rationalised from the 75% de measurement for adduct **263** (Table 5.9) as follows. There are three diastereomers possible (assuming only the *endo* adduct are formed) from the Diels-Alder reaction with the diacrylate system, since two new asymmetric bicyclo adducts are formed per spirodiacrylate (Figure 5.5). The absolute stereochemistry at C-2 of the bicyclo adduct can have the following absolute configurations in the diadduct product: a) both *S*; b) one *S* and one *R*; and c) both *R*. Analysis of the two diastereomers formed indicated that products a) and b) above were formed in a ratio of approximately 88:12 (~75% de). Iodolactonisation (Scheme 5.23) of the two diastereomers provided iodolactones **264** in a ratio of 188 (88+88+12):12 (*S*:*R*), which is consistent with the 89% ee observed. The reaction to form **263** was only tried once and therefore the de may be improved with future work.

The overall conclusion that can be reached is that the 1*S*,5*S*,6*S*-diol **106** produces the *S* configuration at C-2 of the adduct (likewise the 1*R*,5*R*,6*R*-diol **106** produces the *R* stereochemistry at C-2). A possible explanation based on a potential transition state is shown in Figure 5.6. The three diagrams shown in Figure 5.6 are the same transition state viewed from different angles.

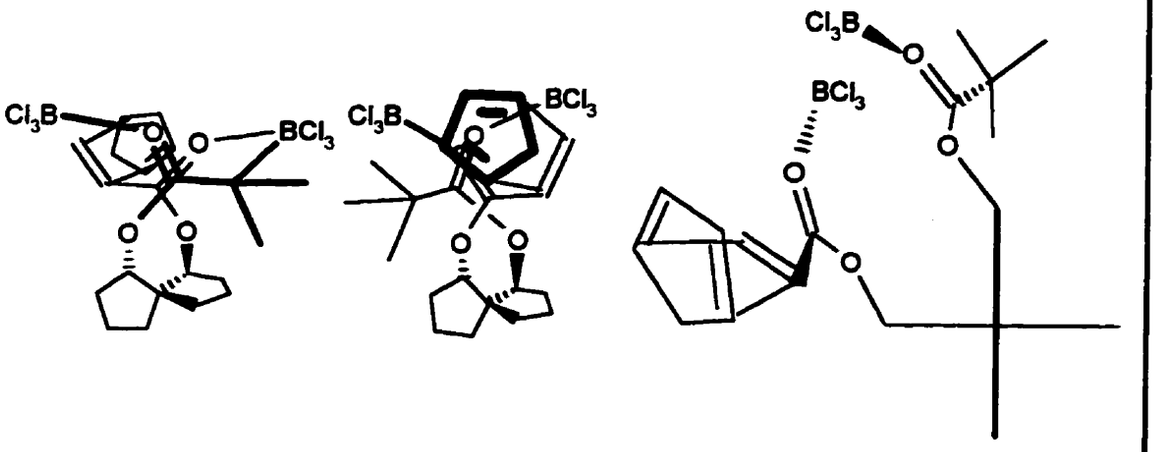
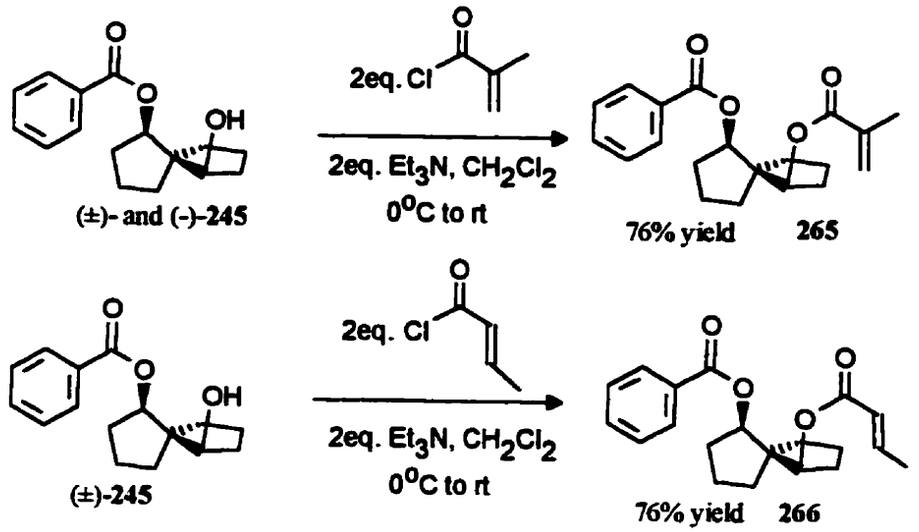


Figure 5.6 Three Orientations of the Same Possible Transition State for the Diels-Alder Reaction of Compound **247** with Cyclopentadiene

Two main points support the transition state shown in Figure 5.6.

1) α,β-unsaturated esters under chelation control adopt an *s-cis* conformation.[215,222]

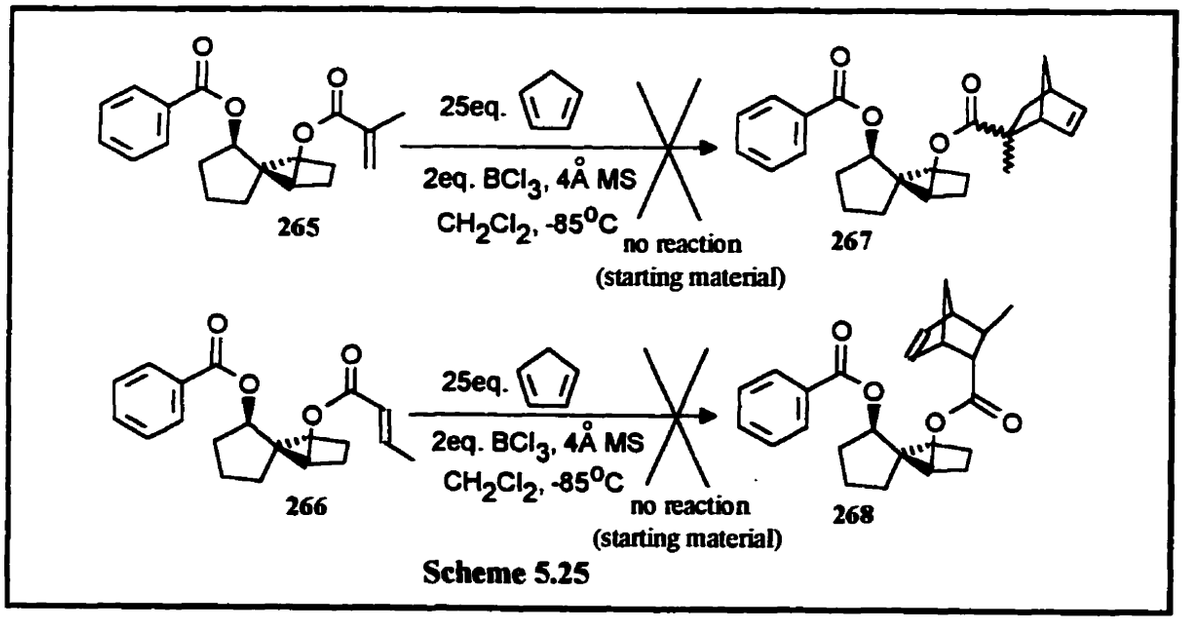
2) the diacrylate system prefers to form the same configuration for both adducts as the main product which suggests that the acrylates prefer to orient themselves in a C_2-symmetric fashion (*i.e.* same face of each acrylate is blocked by the other acrylate).



Scheme 5.24

Attempts at the AM1 semi-empirical level to model the BCl_3 complex of the acrylate dienophiles (**256**, **261** and **263**) in order to lend support for the hypothesised transition state (Figure 5.5) proved futile as the computers continuously failed to complete the calculations.

Endeavors to broaden the scope of the Diels-Alder reaction by extending the methodology to methacrylates and crotonates were attempted. The formation, in moderate yield (76%), of methacrylate **265** and crotonate **266** dienophiles was accomplished by the analogous procedure reported for the acrylate system (Scheme 5.17 and Scheme 5.20). Application of these dienophiles (**265** and **266**) to Diels-Alder reactions using the reaction conditions developed for acrylate **247** (entry 6, Table 5.8) failed to produce any product (**267** and **268**, Scheme 5.25). Unfortunately, further exploration of these reactions (Scheme 5.25) was not possible due to time constraints.



Scheme 5.25

5.3.5 Conclusions

The results for diol **106** as a substrate bound chiral auxiliary were superior to those observed as a Lewis acid bound chiral auxiliary.[223] The greatest achievement as a substrate bound chiral auxiliary was in the Diels-Alder reaction. The optimal conditions for the reaction of an acrylate ester of diol **106** and cyclopentadiene were determined to

be at -85°C for 12 h in the presence of BCl_3. The best results were obtained when the acrylate ester of monopivaloate diol **106** was used (Section 5.3.4), which produced the *endo* Diels-Alder adduct in ≥97% de. This is the first example that uses a pivaloate ester as a blocking group. The Diels-Alder reaction of the diacrylate of diol **106** formed two bicycloadducts for one molecule of chiral auxiliary (diol **106**). After iodolactonisation, the bicycloadducts were proven to be formed in an 89% ee.

Results for diol **151** were obtained in only one reaction in this section (diastereoselective cyclopropanation, Section 5.3.3), but this diol produced mediocre de's and good yields as a substrate bound chiral auxiliary in that reaction. Alteration of the reaction conditions or the investigation of ene-ketals may produce more positive results.

5.4 Future Work

There are many directions that this project could take. Some potential future work for the conversion of the hydroxyl groups in *cis,cis*-spiro[4.4]nonane-1,6-diol (**106**) to other groups functionalities was covered in Section 3.5. The next paragraph broadly summarises where this project could proceed with the application of the C_2-symmetric spiro-diols (**106** and *cis,cis*-2,2′-spirobiindane-1,1′-diol (**151**)) as chiral auxiliaries.

There are many reactions where diols **106** and **151** could be explored as chiral auxiliaries (some examples are epoxidation, epoxide opening, addition of organometallics to aldehydes and ketones, alkylation of esters, conjugate addition, and desymmetrization). Further investigation of some of the reactions reported in this dissertation for chiral auxiliaries diols **106** and **151** could also prove successful. Two examples are: 1) the Diels-Alder reaction reported in Section 5.3.4 where the effects of the alteration of the diene or dienophile could be investigated; and 2) the cyclopropanation (Sections 5.2.3 and 5.3.3) reactions where the solvent and reagents could be optimised. Other extensions for this project in the future could involve development of the next generation of chiral spiro auxiliaries by alteration of the carbon framework (*e.g. cis,cis*-spiro[5.5]undecane-1,7-diol). All of these project continuations are interesting, but time constraints prevented further study for this dissertation.

Chapter 6

6 Experimental Methods

6.1 General Methods

Solvents and reagents were purchased in anhydrous form or were purified by standard methods[224] where necessary. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl, while methylene chloride (CH_2Cl_2) was freshly distilled from calcium hydride. Both solvents (THF and CH_2Cl_2) were distilled immediately before use. Acetone (HPLC grade), acetonitrile, diethyl ether, *N,N*-dimethylformamide (DMF) methanol and pyridine were purchased as anhydrous solvents in Sure/Seal® bottles from the Aldrich Chemical Company. Other solvents and reagents (benzene, *tert*-butanol, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA), toluene and triethylamine) were dried over calcium hydride, distilled, and stored under nitrogen in dried Sure/Seal® bottles.

All glassware, stir bars and metal syringe needles employed in anhydrous reactions were dried in an oven set at 120°C for at least 2 hours. Reaction vessels were cooled to room temperature under a stream of nitrogen, while glass syringes and metal syringe needles were cooled in a desiccator containing Drierite.® In some cases plastic, sterilized, non-pyrogenic syringes (FORTUNA,® Einmalspritze Type A) were used for the addition of anhydrous reagents and solvents. Moisture or oxygen sensitive reactions were performed under a nitrogen atmosphere.

The following cooling baths[225] were used to maintain sub-ambient temperatures: liquid nitrogen-THF (-105°C), liquid nitrogen-ethyl acetate (-85°C), dry ice-acetone (-78°C), dry ice-chloroform (-61°C), dry ice-acetonitrile (-41°C), dry ice-carbon tetrachloride (-23°C), and dry ice-ethylene glycol (-15°C). For extended reaction at low temperatures, as low -85°C, a constant temperature bath was employed (NESLAB, Cryobath CB-80).

Aluminium-backed silica gel plates purchased from E. Merck (0.2 mm silica gel 60, F_{254}) were used for thin layer chromatography (TLC). The plates were visualised with an ultraviolet lamp (254 nm or 366 nm) and/or by heating with a hot air gun after immersion

in a developing solution (118.4 g $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 200 mL concentrated H_2SO_4, and 2 L deionised water). Flash column chromatography was performed using 230-400 mesh silica gel (E. Merck), according to the method of Still *et al.*[226] Radial plate chromatography was accomplished with a Chromatotron (Harrison Research, Model 7924T) with plates bearing 1, 2, or 4 mm of silica gel (EM Science silica gel 60 PF_{254} with gypsum binder). Solvent systems used for TLC or chromatography as the liquid phase were various ratios of hexanes and ethyl acetate, unless otherwise specified, and are listed with the following format: volume of hexanes : volume of ethyl acetate. In some cases with radial plate chromatography the sample was applied with one solvent (*e.g.* $CHCl_3$), dried by blowing air over the plate, and then run using a hexanes and ethyl acetate mixture. In these cases the following format will be used: applied solvent, volume of hexanes : volume of ethyl acetate (*e.g.* $CHCl_3$, 9:1).

Analytical gas liquid chromatography (GC) was performed on a Shimadzu GC-9A gas chromatography equipped with a flame ionization detector using a 25 m × 0.53 mm (i.d.) × 3 μm (film thickness) 007 Series Methyl Silicone (Quadrex Corporation) fused silica column. Chiral phase gas liquid chromatography was performed on the same instrument using a 25 m × 0.33 mm (i.d.) × 0.25 μm (film thickness) Cybex-B (Scientific Glass Engineering) fused silica column. Helium was used as the carrier gas in both cases.

High pressure liquid chromatography (HPLC) analyses were performed on a ICI instrument (LC 1440 system organizer, LL 1150 HPLC pump,) with a UV/VIS detector (LC 12010 UV/VIS detector set at 220 nm, 254 nm or 280nm) using either an ODS AXXIOM-Chromatography column (25 cm , 5 μ) or a Nucleosil® MN(Maherey-Nagel, Et 250/8/4, 120 - $3C_{18}$) column. Unless mentioned otherwise the solvent system used was methanol (~90%) : water (~10%).

Melting points were determined using an Electrothermal® melting point apparatus and are uncorrected. Boiling points refer to the air-bath temperature using a Kugelrohr distillation apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Autopol® III polarimeter using either a 1 cm or a 10 cm path length cell

at $\lambda = 589$ nm. The symbol "α_D" was used to describe the optical rotation of a scalemic mixture.

The infrared spectra were recorded on a Mattson Model Series 4030 FT-IR spectrophotometer. Liquid samples were placed as thin films (neat) between NaCl plates. Solid samples were positioned between NaCl plates by addition of one or two drops of a solution (Et_2O, $CDCl_3$ or $CHCl_3$) of the solid onto one of the plates at which time the solvent was evaporated producing a thin solid layer. The other NaCl plate was then placed on the thin solid layer.

Nuclear magnetic resonance spectra were obtained on either a Bruker ACE-200 (^1H 200 MHz, ^{13}C 50 MHz) or a Bruker AM-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer. Deuteriochloroform, unless otherwise stated, was used as the solvent and the ^1H-NMR spectra were referenced to the ^1H resonance of residual chloroform (δ 7.27), while ^{13}C-NMR spectra were referenced to the ^{13}C resonance of deuteriochloroform (δ 77.0). All ^1H-NMR spectra (run using a 200 MHz instrument unless otherwise stated) listed will have the following format: chemical shift (in ppm), (multiplicity, number of protons, coupling constant(s) (Hz), assignment). The abbreviations used to describe the multiplicities are as follows: br.=broadened, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. The ^{13}C-NMR spectra (run using a 50 MHz instrument unless otherwise stated) are listed with the following format: chemical shift (in ppm), (methyl (CH_3), methylene (CH_2), methine (CH), quaternary carbon (C_q), as determined by DEPT experiments, assignment). In cases where the assignment was ambiguous, the signals and assignments are grouped together. The numbering of atoms in the compounds for the purposes of spectral assignment may differ from the numbering used to name the compound according to IUPAC nomenclature.

Low resolution mass spectra using electron-impact (EI) were recorded using either a Hewlett Packard 5890 Series II gas chromatograph interfaced to a Hewlett Packard 5971A mass selective detector or acquired by Mrs. Q. Wu (University of Calgary) using a VG-7070 spectrometer. Low resolution mass spectra using chemical ionization (CI, NH_3

was the carrier gas) were recorded by Mrs. D. Fox (University of Calgary) on a Kratos MS-80 spectrometer. The data for the low resolution mass spectra is listed using the following format: (method, only if CI was employed) mass (m/e), (relative intensity, assignment). High resolution mass spectra were obtained by Mrs. D. Fox (University of Calgary) on a Kratos MS-80 spectrometer. Microanalyses (Elemental analyses) were also performed by Mrs. D. Fox (University of Calgary) using a Control Equipment Corporation 440 Elemental Analyzer.

X-ray structures were determined either by Dr. M. Parvez (compound **132**, University of Calgary) or Dr. M Kubicki (compound **135**, University of Calgary).

Semi-empirical calculations (AM1 or PM3) were run on a IBM Risc System /6000™ workstation using Spartan® 2.0 (Wavefunction, Inc.).

6.2 General Experimental Procedure

6.2.1 General Procedure 1 for the Preparation of Ketals (or Acetals) with *cis,cis*-Spiro[4.4]nonane-1,6-diol (106) or *cis,cis*-2,2′-Spirobiindane-1,1′-diol (151)

Diol **106** or diol **151** (1 mmol), ketone (or aldehyde) (1 mmol), benzene (15 mL) and $TsOH \cdot 1H_2O$ (catalytic quantities) were placed in a round bottomed flask. The solution was refluxed with azeotropic removal of H_2O until the starting diol was no longer observed by TLC or GC/MS. Anhydrous K_2CO_3 was added and the solution was stirred for 15 min. The mixture was filtered and washed with benzene. The benzene was removed, *in vacuo*, resulting in the formation of the crude product. The crude product was purified by flash column chromatography.

6.2.2 General Procedure 2 for the Preparation of Ketals (or Acetals) with *cis,cis*-Spiro[4.4]nonane-1,6-diol (106) or *cis,cis*-2,2′-Spirobiindane-1,1′-diol (151)

Diol **106** or diol **151** (1 mmol), ketone (or aldehyde) (1 mmol), benzene (15 mL) and PPTS (catalytic quantities) were placed in a round bottomed flask. The solution was refluxed with azeotropic removal of H_2O until the starting diol was no longer observed by

TLC or GC/MS. Anhydrous K_2CO_3 was added and the solution was stirred for 15 min. The mixture was filtered and washed with benzene. The benzene was removed, *in vacuo*, resulting in the formation of the crude product. The crude product was purified by flash column chromatography.

6.2.3 General Procedure 3 for the Cyclopropanation of an Ene-Acetal

This procedure was taken from a paper by Mori, Arai and Yamamoto.[129] Dried acetal (1 eq. distilled for **229** or dried for 1 h under high vacuum (~0.07 Torr) for **230**) was dissolved in hexanes (22 mL for 2 mmol of acetal) and cooled to -20°C. Diethylzinc (5 eq.) was added and the solution was stirred vigorously. After 5 min., CH_2I_2 (5 eq.) was added. The reaction was stirred at -20°C and monitored by GC/MS. If after 6 h the reaction was not complete it was placed in an ice bath until the conversion of starting material was complete by GC/MS. The reaction was quenched by pouring it into a saturated solution of NH_4Cl. The mixture was extracted with Et_2O. The Et_2O layer was dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Radial plate chromatography (~20:1) was used to purify the cyclopropyl product.

6.2.4 General Procedure 4 for the Esterification of an Alcohol

The alcohol (1 eq.) was dissolved in CH_2Cl_2 (~6 mL for 1.5 mmol of alcohol) in a one-necked round bottomed flask and cooled to 0°C. To the solution was added Et_3N (1.1 eq.) followed by the appropriate acid chloride (1 eq.). The reaction was warmed to rt overnight. The reaction was monitored by TLC, and if necessary more Et_3N and acid chloride were added. When the reaction was complete, it was quenched by the addition of more CH_2Cl_2 and the organic layer was extracted with 5% HCl and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and the CH_2Cl_2 was removed *in vacuo*. The crude ester was purified by radial plate chromatography.

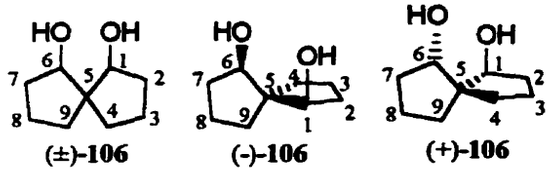
6.2.5 General Procedure 5 for the Diels-Alder reaction of Cyclopentadiene with an Acrylate Ester of Spiro[4.4]nonane-1,6-diol

To the mixture of the acrylate dienophile (1 eq.) and 4Å molecular sieves (200 mg for 0.5 mmol of dienophile, flame dried while under vacuum (~0.1 Torr)) was added

CH_2Cl_2 (30 mL per mmol of dienophile), and the mixture was cooled to -85°C prior to the addition of BCl_3 (2 eq., 1.0 M in heptane). After stirring for 5 min, a precooled (-85°C) solution of freshly cracked cyclopentadiene dimer (3 to 5 eq.) in CH_2Cl_2 (1 to 2 mL) was added *via* a cannula. The reaction was stirred at -85°C in a constant temperature bath for 12 h (overnight) and then filtered through silica gel. The solvent was removed *in vacuo* resulting in crude product. Purification was achieved by separation using radial plate chromatography ($CHCl_3$, 9:1).

6.3 Experimental Procedures Pertaining to Chapter 2

(1*RS*,5*RS*,6*RS*)-, (1*R*,5*R*,6*R*)- and (1*S*,5*S*,6*S*)-Spiro[4.4]nonane-1,6-diol ((±)-, (-)- and (+)-106)



(±)-**106** (-)-**106** (+)-**106**

A. Compound (±)-**106**

DIBAL-H (86.1 mL, 1.0 M in THF) was placed in a 250 mL three-necked round bottom flask and cooled to -78°C. *tert*-Butyllithium (50.6 mL, 1.7 M in pentane) was added slowly turning the solution an orange colour. The solution was allowed to warm to room temperature, where it changed to a light yellow colour, and then was cooled down to -78°C. To this reaction vessel was slowly added, *via* an addition funnel, a solution of freshly distilled (±)-dione **113** (4.37 g, 28.7 mmol) in THF (50 mL). The reaction mixture was warmed to room temperature overnight. The resulting solution was poured into a mixture of 0.5 M $KHSO_4$ (404 mL) and $CHCl_3$ (148 mL) and stirred vigorously. The aluminium salts were removed by filtering through Celite.® The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ and ether. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo* resulting in an oil. Flash column chromatography (1:2) provided a colourless oil, (±)-**106** (4.10 g, 26.2 mmol), in 91% yield. bp 68 - 76°C (air heat)/ 0.052 Torr (literature[153] bp 160 - 165°C (aspirator)); IR 3366 (H-O) cm^{-1}; ^{1}H-NMR 4.17 - 4.13 (m, 2H, H-6 and H-1), 2.77 (br. s, 2H, H on both alcohols), 1.93 - 1.84 (m, 4H), 1.79 - 1.58 (m, 6H), 1.38 - 1.25 (m, 2H); ^{13}C-NMR 79.4

(CH_3, C-6 and C-1), 58.1 (C_q, C-5), 34.0, 33.5 (CH_2, C-9, C-7, C-4 and C-2), 21.0 (CH_2, C-8 and C-3); Mass spectrum 138 (3, $[M-H_2O]^+$), 120 (60, $[M-2H_2O]^+$), 94 (100, $[M-C_2H_6O_2]^+$); Analysis calc'd for $C_9H_{16}O_2$: C, 69.19%; H, 10.32%. Found: C, 69.15%; H, 10.12%.

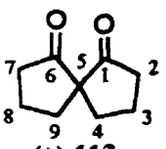
B. Compound (-)-**106**

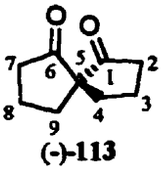
Ketal **133** (0.170 g, 0.585 mmol) was placed in a round bottom flask and CH_2Cl_2 (20 mL), $TsOH \cdot 1H_2O$ (0.040 g, 0.21 mmol) and H_2O (0.5 mL) were added. The solution was refluxed until no starting ketal was observed by GC. More H_2O was added and the solution was extracted with CH_2Cl_2 and EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Purification by flash column chromatography (1:2) produced a white solid, (-)-**106** (0.0869 g, 0.556 mmol), in 95% yield. mp 30.5 - 31°C; IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrum were identical with those obtained for (±)-**106**. Comparison of the optical rotation ($[\alpha]_D^{22.5}$ -101 (c 11.06, 0.1 dm, abs. EtOH)) to the predicted value by Kabuto *et al.* ($[\alpha]_D^{20}$ -99 (α_D^{20} -25.9 (c 1.21, EtOH), 26% ee))[152] indicated that (-)-**106** was almost enantiomerically pure.

C. Compound (+)-**106**

Ketal **134** (0.1784 g, 0.614 mmol) was placed in a round bottomed flask and CH_2Cl_2 (20 mL), $TsOH \cdot 1H_2O$ (0.040 g, 0.21 mmol) and H_2O (0.5 mL) were added. The solution was refluxed until no starting ketal was observed by GC. More H_2O was added and the solution was extracted with CH_2Cl_2 and EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo* to provide crude product. Purification by flash column chromatography (1:2) produced a white solid, (+)-**106** (0.0811 g, 0.519 mmol), in 85% yield. mp 29 - 29.5°C; IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrum were identical with those obtained for (±)-**106**. Comparison of the optical rotation ($[\alpha]_D^{23}$ +97.1 (c 8.70, 0.1 dm, abs. EtOH)) to the predicted value by Kabuto *et al.* ($[\alpha]_D^{20}$ -99 (α_D^{20} -25.9 (c 1.21, EtOH), 26% ee))[152] indicated that (+)-**106** was almost enantiopure (98% ee).

(*RS*)- and (*S*)-Spiro[4.4]nonane-1,6-dione ((±)-113 and (-)-113)


(±)-113


(-)-113

A. Compound (±)-113

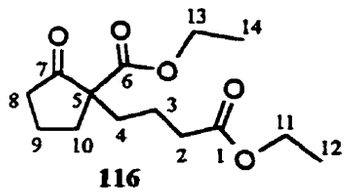
Keto acid **119** (4.35 g, 25.6 mmol) was placed in a 250 mL round bottomed flask and 200 mL of toluene and $TsOH{\cdot}1H_2O$ (2.43 g, 12.8 mmol) were added. The solution was refluxed, with azeotropic removal of water, and the disappearance of starting material was monitored (by GC or TLC (n-butanol (4) : acetic acid (1) : H_2O (5)). Saturated $NaHCO_3$ was added and the two phases were vigorously stirred for 15 min. The aqueous layer was extracted with ether. The ether and toluene layers were combined, dried over anhydrous Na_2SO_4, filtered and the solvents removed *in vacuo* to produce a dark oil. Unreacted starting material could be reisolated by: acidification of the aqueous layer, extraction with ether, drying of the organic layer, and removal of the ether *in vacuo* which produced an oil. Spiro[4.4]nonane-1,6-dione (**113**) was purified by distillation (bulb-to-bulb), 99 - 104°C (air heat)/ aspirator (literature[147] 91 - 92°C / 9 Torr), which yielded a white solid (2.80 g, 18.4 mmol (72%)). Compound **113** was previously synthesised by Cram and Steinberg,[145] Carruthers and Orridge,[146] Gerlach and Muller.[147] mp 37 - 38°C (literature[147] mp 38 - 40°C); IR 1746, 1723 (C=O) cm^{-1} (two C=O also observed by Carruthers and Orridge);[146] ^{1}H-NMR 2.45 - 2.00 (m, 8H, H-9, H-7, H-4, and H-2), 1.95 - 1.72 (m, 4H, H-8 and H-3); ^{13}C-NMR 217.3 (C_q, C-6 and C-1), 65.0 (C_q, C-5), 39.1 (CH_2, C-7 and C-2), 34.9 (CH_2, C-9 and C-4), 20.4 (CH_2, C-8 and C-3); Mass spectrum 152 (25, $M^{+\cdot}$), 97 (100, $[M\text{-}CH_2{=}CHC{=}O]^+$)[227] ; Exact mass calc'd for $C_9H_{12}O_2$: 152.0837. Found: 152.0831. Analysis calc'd for $C_9H_{12}O_2$: C, 71.03%; H, 7.95%. Found: C, 69.65%; H, 7.76%.

B. Compound (-)-113

Purified (+)-diol **106** (0.0302 g, 0.193 mmol) was placed in a 10 mL one-necked round bottom flask along with CH_2Cl_2 (1 mL). To the solution was added PCC (0.146 g, 5.80 mmol)[200] and the reaction was stirred at rt. Complete disappearance of starting material (diol **106**) was observed by GC after 1.5 h. Addition of 1 mL of ether (1 mL) to

the reaction followed by stirring for 15 min produced a dark solid. The suspension was filtered through Celite® and washed with ether. The ether was removed *in vacuo* resulting in an oil. Purification of the product by distillation (bulb-to-bulb), 120°C (air bath) /aspirator, produced (-)-**113** as a white solid (0.0208 g, 0.137 mmol) in 71% yield. This compound was previously synthesised by Gerlach (Scheme 2.3).[149] mp 60.5 - 62.0°C (literature[149] 65.5 -66°C); the IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrum were identical to those obtained for (±)-**113**. Analysis calc'd for $C_9H_{12}O_2$: C, 71.03%; H, 7.95%. Found: C, 70.76%; H, 7.84%. Optical rotation comparison ($[\alpha]_D^{21}$ -131 (c 3.72, 0.1 dm, cyclohexane)) to the published value ($[\alpha]_D$ -135 (cyclohexane))[149] indicated that the ee was at least 97%.

(*RS*)-Ethyl 4-(1-Ethoxycarbonyl-2-oxocyclopentyl)butanoate ((±)-116)

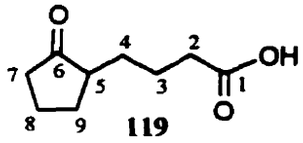


116

Potassium hydride (0.86 g of 35% dispersion, 7.5 mmol of KH) was placed in a 100 mL three-necked round bottom flask under nitrogen. The mineral oil was removed by washing three times with 10 mL aliquots of anhydrous THF. To the dried KH was added 35 mL of dry THF, and after cooling to -78°C, freshly distilled (bulb-to-bulb) ethyl 2-oxocyclopentanecarboxylate (**115**) (1.06 g, 6.79 mmol) was washed into the reaction vessel with THF (5 mL). The reaction mixture was warmed to room temperature and when all the precipitate had dissolved (in some cases additional THF was needed to solvate all the precipitate), freshly distilled (bulb-to-bulb) 4-bromobutanoate (**110**) (1.07 mL, 7.47 mmol) was added. The reaction was refluxed for 30 h, after which the THF was removed *in vacuo*. Water was added and the resulting solution was extracted with chloroform and ether. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvents removed *in vacuo* to produce an oil. Purification by distillation (bulb-to-bulb), bp 80 - 85°C (air heat)/ 0.04 Torr (literature[156] 140 - 145°C at 0.4 mm Hg), yielded 1.78 g (6.60 mmol) of a colourless oil (**116**) in 97% yield. Compound **116** was previously synthesised by Cram and Steinberg[145] and

Bachmann and Struve.[156] IR 1739 (C=O), 1728 (C=O) cm^{-1}; ^{1}H-NMR 4.08 (q, 2H, $J_{13,14}$ or $J_{11,12}$ = 7.2 Hz, H-13 or H-11), 4.04 (q, 2H, $J_{13,14}$ or $J_{11,12}$ = 7.2 Hz, H-13 or H-11), 2.46 - 2.18 (m, 5H), 1.95 - 1.83 (m, 4H), 1.56 - 1.48 (m, 3H), 1.17 (t, 6H, $J_{14,13}$ and $J_{12,11}$ = 7.2 Hz, H-14 and H-12); ^{13}C-NMR 214.3 (C_q, C-7), 172.6 (C_q, C-6 or C-1), 170.4 (C_q, C-6 or C-1), 61.2 (CH_2, C-13 or C-11), 60.1 (CH_2, C-13 or C-11), 60.0 (C_q, C-5), 37.6, 34.1, 32.9, 32.5, 20.1, 19.4 (CH_2, C-10, C-9, C-8, C-4, C-3, and C-2), 14.0 (CH_3, C-14 or C-12), and 13.9 (CH_3, C-14 or C-12); Mass spectrum 280 (1, $M^{+\cdot}$), 242 (32, $[M-C_2H_4]^+$), 224 (46, $[M-HOEt]^+$), 156 (100, $\{M-CH_2CHCH_2CO_2Et]^+$).

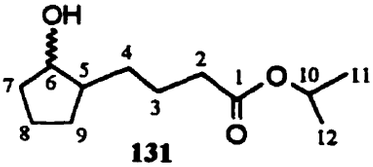
(*RS*)-4-(2-Oxocyclopentyl)butanoic Acid ((±)-119)



119

Compound **116** (0.27 g, 1.0 mmol) was placed in a 50 mL round bottomed flask with 8 mL of 10% HCl and refluxed for 12 h (disappearance of starting material was monitored by GC). Upon completion, the reaction mixture was extracted with ether. The combined ether layers were combined and extracted with saturated $NaHCO_3$. The combined saturated $NaHCO_3$ layer was acidified (to pH≤2) and extracted with ether. The combined ether layers were dried over anhydrous Na_2SO_4, filtered and the ether was removed *in vacuo* to produce an oil. Distillation (bulb-to-bulb), bp 110-115°C (air heat)/ 0.05 Torr (literature[156] 153 - 156°C / 0.2 mm Hg), produced 0.147 g (0.864 mmol) of a colourless liquid (**119**) in 86% yield. Compound **119** was characterised by Bachmann and Struve.[156] ^{1}H-NMR 2.41 (t, 2H, $J_{2,3}$ = 6.5 Hz, H-2), 2.31 - 1.93 (m, 4H), 1.92 - 1.25 (m, 7H); ^{13}C-NMR 221.4 (C_q, C-6), 179.2 (C_q, C-1), 47.9 (CH, C-5), 37.9, 33.9, 29.4, 28.9, 22.6, 20.6 (CH_2, C-9, C-8, C-7, C-4, C-3 and C-2); Mass spectrum 170 (3, $M^{+\cdot}$), 152 (15, $[M-H_2O]^+$), 84 (100, $[M-CH_2CHCH_2CO_2H]^+$).

Isopropyl 4-(2-Hydroxycyclopentyl)butanoate (131)

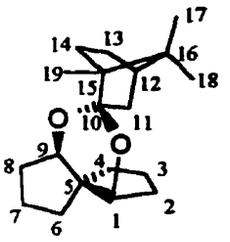


131

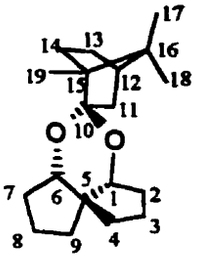
The Meerwein-Ponndorf-Verley reduction of (±)-dione **113** was done according to the typical procedure published in a review by Wilds.[163] In a round bottom flask (50mL) was placed $AlMe_3$ (7.85 mL, 2.0 M in hexanes) and

the solution was cooled to -78°C. Isopropyl alcohol was added (2 mL) and the resulting mixture was warmed to rt. (±)-Dione **113** (0.238 g, 1.56 mmol) was added in isopropyl alcohol (20 mL). The solution was heated and isopropyl alcohol was distilled off at a rate of about 5 to 10 drops per min. More isopropyl alcohol was added to the reaction mixture as the distillation progressed. The distillate was tested for acetone using a 2,4-DNP test, but no precipitate was observed. (The solution was refluxed when the reaction could not be monitored) The reaction was continued until no more starting material was present by GC. The solution was cooled, 12% HCl was added and the mixture was extracted with ethyl acetate. The combined organic layer was extracted with water, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. Flash column chromatography (5:1) resulted in a light yellow oil (0.229 g, 1.07 mmol) which was identified as compound **131** (68% yield). IR 3473 (O-H), 1730 (C=O) cm^{-1}; ^{1}H-NMR 5.01 (septet, 1H, $J_{10,12}$ and $J_{10,11}$ = 6.3 Hz, H-10), 4.19 (br. s, 0.24H, H-6 (minor diastereomer)), 3.82 (q, 0.76H, $J_{6,7}$ and $J_{6,5}$ = 5.6 Hz, H-6 (major diastereomer)), 2.28 (t, 2H, $J_{2,3}$ = 7.4 Hz, H-2), 2.02 - 1.80 (m, 2H), 1.80 - 1.42 (m, 9H), 1.48 - 1.07 (m, 1H) 1.23 (d, 6H, $J_{12,10}$ and $J_{11,10}$ = 6.3 Hz, H-12 and H-11); ^{13}C-NMR (major diastereomer) 173.3 (C_q, C-1), 78.7 (CH, C-6), 67.3 (CH, C-10), 47.6 (CH, C-5), 34.7, 34.4, 33.1, 29.7, 23.5, 21.6 (CH_2, C-9, C-8, C-7, C-4, C-3, and C-2), 21.7 (CH_3, C-12 and C-11); ^{13}C-NMR (minor diastereomer) 173.5 (C_q, C-1), 74.0 (CH, C-6), 67.4 (CH, C-10), 45.5 (CH, C-5), 34.6, 34.5, 28.7, 28.5, 23.6 (CH_2, C-9, C-8, C-7, C-4, C-3, and C-2 (one resonance was not observed)), 21.7 (CH_3, C-12 and C-11); Mass spectrum 197 (20, $[M\text{-}OH]^+$), 155 (84, $[M\text{-}OCHMe_2]^+$), 137 (100, $[M\text{-}H_2O$ and $OCHMe_2]^+$), 41 (100, $[C_3H_5]^+$); Exact mass calc'd for $C_{12}H_{22}O_3$: 214.1579. Found: 214.1549.

(1*R*,5*R*,6*R*)-Spiro[4.4]nonane-1,6-diol (1'*R*)-(+)-Camphor Ketal ((-)-133) and (1*S*,5*S*,6*S*)-Spiro[4.4]nonane-1,6-diol (1'*R*)-(+)-Camphor Ketal ((+)-134)



133



134

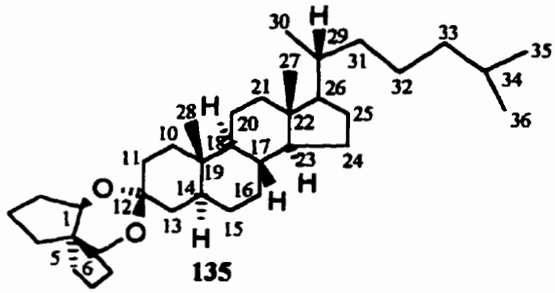
Freshly distilled (±)-diol **106** (4.10 g, 26.2 mmol), (+)-1*R*-camphor (14.0 g, 91.7 mmol), benzene (350 mL) and $TsOH{\cdot}1H_2O$ (0.045 g, 0.24 mmol) were placed in a 500 mL round bottom flask. The solution was refluxed with azeotropic removal of H_2O until (±)-diol **106** was no longer observed by TLC (1:2). Anhydrous K_2CO_3 was added and the solution was stirred for 15 minutes. The mixture was filtered and washed with hexanes and ether. The organic phases were combined, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. The diastereomers were separated by flash column chromatography (hexanes) which provided two compounds **133** (3.40 g, 11.7 mmol, $R_f = 0.36$) and **134** (3.42 g, 11.8 mmol, $R_f = 0.19$) in 89% and 90% yield respectively.

Compound **133** was a colourless oil that solidified on standing producing a clear colourless solid. mp 34 - 36°C; bp 84 - 90°C (air heat)/ 0.06 Torr; IR 2951, 2940, 2930 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 3.85 (dd, 1H, $J_{6,7}$ or $J_{1,2}$ = 1.3 and 3.4 Hz, H-6 or H-1), 3.75 (dd, 1H, $J_{6,7}$ or $J_{1,2}$ = 1.8 and 5.6 Hz, H-6 or H-1), 2.03 - 1.47 (m, 15H), 1.40 - 1.06 (m, 4H), 1.01 (s, 3H, H-19, H-18 or H-17), 0.89 (s, 3H, H-19, H-18 or H-17), 0.81 (s, 3H, H-19, H-18 or H-17); ^{13}C-NMR 107.6 (C_q, C-10), 79.8 (CH, C-6 or C-1), 79.7 (CH, C-6 or C-1), 55.9, 54.0, 46.1 (C_q, C-16, C-15, and C-5), 44.8 (CH, C-12), 43.5, 37.5, 36.8, 33.3, 31.5, 26.5, 27.0, 24.5, 23.7 (CH_2, C-14, C-13, C-11, C-8, C-7, C-6, C-4, C-3, C-2), 20.8, 20.7, 10.7 (CH_3, C-19, C-18 and C-17); Mass spectrum 290 (19, $M^{+\cdot}$), 219 (14, $[M-C_4H_7O]^+$), 121 (100, $[C_9H_{13}]^+$); Analysis calc'd for $C_{19}H_{30}O_2$: C, 78.57%; H, 10.41%. Found: C, 78.74%; H, 10.45%. Optical rotation obtained was $[\alpha]_D^{21.5}$ +4.30 (c 18.4, 0.1 dm, CH_2Cl_2).

Compound **134** was a colourless oil. bp 81 - 88°C (air heat)/ 0.057 Torr, IR 2953, 2917, 2874 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 3.84 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 5.4 Hz, H-6 or H-1), 3.80

(d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.8 Hz, H-6 or H-1), 2.16 (dt, 1H, $J_{12,13}$ and $J_{12,11} \approx 3$ and 12 Hz, H-12), 2.03 - 1.43 (m, 12H), 1.38 - 1.10 (m, 6H), 0.97 (s, 3H, H-17, H-19 or H-18), 0.91 (s, 3H, H-19, H-18 or H-17), 0.81 (s, 3H, H-19, H-18 or H-17); ^{13}C-NMR 107.3 (C_q, C-10), 80.5 (CH, C-6 or C-1), 78.2 (CH, C-6 or C-1), 56.9, 53.7, 48.7 (C_q, C-16, C-15, and C-5), 44.9 (CH, C-12), 43.8, 37.2, 36.7, 32.8, 31.9, 29.2, 27.2, 24.6, 23.9 (CH_2, C-14, C-13, C-11, C-8, C-7, C-6, C-4, C-3, and C-2), 20.9, 20.8, 11.6 (CH_3, C-19, C-18 and C-17); Mass spectrum 290 (19, $M^{+\cdot}$), 219 (14, $[M-C_4H_7O]^+$), 121 (100, $[C_9H_{13}]^+$); Analysis calc'd for $C_{19}H_{30}O_2$: C, 78.57%; H, 10.41%. Found: C, 78.73%; H, 10.54%. Optical rotation obtained was $[\alpha]_D^{21}$ -18.10 (c 17.1, 0.1 dm, CH_2Cl_2).

(1*R*,5*R*,6*R*)-Spiro[4.4]nonane-1,6-diol (+)-5α-Cholestan-3-one Ketal ((+)-135)



135

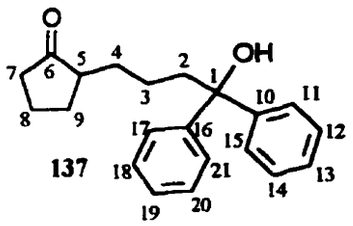
(-)-Diol **106** (0.0513 g, 0.328 mmol) was mixed with (+)-5α-cholestan-3-one (0.140 g, 0.361 mmol) in benzene (6 mL) according to general procedure 1. The crude product was purified by flash column chromatography (20:1) which produced compound **135** (0.149 g, 0.284 mmol) as a colourless solid in 87% yield. mp 122 - 122.5°C; IR 2872, 2925 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 3.88 (d, 1H, $J_{6,5}$ or $J_{1,2}$ = 5.3 Hz, H-6 or H-1), 3.77 (d, 1H, $J_{6,5}$or $J_{1,2}$ = 5.4 Hz, H-6 or H-1), 1.99 - 0.96 (m, 43H), 0.90 (d, 3H, $J_{30,29}$ = 6.6 Hz, H-30), 0.87 (d, 6H, $J_{36,34}$ and $J_{35,34}$ = 6.7 Hz, H-36 and H-35), 0.80 (s, 3H, H-28 or H-27), 0.65 (s, 3H, H-28 or H-27); ^{13}C-NMR 99.2 (C_q, C-12), 78.3, 77.9 (CH, C-6 and C-1), 57.3 (C_q, C-5), 56.5, 56.3, 53.9, 42.4, 35.8, 35.5, 28.0 (CH, C-34, C-29, C-26, C-23, C-18, C-17 and C-14), 42.6, 35.7 (C_q, C-22 and C-19), 39.5, 40.1, 36.9, 36.7, 36.2, 35.3, 35.2, 32.3, 32.1, 32.0, 31.4, 29.7, 28.5, 28.3, 24.2, 24.1, 23.9, 21.2 (CH_2, C-33, C-32, C-31, C-25, C-24, C-21, C-20, C-16, C-15, C-13, C-11, C-10, C-9, C-8, C-7, C-4, C-3 and C-2), 22.8, 22.6, 12.0, 11.5, 18.6 (CH_3, C-36, C-35, C-30, C-28 and C-27); Mass spectrum 524 (14, $M^{+\cdot}$), 193 (94, $[M-C_{12}H_{17}O]^+$), 121 (100, $[C_9H_{13}]^+$); Exact mass calc'd for $C_9H_{12}O_2$: 524.4593. Found: 524.4585. Analysis calc'd for $C_{36}H_{60}O_2$: C,

82.38%; H, 11.52%. Found: C, 81.86%; H, 11.13%. Optical rotation obtained was $[\alpha]_D^{22.5}$ +23.8 (c 6.02, 0.1 dm, $CHCl_3$).

Crystal data: orthorhombic $P2_12_12$; a = 41.261(2) Å; b = 12.2083(8) Å; c = 6.4622(4) Å; V = 3255.2(4) $Å^3$; Z = 4; d_x = 1.07 Mgm^{-3}; Cu-Kα radiation (23°C) total of 3775 reflections in the range $23.4 \leq \theta \leq 36.31$, of which 2278 were used (I>0) in the structure solution; R = 0.079 and S=1.5.

6.3 Experimental Procedures Pertaining to Chapter 3

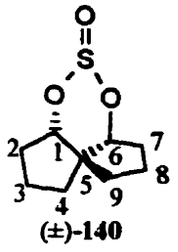
4-(2-Oxocyclopentyl)-1,1-diphenylbutan-1-ol ((±)-137)



137

Iodobenzene (0.114 mL, 1.02 mmol) was passed through basic alumina and placed in a 50 mL three-necked round bottom flask along with THF (5 mL) and cooled to -78°C. *tert*-Butyllithium (2.230 mmol, 1.7 M in pentane) was added slowly. After 5 min the flask was removed from the cold bath and warmed to rt. The flask was cooled to -78°C and freshly distilled (±)-dione **113** (0.0707 g, 0.465 mmol) was added slowly as a solution in THF (5mL) from an addition funnel. The reaction mixture was warmed to rt (overnight). The reaction was quenched with saturated NH_4Cl and extracted with ether. The ether layers were combined and dried over Na_2SO_4. The dried solution was filtered and the ether was removed *in vacuo*. The product was purified by flash column chromatography (3:1) which produced a white solid, **137** (0.0503 g, 0.163 mmol), in 35% yield. mp 111 - 112 °C; IR 3438 (H-O), 1719 (C=O) cm^{-1}; ^{1}H-NMR 7.47 (m, 10H, H-21, H-20, H-19, H-18, H-17, H-15, H-14, H-13, H-12 and H-11), 2.38-1.57 (m, 9H), 1.52 (m, 4H); ^{13}C-NMR 222.4 (C_q, C-6), 148.0, 147.8 (C_q, C-16 and C-10), 129.0 (CH, (C-21, C-17, C-15 and C-11) or (C-20, C-18, C-14 and C-12)), 127.7, 127.6 (CH, C-17 and C-13), 126.8 (CH, (C-21, C-17, C-15 and C-11) or (C-20, C-18, C-14 and C-12)), 79.0 (C_q, C-1), 49.9 (CH, C-5), 42.6, 38.9, 30.8, 30.4, 22.7, 21.5 (CH_2, C-9, C-8, C-7, C-4, C-3 and C-2); Mass spectrum 290 (3, $[M-H_2O]^+$), 206 (100), 91 (70, $[C_7H_7]^+$); Exact mass calc'd for $C_{21}H_{22}O$: 290.1671. Found: 290.1677.

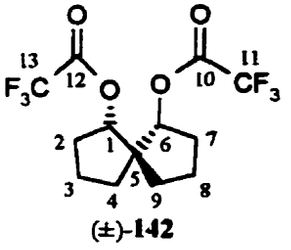
(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diyl Sulfite ((±)-140)



(±)-140

(±)-Diol **106** (0.0644 g, 0.415 mmol) was dissolved in anhydrous pyridine (10 mL) in a one-necked round bottom flask (50 mL). Thionyl chloride (0.2 mL) was added and the reaction was stirred at rt. The reaction was monitored by TLC and after 0.5 h no starting material was observed. To the finished reaction mixture was added 10% HCl (50 mL) and the mixture was extracted with chloroform. The organic layer was subsequently extracted with water. The resulting organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. Compound (±)-**140** was purified by flash column chromatography (20:1) which produced a clear liquid (0.0702 g, 0.347 mmol) in 84% yield. bp 115 - 122 °C (air heat)/ aspirator; IR 2953, 2874 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 4.74 (dd, 1H, $J_{6,7}$ or $J_{1,2}$ = 5.8 and 1.3 Hz, H-6 or H-1), 4.18 (dd, 1H, $J_{6,7}$ or $J_{1,2}$ = 5.8 and 1.3 Hz, H-6 or H-1), 2.08 (m, 6H), 1.80 - 1.59 (m, 4H), 1.59 - 1.38 (m, 2H); ^{13}C-NMR 84.3 (CH, C-6 or C-1), 78.7 (CH, C-6 or C-1), 57.6 (C_q, C-5), 36.6, 36.1 (CH_2, C-7 and C-2), 31.9, 31.8 (CH_2, C-9 and C-4), 23.4_1, 23.3_6 (CH_2, C-8 and C-3); Mass spectrum (CI) 220 (20, $[M+NH_4]^+$), 203 (3, $[M+H]^+$), 121 (100, $[C_9H_{13}]^+$); Analysis calc'd for $C_9H_{14}SO_3$: C, 53.44%; H, 6.98%. Found: C, 53.59%; H, 6.72%.

(1*RS*,5*RS*,6*RS*)-1,6-Di(trifluoroacetoxy)spiro[4.4]nonane ((±)-142)

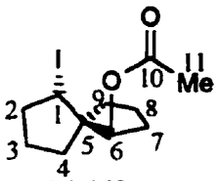


(±)-142

(±)-Diol **106** (0.1010 g, 0.6465 mmol) was dissolved in CH_2Cl_2 (5 mL) in a one-necked round bottom flask. Triethylamine (0.198 mL, 1.42 mmol) was added and the solution was cooled to 0°C. Trifluoroacetic anhydride (0.201 mL, 1.42 mmol) was added and the reaction was warmed to rt (overnight). To the reaction mixture was added CH_2Cl_2 and the organic phase was extracted with 10% HCl and H_2O. The organic phase was dried over Na_2SO_4. The solution was filtered and the CH_2Cl_2 was removed *in vacuo*. Flash column chromatography (9:1) was used to purify the product producing an 98% yield of (±)-diester **142** (0.2213 g, 0.6355 mmol) which was a white solid. mp 41 - 42°C; IR 1778 (C=O (ester)) cm^{-1}; ^{1}H-NMR 5.23 (d, 2H, $J_{6,7}$ and $J_{1,2}$ =

3.9 Hz, H-6 and H-1), 2.15 - 1.52 (m, 12H); ^{13}C-NMR 156.4 (q, $J_{C,F}$ = 42.4 Hz, C_q, C-12 and C-10), 114.4 (q, $J_{C,F}$ = 285.9 Hz, C_q, C-13 and C-10), 85.9 (CH, C-6 and C-1), 58.1 (C_q, C-5), 33.1, 31.3 (CH_2, C-9, C-7, C-4 and C-2), 20.6 (CH_2, C-8 and C-3); Mass spectrum 348 (0.2, M^+), 235 (14, $[M-O_2CCF_3]^+$), 121 (100, $[C_9H_{13}]^+$); Analysis calc'd for $C_{13}H_{14}F_6O_4$: C, 44.84%; H, 4.05%. Found: C, 45.23%; H, 3.70%.

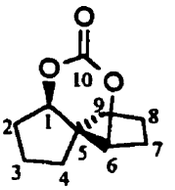
(1*SR*,5*RS*,6*RS*)-6-Acetoxy-1-iodospiro[4.4]nonane ((±)-143)



(±)-143

Freshly distilled (±)-diol **106** (0.0470 g, 0.301 mmol) was transferred to a three-necked round bottom flask using acetonitrile (2 mL). Anhydrous NaI (0.184 g, 1.23 mmol) and Me_3SiCl (0.156 mL, 1.23 mmol) were added. The reaction was monitored by TLC and was quenched after 4 h by the addition of ether. The organic layer was extracted with H_2O, saturated $Na_2S_2O_3$ solution and brine. The organic layer was dried (over anhydrous Na_2SO_4), filtered and the solvent was removed *in vacuo*. The product obtained, (±)-**143**, initially was very pure (98% yield, 0.0912 g, 0.296 mmol), but readily decomposed. Further purification could be performed by distillation (bulb-to-bulb), bp 64 - 72°C (air heat)/ 0.06 Torr, which produced a clear liquid. IR 1736 (C=O(ester)) cm^{-1}; ^{1}H-NMR 4.87 (d, 1H, $J_{6,7}$ = 5.4 Hz, H-6), 4.51 (t, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 2.28 - 1.90 (m, 7H), 1.90 - 1.47 (m, 9H), 2.06 (s, 3H, H-11); ^{13}C-NMR 170.6 (C_q, C-10), 78.3 (CH, C-6), 58.7 (C_q, C-5), 38.4 (CH, C-1), 39.6, 38.6, 34.3, 32.6, 22.3, 20.8 (CH_2, C-9, C-8, C-7, C-4, C-3 and C-2), 21.3 (CH_3, C-11); Mass spectrum (CI) 362 (15, $[M+NH_4]^+$), 309 (0.7, $[M+H]^+$), 249 (56, $[M-OAc]^+$), 181 (59, $[M-I]^+$), 121 (100, $[C_9H_{13}]^+$).

(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diyl Carbonate ((±)-147)



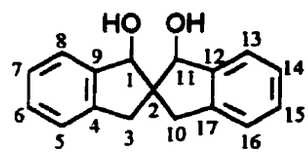
(±)-147

(±)-Diol **106** (0.130 g, 0.831 mmol), anhydrous K_2CO_3 (0.050 mg, 0.036 mmol), and dimethyl carbonate (2 mL) were placed in a round bottom flask and refluxed overnight. The reaction was filtered, washed with ether, and the solvent was removed *in vacuo*. Purification by radial plate chromatography (3:1) produced (±)-carbonate **147** (0.146 g, 0.801 mmol) as a colourless oil in 96% yield. IR 2953, 2870 (H-C(sp^3)), 1758

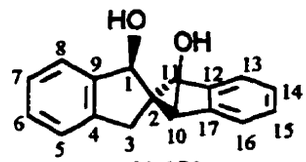
(C=O(carbonate)) cm^{-1}; ^{1}H-NMR 4.42 (t, 2H, $J_{6,7}$ and $J_{1,2}$ = 4.0 Hz, C-6 and C-1), 2.08 - 1.97 (m, 4H), 1.97 - 1.51 (m, 8H); ^{13}C-NMR 152.1 (C_q, C-10), 87.8 (C_q, C-6 and C-1), 53.0 (C_q, C-5), 37.2 (CH_2, C-7 and C-2), 32.6 (CH_2, C-9 and C-4), 22.8 (CH_2, C-8 and C-3); Mass spectrum 172 (0.19, $M^{+\cdot}$), 120 (36, $[C_9H_{12}]^{+\cdot}$), 94 (100); Analysis calc'd for $C_{10}H_{14}O_3$: C, 65.92%; H, 7.74%. Found: C, 65.41%; H, 8.09%.

6.5 Experimental Procedures Pertaining to Chapter 4

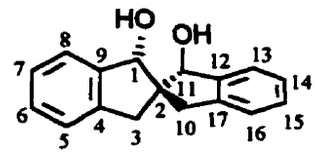
(1*RS*,1'*RS*,2*RS*)-, (1*R*,1'*R*,2*R*)- and (1*S*,1'*S*,2*S*)-2,2'-Spirobiindane-1,1'-diol ((±)-, (-)- and (+)-151)



(±)-**151**



(-)-**151**



(+)-**151**

A. Compound (±)-**151**

tert-Butyllithium (8.20 mL, 1.7 M in pentane) was slowly added to a solution of DIBAL-H (13.94 mL, 1.0 M in THF) at -78°C. The solution was stirred 5 minutes, warmed to room temperature and immediately cooled to -78°C. To this mixture freshly distilled (±)-dione **152** (1.15 g, 4.65 mmol) in THF (30 mL) was added very slowly and the resulting mixture warmed to rt (overnight). Saturated NH_4Cl was added dropwise until the evolution of H_2 ceased. The mixture was poured into a beaker containing $CHCl_3$ (200 mL) and saturated ammonium chloride (100 mL), followed by vigorous stirring (precipitation of the aluminum salts). The solids were filtered through Celite® and the solution extracted with methylene chloride or chloroform. The organic layer was dried (Na_2SO_4) and removed *in vacuo*. Column chromatography using silica gel[228] ($CHCl_3$:EtOH (97.5:2.5)) provided a white powder (1.14 g, 4.52 mmol, 97%).[229] mp 234.5-236.0°C (literature[152] 241-242°C), sublimes 159 - 172°C (air bath)/ 0.045 Torr; IR 3498 (O-H), 3360 (O-H) cm^{-1}; ^{1}H-NMR 7.51 - 7.47 (m, 2H), 7.32-7.21 (m, 6H), 5.21 (s, 2H, H-10 and H-1), 3.19 (d, 2H, J_{gem} = 15.5 Hz, 1H-11 and 1H-3), 2.95 (br. s, 2H, H's on the alcohols), 2.56 (d, 2H, J_{gem} = 15.5 Hz, 1H-11 and 1H-3). ^{13}C-NMR (D_6-DMSO,

reference peak = 39.5) 144.7, 142.7 (C_q, C-17, C-12, C-9 and C-4), 128.0, 126.4, 2×125.0 (CH, C-16, C-15, C-14, C-13, C-8, C-7, C-6 and C-5), 80.0 (CH, C-10 and C-1), 58.3 (C_q, C-2), 41.7 (CH_2, C-11 and C-3); The ^{1}H-NMR spectrum was consistent with that reported by Kabuto *et al.*[152] Mass spectrometry 234 (61, $[M-H_2O]^+$), 216 (82, $[M-(2 \times H_2O)]^+$), 118 (100, $[C_9H_{10}]^+$ or $[C_8H_6O]^+$).

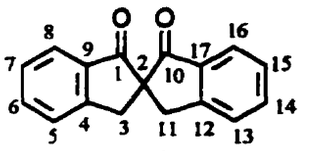
B. Compound (-)-**151**

To a solution of compound **201** (0.0766 g, 0.153 mmol) in methanol (10 mL) was added 10% KOH (5 mL) at room temperature. A white precipitate formed slowly. When TLC indicated there was no starting material remaining, the solution was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. Column chromatography ($CHCl_3$: EtOH (97.5:2.5)) provided a white solid (0.0312 g, 0.124 mmol, 87%). All the spectroscopic data for (–)-**151** were identical with the data obtained from (±)-diol **151**. mp 243-244°C (dec.). $[\alpha]_D^{21}$ –41.4 (c 0.084, 1 dm, dry acetone) (literature[152] α_D^{20} -8.6 (c 0.42, 21% ee by MTPA ester, acetone)).

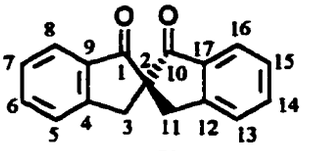
C. Compound (+)-**151**

To a solution of compound **202** (0.159 g, 0.317 mmol) in methanol (20 mL) was added 10% KOH (10 mL) at room temperature. A white precipitate formed slowly. When TLC indicated there was no starting material remaining the solution was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. Column chromatography ($CHCl_3$: EtOH (97.5:2.5)) provided a white solid (0.0695 g, 0.275 mmol, 87%). All the spectroscopic data for (+)-**151** were identical with the data obtained from (±)-diol **151**. mp 236- 237°C (dec.). $[\alpha]_D^{22}$ +38.6 (c 0.102, 1 dm, dry acetone) (literature[152] α_D^{20} -8.6 (c 0.42, 21% ee by MTPA ester, acetone)).

(2*RS*)- and (2*S*)-2,2'-Spirobiindane-1,1'-dione ((±)- and (+)-152)



(±)-**152**



(+)-**152**

A. Compound (±)-**152**

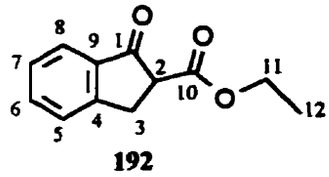
A solution of diester **6** (215 mg, 0.587 mmol) in 70% sulfuric acid (35 mL)[193] was heated from 50°C to 130°C over 1 h (the solution turned black while being monitored by GC). The mixture was cooled to room temperature and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and removed *in vacuo*. The product was purified by bulb-to-bulb sublimation, 162°C - 180°C (air bath)/ 0.05 Torr, to provide a light yellow solid (129 mg, 0.520 mmol, 89%). No further purification was necessary for the subsequent steps; however, silica gel column chromatography ($CHCl_3$) or recrystallisation from benzene[188] yielded a white solid. mp 172.6 - 175.5°C (literature[183] 173.6 - 176°C); IR 1687 (C=O (ketone)) cm^{-1}; ^{1}H-NMR 7.76 (d, 2H, $J_{16,15}$ and $J_{8,7}$ = 7.6 Hz, H-16 and H-8), 7.65 (t, 2H, $J_{14,15}$ and $J_{14,13}$ and $J_{6,7}$ and $J_{6,5}$ = 7.6 Hz, H-14 and H-6), 7.55 (d, 2H, $J_{12,13}$ and $J_{5,6}$ = 7.6 Hz, H-12 and H-5), 7.40 (t, 2H, $J_{15,16}$ and $J_{15,14}$ and $J_{7,8}$ and $J_{7,6}$ = 7.6 Hz, H-15 and H-7), 3.72 (d, 2H, J_{gem} = 17.0 Hz, 1H-11 and 1H-3), 3.19 (d, 2H, J_{gem} = 17.0 Hz, 1H-11 and 1H-3); ^{13}C-NMR 202.6 (C_q, C-10 and C-1), 153.8, 135.3 (C_q, C-17, C-12, C-9 and C-4), 135.2 (CH, C-14 and C-6), 127.7, 126.3, 124.7 (CH, C-16, C-15, C-13, C-8, C-7 and C-5), 65.2 (C_q, C-2), 39.9 (CH_2, C-11 and C-3). The ^{1}H-NMR spectrum was consistent with that reported by Dynesen.[183]

B. Compound (+)-**152**

To diol (+)-**151** (21.3 mg, 0.0844 mmol) in CH_2Cl_2 (12 mL) was added PDC (381 mg, 1.01 mmol). After 2 hours at room temperature (TLC showed no starting material) diethyl ether was added. The mixture was stirred for 15 minutes, filtered through Celite® and the solvent removed *in vacuo*. Flash column chromatography ($CHCl_3$) provided a white solid (17.7 mg, 0.0713 mmol) in 85% yield whose spectroscopic data were the same

as those of (±)-dione **152**. $[\alpha]_D^{22.5}$ +147.4 (c 1.25, 0.1 dm, $CHCl_3$); literature[188] $[\alpha]_D^{25}$ +151.86 (c 3.22, $CHCl_3$).

2-Ethoxycarbonyl-1-indanone (192)

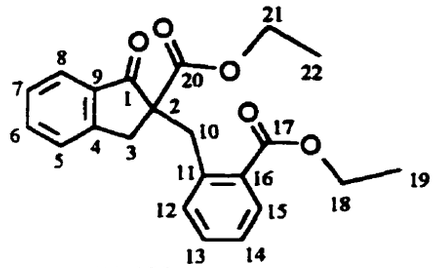


192

A 60% dispersion of sodium hydride (4.36 g, 109 mmol) was washed three times with diethyl ether (Sure/Seal®). The residual ether was removed by passing a stream of nitrogen gas over the mixture. Benzene (45 mL) and diethyl carbonate (8.80 mL, 72.6 mmol) were added and the resulting solution was mechanically stirred and refluxed (the reaction mixture turned green).[192] Freshly distilled 1-indanone (4.80 g, 36.3 mmol) in benzene (15 mL) was added slowly to the refluxing solution over 4.5 h. The addition funnel was washed with benzene (5 mL) and the reaction mixture was refluxed for an additional 0.5 h. Acetic acid and water were added until all the solid dissolved and the aqueous layer was approximately pH 5. The aqueous layer was extracted three times with benzene and the combined benzene extracts were washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude product was purified by bulb-to-bulb distillation to give a colourless liquid (6.61 g, 32.4 mmol, 89%): bp 72 - 88°C (air bath)/ 0.045 Torr; IR 1741 (C=O), 1716 (C=O), 1649, 1573 (aromatic C-C) cm^{-1}; ^1H NMR spectrum indicated the ratio of keto:enol was 76:24; ^1H NMR (both keto and enol form, however only keto form assigned) 10.43 (br. s, 0.24H, enol), 7.81-7.37 (m, 4H, keto and enol, H-8, H-7, H-6, and H-5), 4.33 (q, 0.48H, J=7.1 Hz, enol), 4.26 (q, 1.52H, $J_{11,12}$ = 7.1 Hz, keto, H-11), 3.73 (dd, 0.76H, $J_{2,3}$ = 8.2 and 4.1 Hz, keto, H-2), 3.58 (dd, 0.76H, J_{gem} = 17.3 Hz and $J_{3,2}$ = 4.1 Hz and, keto, 1H-3), 3.53 (s, 0.24H, enol), 3.38 (dd, 0.76H, J_{gem} = 17.3 Hz and $J_{3,2}$ = 8.2, keto, 1H-3), 1.38 (t, 0.72H, J = 7.1 Hz, enol), 1.32 (t, 2.28H, $J_{12,11}$ = 7.1 Hz, keto, H-12); ^{13}C-NMR spectrum indicated both the keto and enol forms were present. ^{13}C-NMR (keto only) 199.3 (C_q, C-1), 168.9 (C_q, C-10), 153.4 (C_q, C-9), 135.1 (C_q, C-4), 135.2, 127.6, 126.4, 124.4 (CH, C-8, C-7, C-6 and C-5), 61.5 (CH_2, C-11), 53.1 (CH, C-2), 30.1 (CH_2, C-3), 14.0 (CH_3, C-12); Mass spectrum 204

(42, $M^{+\cdot}$), 159 (22, $[M\text{-}OEt]^+$), 130 (100, $[M\text{-}HCO_2Et]^{+\cdot}$); Analysis calc'd for $C_{12}H_{12}O_3$: C, 70.58%; H, 5.92%. Found: C, 70.76%; H, 6.07%.

(2*RS*)-2-Ethoxycarbonyl-2-(2-(ethoxycarbonyl)phenylmethyl)-1-indanone ((±)-193)

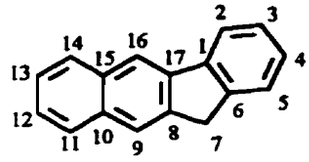


(±)-**193**

Freshly distilled ester **192** (4.86 g, 23.8 mmol) in DMF (10 mL, Sure/Seal®) was slowly added to a 60% dispersion of sodium hydride (1.05 g, 26.2 mmol). Once the vigorous evolution of H_2 had ceased, the solution was heated to 60°C for one hour (turned dark red-purple) and ethyl 2-(bromomethyl)benzoate[191] (6.31 g, 26.0 mmol) was added in DMF (15 mL, Sure/Seal®).[183] The reaction mixture was heated at 60°C for 87 h (the disappearanceof starting material was monitored by GC/MS). The reaction was cooled to room temperature and a few drops of water were added. The mixture was extracted with ether and was washed with brine. The ether layer was dried (Na_2SO_4), filtered and the ether removed *in vacuo*. The crude product was distilled bulb-to-bulb yielding a yellow solid. Purification by silica gel chromatography (5:1) produced (±)-**193** (7.72 g, 21.1 mmol) as a white solid in 89% yield: mp 93.5-94.0°C, bp 178-190°C (air bath) /0.05 Torr (slight dec.). IR 1737 (C=O (ester)), 1711 (C=O (ester and ketone)) cm^{-1}; ^{1}H-NMR 7.80 (d, 1H, $J_{15,14}$ or $J_{8,7}$ = 7.1 Hz, H-15 or H-8), 7.23 (d, 1H, $J_{15,14}$ or $J_{8,7}$ = 7.6 Hz, H-15 or H-8), 7.50 (t, 1H, ($J_{13,12}$ and $J_{13,11}$) or ($J_{6,7}$ and $J_{6,5}$ = 7.4 Hz, H-13 or H-6), 7.33-7.13 (m, 5H, H-14, H-12, H-7, H-5 and H-13 or H-6), 4.30 (q, 2H, $J_{21,22}$ = 7.1 Hz, H-21), 4.15 (q, 2H, $J_{18,19}$ = 7.1 Hz, H-18), 4.08 (d, 1H, J_{gem} = 14.1 Hz, 1H-10), 3.68 (d, 1H, J_{gem} = 14.1 Hz, 1H-10), 3.60 (d, 1H, J_{gem} = 16.7 Hz, 1H-3), 3.07 (d, 1H, J_{gem} = 16.7 Hz, 1H-3), 1.32 (t, 3H, $J_{22,21}$ = 7.1 Hz, H-22), 1.17 (t, 3H, $J_{19,18}$ = 7.1 Hz, H-19); ^{13}C-NMR 202.6 (C_q, C-1), 170.8, 167.7 (C_q, C-20 and C-17), 153.7, 137.9 (C_q, C-19, C-11, C-9 and/or C-4, other C_q's are not observed), 135.1, 131.5, 131.2, 130.4, 127.4, 126.6, 126.0, 124.4 (CH, C-15, C-14, C-13, C-12, C-8, C-7, C-6, C-5 and C-4), 61.7, 61.0 (CH_2, C-21 and C-18), 35.6, 35.5 (CH_2, C-10 and C-3), 14.1, 13.9 (CH_3, C-22 and C-19); Mass spectrum 366 (1, $M^{+\cdot}$), 320 (46, $[M\text{-}EtOH]^{+\cdot}$), 247 (100, [M-EtOH and

$CO_2Et]^+$), 157 (94); Analysis calc'd for $C_{22}H_{22}O_5$: C, 72.12%; H, 6.05% Found: C, 72.10%; H, 6.17%.

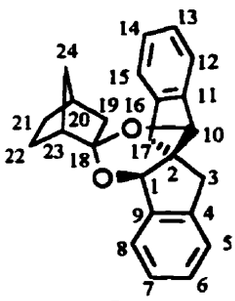
2,3-Benzofluorene (194)



194

(±)-Diol **151** (0.0210 g, 0.0832 mmol), (1*R*)-camphor (0.038 g, 0.25 mmol), and TsOH (catalytic quantities), were placed in a round bottomed flask and dissolved in benzene (10 mL). The solution was refluxed with azeotropic removal of water. The reaction was monitored for loss of starting diol by TLC or GC/MS. To the solution at rt was added anhydrous K_2CO_3. After 15 minutes the mixture was filtered and the flask was washed with benzene. The solvent was removed *in vacuo*. Purification by flash column chromatography (20:1) resulted in the isolation of **194** as a white solid, (64% yield, 0.0166 g, 0.0536 mmol). mp 196.7 - 197.0°C (literature[230] 208°C); IR[231] (Nujol mull) 3055, 3046, 3019 (H-C(sp^2)) cm^{-1}; ^{1}H-NMR 8.22 (s, 1H), 8.05 - 7.93 (m, 4H), 7.64 - 7.36 (m, 5H), 4.10 (s, 2H, H-7); ^{13}C-NMR 143.8, 141.2$_2$, 141.1$_7$, 140.6, 133.2, 133.1 (C_q, C-17, C-15, C-10, C-8, C-6, C-1), 128.2, 127.8, 127.6, 2×127.0, 125.4, 125.3, 123.4, 120.6, 117.8 (CH, C-16, C-14 to C-11, C-9 and C-5 to C-2), 36.4 (CH_2, C-7): Mass spectrum 216 (100, $M^{+\cdot}$).

(1*RS*,1'*RS*,2*RS*)-2,2'-Spirobiindane-1,1'-diol (1''*RS*,4''*RS*)-Bicyclo[2.2.1]hexan-2-one Ketal ((±)-197)

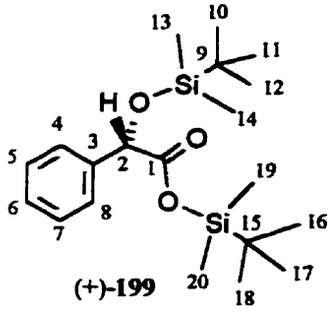


(±)-**197**

(±)-Ketal **197** was prepared from (±)-diol **151** (0.0637g, 0.252 mmol) and (±)-bicyclocompound **196** (0.031 g, 0.28 mmol) using general procedure 2. Radial plate chromatography (20:1) produced (±)-ketal **197** (0.0392 g, 0.114 mmol) as a light yellow oil in 41% yield. IR 3072, 3037 (H-C(sp^2)), 2956, 2873 (H-(sp^3)) cm^{-1}; ^{1}H-NMR (2:1 ratio of diastereomers: main diastereomer reported) 7.57 - 7.48 (m, 2H), 7.39 - 7.24 (m, 6H), 4.87, 4.86 (s, 2H, H-10 and H-1), 3.24, 3.18 (d, 2H, J_{gem} = 15.9 and 15.7 Hz, 1H-17 and 1H-3), 2.74, 2.71 (d, 2H, J_{gem} = 15.9 and 15.7 Hz, 1H-17 and 1H-3), 2.48 (br. d, 1H, $J_{23,22}$ = 3.5 Hz, H-23), 2.28 (br. s,

1H, H-20), 1.89 - 1.70, 1.67 -1.28 (m, 8H); ^{13}C-NMR (main diastereomer) 144.7, 144.4, 140.9, 140.8 (C_q, C-16, C-11, C-9 and C-4), 128.7, 126.7, 126.5, 126.2, 126.0, 125.7, 125.1, 125.0 (CH, C-15 to C-12 and C-8 to C-5), 109.0 (C_q, C-18), 82.1, 81.4 (CH, C-10 and C-1), 54.3 (C_q, C-2), 43.3_2, 35.5 (CH, C-23 and C-20), 44.2, 43.2_7, 43.2, 36.7, 28.6, 21.4 (CH_2, C-24, C-22, C-21, C-19, C-17 and C-3); Mass spectrum 344 (14, $M^{+\cdot}$), 234 (79, $[M-C_7H_{10}O]^+$), 218 (100, $[M-C_7H_{10}O_2]^+$); Exact mass calc'd for $C_{24}H_{24}O_2$: 344.1776. Found: 344.1782.

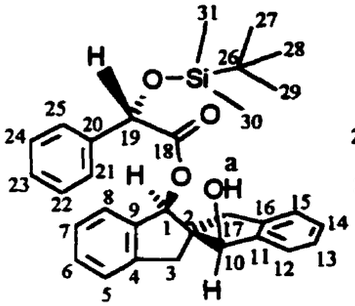
***tert*-Butyldimethylsilyl (2*S*)-(*O*-*tert*-Butyldimethylsilyl)mandelate ((+)-199)**



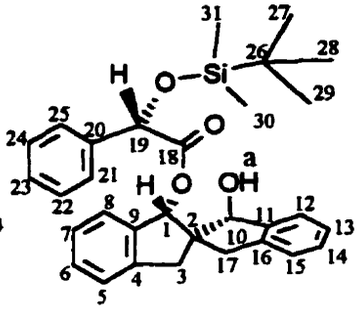
(+)-199

(+)-(2*S*)-Mandelic acid (**198**, 10.0 g, 65.7 mmol), imidazole (18.8 g, 276 mmol) and *tert*-butyldimethylsilyl chloride (29.7 g, 197 mmol) were dissolved in DMF (110 mL) at 0°C. The mixture was stirred at rt for 84 h, extracted with diethyl ether and the ether was washed three times with brine. The organic layer was dried (Na_2SO_4) and removed *in vacuo* to give a colourless oil. Bulb-to-bulb distillation yielded a colourless oil (24.3 g, 63.8 mmol) in 97% yield. bp 90°C-110°C (air bath)/ 0.045 Torr. IR 3031 (H-C(sp^2)), 2956, 2930 (H-C(sp^3)), 1741, 1717 cm^{-1}; ^{1}H-NMR 7.49-7.42 (m, 2H, H-8 and H-4), 7.42-7.28 (m, 3H, H-7, H-6 and H-5), 5.15 (s, 1H, H-2), 0.92 (s, 9H, (H-18, H-17 and H-16) or (H-12, H-11, and H-10)), 0.83 (s, 9H, (H-18, H-17 and H-16) or (H-12, H-11, and H-10)), 0.20 (s, 3H, H-20, H-19, H-14 or H-13), 0.15 (s, 3H, H-20, H-19, H-14 or H-13), 0.12 (s, 3H, H-20, H-19, H-14 or H-13), 0.02 (s, 3H, H-20, H-19, H-14 or H-13); ^{13}C-NMR 172.1 (C_q, C-1), 139.6 (C_q, C-3), 127.9 (CH, C-6), 128.1, 126.5 (CH, C-8, C-7, C-5 and C-4), 75.3 (CH, C-2), 25.6, 25.3 (CH_3, C-18, C-17, C-16, C-12, C-11, and C-10), 18.2, 17.6 (C_q, C-15 and C-9), 2×-5.0, -5.1, -5.2 (CH_3, C-20, C-19, C-14 and C-13); Mass spectrum 365 (0.8, $[M-Me]^+$), 323 (44, $[M-t-Bu]^+$), 221 (62, $[M-CO_2SiMe_2t-Bu]^+$), 73 (100, $[OSiMe_2]^+$ or $[Ot-Bu]^+$); Exact mass calc'd for $C_{19}H_{33}O_3Si_2$ ($[M-CH_3]^+$): 365.1968. Found: 365.1955. $[\alpha]_D^{22}$ +46.17 (c 1.62, 0.1 dm, chloroform).

(1*S*,1'*S*,2*S*)- and (1*R*,1'*R*,2*R*)-1-((2*S*)-(*O*-*tert*-Butyldimethylsilyl)mandeloxy)-2,2'-spirobiindan-1'-ol ((-)-201 and (+)-202)



(-)-**201**



(+)-**202**

To a solution of compound (+)-**199** (205 mg, 0.540 mmol)[232] in CH_2Cl_2 (10 mL) at 0°C was added DMF (3 drops) and oxalyl chloride (61.3 μL, 0.702 mmol).[199,233] The solution was stirred for 0.5 h, warmed to rt and stirred overnight. The solvent was removed *in vacuo* and the flask back purged with dry N_2 to provide compound **200**. Tetrahydrofuran (10 mL) was added and the mixture cooled to -78°C.

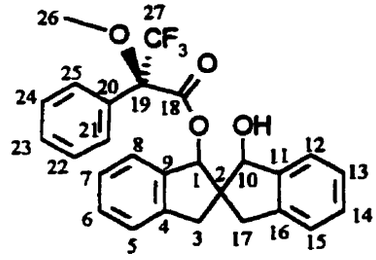
In a separate round bottom flask, (±)-diol **151** (54.5 mg, 0.216 mmol) was placed under a vacuum (approximately 0.1 Torr) for 1 h. After back purging with N_2, THF (5 mL) was added and the suspension cooled to -78°C whereupon *n*-butyllithium (97.2 μL, 1M in THF) was added. After stirring 5 min., the solution was warmed to rt and transferred to an equalised dropping funnel. This solution was added slowly to the acid chloride **200** solution (at -78°C). The resulting solution was slowly warmed to rt overnight. Saturated $NaHCO_3$ was added and the aqueous layer extracted numerous times with diethyl ether. The combined ether layers were dried (Na_2SO_4) and removed *in vacuo*. The diastereomers were separated from other impurities by flash column chromatography (9:1). This procedure provided an oil (78 mg, 0.16 mmol, 72%) which solidified on standing. The mixture of diastereomers was separated using a column of silica gel ($CHCl_3$) (R_f of **202** = 0.14; R_f of **201** = 0.24).

Diastereomer **201**: IR 3582 (O-H), 1730 (C=O(ester)) cm^{-1}; ^{1}H-NMR 7.54-7.17 (m, 13H, H-25 to H-21, H-15 to H-12, and H-8 to H-5), 6.12 (s, 1H, H-1), 5.21 (s, 1H, H-19), 5.07 (d, 1H, $J_{10,a}$ = 4.8 Hz, H-10), 3.16 (d, 1H, J_{gem} = 15.4 Hz, 1H-17 or 1H-3), 3.14 (d, 1H, J_{gem} = 15.4 Hz, 1H-17 or 1H-3), 2.51 (d, 1H, J_{gem} = 15.4 Hz, 1H-17 or 1H-

3), 2.47 (d, 1H, J_{gem} = 15.4 Hz, 1H-17 or 1H-3), 2.03 (d, 1H, $J_{a,10}$ = 4.8 Hz, H-a), 0.84 (s, 9H, H-29, H-28 and H-27), -0.04 (s, 3H, H-31 or H-30), -0.11 (s, 3H, H-31 or H-30); ^{13}C-NMR 171.5 (C_q, C-18), 144.1, 143.6, 142.3, 140.2, 138.9 (C_q, C-20, C-16, C-11, C-9, C-4), 129.3, 128.6, 128.5, 128.3, 127.1, 126.9, 126.7, 125.7, 125.3, 125.0 (CH, C-25 to C-21, C-15 to C-12 and C-8 to C-5 (one C resonance hidden)), 83.4, 80.2, 74.9, (CH, C-19, C-10 and C-1), 59.0 (C_q, C-2), 42.3, 42.1 (CH_2, C-17 and C-3), 25.5 (CH_3, C-29, C-28 and C-27), 18.1 (C_q, C-26), -5.4 (CH_3, C-31 and C-30); Mass spectrum 483 (5, [M-OH]$^+$), 217 (100); Exact mass calc'd for $C_{31}H_{34}O_3Si$ ([M-OH]$^+$): 483.2355. Found: 483.2347. $[\alpha]_D^{22.5}$ –79.99 (c 11.25, 0.1 dm, chloroform).

Diastereomer **202**: IR 3567 (O-H), 1750 (C=O(ester)) cm^{-1}; ^{1}H-NMR 7.63 (dd, 1H, J = 7.0 and 1.6 Hz), 7.51-7.15 (m, 11H), 6.12 (s, 1H, H-1), 5.14 (s, 1H, H-19), 4.77 (d, 1H, $J_{10,a}$ = 4.5 Hz, H-10), 3.12 (d, 1H, J_{gem} = 15.3 Hz, 1H-17 or 1H-3), 3.09 (d, 1H, J_{gem} = 15.3 Hz, 1H-17 or 1H-3), 2.41 (d, 1H, J_{gem} = 15.3 Hz, 1H-17 or 1H-3), 2.37 (d, 1H, J_{gem} = 15.3 Hz, 1H-17 or 1H-3), 1.55 (d, 1H, $J_{a,10}$ = 4.5 Hz, H-a), 0.90 (s, 9H, H-29, H-28 and H-27), 0.09 (s, 3H, H-31 or H-30), -0.04 (s, 3H, H-31 or H-30); ^{13}C-NMR 170.9 (C_q, C-18), 144.4, 143.3, 142.6, 140.4, 139.4 (C_q, C-20, C-16, C-11, C-9, C-4), 129.3, 128.7, 128.6, 127.4, 126.9, 126.8, 126.5, 125.3, 125.2, 125.1 (CH, C-25 to C-21, C-15 to C-12 and C-8 to C-5 (one C resonance hidden)), 82.7, 79.6, 74.7, (CH, C-19, C-10 and C-1), 58.9 (C_q, C-2), 42.4, 42.2 (CH_2, C-17 and C-3), 25.7 (CH_3, C-29, C-28 and C-27), 18.2 (C_q, C-26), -4.9, -5.2 (CH_3, C-31 and C-30); Mass spectrum 483 (5, [M-OH]$^+$), 443 (2, [M-*t*-Bu]$^+$), 217 (100); Exact mass calc'd for $C_{31}H_{34}O_3Si$ ([M-OH]$^+$): 483.2355. Found: 483.2348. $[\alpha]_D^{22.5}$ +102.34 (c 7.0, 0.1 dm, chloroform).

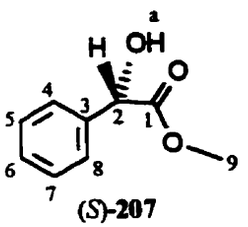
(1*RS*,1'*RS*,2*RS*)-1-(((2''*R*)-2''-Methoxy-2''-(trifluoromethyl)phenylacetoxy)-2,2'-spirobiindan-1'-ol (203 and 204)



203 and 204

(±)-Diol **151** (0.056 g, 0.22 mmol) was added to a round bottomed flask containing MTPA-Cl (0.22 mmol) in $CHCl_3$ or $CDCl_3$ (2 mL).[201] To the solution was added DMAP (catalytic quantities) and Et_3N (0.078 mL, 0.56 mmol) and the reaction stirred overnight. More $CHCl_3$ was added and the organic layer was extracted with 5% HCl and water. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified by radial plate chromatography ($CHCl_3$) which provided **203** and **204** (0.0896 g, 0.191 mmol, 85% yield) as a light yellow solid. IR 3566 (H-O), 1741 (C=O (ester)) cm^{-1}; ^{1}H-NMR (400 MHz, diastereomer from 1*R*,1'*R*,2*R*-diol **151**) 7.71 (d, 1H, J = 7.4 Hz), 7.48 - 7.19 (m, 12H), 6.38 (s, 1H, H-1), 5.09 (s, 1H, H-10), 3.47 (s, 3H, H-26), 3.23 (d, 1H, J_{gem} = 15.4 Hz, 1H-17 or 1H-3), 3.06 (d, 1H, J_{gem} = 15.6 Hz, 1H-17 or 1H-3), 2.45 (d, 1H, J_{gem} = 15.4 Hz), 2.41 (d, 1H, J_{gem} = 15.4 Hz); ^{1}H-NMR (400 MHz, diastereomer from 1*S*,1'*S*,2*S*-diol **151**) 7.71 (d, 1H, J = 7.4 Hz), 7.48 - 7.19 (m, 12H), 6.38 (s, 1H, H-1), 4.96 (s, 1H, H-10), 3.41 (s, 3H, H-26), 3.23 (d, 1H, J_{gem} = 15.4 Hz, 1H-17 or 1H-3), 3.11 (d, 1H, J_{gem} = 15.6 Hz, 1H-17 or 1H-3), 2.47 (d, 1H, J_{gem} = 15.4 Hz), 2.44 (d, 1H, J_{gem} = 15.4 Hz); ^{13}C-NMR (400MHz, both diastereomers) 166.1, 165.8 (C_q, C-18), 144.7, 144.6, 143.8, 143.3, 142.6, 139.6$_4$, 139.5$_9$ (C_q, C-20, C-16, C-11, C-9 and C-4), 129.9, 129.7, 129.6, 129.4, 129.0, 128.9, 128.4, 128.2, 127.6, 127.5, 127.4, 127.2, 127.1, 126.9, 126.7, 125.6, 125.3, 125.1 (CH, C-25 to C-21, C-15 to C-12 and C-8 to C-5), 84.3, 84.1, 79.2 (CH, C-10 and C-1), 59.4, 59.2 (CH_3, C-26), 55.3, 55.2 (C_q, C-2), 42.1, 41.9, 41.8, 41.7 (CH_2, C-17 and C-3); Mass spectrum 468 (4, $M^{+\cdot}$), 451 (18, $[M\text{-}OH]^+$), 217 (100); Exact mass calc'd for $C_{27}H_{23}O_4F_3$: 468.1548. Found: 468.1515.

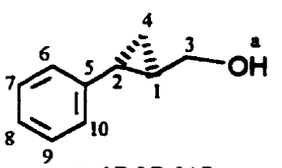
Methyl (*S*)-Mandelate ((+)-207)


(*S*)-207

To (+)-(*S*)-mandelic acid in a round bottom flask was added CH_2N_2 (in ether) until the resulting solution stayed slightly yellow. The ether and any excess CH_2N_2 were removed *in vacuo*. ^{1}H-NMR (200MHz) 7.48 - 7.33 (m, 5H, C-8 to C-4), 5.19 (d, 1H, $J_{2,a}$ = 5.6 Hz, H-2), 3.77 (s, 3H, H-9), 3.47 (d, 1H, $J_{a,2}$ = 5.6 Hz, Ha); Mass spectrum 166 (15, $M^{+\cdot}$), 107 (100, $[M\text{-}CO_2Me]^+$), 77 (50, $[C_6H_5]^+$). The ^{1}H-NMR corresponded to that published, thus this compound was not fully characterised.[234] Chiral GC analysis of a mixture of the (+)- and (-)-methyl mandelate (**207**) showed that enantiomeric separation occurred by heating the column at 95°C for 40 min.

Experimental Procedure Pertaining to Chapter 5

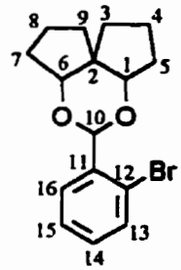
(1*R*,2*R*)-1-Hydroxymethyl-2-phenylcyclopropane ((-)-215)


(-)-1*R*,2*R*-215

Cinnamyl alcohol (**214**, 0.058 g, 0.43 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0°C.[32a] Diethylzinc (0.48 mL, 1M in hexanes) was added and the solution stirred for 15 min. Freshly distilled (-)-1*R*,5*R*,6*R*-diol **106** was washed into the solution with CH_2Cl_2 (4 mL) and stirred for 1 h. More Et_2Zn (0.87 mL) was added and the solution was cooled to -20°C and stirred for 10 min. Diiodomethane (0.1394 mL, 1.73 mmol) was added and the reaction stirred for 10 min. at -20°C before placing the reaction in an ice bath, and warming to rt overnight. When TLC (1:1) showed no starting material, the reaction was quenched by pouring it into a saturated solution of NH_4Cl followed by extraction with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Radial plate chromatography (5:1 followed by 1:1) produced purified cyclopropane product **215** (0.0371 g, 0.250 mmol) and diol **106** (0.0687 g, 92% reisolated yield). Compound **215** was a clear liquid. bp 142 - 156°C (air bath)/ aspirator; IR 3392 (H-O), 3062 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 7.34 - 7.06 (m, 5H, H-10 to H-6), 3.62 (d, 2H, $J_{3,1}$ = 6.8 Hz, H-3), 1.94 (br. s, 1H, H-a), 1.90 - 1.78 (m, 1H, H-2 or H-1), 1.56 - 1.40 (m, 1H, H-2 or H-1), 1.04 - 0.90 (m, 2H, H-4); ^{13}C-NMR 142.4 (C_q, C-5), 128.2, 125.7 (CH,

C-10, C-9, C-7 and C-6), 125.6 (CH, C-8), 66.4 (CH_2, C-3), 25.2, 21.2 (CH, C-2 and C-1), 13.8 (CH_2, C-4); Mass spectrum 148 (27, M^+), 130 (25, $[M-H_2O]^+$), 117 (100, $[M-CH_2OH]^+$); Exact mass calc'd for $C_{10}H_{12}O$: 148.0888. Found: 148.0899. Optical rotation obtained was α_D^{23} -16.2 (c 2.45, 0.1 dm, EtOH) (literature[32a] $[\alpha]_D^{12}$ -90.8).

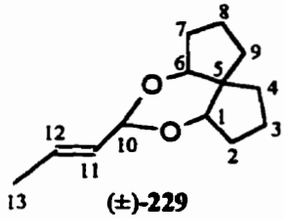
(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol *o*-Bromobenzaldehyde Acetal ((±)-221)



(±)-221

Acetal (±)-**221** was prepared according to general procedure 1 by mixing (±)-diol **106** (0.151 g, 0.967 mmol) with *o*-bromobenzaldehyde (**220**, 0.179 g, 0.967 mmol). Flash column chromatography (20:1) provided acetal **221** (0.301 g, 0.930 mmol) in 96% yield which was a colourless liquid that solidified on standing. mp 59.0 - 59.5°C, bp 113 - 122°C (air bath)/ 0.05 Torr; IR 2956, 2867 (H-C(sp^3)), 1097 (C-O) cm^{-1}; ^{1}H-NMR 7.72 (dd, 1H, $J_{16,15}$ or $J_{13,14}$ = 7.6 Hz and $J_{16,14}$ or $J_{13,15}$ = 1.8 Hz, H-16 or H-13), 7.54 (dd, 1H, $J_{16,15}$ or $J_{13,14}$ = 7.8 Hz and $J_{16,14}$ or $J_{13,15}$ = 1.2 Hz, H-16 or H-13), 7.35 (dt, 1H, $J_{15,16}$ and $J_{15,14}$ or $J_{14,15}$ and $J_{14,13}$ = 7.6 Hz and $J_{15,13}$ or $J_{14,16}$ = 1.2 Hz, H-15 or H-14), 7.19 (dt, 1H, $J_{15,16}$ and $J_{15,14}$ or $J_{14,15}$ and $J_{14,13}$ = 7.8 Hz and $J_{15,13}$ or $J_{14,16}$ = 1.8 Hz, H-15 or H-14), 5.97 (s, 1H, H-10), 4.31 (t, 1H, $J_{6,7}$ or $J_{1,5}$ = 7.9 Hz, H-6 or H-1), 4.02 (d, 1H, $J_{6,7}$ or $J_{1,5}$ = 5.0 Hz, H-6 or H-1), 2.40 - 1.35 (m, 12H)); ^{13}C-NMR 137.8 (C_q, C-11), 132.8, 130.1, 128.2, 127.5 (CH, C-16 to C-13), 122.6 (C_q, C-12), 93.4 (CH, C-10), 83.0, 80.8 (CH, C-6 and C-1), 49.2 (C_q, C-2), 34.9, 31.6, 27.8, 22.1, 21.1 (CH_2, C-9, C-8, C-7, C-5, C-4, C-3 (one resonance missing)); Mass spectrum (CI) 325 (27, $[M+2+H]^+$), 323 (31, $[M+H]^+$), 120 (100, $[C_9H_{12}]^+$); Analysis calc'd for $C_{16}H_{19}O_2Br$: C, 59.45%; H, 5.92%. Found: C, 59.73%; H, 5.57%.

(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol Crotonaldehyde Acetal ((±)-229 (R = Me))

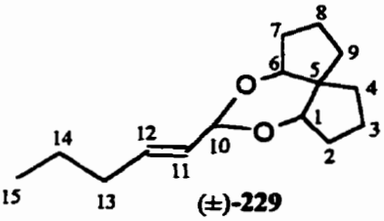


(±)-229

(±)-Diol **106** (0.102 g, 0.654 mmol) and crotonaldehyde (0.0596 mL, 0.719 mmol), in benzene (11 mL), were converted to (±)-acetal **229** by general procedure 1 (double bond isomerisation, however, could be minimised if general procedure 2 was employed). Purification of the product by radial plate

chromatography (20:1) provided (±)-**229** as a clear liquid in 83% yield (0.141 g, 0.676 mmol). bp 112 - 124°C (air heat)/ aspirator; IR 3019 (H-C(sp^2)), 2956, 2872 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 5.90 (dq, 1H, $J_{12,11}$ = 15.5 Hz and $J_{12,13}$ = 6.5 Hz, H-12), 5.56 (dd, 1H, $J_{11,12}$ = 15.5 Hz and $J_{11,10}$ = 5.7 Hz, H-11), 5.10 (d, 1H, $J_{10,11}$ = 5.7 Hz, H-10), 4.13 (t, 1H, $J_{6,7}$ or $J_{1,2}$ = 7.3 Hz, H-7 or H-1), 3.78 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 5.1 Hz, H-7 or H-1), 2.13 - 1.26 (m, 12H), 1.72 (d, 3H, $J_{13,12}$ = 6.5 Hz, H-13); ^{13}C-NMR 130.2, 128.5 (CH, C-12 and C-11), 94.2 (CH, C-10), 82.3, 79.4 (CH, C-6, C-1), 35.0, 34.9, 31.5, 28.3, 22.1, 21.1 (CH_2, C-9, C-8, C-7, C-4, C-3 and C-2), 17.5 (CH_3, C-13); Mass spectrum 208 (0.4, $M^{+\cdot}$), 207 (0.8, $[M-H]^+$), 120 (95), 94(100); Exact mass calc'd for $C_{13}H_{20}O_2$: 208.1463. Found: 208.1467.

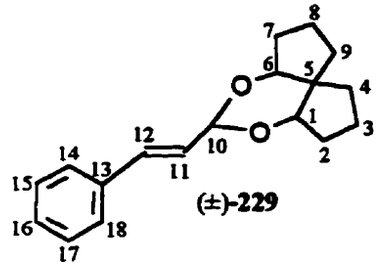
(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol *trans*-2-Hexenal Acetal ((±)-229 (R = *n*-Pr))



(±)-**229**

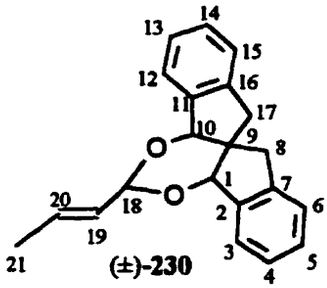
(±)-Diol **106** (0.331 g, 2.12 mmol) and *trans*-2-hexenal (0.271 mL, 2.33 mmol), in benzene (15 mL), were converted to (±)-acetal **229** by general procedure 1 (double bond isomerisation, however, could be minimised if general procedure 2 was employed). Purification of the product by radial plate chromatography (30:1) provided (±)-**229** as a clear liquid in 86% yield (0.430 g, 1.82 mmol). bp 58 - 65°C (air bath)/ 0.06 Torr; IR 2931, 2873 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 5.90 (dt, 1H, $J_{12,11}$ = 15.6 Hz and $J_{12,13}$ = 6.5 Hz, H-12), 5.55 (dd, $J_{11,12}$ = 15.6 Hz and $J_{11,10}$ = 5.7 Hz, H-11), 5.12 (d, 1H, $J_{10,11}$ = 5.7Hz, H-10), 4.14 (t, 1H, $J_{6,7}$ or $J_{1,2}$ = 7.3 Hz, H-6 or H-1), 3.79 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 5.1 Hz, H-6 or H-1), 2.12 -1.32 (m, 14H), 0.91 (t, 3H, $J_{15,14}$ = 7.3 Hz, H-15); ^{13}C-NMR 135.3, 127.2 (CH, C-12 and C-11), 94.4 (CH, C-10), 82.3, 79.5 (CH, C-6 and C-1), 49.9 (C_q, C-5), 35.0, 34.9, 34.8, 31.5, 28.3, 22.2, 22.0, 21.2 (CH_2, C-14, C-13, C-9, C-8, C-7, C-4, C-3 and C-2), 13.7 (CH_3, C-15); Mass spectrum 236 (0.4, $M^{+\cdot}$), 235 (0.8, $[M-H]^+$), 193 (9, $[M-CH_2CH_2CH_3]^+$), 121 (100, $[C_9H_{13}]^+$), 94 (100); Exact mass calc'd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1775.

(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol *trans*-Cinnamaldehyde Acetal ((±)-229 (R = Ph))



(±)-Diol **106** (0.178 g, 1.14 mmol) and *trans*-cinnamaldehyde (0.158 mL, 1.26 mmol), in benzene (14 mL), were converted to (±)-acetal **229** by general procedure 1. Purification of the product by radial plate chromatography (20:1) provided (±)-**229** as a clear liquid in 93% yield (0.289 g, 1.07 mmol). bp 124 - 138°C (air bath)/ 0.05 Torr; IR 3057, 3026 (H-C(sp^2)), 2956, 2868 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 7.42 (d, 2H, $J_{14,15}$ and $J_{18,17}$ = 8.1 Hz, H-18 and H-14), 7.36 -7.24 (m, 3H, H-17, H-16 and H-15), 6.79 (d, 1H, $J_{12,11}$ = 16.1 Hz, H-10), 6.25 (dd, 1H, $J_{11,12}$ = 16.1 Hz and $J_{11,10}$ = 5.0 Hz, H-11), 5.35 (d, 1H, $J_{10,11}$ = 5.0 Hz, H-10), 4.20 (t, 1H, $J_{6,7}$ or $J_{1,2}$ = 7.1 Hz, H-6 or H-1), 3.86 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 5.0 Hz, H-6 or H-1), 2.19 -1.77 and 1.77 -1.32 (m, 12H); ^{13}C-NMR 136.1 (C_q, C-13), 132.9, 128.3, 128.3, 127.8, 126.7, 126.1 (CH, C-18 to C-14, C-12 and C-11), 94.0 (CH, C-10), 82.5, 79.5 (CH, C-6 and C-1), 50.3 (C_q, C-5), 25.0, 31.5, 28.4, 22.3, 22.2, 21.3 (CH_2, C-9, C-8, C-7, C-4, C-3 and C-2); Mass spectrum 270 (4, $M^{+\cdot}$), 121 (100, $[C_9H_{13}]^+$); Exact mass calc'd for $C_{18}H_{22}O_2$: 270.1620. Found: 270.1607.

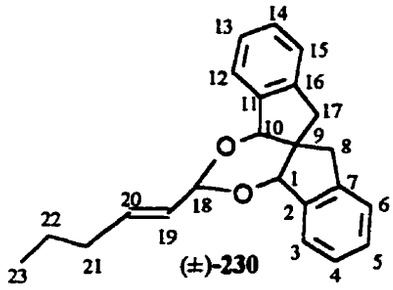
(1*RS*,1′*RS*,2*RS*)-2,2′-Spirobiindane-1,1′-diol Crotonaldehyde Acetal ((±)-230 (R = Me))



(±)-Diol **151** (0.0384 g, 0.152 mmol) and crotonaldehyde (13.9 μL, 0.167 mmol), in benzene (15 mL), were converted to (±)-acetal **230** by general procedure 2. Purification of the product was not needed, but could be performed by radial plate chromatography (~20:1). (±)-Acetal **230** was a light yellow liquid (97% yield (based on aldehyde), 0.0493 g). IR 3073, 3044 (H-C(sp^2)), 2922, 2914 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 7.53 - 7.17 (m, 8H, H-15 to H-12 and H-6 to H-3), 5.95 (dq, 1H, $J_{20,19}$ = 15.5 Hz and $J_{20,21}$ = 6.5 Hz, H-20), 5.61 (dd,

1H, $J_{19,20}$ = 15.5 Hz and $J_{19,18}$ = 5.4, H-19), 5.59 (s, 1H, H-10 or H-1), 5.12 (d, 1H, $J_{18,19}$ = 5.4 Hz, H-18), 4.56 (s, 1H, H-10 or H-1), 3.80 (d, 1H, $J_{17,17}$ or $J_{8,8}$ = 15.6, H-17 or H-8), 2.98 (d, 1H, $J_{17,17}$ or $J_{8,8}$ = 15.6, H-17 or H-8), 2.72 (complex AB, 2H, H-17 or H-8), 1.76 (d, 3H, $J_{21,20}$ = 6.5 Hz, H-21); ^{13}C-NMR 145.0, 140.8, 140.4_9, 140.4_5 (C_q, C-16, C-11, C-7 and C-2), 130.8, 129.1, 128.4, 128.1, 127.2, 126.8, 126.4, 125.4, 125.1, 124.1 (CH, C-20, C-19, C-15 to C-12, C-6 to C-3), 93.3 (CH, C-18), 83.6, 82.4 (CH, C-10 and C-1), 49.4 (C_q, C-9), 40.8, 39.7 (CH_2, C-17 and C-8), 17.6 (CH_3, C-21); Mass spectrum 304 (0.8, $M^{+\cdot}$), 217 (100); Exact mass calc'd for $C_{21}H_{20}O_2$: 304.1463. Found: 304.1452.

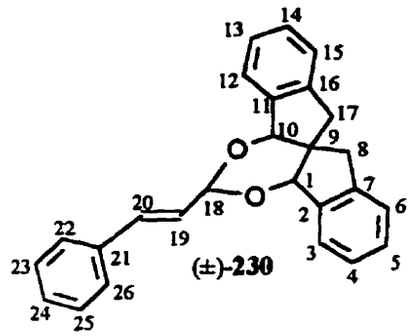
(1*RS*,1'*RS*,2*RS*)-2,2'-Spirobiindane-1,1'-diol *trans*-2-Hexenal Acetal ((±)-230 (R = *n*-Pr))



(±)-**230**

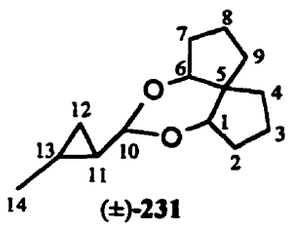
(±)-Diol **151** (0.0976 g, 0.387 mmol) and *trans*-2-hexenal (0.0494 mL, 0.4255 mmol), in benzene (15 mL), were converted to (±)-acetal **230** by general procedure 2. Purification of the product was not needed, but could be performed by radial plate chromatography (~20:1). (±)-Acetal **230** was a light yellow liquid (96% yield (based on aldehyde), 0.1358 g). IR 3073 (H-C(sp^2)), 2929 (H-C(sp^2)) cm^{-1}; ^{1}H-NMR 7.52 - 7.15 (m, 8H, H-15 to H-12 and H-6 to H-3), 5.92 (dt, 1H, $J_{20,19}$ = 15.6 Hz and $J_{20,21}$ = 6.5 Hz, H-20), 5.58 (s, 1H, H-10 or H-1), 5.57 (dd, 1H, $J_{19,20}$ = 15.6 Hz and $J_{19,18}$ = 5.5 Hz, H-19), 5.12 (d, 1H, $J_{18,19}$ = 5.5 Hz, H-18), 4.55 (s, 1H, H-10 or H-1), 3.80 (d, 1H, $J_{17,17}$ or $J_{8,8}$ = 15.6 Hz, 1H-17 or 1H-8), 2.96 (d, 1H, $J_{17,17}$ or $J_{8,8}$ = 15.6 Hz, 1H-17 or 1H-8), 2.71 (complex AB, 2H, H-17 or H-8), 2.05 (q, 2H, $J_{21,22}$ and $J_{21,20}$ = 7.1 Hz, H-21), 1.44 (septet, 2H, $J_{22,23}$ and $J_{22,21}$ = 7.3 Hz), 0.92 (t, 3H, $J_{23,22}$ = 7.3 Hz); ^{13}C-NMR 145.1, 140.9, 2×140.5 (C_q, C-16, C-11, C-7 and C-2), 135.8, 129.1, 128.4, 127.2, 126.8, 126.7, 126.5, 125.4, 125.2, 124.2 (CH, C-20, C-19, C-15 to C-12 and C-6 to C-3), 93.5 (CH, C-18), 83.7, 82.4 (CH, C-10 and C-1), 49.4 (C_q, C-9), 40.8, 39.7, 34.1, 21.7 (CH_2, C-22, C-21, C-17 and C-8), 13.8 (CH_3, H-23); Mass spectrum 332 (1, $M^{+\cdot}$), 217 (100); Exact mass calc'd for $C_{23}H_{24}O_2$: 332.1776. Found: 332.1773.

(1*RS*,1'*RS*,2*RS*)-2,2'-Spirobiindane-1,6-diol *trans*-Cinnamaldehyde Acetal ((±)-230 (R = Ph))


(±)-230

(±)-Diol **151** (0.1028 g, 0.407 mmol) and *trans*-cinnamaldehyde (0.0565 mL, 0.448 mmol), in benzene (15 mL), were converted to (±)-acetal **230** by general procedure 2. Purification of the product was not needed, but could be performed by radial plate chromatography (~20:1). (±)-Acetal **230** was a light yellow liquid (99% yield, 0.165 g) that crystallised on standing. mp 147 - 148°C; IR 3047, 3027 (H-C(sp^2)), 2923, 2869 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 7.55 - 7.19 (m, 12H), 6.78 (d, 1H, $J_{20,19}$ = 16.1 Hz, H-20), 6.25 (dd, 1H, $J_{19,20}$ = 16.1 Hz and $J_{19,18}$ = 5.0 Hz, H-19), 5.64 (s, 1H, H-10 and H-1), 5.32 (d, 1H, $J_{18,19}$ = 5.0 Hz, H-18), 4.62 (s, 1H), 3.83 (d, 1H, $J_{17,17}$ or $J_{8,8}$ =15.6 Hz, H-17 or H-8), 3.00 (d, 1H, $J_{17,17}$ or $J_{8,8}$ =15.6 Hz, H-17 or H-8), 2.73 (complex AB, 2H, H-17 or H-8); ^{13}C-NMR 145.1, 140.7, 140.6, 140.4, 136.0 (C_q, C-21, C-16, C-11, C-7 and C-2), 133.5, 129.2, 128.5, 128.3, 128.0, 127.3, 126.9, 126.8, 126.4, 125.5, 125.4, 125.2, 124.2 (CH, C-26 to C-22, C-15 to C-12, C-6 to C-3), 93.2 (CH, C-18), 83.8, 82.6 (CH, C-10 and C-1), 49.5 (C_q, C-9), 40.8, 39.8 (CH_2, C-17 and C-8); Mass spectrum 366 (3, $M^{+\cdot}$), 234 (84), 217 (100); Exact mass calc'd for $C_{26}H_{22}O_2$: 366.1620. Found: 366.1619.

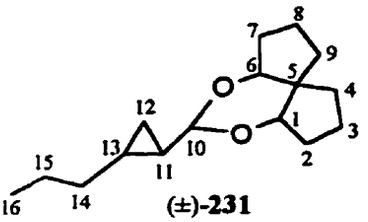
(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol (1*RS*,2*RS*)-(2-Methylcyclopropane)-carbaldehyde Acetal ((±)-231 (R = Me))


(±)-231

(±)-Compound **231** was prepared from (±)-acetal **229** (R= Me (0.0458 g, 0.220 mmol)), $ZnEt_2$ (1.10 mL, 1.0 M in hexane), CH_2I_2 (0.0885 mL, 1.10 mmol) and hexanes (2.4 mL) using general procedure 3. The colourless oil obtained was not purified (0.0483 g, 0.217 mmol, 99% yield). IR 2954, 2857 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR (major diastereomer (53% de) all *R* or all *S* stereocentres), 4.19 (d, 1H, $J_{10,11}$ = 6.0 Hz, H-10), 4.13 (q, 1H, $J_{6,7}$ or $J_{1,2}$ = 7.5 Hz, H-6 or H-1), 3.66 (d, 1H, $J_{6,7}$ or

$J_{1,2}$ = 4.8Hz, H-6 or H-1), 2.18 - 1.17 (m, 12H), 1.06 (d, 3H, $J_{14,13}$ ~ 6 Hz, H-14), 0.88 - 0.69 (m, 2H, H-12), 0.60 - 0.48 (m, 1H, H-13 or H-11), 0.33 - 0.19 (m , 1H, H-13 or H-11); ^{13}C-NMR 97.2 (CH, C-10), 82.3, 79.7 (CH, C-6 and C-1), 49.4 (C_q, C-5), 34.9, 31.5, 28.0, 22.2, 22.1 (CH_2, C-9 to C-7 and C-4 to C-2), 23.3, 18.3 (CH, C-13 and C-11), 9.6 (CH_2, C-12); Mass spectrum 222 (0.2, $M^{+\cdot}$), 221 (3, $[M-H]^+$), 120 (100); Exact mass calc'd for $C_{14}H_{22}O_2$: 222.1620. Found: 222.1598.

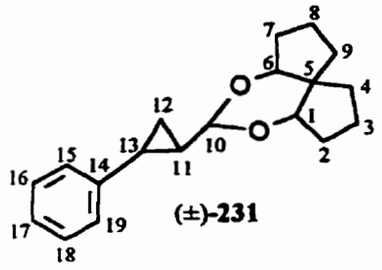
(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol (1*RS*,2*RS*)-(2-*n*-Propylcyclopropane)-carbaldehyde Acetal ((±)-231 (R = *n*-Pr))

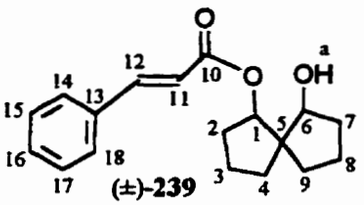


(±)-**231**

(±)-Compound **231** was prepared from (±)-acetal **229** ((R = *n*-Pr), 0.0720 g, 0.305 mmol), $ZnEt_2$ (1.52 mL, 1.0 M in hexane), CH_2I_2 (0.123 mL, 1.52 mmol) and hexanes (3.4 mL) using general procedure 3. Radial plate chromatography (20.:1) provided (±)-**231** as a colourless liquid (0.0651 g, 0.260 mmol) in 85% yield. IR 2956, 2868 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR (major diastereomer (36% de)) 4.22 (d, 1H, $J_{10,11}$ = 5.9 Hz, H -10), 4.13 (t, 1H, $J_{6,7}$ or $J_{1,2}$ = 7.1 Hz, H-6 or H-1), 3.66 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.7 Hz, H-6 or H-1), 2.14 - 1.03 (m, 14H), 0.9 (t, 3H, $J_{16,15}$ = 7.0 Hz, H-16), 0.95 - 0.69 (m, 2H, C-12), 0.61 - 0.51 (m, 1H, H-13 or H-11), 0.48 - 0.23 (m, 1H, H-13 or H-11); ^{13}C-NMR (major diastereomer) 97.1 (C_q, C-10), 82.3, 79.6 (CH, C-6 and C-1), 49.8 (C_q, C-5), 35.5, 35.0, 31.6, 28.1, 22.8, 22.4 (CH_2, C-15, C-14, C-9, C-8, C-7, C-4, C-3 and C-2), 22.0 (CH_3, C-16), 15.0, 13.8 (CH, C-13 and C-11), 8.3 (CH_2, C-12); Mass spectrum 250 (0.2, $M^{+\cdot}$), 249 (2, $[M-H]^+$), 120 (100); Exact mass calc'd for $C_{16}H_{26}O_2$: 250.1933. Found: 250.1937.

(1*RS*,5*RS*,6*RS*)-Spiro[4.4]nonane-1,6-diol (1*RS*,2*RS*)-(2-Phenylcyclopropane)-carbaldehyde Acetal ((±)-231 (R = Ph)) and (1*RS*,5*RS*,6*RS*)-6-Hydroxyspiro[4.4]nonan-1-yl *trans*-Cinnamate ((±)-239)





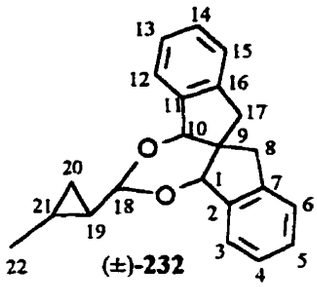
(±)-Compounds **231** and (±)-**239** were prepared from (±)-acetal **229** ((R = Ph), 0.092 g, 0.34 mmol), $ZnEt_2$ (1.70 mL, 1.0 M in hexane), CH_2I_2 (0.274 mL, 3.40 mmol) and hexanes (3.7 mL) using general procedure 3. Radial plate chromatography (20:1 followed by 5:1) provided compounds (±)-**231** (0.0344 g, 0.121 mmol, 36% yield) and (±)-**239** (0.0284 g, 0.100 mmol, 29% yield).

(±)-**231**: IR 3027 (H-C(sp^2)), 2951, 2868 (H-C(sp^3)),1116 (C-O) cm^{-1}; ^{1}H-NMR (major diastereomer (67%)) 7.32 - 7.07 (m, 5H, H-19 to H-15), 4.56 (d, 1H, $J_{10,11}$ = 5.1 Hz, H-10), 4.16 (t, 1H, $J_{6,7}$ or $J_{1,2}$ = 7.3 Hz, H-6 or H-1), 3.73 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.9 Hz, H-6 or H-1), 2.16 - 1.22 (m, 13H), 1.20 -1.09 (m, 1H, C-13 or C-11), 0.98 - 0.86 (m, 2H, C-12); ^{13}C-NMR 128.1, 126.0 (CH, C-19, C-18, C-16, C-15), 125.5 (CH, C-17), 121.3 (C_q, C-14), 95.7 (CH, C-10), 79.7 (CH, C-6 and C-1), 50.0 (C_q, C-5), 35.0, 34.9$_6$, 31.6, 28.2, 22.8, 21.2 (CH_2, C-9 to C-7 and C-4 to C-2), 26.0, 19.3 (CH, C-13 and C-11), 12.1 (CH_2, C-12); Mass spectrum 284 (0.1, $M^{+\cdot}$), 180 (13, $[M-C_8H_8]^+$), 121 (100); Exact mass calc'd for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1773.

(±)-**239**: IR 3587 (H-O), 1705 (C=O) cm^{-1}; ^{1}H-NMR 7.71 (d, 1H, $J_{12,11}$ = 16.0 Hz, H-12), 7.57 - 7.52 (m, 2H), 7.43 - 7.37 (m, 3H), 6.46 (d, 1H, $J_{11,12}$ = 16.0 Hz, H-11), 5.20 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 3.88 (s, 1H, H-6), 3.22 (br. s, 1H, H-a), 2.00 - 1.26 (m, 12H< H-9 to H-7 and C-4 to C-3); ^{13}C-NMR 167.7 (C_q, C-10), 134.3 (C_q, C-13), 145.5, 130.4, 128.9, 128.1, 118.1 (CH, C-18 to C-14, C-12 and C-11), 82.3, 77.5 (CH, C-6 and C-1), 61.0 (C_q, C-5), 32.4, 32.3, 32.1, 32.5, 20.7, 20.5 (CH_2, C-9 to C-7 and C-4 to C-2); Mass

spectrum 286 (0.1, $M^{+\cdot}$), 13 (100, $[PhCH{=}CH{-}CO]^{+}$), 121 (91, $[C_9H_{12}]^{+}$); Exact mass calc'd for $C_{18}H_{22}O_3$: 286.1570. Found: 286.1577.

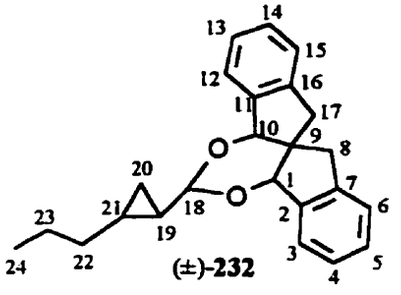
(1*RS*,1'*RS*,2*RS*)-2,2'-Spirobiindane-1,1'-diol (1*RS*,2*RS*)-(2-Methylcyclopropane)-carbaldehyde Acetal ((±)-232 (R = Me))



(±)-**232**

(±)-Compound **232** was prepared using general procedure 3 with (±)-acetal **230** ((R = Me), 0.0493 g, 0.162 mmol), $ZnEt_2$ (0.810 mL, 1.0 M in hexane), CH_2I_2 (0.0652 mL, 0.810 mmol) and hexanes (1.8 mL). The product was purified by radial chromatography ($CHCl_3$, 20:1) and provided compound **232** (0.0442 g, 0.138 mmol) as a colourless oil in 86% yield. IR 3071, 3024 (H-C(sp^2)), 2898, 2866 (H-C(sp^3)), 1085 (C-O) cm^{-1}; ^{1}H-NMR 7.57 - 7.13 (m, 8H, H-15 to H-12 and H-6 to H-3), 5.54 (s, 1H, H-10 or H-1), 4.15 (d, 1H, $J_{18,19}$ = 6.3 Hz, H-18), 3.79 (d, 1H, J_{gem} = 15.6 Hz, H-17 or H-8), 2.94 (d, 1H, J_{gem} = 15.6 Hz, H-17 or H-8), 2.66 (complex AB, 2H, H-17 or H-8), 1.10 (d, 3H, $J_{22,21}$ = 5.8 Hz, H-22), 0.95 - 0.77 (m, 2H, H-20), 0.61 - 0.50 (m, 1H, H-21 or H-19), 0.38 - 0.24 (m, 1H, H-21 or H-19); ^{13}C-NMR 145.1, 141.1, 140.7, 140.6 (C_q, C-16, C-11, C-7 and C-2), 129.0, 128.3, 127.2, 126.8, 126.5, 125.4, 125.2, 124.0 (CH, C-15 to C-12 and C-6 to C-3), 96.7 (CH, C-18), 83.9, 82.3 (CH, C-10 and C-1), 49.5 (Cq, C-9), 40.8, 39.8 (CH, C-17 and C-8), 23.0, 9.6 (CH, C-21 and C-19), 18.3 (CH_3, C-22), 10.1 (CH_2, C-20); Mass spectrum 318 (1, $M^{+\cdot}$), 317 (3, $[M-H]^{+}$), 263 (12, $[M-C_4H_7]^{+}$), 218 (100), 217 (100), 118 (89); Exact mass calc'd for $C_{22}H_{22}O_2$: 318.1620. Found: 318.1590.

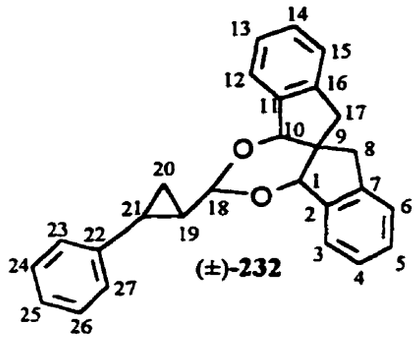
(1*RS*,1'*RS*,2*RS*)-2,2'-Spirobiindane-1,1'-diol (1*RS*,2*RS*)-(2-*n*-Propylcyclopropane)-carbaldehyde Acetal ((±)-232 (R = *n*-Pr))



(±)-**232**

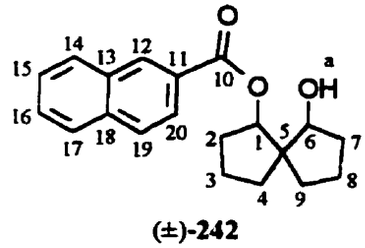
(±)-Compound **232** was prepared using general procedure 3 with (±)-acetal **230** ((R = *n*-Pr), 0.050 g, 0.150 mmol), $ZnEt_2$ (0.925 mL, 1.0 M in hexane), CH_2I_2 (0.149 mL, 1.85 mmol) and hexanes (2.04 mL). The product was purified by radial chromatography ($CHCl_3$, 20:1) which provided compound **232** (0.0383 g, 0.1105 mmol) as a viscous colourless oil in 74% yield. IR 3024 (H-C(sp^2)), 2922 (H-C(sp^3)), 1085 (C-O) cm^{-1}; ^{1}H-NMR 7.47 - 7.11 (m, 8H), 5.53 (s, 1H, H-10 or H-1), 4.41 (s, 1H, H-10 or H-1), 4.11 (d, 1H, $J_{18,19}$ = 5.6 Hz, H-18), 3.78 (d, 1H, J_{gem} = 15.6 Hz, H-17 or H-8), 2.93 (d, 1H, J_{gem} = 15.6 Hz, H-17 or H-8), 2.66 (complex AB, 2H, H-17 or H-8), 1.48 - 1.07 (m, 5H), 0.95 (t, 3H, $J_{24,23}$ = 7.4 Hz, H-24), 0.92 - 0.70 (m, 2H, H-21, H-20 and/or H-19), 0.55 - 0.46 (m, 1H, H-21, H-20 and/or H-19), 0.37 - 0.26 (m, 1H, H-21, H-20 and/or H-19); ^{13}C-NMR 145.2, 141.2, 140.7, 140.6 (C_q, C-16, C-11, C-7 and C-2), 129.0, 128.3, 127.2, 126.8, 126.5, 125.4, 125.1, 124.0 (CH, C-15 to C-12 and C-6 to C-3), 97.0 (CH, C-18), 84.0, 82.3 (CH, C-10 and C-1), 49.5 (C_q, C-9), 40.8, 39.9, 35.5, 22.5 (CH_2, C-23, C-22, C-17 and C-8), 21.8, 15.5 (CH, C-21 and C-19), 13.9 (CH_3, C-24), 8.8 (CH_2, C-20); Mass spectrum 345 (0.2, $[M-H]^+$), 217 (100); Exact mass calc'd for $C_{24}H_{26}O_2$: 346.1933. Found: 346.1910.

(1*RS*,1'*RS*,2*RS*)-2,2'-Spirobiindane-1,1'-diol (1*RS*,2*RS*)-(2-Phenylcyclopropane)-carbaldehyde Acetal ((±)-232 (R = Ph))



(±)-Compound **232** was prepared using general procedure 3 with (±)-acetal **230** (0.0694 g, 0.189 mmol), $ZnEt_2$ (1.28 mL, 1.0 M in hexane), CH_2I_2 (0.207 mL, 2.57 mmol) and hexanes (2.8 mL). The product was purified by radial chromatography ($CHCl_3$, 20:1) provided compound **232** (0.0542 g, 0.142 mmol), which was a colourless liquid, in 75% yield. IR 3073, 3025 (H-C(sp^2)), 2896 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 7.56 - 7.08 (m, 13H, H-27 to H-23, H-15 to H-12 and H-6 to H-3), 5.59 (s, 1H, H-10 or H-1), 4.52 (s, 1H, H-10 or H-1), 4.50 (d, 1H, $J_{18.19}$ = 5.7 Hz, H-18), 3.44 (d, 1H, J_{gem} = 15.6 Hz, 1H-17 or 1H-8), 2.98 (d, 1H, J_{gem} = 15.6 Hz, 1H-17 or 1H-8), 2.71 (complex AB, 1H, H-17 or H-8), 2.09 - 1.99 (m, 1H, H-21, 1H-20 or H-19), 1.66 - 1.54 (m, 1H, H-21, 1H-20 or H-19), 1.21 - 1.02 (m, 1H, H-21, 1H-20 or H-19), 1.01 - 0.91 (m, 1H, H-21, 1H-20 or H-19); ^{13}C-NMR 145.1, 142.2, 141.0, 140.6_3, 140.5_8 (C_q, C-22, C-16, C-11, C-7 or C-2), 129.1, 128.4, 128.2, 127.2, 126.8, 126.5, 126.1, 125.6, 125.5, 125.1, 124.0 (CH, C-27 to C-23, C-15 to C-12 and C-6 to C-3), 95.4 (C_q, C-18), 83.9, 82.3 (CH, C-10 and C-1), 49.6 (C_q, C-9), 40.8, 39.8 (CH_2, C-17 and C-7), 25.6, 19.8 (CH, C-21 and C-19), 12.2 (CH_2, C-20); Mass spectrum 380 (0.7, $M^{+\cdot}$), 362 (1, $[M-H_2O]^+$), 218 (100); Exact mass calc'd for $C_{27}H_{24}O_2$: 380.1776. Found: 380.1784.

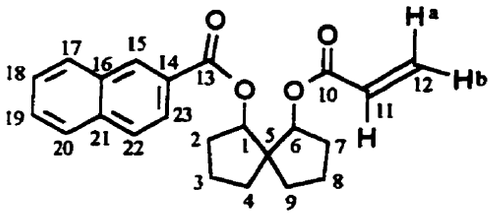
(1*RS*,5*RS*,6*RS*)-6-Hydroxyspiro[4.4]nonan-1-yl 2-Naphthoate ((±)-242)



Esterification of (±)-diol **106** (0.260 g, 1.66 mmol) was performed using general procedure 4 with 2-naphthoyl chloride (0.317 g, 1.66 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided compound (±)-**242** (0.505 g, 0.163 mmol) as a white solid in 98% yield. mp 77.2 - 78.0°C; IR 3479 (H-O), 3063 (H-C(sp^2)), 2958 (H-C(sp^3)), 1783

(C=O) cm^{-1}; ^{1}H-NMR 8.59 (s, 1H, H-12), 8.04 (d, 1H, J = 8.7 Hz, H-20, H-19, H-17 or H-14), 7.96 (d, 1H, J = 8.2 Hz, H-20, H-19, H-17 or H-14), 7.88 (d, 2H, J = 8.7 Hz, H-20, H-19, H-17 and/or H-14), 7.64 - 7.51 (m, H, H-16 and H-15), 5.38 (s, 1H, H-1), 3.98 (s, 1H, H-6), 3.20 (br. s, 1H, H-a), 2.15 - 1.62 (m, 10H), 1.53 - 1.46 (m, 2H); ^{13}C-NMR 167.0 (C_q, C-10), 135.3, 132.1, 127.2 (C_q, C-18, C-13 and C-11), 130.9, 129.0, 128.0, 127.9, 127.5, 126.4, 124.9 (CH, C-20, C-19, C-17 to C-14 and C-12), 82.6, 77.2 (CH, C-6 and C-1), 60.8 (C_q, C-5), 2x32.2, 31.8, 31.3, 20.5, 20.3 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 310 (4, $M^{+\cdot}$), 172 (100, $[C_{11}H_8O_2]^+$), 155 (90, [2-Np-C=O]$^+$); Exact mass calc'd for $C_{20}H_{22}O_3$: 310.1569. Found: 310.1602.

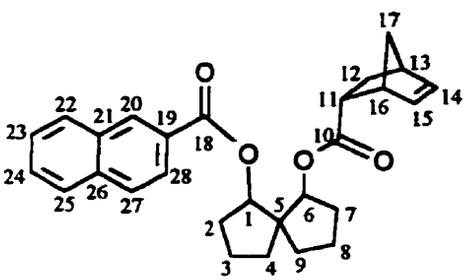
(1*RS*,5*RS*,6*RS*)-6-Acryloxy-1-(2-naphthylcarbonyloxy)spiro[4.4]nonane ((±)-243)



(±)-**243**

Esterification of (±)-**242** (0.225 g, 0.725 mmol) was performed using general procedure 4 with acryloyl chloride (0.118 mL, 1.45 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided compound (±)-**243** (0.186 g, 0.510 mmol) as a white solid in 70% yield. mp 84 - 85°C; IR 3054 (H-C(sp^2)), 2966 (H-C(sp^3)), 1719 (C=O) cm^{-1}; ^{1}H-NMR 8.48 (s, 1H, H-15), 7.95 (d, 2H, J = 8.6 Hz), 7.88 - 7.82 (m, 2H), 7.62 - 7.48 (m, 2H), 6.10 (dd, 1H, $J_{12a,11}$ = 17.3 Hz and J_{gem} = 1.8 Hz, H-a), 5.88 (dd, 1H, $J_{11,12a}$ = 17.3 Hz and $J_{11,12b}$ = 10.1 Hz, H-11), 5.57 (dd, 1H, $J_{12b,11}$ = 10.1 Hz and J_{gem} = 1.8 Hz, H-b), 5.41 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.9 Hz, H-6 or H-1), 5.36 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.1 Hz, H-6 or H-1), 2.13 - 1.75 (m, 10H), 1.75 - 1.52 (m, 2H); ^{13}C-NMR 166.0, 165.4 (C_q, C-13 and C-10), 135.4, 132.5, 127.9 (C_q, C-21, C-16 and C-14), 130.1 (CH_2, C-12), 130.8, 129.4, 128.5, 128.0_1, 127.9_8, 127.7, 126.4, 125.1 (CH, C-23, C-22, C-20 to C-17 and C-11), 82.1, 81.6 (CH, C-6 and C-1), 58.3 (C_q, C-5), 34.0, 33.8, 31.9, 31.8, 21.1_2, 21.0_6 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 364 (28, $M^{+\cdot}$), 292 (0.4, [M-$HO_2CCH{=}CH_2$]$^+$), 226 (30), 155 (100, [2-Np-C=O]$^+$), 55 (35, [$H_2C{=}CH{-}C{=}O$]$^+$); Exact mass calc'd for $C_{23}H_{24}O_4$: 364.1675. Found: 364.1654.

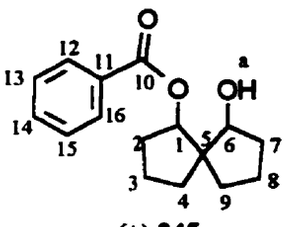
(1*RS*,5*RS*,6*RS*)-1-(2-Naphthylcarbonyloxy)-6-(5-norbornenyl-*endo*-2-carbonyloxy)-spiro[4.4]nonane ((±)-244)



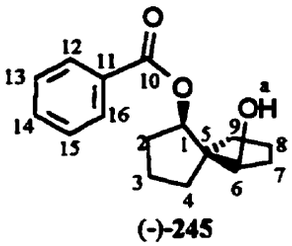
(±)-244

Compound (±)-**243** (0.1022g , 0.2804 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 9:1) provided a 79% yield (79% de) of (±)-**244** (0.0951 g, 0.2209 mmol), which was a light yellow oil that crystallised on standing, forming a white solid. mp 118 - 120°C; IR 3069 (H-C(sp^2)), 2949, 2865 (H-C(sp^3)), 1714 (C=O) cm^{-1}; ^{1}H-NMR (major diastereomer) 8.53 (s, 1H, H-20), 8.00 (d, 1H, J = 8.5 Hz, H-28, H-27, H-25 or H-22), 7.96 (d, 1H, J = 8.1 Hz, H-28, H-27, H-25 or H-22), 7.87 (d, 2H, J = 8.5 Hz, H-28, H-27, H-25 or H-22), 7.59 - 7.51 (m, 2H, H-24 and H-23), 5.88 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.1 Hz, H-15 or H-14), 5.40 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 2.8 Hz, H-15 or H-14), 5.35 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.9 Hz, H-6 or H-1), 5.19 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.3 Hz, H-6 or H-1), 2.94 (br. s, 1H, H-16), 2.73 - 2.69 (m, 2H, H-11 and H-13), 2.09 - 1.63 (m, 10H), 1.61 - 1.52 (m, 3H), 1.26 (d, 1H, J = 7.8 Hz), 1.22 - 1.18 (m, 1H), 1.11 (d, 1H, J = 8.2 Hz); ^{13}C-NMR (major diastereomer) 174.0 (C_q, C-10), 166.0 (C_q, C-18), 135.4, 132.4, 127.9 (C_q, C-26, C-21 and C-14), 137.1, 132.0, 130.5, 129.4, 128.1$_0$, 128.0$_6$, 127.6, 126.5, 125.1 (CH, C-28, C-27, C-25 to C-22, C-20, C-15 and C-14), 82.2, 81.1 (CH, C-6 and C-1), 57.9 (C_q, C-5), 45.8, 43.3, 42.3, (CH, C-16, C-13 and C-11), 49.6, 33.6, 33.5, 31.7, 29.3, 20.8, 20.7 (CH_2, C- 17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 364 (5, $[M-C_5H_6]^+$, retroDiels-Alder), 155 (100, $[2\text{-Np-C=O}]^+$), 127 (78, $[Np]^+$), 55 (46, $[O{=}CCH{=}CH_2]^+$); Exact mass calc'd for $C_{28}H_{30}O_4$: 430.2144. Found: 430.2168.

(1*RS*,5*RS*,6*RS*)- and (1*R*,5*R*,6*R*)-6-Hydroxyspiro[4.4]nonan-1-yl Benzoate ((±)- and (-)-245)



(±)-245



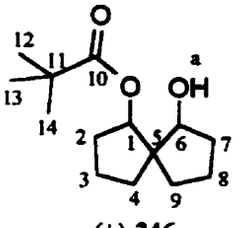
(-)-245

Esterification of diol **106** (0.2392 g, 1.53 mmol) was performed using general procedure 4 with benzoyl chloride (0.187 mL, 1.61 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided compound **245** (0.375 g, 1.44 mmol) as a colourless oil in 93% yield.

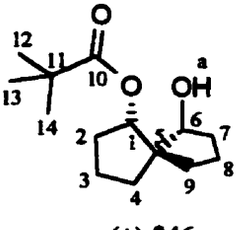
(±)-**245** bp 119 -126°C (air heat)/ 0.07 Torr; IR 3486 (H-O), 1717 (C=O) cm^{-1}; ^{1}H-NMR 8.04 (d, 2H, $J_{16,15}$ and $J_{11,12}$ = 7.5 Hz, H-16 and H-11), 7.58 (t, 1H, $J_{14,15}$ and $J_{14,13}$ = 7.5 Hz, H-14), 7.46 (t, 2H, $J_{15,16}$ and $J_{15,14}$ and $J_{13,14}$ and $J_{13,12}$ = 7.5 Hz, H-15 and H-13), 5.32 (s, 1H, H-1), 3.92 (s, 1H, H-6), 3.06 (br. s, 1H, H-a), 2.03 - 1.55 (m, 10H), 1.51 - 1.33 (m, 2H); ^{13}C-NMR 167.0 (C_q, C-10), 133.0 (CH, C-14), 130.2 (C_q, C-11), 129.5, 128.3 (CH, C-16, C-15, C-13 and C-12), 82.7, 77.4 (CH, C-6 and C-1), 60.9 (C_q, C-5), 32.3_4, 32.2_9, 31.9, 31.4, 20.7, 20.4 (CH, C-9 to C-7 and C-4 to C-2); Mass spectrum 242 (0.8, $[M-H_2O]^+$), 155 (2, $[M-C_7H_5O]^+$), 105 (100, $[PhC{=}O]^+$); Exact mass calc'd for $C_{16}H_{18}O_2$ ($C_{16}H_{20}O_3$ - H_2O): 242.1307. Found: 242.1306.

(-)-**245** ^{1}H-NMR, ^{13}C-NMR and mass spectrum corresponded to those for (±)-**245**. Optical rotation obtained was $[\alpha]_D^{25.5}$ -76.4 (c 15.77, 0.1 dm, $CHCl_3$).

(1*RS*,5*RS*,6*RS*)- and (1*S*,5*S*,6*S*)-6-Hydroxyspiro[4.4]nonan-1-yl Pivalate ((±)-and (+)-246)



(±)-246



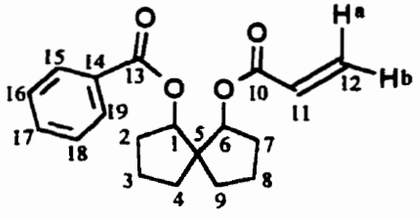
(+)-246

Esterification of diol **106** (0.2215 g, 1.418 mmol) was performed using general procedure 4 with pivaloyl chloride (0.227 mL, 1.84 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided compound **246** (0.314 g, 1.31 mmol) as a colourless oil in 92% yield.

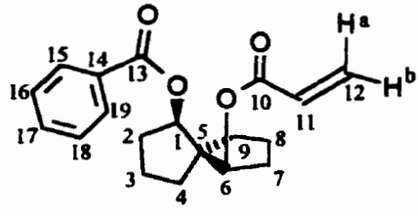
(±)-246 IR 3471 (H-O), 2963 (H-C(sp^3)), 1726, 1706 (C=O) cm^{-1}; ^{1}H-NMR 5.01 (s, 1H, H-1), 3.77 (s, 1H, H-6), 3.40 (br. s, 1H, H-a), 1.93 - 1.61 (m, 10H,), 1.56 - 1.22 (m, 2H), 1.19 (s, 9H, H-14, H-13 and H-12); ^{13}C-NMR 81.7, 77.4 (CH, C-6 and C-1), 60.9 (C_q, C-5), 38.9 (C_q, C-11), 2x32.2, 31.9, 31.2, 20.6, 20.4 (CH_2, C-9, C-8, C-7, C-4, C-3 and C-2), 27.1 (CH_3, C-14, C-13, and C-12); Mass spectrum 121 (40, $[C_9H_{13}]^+$), 57 (100, $[Me_3C]^+$), 41 (78, $[C_3H_5]^+$).

(-)-246 ^{1}H-NMR, ^{13}C-NMR and mass spectrum corresponded to those for **(±)-246**. Optical rotation obtained was $[\alpha]_D^{25}$ +39.3 (c 2.66, 0.1 dm, $CHCl_3$).

(1*RS*,5*RS*,6*RS*)- and (1*R*,5*R*,6*R*)-6-Acryloxy-1-(phenylcarbonyloxy)spiro[4.4]nonane ((±)- and (-)-247)



(±)-247

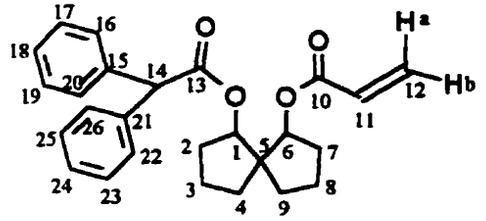


(-)-247

Esterification of **245** (0.0988 g, 0.380 mmol) was performed using general procedure 4 with acryloyl chloride (0.062 mL, 0.759 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 9:1) which provided compound **247** (0.100 g, 0.319 mmol) as a colorless oil in 84% yield. IR 1721 (C=O), 1277 (C-O) cm^{-1}; ^{1}H-NMR 7.90 (d, 2H, $J_{19,18}$ and $J_{15,16}$ = 7.0 Hz, H-19 and H-15), 7.45 - 7.52 (m, 1H, H-17), 7.37 (t, 2H, $J_{18,19}$ and $J_{16,15}$ and $J_{18,17}$ and $J_{16,17}$ = 7.0 Hz, H-18 and H-14), 6.11 (dd, 1H, $J_{12a,11}$ = 17.3 Hz and J_{gem} = 1.7 Hz, H-a), 5.87 (dd, 1H, $J_{11,12a}$ = 17.3 Hz and $J_{11,12b}$ = 10.2 Hz, H-11), 5.58 (dd, 1H, $J_{12b,11}$ = 10.1 Hz and J_{gem} = 1.7 Hz, H-b), 5.33 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.8 Hz, H-6 or H-1), 4.05 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.1 Hz, H-6 or H-1), 2.10 - 1.68 (m, 10H), 1.68 - 1.47 (m, 2H); ^{13}C-NMR 165.7, 165.2 (C_q, C-13 and C-10), 130.0 (CH_2, C-12), 130.5 (C_q, C-14), 132.6, 129.3, 128.4, 128.1 (CH, C-19 to C-15), 81.8, 81.4 (CH, C-6 and C-1), 58.1 (C_q, C-5), 33.7, 33.6, 2x31.7, 2x20.9 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 314 (0.6, M^+), 242 (19, $[M\text{-}HO_2CCH{=}CH_2]^+$), 105 (100, $[PhCO]^+$); Analysis

calc'd for $C_{19}H_{22}O_4$: C, 72.59%; H, 7.05%. Found: C, 72.07%; H, 7.00%. Exact mass calc'd for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1549.

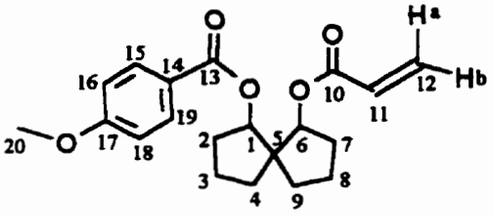
(1*RS*,5*RS*,6*RS*)-6-Acryloxy-1-(diphenylacetoxy)spiro[4.4]nonane ((±)-248)



(±)-**248**

(±)-Compound **248** was formed in two steps. First, (±)-diol **106** (0.1235 g, 0.791 mmol) was esterified with diphenylacetyl chloride (0.238 g, 1.03 mmol) according to general procedure 4. The product was purified (0.213 g, 0.608 mmol, 77% yield) by radial plate chromatography ($CHCl_3$, 5:1) and immediately reacted (step 2) with acryloyl chloride (0.141 mL, 1.22 mmol) according to general procedure 4. The diester was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided compound (±)-**248** (0.186 g, 0.510 mmol) as a white solid in 80% yield (62% overall yield). mp 84.7 - 85.4°C; IR 3062, 3029 (H-C(sp^2)), 2950 (H-C(sp^3)), 1730, 1726 (C=O) cm^{-1}; ^{1}H-NMR 7.32 - 7.21 (m, 10H, H-26 to H-22 and H-20 to H-16), 6.22 (dd, 1H, $J_{12a,11}$ = 17.2 Hz and J_{gem} = 1.7 Hz, H-a), 5.91 (dd, 1H, $J_{11,12a}$ = 17.3 Hz and $J_{11,12b}$ = 10.3 Hz, H-11), 5.64 (dd, 1H, $J_{12b,11}$ = 10.3 Hz and J_{gem} = 1.7 Hz, H-b), 5.17 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.8 Hz, H-6 or H-1), 4.98 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.4 Hz, H-6 or H-1), 4.92 (s, 1H, H-14), 1.94 - 1.59 (m, 10H), 1.59 - 1.40 (m, 2H); ^{13}C-NMR 171.3 (C_q, C-13), 165.0 (C_q, C-10), 138.6, 138.5 (C_q, C-21 and C-15), 123.0 (CH_2, C-12), 128.6, 128.4, 128.1 (CH, C-26, C-25, C-23, C-22, C-20, C-19, C-17 and C-16), 126.8_4, 126.8_0 (CH, C-24 and C-18), 81.7, 81.2 (CH, C-6 and C-1), 57.7 (C_q, C-5), 33.2, 32.9, 31.3, 31.2, 20.6, 21.4 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 404 (1, M^+), 332 (8, [M-$HO_2CCH{=}CH_2$]$^+$), 194 (75), 167 (96), 121 (100, [C_9H_{13}]$^+$), 55 (88, [$H_2C{=}CH{-}C{=}O$]$^+$); Exact mass calc'd for $C_{26}H_{28}O_4$: 404.1988. Found: 404.2023.

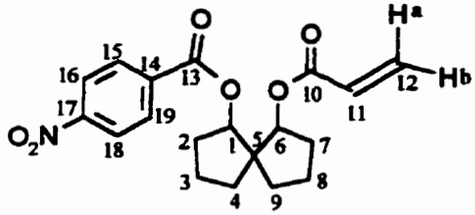
(1*RS*,5*RS*,6*RS*)-6-Acryloxy-1-(*p*-methoxyphenylcarbonyloxy)spiro[4.4]nonane ((±)-249)



(±)-249

(±)-Compound **249** was formed in two steps. First, (±)-diol **106** (0.3195 g, 2.045 mmol) was esterified with *p*-methoxybenzoyl chloride (0.384 g, 2.25 mmol) according to general procedure 4. The product was purified (0.4854 g, 1.672 mmol, 82% yield) by radial plate chromatography ($CHCl_3$, 5:1) and a portion of it was immediately reacted (0.2200 g, 0.758 mmol) with acryloyl chloride (0.176 mL, 1.52 mmol) according to general procedure 4 (step 2). The crude diester was purified by radial plate chromatography ($CHCl_3$, 5:1) provided compound (±)-**249** (0.1348 g, 0.392 mmol) as a colourless oil in 52% yield (43% overall yield). IR 2953 (H-C(sp^3)), 1720, 1711 (C=O), 1279, 1257 (C-O) cm^{-1}; ^{1}H-NMR 7.86 (d, 2H, $J_{19,18}$ and $J_{16,15}$ = 9.0 Hz, H-19 and H-15), 6.86 (d, 2H, $J_{18,19}$ and $J_{16,15}$ = 9.0 Hz, H- 18 and H-16), 6.12 (dd, 1H, $J_{12a,11}$ = 17.2 Hz and J_{gem} = 1.8 Hz, H-a), 5.88 (dd, 1H, $J_{11,12a}$ = 17.2 Hz and $J_{11,12b}$ = 10.2 Hz, H-11), 5.66 (dd, 1H, $J_{12b,11}$ = 10.2 Hz and J_{gem} = 1.8 Hz, H-b), 5.29 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.8 Hz, H-6 or H-1), 5.25 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.1 Hz, H-6 or H-1), 3.83 (s, 3H, H-20), 2.03 - 1.74 (m, 10H), 1.74 - 1.54 (m, 2H); ^{13}C-NMR 165.4, 165.2, 163.1 (C_q, C-17, C-13and C-10), 129.8 (CH_2, C-12), 131.3 (CH, C-11), 128.5 (CH, C-19 and C-15 or C-18 and C-16), 123.0 (C_q, C-14), 113.4 (CH, C-19 and C-15 or C-18 and C-16), 2×81.4 (CH, C-6 and C-1), 58.1 (C_q, C-5), 55.2 (CH_3, C-20), 33.8, 33.7, 31.7_0, 31.6_7, 2×21.0 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 344 (27, M^+), 272 (4, $[M\text{-}HO_2CCH{=}CH_2]^+$), 135 (100, $[MeOPh\text{-}C{=}O]^+$), 120 (85, $[C_9H_{12}]^+$), 55 (69, $[H_2C{=}CH\text{-}C{=}O]^+$); Exact mass calc'd for $C_{20}H_{24}O_5$: 344.1624. Found: 344.1640.

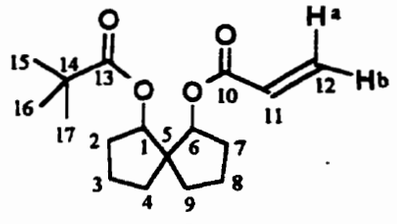
(1*RS*,5*RS*,6*RS*)-6-Acryloxy-1-(*p*-nitrophenylcarbonyloxy)spiro[4.4]nonane ((±)-250)



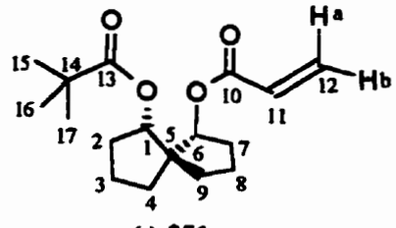
(±)-250

(±)-Compound **250** was formed in two steps. First, (±)-diol **106** (0.2114 g, 1.35 mmol) was esterified with *p*-nitrobenzoyl chloride (0.264 g, 1.42 mmol) according to general procedure 4. The product was purified by radial plate chromatography ($CHCl_3$, 3:1) and the second reaction was with acryloyl chloride (0.340 mL, 2.93 mmol) according to general procedure 4. The crude diester was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided compound (±)-**250** (0.4167 g, 1.16 mmol) as a white solid in 86% overall yield. mp 90.0 - 90.7°C; IR 1722 (C=O), 1517 (NO_2 asymmetric) 1348 (NO_2 symmetric) cm^{-1}; ^{1}H-NMR 8.25 (d, 2H, $J_{18,19}$ and $J_{16,15}$ = 9.0 Hz, H- 18 and H-16), 8.08 (d, 2H, $J_{19,18}$ and $J_{16,15}$ = 9.0 Hz, H-19 and H-15), 6.12 (dd, 1H, $J_{12a,11}$ = 17.2 Hz and J_{gem} = 1.8 Hz, H-a), 5.88 (dd, 1H, $J_{11,12a}$ = 17.2 Hz and $J_{11,12b}$ = 10.2 Hz, H-11), 5.63 (dd, 1H, $J_{12b,11}$ = 10.2 Hz and J_{gem} = 1.8 Hz, H-b), 5.37 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.0 Hz, H-6 or H-1), 5.29 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.1 Hz, H-6 or H-1), 2.11 - 1.70 (m, 10H), 1.70 - 1.53 (m, 2H); ^{13}C-NMR 165.1, 163.8, (C_q, C-13 and C-10), 150.3 (C_q, C-17), 135.8 (C_q, C-14), 130.3 (CH_2, C-12), 130.4, 123.3 (CH, C-19, C-18, C-16 and C-15), 128.3 (CH, C-11), 83.0, 81.1 (CH, C-6 and C-1), 58.3 (C_q, C-5), 33.7, 33.6, 31.7, 31.6, 2×21.0 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 150 (33, $[O_2NPhC{=}O]^+$), 120 (67, $[C_9H_{12}]^+$), 55 (100, $[H_2C{=}CH\text{-}C{=}O]^+$); Analysis calc'd for $C_{19}H_{21}NO_6$: C, 63.50%; H, 5.89%; N, 3.90%. Found: C, 63.38%; H, 5.59%; N 4.27%.

(1*RS*,5*RS*,6*RS*)- and (1*S*,5*S*,6*S*)-6-Acryloxy-1-(pivaloxy)spiro[4.4]nonane (251)



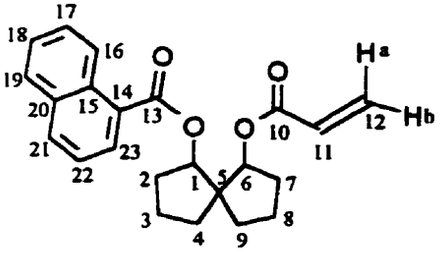
(±)-251



(-)-251

Compound **251** was prepared by reacting diol **106** (0.0900 g, 0.374 mmol) with acryloyl chloride (0.061 mL, 0.749 mmol) using general procedure 4. Purification of **251** by radial plate chromatography ($CHCl_3$, 20:1) provided a white solid in 76% yield (0.0839 g, 0.273 mmol). mp 36 - 37°C; IR 1728 (C=O(ester)) cm^{-1}; ^1H NMR 6.30 (dd, 1H, $J_{12a,11}$ = 17.2 Hz and J_{gem} = 1.8 Hz, H-a), 6.02 (dd, 1H, $J_{11,12a}$ = 17.2 Hz and $J_{11,12b}$ = 10.3 Hz, H-11), 5.75 (dd, 1H, $J_{12b,11}$ = 10.3 Hz and J_{gem} = 1.8 Hz, H-b), 5.07 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.7 Hz), 5.04 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.9 Hz), 1.9 - 1.4 (m, 14H), 1.08 (s, 9H, H-17, H-16 and H-15); ^{13}C-NMR 177.4 (C_q, C-13), 165.4 (C_q, C-10), 130.3 (CH_2, C-12), 128.9 (CH, C-11), 81.8, 80.7 (CH, C-6 and C-1), 57.9 (C_q, C-5), 38.7 (C_q, C-14), 33.4, 33.3, 2×31.5, 2×20.8 (CH, C-9 to C-7 and C-4 to C-2), 27.1 (CH_3, C-17, C-16 and C-15); Mass spectrum 121 (63, $[C_9H_{13}]^+$), 55 (100, $[H_2C{=}CHCO]^+$); Analysis calc'd for $C_{17}H_{26}O_4$: C, 69.36%; H, 8.90%. Found: C, 69.78%; H, 8.79%.

(1*R*,5*R*,6*R*)-6-Acryloxy-1-(1-naphthylcarbonyloxy)spiro[4.4]nonane (252)

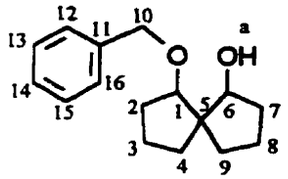


252

Compound **252** was formed in two reactions. First, (-)-diol **106** (0.2348 g, 1.50 mmol) was esterified with 1-naphthoyl chloride (0.3008 g, 1.578 mmol) according to general procedure 4. The monoester was purified (0.4254g, 1.371 mmol, 91% yield) by radial plate chromatography ($CHCl_3$, 5:1) and the second reaction was with acryloyl chloride (0.223 mL, 2.74 mmol) according to general procedure 4. The crude diester was purified by radial plate chromatography ($CHCl_3$, 9:1) which provided compound **252** (0.3727 g, 1.023 mmol) as a colourless oil in 75% yield (68% overall yield). IR 3051 (H-C(sp^2)), 2891, 2968 (H-C(sp^3)), 1711 (C=O) cm^{-1}; ^1H-NMR 8.84 (d, 1H, J = 8.5 Hz, H-23, H-21, H-19 or H-16), 8.02 (d, 1H, J = 7.2 Hz, H-23, H-21, H-19 or H-16), 7.97 (d, 1H, J = 8.2 Hz, H-23, H-21, H-19 or H-16), 7.85 (d, 1H, J = 7.8 Hz, H-23, H-21, H-19 or H-16), 7.63 - 7.44 (m, 4H, H-23, H-22, H-18 and H-17), 6.22 (dd, 1H, $J_{12a,11}$ = 17.3 Hz and J_{gem} = 1.8 Hz, H-a), 5.98 (dd, 1H, $J_{11,12a}$ = 17.3 Hz and $J_{11,12b}$ = 10.1 Hz, H-11), 5.63 (dd, 1H, $J_{12b,11}$ = 10.1 Hz and J_{gem} = 1.8 Hz,

H-b), 5.51 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.5 Hz, H-6 or H-1), 5.30 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.9 Hz, H-6 or H-1), 2.09 - 1.78 (m, 10H), 1.76 - 1.52 (m, 2H); ^{13}C-NMR 166.6, 165.4 (C_q, C-13 and C-10), 133.6, 131.2, 127.5 (C_q, C-20, C-15 and C-14), 130.2 (CH_2, C-12), 132.9, 129.6. 128.5, 128.3, 127.3, 125.9, 125.6, 124.4 (CH, C-23, C-22, C-21, C-19, C-18, C-17, C-16, C-11), 81.7, 81.6 (CH, C-6 and C-1), 58.1 (C_q, C-5), 33.6, 33.5, 31.8, 31.6, 2×20.8 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 364 (15, $M^{+\cdot}$), 226 (12), 155 (100, [1-Np-C=O]$^+$), 127 (99, [Np]$^+$), 55 (65, [H_2C=CH-C=O]$^+$); Exact mass calc'd for $C_{23}H_{24}O_4$: 364.1675. Found: 364.1676.

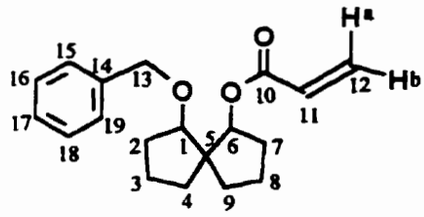
(1*RS*,5*RS*,6*RS*)-1-(Benzyloxy)spiro[4.4]nonan-6-ol ((±)-253)



(±)-**253**

(±)-Diol **106** (0.124 g, 0.792 mmol) was dissolved in THF (5 mL) in a one-necked round bottomed flask and cooled to 0°C. Sodium hydride (0.033 g (60% dispersion), 0.83 mmol) was added followed after 5 min. by benzyl bromide (0.099 mL, 0.832 mmol) and the reaction was warmed to rt overnight. The disappearance of diol **106** was monitored by TLC and the reaction was quenched by addition of water. The mixture was extracted with CH_2Cl_2 and the organic layer dried over Na_2SO_4. The CH_2Cl_2 layer was filtered and the CH_2Cl_2 removed *in vacuo*. The product was purified by radial plate chromatography ($CHCl_3$, 5:1) which provided an 89% yield of (±)-ether **253** (0.174 g, 0.705 mmol), which was as a colourless oil. IR 3488 (H-O), 3029 (H-C(sp^2)), 2929 (H-C(sp^3)) cm^{-1}; ^{1}H-NMR 7.34 (s, 5H, H-16 to H-12), 4.64 (d, 1H, J_{gem} = 11.8 Hz, 1H-10), 4.34 (d, 1H, J_{gem} = 11.8 Hz, 1H-10), 4.09 (br. s, 1H, H-6), 3.90 (t, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 1.92 - 1.53 (m, 10H), 1.40 - 1.26 (m, 2H); ^{13}C-NMR 138.0 (C_q, C-11), 128.4, 127.5 (CH, C-16, C-15, C-13 and C-12), 127.7 (CH, C-14), 86.9, 79.0 (CH, C-6 and C-1), 70.4 (CH_2, C-10), 58.3 (C_q, C-5), 34.5, 34.4, 32.4, 29.7, 21.4, 20.8 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 228 (1, [M-H_2O]$^+$), 91 (100, [C_7H_7]$^+$); Analysis calc'd for $C_{16}H_{22}O_2$: C, 78.01%; H, 9.00%. Found: C, 77.68%; H, 8.79%.

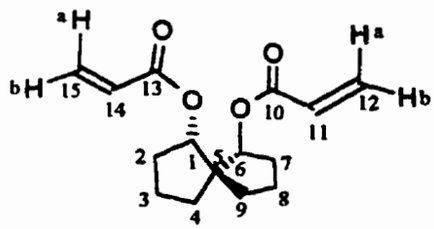
(1*RS*,5*RS*,6*RS*)-1-Acryloxy-6-(benzyloxy)spiro[4.4]nonane ((±)-254)



(±)-254

Esterification of (±)-**253** (0.3426 g, 1.391 mmol) was done using general procedure 4 with acryloyl chloride (0.323 mL, 2.78 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 9:1) which provided compound (±)-**254** (0.1898 g, 0.6318 mmol) as a colourless oil in 45% yield. IR 3066 (H-C(sp^2)), 2836 (H-C(sp^3)), 1720 (C=O(ester)) cm^{-1}; ^{1}H-NMR 7.33 - 7.18 (m, 5H, H-19 to H-15), 6.32 (dd, 1H, $J_{12a,11}$ = 17.2 Hz and J_{gem} = 1.8 Hz, H-a), 6.05 (dd, 1H, $J_{11,12a}$ = 17.2 Hz and $J_{11,12b}$ = 10.2 Hz, H-11), 5.73 (dd, 1H, $J_{12b,11}$ = 10.2 Hz and J_{gem} = 1.8 Hz, H-b), 5.26 (d, 1H, $J_{6,7}$ = 3.5 Hz, H-6), 4.46 (d, 1H, J_{gem} = 11.7 Hz, 1H-13), 4.27 (d, 1H, J_{gem} = 11.7 Hz, 1H-13), 3.76 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 1.99 - 1.58 (m, 10H), 1.52 - 1.42 (m, 2H); ^{13}C-NMR 165.4 (C_q, C-10), 138.9 (C_q, C-14), 129.6 (CH_2, C-12), 129.3, 128.1, 127.4, 127.1, (CH, C-19 to C-15 and C-11), 85.5, 81.7 (CH, C-6 and C-1), 70.4 (CH_2, C-13), 58.3 (C_q, C-5), 33.4, 32.8, 31.4, 28.9, 20.7, 21.6 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 228 (7, [M-$HO_2CCH{=}CH_2$]$^+$), 227 (7, [M-H+$HO_2CCH{=}CH_2$]$^+$), 122 (81), 91 (100, [$PhCH_2$]$^+$), 55 (96, [$H_2C{=}CH\text{-}C{=}O$]$^+$); Analysis calc'd for $C_{19}H_{24}O_3$: C, 75.97%; H, 8.05%. Found: C, 75.89%; H, 8.41%.

(1*S*,5*S*,6*S*)-1,6-Di(acryloxy)spiro[4.4]nonane (255)

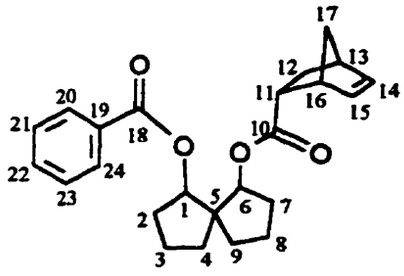


255

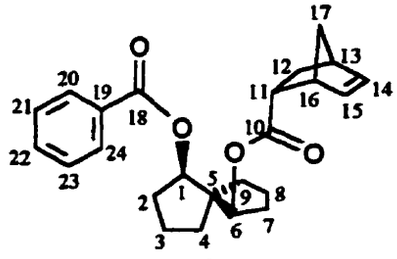
Esterification twice of (+)-diol **106** (0.1478 g, 0.946 mmol) with acryloyl chloride (0.307 mL, 3.78 mmol) was accomplished using general procedure 4. Radial plate chromatography ($CHCl_3$, 9:1) was used to purify compound **255**, which was formed as a colourless oil in 51% yield (0.1280 g, 0.484 mmol). IR 1724 (C=O), 1197 (C-O) cm^{-1}; ^{1}H NMR 6.27 (dd, 2H, $J_{12a,11}$ = 17.2 Hz and J_{gem} = 1.8 Hz, H-a), 5.99 (dd, 2H, $J_{11,12a}$ = 17.2 Hz and $J_{11,12b}$ = 10.3 Hz, H-11), 5.73 (dd, 2H, $J_{12b,11}$ = 10.3 Hz and J_{gem} = 1.8 Hz, H-b), 5.16 (d, 2H, J=3.9 Hz), 2.05 - 1.45 (m, 12H); ^{13}C NMR

165.3 (C_q, C-13 and C-10), 130.1 (CH_2, C-15 and C-12), 128.6 (CH, C-14 and C-11), 81.2 (CH, C-6 and C-1), 58.0 (C_q, C-5), 33.6, 31.6, 20.9 (CH_2, C-9 to C-7 and C-4 to C-2); Mass spectrum 120 (16, $[C_9H_{12}]^+$), 55 (100, $[H_2C{=}CHCO]^+$); Analysis calc'd for $C_{15}H_{20}O_4$: C, 68.16%; H, 7.84%. Found: C, 68.09%; H, 7.63%.

(1*RS*,5*RS*,6*RS*)- and (1*R*,5*R*,6*R*)-1-Phenylcarbonyloxy-6-(5-norbornenyl-*endo*-2-carbonyloxy)spiro[4.4]nonane (256)



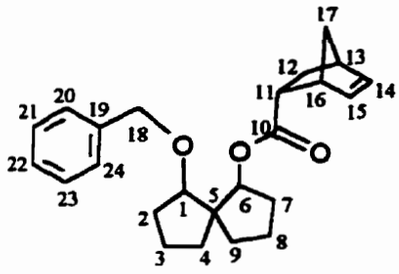
(±)-256



256

Compound **247** (0.0512 g, 0.163 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 9:1) was used to purify **256** which produced a 72% yield (0.0448 g, 0.118 mmol) of a colourless oil (88% de). IR 1729 (C=O(ester)), 1715 (C=O(conjugated ester)), 1276 (C-O) cm^{-1}; ^{1}H-NMR (major diastereomer) 8.01 - 7.92 (m, 2H, H-24 and H-20), 7.58 - 7.38 (m, 3H, H-23 to H-21), 5.94 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.1 Hz, H-15 or H-14), 5.34 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 2.9 Hz, H-15 or H-14), 5.28 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.5 Hz, H-6 or H-1), 5.08 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.6 Hz, H-6 or H-1), 2.92 (br. s, 1H, H-16), 2.77-2.67 (m, 2H, H-11 and H-13), 2.07-1.52 (m, 13H), 1.31-1.12 (m, 3H); ^{13}C-NMR (major diastereomer) 173.9 (C_q, C-10), 165.8 (C_q, C-18), 137.1, 132.7, 132.0 (CH, C-22, C-15 and C-14), 130.7 (C_q, C-19), 129.4, 128.3 (CH, C-24, C-23, C-21 and C-20), 82.0, 81.1 (CH, C-6 and C-1), 57.9 (C_q, C-5), 45.9, 43.3, 42.4 (CH, C-16, C-13 and C-11), 49.7, 33.5, 33.4, 2×31.7, 29.4, 20.8, 20.7 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 380 (4, $M^{+\cdot}$), 243 (60,$[M\text{-}HO_2C\text{-}(C_7H_9)]^+$), 121 (100, $[C_9H_{13}]^+$), 105 (98, [PhCO]+); Exact mass calc'd for $C_{24}H_{28}O_4$: 380.1988. Found: 380.2002.

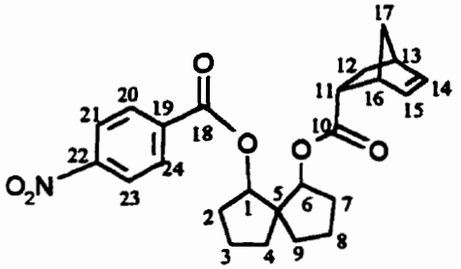
(1*RS*,5*RS*,6*RS*)-6-Benzyloxy-1-(5-norbornenyl-*endo*-2-carbonyloxy)spiro[4.4]nonane ((±)-257)



(±)-257

Compound **254** (0.1149 g, 0.384 mmol) was reacted with cyclopentadiene according to general procedure 5, except only 1 eq. of BCl_3 was added. Radial plate chromatography ($CHCl_3$, 20:1) was used to purify (±)-**257** which produced a 100% yield (0.1408 g, 0.384 mmol) of a colourless oil (75% de). IR 3060 (H-C(sp^2)), 2964 (H-C(sp^3)), 1728 (C=O(ester)) cm^{-1}; ^{1}H-NMR (400 MHz, major diastereomer) 7.34 - 7.23 (m, 5H, H-24 to H-20), 6.09 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.1 Hz, H-15 or H-14), 5.84 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 2.9 Hz, H-15 or H-14), 5.09 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.6 Hz, H-6 or H-1), 4.53 (d, 1H, J_{gem} = 11.9 Hz, 1H-18), 4.36 (d, 1H, J_{gem} = 11.9 Hz, 1H-18), 3.79 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.6 Hz, H-6 or H-1), 3.15 (br. s, 1H, H-16), 2.86 - 2.80 (m, 2H, H-11 and H-13), 1.98 - 1.57(m, 10H), 1.43 - 1.29 (m, 5H), 1.23 (d, 1H, J = 8.2 Hz); ^{13}C-NMR (100 MHz, major diastereomer) 173.6 (C_q, C-10), 139.2 (C_q, C-19), 137.1, 132.6 (CH, C-15 and C-14), 128.1, 127.0 (CH, C-24, C-23, C-21 and C-20), 127.1 (CH, C-22), 85.6, 81.3 (CH, C-6 and C-1), 70.9 (CH_2, C-18), 58.9 (C_q, C-5), 46.0, 43.2, 42.5 (CH, C-16, C-13 and C-11), 49.5, 33.2, 32.7, 31.3, 29.3, 28.7, 20.5, 20.3 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 366 (0.7, M^+), 260 (23), 121 (84, $[C_9H_{13}]^+$), 91 (100, $[PhCH_2]^+$), 55 (87, $[OCCH{=}CH_2]^+$); Exact mass calc'd for $C_{24}H_{30}O_3$: 366.2195. Found: 366.2179.

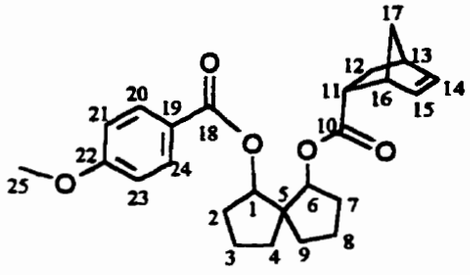
(1*RS*,5*RS*,6*RS*)-1-(*p*-Nitrophenylcarbonyloxy)-6-(5-norbornenyl-*endo*-2-carbonyloxy)spiro[4.4]nonane (258)



(±)-**258**

Compound **249** (0.1296 g, 0.3763 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 9:1) was used to purify **258** which produced an 83% yield (0.1288 g, 0.3138 mmol) of a light yellow oil that crystallised on standing to a light yellow solid (88% de). mp 108.5 - 109.0°C; IR 3065 (H-C(sp^2)), 2964 (H-C(sp^3)), 1722 (C=O(ester)), 1527 (asymmetric NO_2), 1342 (symmetric NO_2) cm^{-1}; ^{1}H-NMR (400 MHz, major diastereomer) 8.23 (d, 2H, $J_{23,24}$ and $J_{21,20}$ = 8.9 Hz, H-23 and H-22), 8.10 (d, 2H, $J_{24,23}$ and $J_{20,21}$ = 8.9 Hz, H-24 and H-20), 5.90 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.1 Hz, H-15 or H-14), 5.39 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 2.8 Hz, H-15 or H-14), 5.26 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.1 Hz, H-6 or H-1), 5.10 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.7 Hz, H-6 or H-1), 2.90 (br. s, 1H, H-16), 2.73 (br. s, 1H, H-13), 2.67 (dt, 1H, $J_{11,12}$ = 9.3 and 4.4 Hz, H-11), 2.08-1.95 (m, 1H), 1.95 - 1.63 (m, 10H), 1.57 - 1.48 (m, 2H), 1.26 (dd, 1H, J = 8.2 and 3.1 Hz), 1.14 (dd, 1H, J = 4.3 and 2.7 Hz), 1.11 (d, 1H, J = 8.0 Hz); ^{13}C-NMR (100 MHz, major diastereomer) 173.6 (C_q, C-10), 163.8(C_q, C-18), 150.3 (C_q, C-22), 135.9 (C_q, C-19), 137.3, 131.81(CH, C-15 and C-14), 30.4, 123.4 (CH, C-24, C-23, C-21 and C-20), 83.1, 80.6 (CH, C-6 and C-1), 57.9 (C_q, C-5), 45.6, 43.3, 42.2 (CH, C-16, C-13 and C-11), 49.5, 33.2, 33.1, 31.7, 31.4, 29.2, 20.5_8, 20.5_3 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 207 (14), 150 (50, $[O_2NPhCO]^+$), 120 (85, $[C_9H_{12}]^+$), 55 (100, $[OCCH{=}CH_2]^+$); Exact mass calc'd for $C_{24}H_{27}NO_6$: 425.1838. Found: 425.1868.

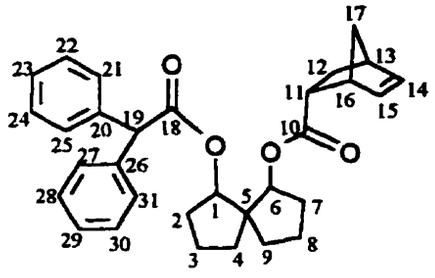
(1*RS*,5*RS*,6*RS*)-1-(*p*-Methoxyphenylcarbonyloxy)-6-(5-norbornenyl-*endo*-2-carbonyloxy)spiro[4.4]nonane (259)



(±)-**259**

Compound **250** (0.197 g, 0.548 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 9:1) was used to purify **258** which produced a 98% yield (0.229 g, 0.538 mmol) of a light yellow oil that crystallised on standing to a light yellow solid (84% de). mp 64.5 - 65.5°C; IR 3063 (H-C(sp^2)), 2969, 2946 (H-C(sp^3)), 1729 ,1710 (C=O(ester)) cm^{-1}; ^{1}H-NMR (400 MHz, major diastereomer) 7.90 (d, 2H, $J_{24,23}$ and $J_{20,21}$ = 8.8 Hz, H-24 and H-20), 6.88 (d, 2H, $J_{23,24}$ and $J_{21,20}$ = 8.8 Hz, H-23 and H-21), 5.93 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.6 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.1 Hz, H-15 or H-14), 5.38 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.6 Hz and $J_{15,11}$ or $J_{14,12}$ = 2.8 Hz, H-15 or H-14), 5.22 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.0 Hz, H-6 or H-1), 5.06 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.1 Hz, H-6 or H-1), 3.82 (s, 3H, H-25), 2.92 (br. s, 1H, H-16), 2.75 (br. s, 1H, H-13), 2.69 (dt, 1H, $J_{11,12}$ = 9.2 and 4.1 Hz, H-11), 2.01-1.66 (m, 11H), 1.54 - 1.46 (m, 2H), 1.30 - 1.14 (m, 2H), 1.12 (d, 1H, J = 8.3); ^{13}C-NMR (100 MHz, major diastereomer) 173.9 (C_q, C-10), 165.5, 163.1 (C_q, C-18 and C-22), 137.1, 132.0 (C_q, C-15 and C-14), 131.4 (CH, C-24 and C-20), 123.0 (C_q, C-19), 113.5 (CH, C-23 and C-21), 81.6, 81.1 (CH, C-6 and C-1), 57.8 (C_q, C-5), 55.3 (CH_3, C-25), 45.8, 43.2, 42.4 (CH, C-16, C-13 and C-11), 49.6, 33.4, 33.3, 2×31.6, 29.3, 20.7, 20.6 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 344 (1, $[M\text{-}C_5H_6]^+$, retroDiels-Alder), 135 (100, $[MeOPhCO]^+$), 120 (18, $[C_9H_{12}]^+$), 55 (26, $[OCCH{=}CH_2]^+$); Exact mass calc'd for $C_{25}H_{30}O_5$: 410.2093. Found: 410.2086.

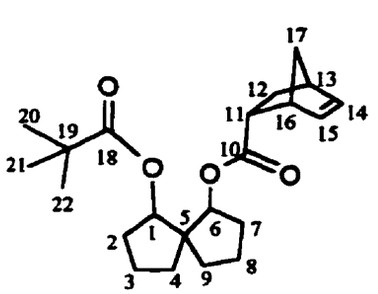
(1*RS*,5*RS*,6*RS*)-1-(Diphenylacetoxy)-6-(5-norbornenyl-*endo*-2-carbonyloxy)-spiro[4.4]nonane ((±)-260)



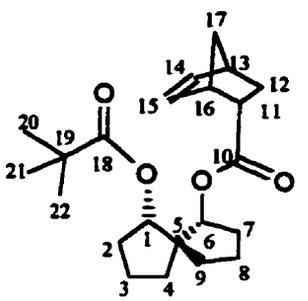
(±)-260

Compound **248** (0.1091 g, 0.2697 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 9:1) was used to purify (±)-**260** which produced a 100% yield (0.1276 g, 0.2711 mmol) of a colourless oil that crystallised on standing to a colourless solid (90% de). mp 104.0 - 104.5°C; IR 2968 (H-C(sp^3)), 1727 (C=O(ester)) cm^{-1}; ^{1}H-NMR (400 MHz, major diastereomer) 7.34 - 7.02 (m, 10 H), 6.01 (dd, 1H, $J_{15.14}$ or $J_{14.15}$ = 5.7 Hz and $J_{15.11}$ or $J_{14.12}$ = 3.1 Hz, H-15 or H-14), 5.84 (dd, 1H, $J_{15.14}$ or $J_{14.15}$ = 5.6 Hz and $J_{15.11}$ or $J_{14.12}$ = 2.9 Hz, H-15 or H-14), 5.08 (d, 1H, $J_{6.7}$ or $J_{1.2}$ = 3.9 Hz, H-6 or H-1),4.95 (s, 1H, H-19), 4.91 (d, 1H, $J_{6.7}$ or $J_{1.2}$ = 3.6 Hz, H-6 or H-1), 3.04 (br. s, 1H, H-16), 2.80 (br. s, 1H, H-13), 2.58 (dt, 1H, $J_{11.12}$ = 9.4 and 4.1 Hz, H-11), 1.87 - 1.32 (m, 14H), 1.23 - 1.19 (m, 1H), 1.13 (d, 1H, J = 8.2 Hz); ^{13}C-NMR (100 MHz, major diastereomer) 173.9, 171.4 (C_q, C-18 and C-10), 138.7_4, 138.6_8 (C_q, C-26 and C-20), 137.1, 132.8 (CH, C-15 and C-14), 128.6, 128.5, 128.3_0, 128.2_6 (CH, C-31, C-30, C-28, C-27, C-25, C-24, C-22, C-21), 127.0_2, 126.9 (CH, C-29, C-23), 81.9, 80.8 (CH, C-6 and C-1), 57.7 (C_q, C-5), 57.3 (CH, C-19), 45.5, 43.8, 42.3 (CH, C-16, C-13 and C-11), 49.4, 33.1, 32.8, 31.4, 31.2, 29.4, 20.5, 20.4 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 470 (0.9, $M^{+\cdot}$), 333 (33), 167 (88, $[Ph_2CH]^+$), 121 (100, $[C_9H_{13}]^+$), 55 (84, $[OCCH{=}CH_2]^+$); Analysis calc'd for $C_{31}H_{34}O_4$: C, 79.13%; H, 7.28%. Found: C, 79.01%; H, 7.66%.

(1*RS*,5*RS*,6*RS*)- and (1*R*,5*R*,6*R*)-6-(5-Norbornenyl-*endo*-2-carbonyloxy)-1-(pivaloxy)spiro[4.4]nonane (261)



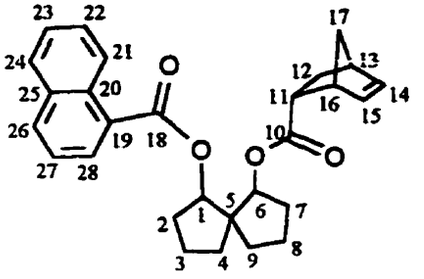
(±)-**261**



(-)-**261**

Compound **251** (0.0761 g, 0.259 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 20:1) was used to purify **261** which produced a 80% yield (0.0748 g, 0.2075 mmol) of a colourless oil that crystallised on standing to a white solid (>97% de). mp 74.8 - 76.5°C; IR 2972 (H-C(sp^3)), 1728 (C=O) cm^{-1}; ^1H NMR (major diastereomer) 6.11 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.0 Hz, H-15 or H-14), 5.89 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 2.8 Hz, H-15 or H-14), 4.96 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.5 Hz, H-6 or H-1), 4.93 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.1 Hz, H-6 or H-1), 3.12 (br. s, 1H, H-16), 2.86 - 2.77 (m, 2H, H-13 and H-11), 1.87 - 1.20 (m, 18H), 1.11 (s, 9H, H-22, H-21 and H-20), ^{13}C NMR (major diastereomer) 177.4, 173.8 (C_q, C-18 and C-10), 137.2, 132.8 (CH, C-15 and C-14), 80.9, 80.7 (CH, C-6 and C-1), 57.8 (C_q, C-5), 45.6, 43.9, 42.4 (CH, C-16, C-13 and C-11), 49.6, 38.7, 2x33.0, 31.5, 31.3, 29.5, 20.5, 20.4 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2), 27.0 (CH_3, C-22, C-21 and C-20); Mass spectrum 360 (9, $M^{+\cdot}$), 258 (7, $[M\text{-}HO_2CCMe_3]^+$), 223.1 (51, $[M\text{-}O_2C\text{-}(C_7H_9)]^+$), 121 (100, $[C_9H_{13}]^+$); Exact mass calc'd for $C_{22}H_{32}O_4$: 360.2301. Found: 360.2270.

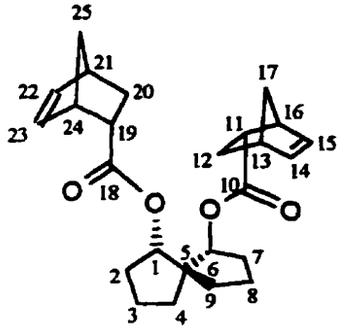
(1*R*,5*R*,6*R*)-1-(1-Naphthylcarbonyloxy)-6-(5-norbornenyl-*endo*-2-carbonyloxy)-spiro[4.4]nonane (262)



262

Compound **252** (0.1577 g, 0.4327 mmol) was reacted with cyclopentadiene according to general procedure 5. Radial plate chromatography ($CHCl_3$, 9:1) provided an 89% yield (75% de) of **262** (0.1662 g, 0.3860 mmol) which was a colourless oil that crystallised on standing forming a white solid. mp 146 - 147°C; IR 3063 (H-C(sp^2)), 2944 (H-C(sp^3)), 1709 (C=O) cm^{-1}; ^{1}H-NMR (major diastereomer) 8.93 (d, 1H, $J_{28,27}$ = 8.6 Hz, H-28), 8.08 (d, 1H, J = 7.3 Hz, H-26, H-24 or H-21), 8.01 (d, 1H, J = 8.0 Hz, H-26, H-24 or H-21), 7.87 (d, 1H, J = 8.6 Hz, H-26, H-24 or H-21), 7.65 - 7.44 (m, 3H, H-27, H-23 and H-22), 5.94 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,11}$ or $J_{14,12}$ = 3.0 Hz, H-15 or H-14), 5.53 (dd, 1H, $J_{15,14}$ or $J_{14,15}$ = 5.7 Hz and $J_{15,16}$ or $J_{14,12}$ = 2.8 Hz, H-15 or H-14), 5.41 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 2.6 Hz, H-6 or H-1), 5.14 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.4 Hz, H-6 or H-1), 3.00 (br. s, 1H, H-16), 2.82 - 2.74 (m, 2H, H-11 and H-13), 2.13 - 1.58 (m, 10H), 1.42 -1.22 (m, 2H), 1.13 (d, 1H, J = 7.9 Hz); ^{13}C-NMR (major diastereomer) 174.0 (C_q, C-10), 166.7 (C_q, C-18), 133.7, 131.2, 127.4 (C_q, C-25, C-20 and C-19), 137.0, 133.1, 132.1, 129.9, 128.4, 127.5, 126.0, 125.6, 124.5 (CH, C-28 to C-26 and C-24 to C-21), 82.0, 81.9 (CH, C-6 and C-1), 57.8 (C_q, C-5) 45.7, 43.4, 42.3, (CH, C-16, C-13 and C-11), 49.5, 2×33.2, 31.6_3, 31.5_8, 29.3, 20.6, 20.5 (CH_2, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 430 (4, $M^{+\cdot}$), 364 (7, $[M-C_5H_6]^+$, retroDiels-Alder), 155 (100, $[1\text{-Np-C=O}]^+$), 127 (79, $[Np]^+$), 55 (75, $[O{=}CCH{=}CH_2]^+$); Exact mass calc'd for $C_{28}H_{30}O_4$: 430.2144. Found: 430.2137.

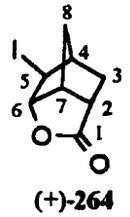
(1*S*,5*S*,6*S*)-1,6-Di(5-norbornenyl-*endo*-2-carbonyloxy)spiro[4.4]nonane (263)



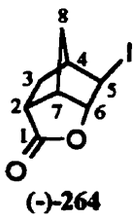
263

Compound **255** (0.125 g, 0.471 mmol) was reacted with cyclopentadiene according to general procedure 5, except that the quantity of cyclopentadiene was double. Radial plate chromatography ($CHCl_3$, 9:1) provided **263** in 84% yield (0.1559 g, 0.3932 mmol) of a colourless oil (75% de). IR 3057 (H-C(sp^2)), 2968 (H-C(sp^3)), 1729 (C=O) cm^{-1}; ^1H NMR (major diastereomer) 6.09 (dd, 1H, $J_{23,22}$ and $J_{15,14}$ or $J_{22,23}$ and $J_{14,15}$ = 5.7 Hz and $J_{23,19}$ and $J_{15,11}$ or $J_{22,21}$ and $J_{14,12}$ = 3.0 Hz, H-15 and H-23 or H-22 H-14), 5.83 (dd, 1H, $J_{23,22}$ and $J_{15,14}$ or $J_{22,23}$ and $J_{14,15}$ = 5.7 Hz and $J_{23,19}$ and $J_{15,11}$ or $J_{22,21}$ and $J_{14,12}$ = 2.8 Hz, H-15 and H-23 or H-22 H-14), 4.88 (d, 2H, $J_{6,7}$ and $J_{1,2}$ = 2.7 Hz, H-6 and H-1), 3.09 (br s, 2H), 2.84 - 2.76 (m, 4H), 1.89 - 1.16 (m, 22H); ^{13}C NMR (major diastereomer) 173.7 (C_q, C-10 and C-18), 137.2, 132.5 (CH, C-23, C-22, C-15 and C-14), 80.7 (CH, C-6 and C-1), 57.5 (C_q, C-5), 45.6, 43.7, 42.4 (CH, C-24, C-21, C-19, C-16, C-13 and C-11), 49.5, 32.7, 31.3, 29.3, 20.3 (CH_2, C-25, C-20, C-17, C-12, C-9 to C-7 and C-4 to C-2); Mass spectrum 396 (1.5, M^{+}), 259 (43, [M - O_2C-(C_7H_9)]$^+$), 121 (100, [C_9H_{13}]$^+$), 55 (94, [OCCH=CH_2]$^+$); Exact mass calc'd for $C_{25}H_{32}O_4$: 396.2301. Found: 396.2262.

(1*S*,4*S*,6*S*,8*R*,9*S*)- and (1*R*,4*R*,6*R*,8*S*,9*R*)-9-Iodo-2-oxatricyclo[4.2.1^{1,6}.0^{4,8}]nonane-3-one ((+)- and (-)-264)



(+)-**264**



(-)-**264**

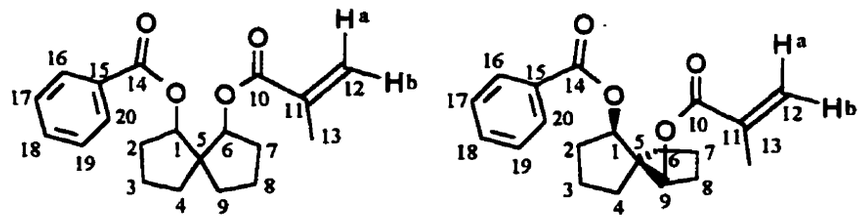
The procedure published by Mathivanan and Maitra was followed for the formation of iodolactone **264**.[215] Compound **261** (0.0722 g, 0.200 mmol) was dissolved in CH_2Cl_2 (8.4 mL) in a 25 mL round-bottomed flask. To this solution was added KI (0.1995 g, 1.202 mmol), $NaHCO_3$ (0.168 g, 2.00 mmol) and water (0.5 mL), and the solution was vigorously stirred. Sublimed I_2 (0.102 g, 0.401 mmol) was added and the reaction was stirred at rt. The disappearance of starting material was followed by TLC and upon completion of the

reaction more CH_2Cl_2 was added and the solution was extracted with a 10% $Na_2S_2O_3$ solution. The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Radial plate chromatography ($CHCl_3$, 5:1) was used to purify the iodolactone **264** (0.0518 g, 0.196 mmol), which was formed in 98% yield (33% of (+)-**246** was recovered). ^{1}H-NMR 5.14 (d, 1H, J = 6.5 Hz), 3.90 (d, 1H, J = 2.5 Hz), 3.21 (br. s, 1H), 2.73 (br. s, 1H), 2.58 (dd, 1H, J = 10.7 and 3.9 Hz), 2.40 (d, 1H, J = 11.5 Hz), 2.08 (td, 1H, J = 11.5 and 3.9 Hz), 1.91 - 1.26 (m, 2H); ^{13}C-NMR 179.2 (C_q, C-1), 89.0 (CH, C-6), 46.8, 46.6, 37.4$_1$, 29.6 (CH, C-7, C-5, C-4 and C-2), 34.6, 37.4$_5$ (CH_2, C-8 and C-3); Mass spectrum 264 (40, $M^{+\cdot}$), 137 (94, $[M-I]^+$), 93 (100, $[M-CO_2$ and $I]^+$). The ^{1}H-NMR spectrum and mass spectrum agreed with those published in the literature and therefore a full characterisation of **264** was not performed.[215] The optical rotation for iodolactone **264** produced from Diels-Alder adduct **261** was $[\alpha]_D^{26}$ +112.4 (c 2.83, 0.1 dm, benzene) (literature[220] $[\alpha]_D^{28}$ -116 (c 2.2, benzene).

Iodolactonisation of **256** produced **264** in 79% yield with $\alpha_D^{25.5}$-92.1 (c 1.69, 0.1 dm, $CHCl_3$) = -102.7 (benzene), and allowed the recovery of (-)-**245** in 79% yield.

Double iodolactonisation of **263** produced **264** in 97% yield with $\alpha_D^{22.5}$+102.7 (c 3.16, 0.1 dm, benzene).

(1*RS*,5*RS*,6*RS*)- and (1*R*,5*R*,6*R*)-1-Phenylcarbonyloxy-6-(methacryloxy)-spiro[4.4]nonane (265)

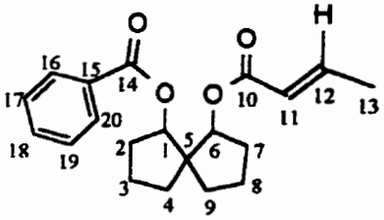


(±)-**265** **265**

Esterification of **245** (0.0457 g, 0.176 mmol) was done using general procedure 4 with methacryloyl chloride (0.0343 mL, 0.351 mmol). The product was purified by radial plate chromatography ($CHCl_3$, 9:1) providing compound **265** (0.0439 g, 0.134 mmol) as a

colourless oil in 76% yield. IR 2961 (H-C(sp^3)), 1715 (C=O(ester)) cm^{-1}; ^{1}H-NMR 7.92 (d, 2H, $J_{20,19}$ and $J_{16,15}$ = 7.0 Hz, H-20 and H-16), 7.52 (t, 1H, $J_{18,19}$ and $J_{18,17}$ = 7.0 Hz, H-18), 7.41 (t, 2H, $J_{19,20}$ and $J_{19,18}$ and $J_{17,18}$ and $J_{17,16}$ = 7.0 Hz, H-19 and H-17), 5.87 (s, 1H, H-a or H-b), 5.36 (t, 1H, H-a or H-b), 5.31 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.9 Hz, H-6 or H-1), 5.26 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.0 Hz, H-6 or H-1), 2.06 - 1.78 (m, 10H), 1.63 - 1.52 (m, 2H) and 1.69 (s, 3H, H-13); ^{13}C-NMR 165.5, 165.9 (C_q, C-14 and C-10), 136.4, 130.5 (C_q, C-15 and C-11), 132.7, 129.4, 128.2 (CH, C-20 to C-16), 125.0 (CH_2, C-12), 82.1, 81.6 (CH, C-6 and C-1), 58.2 (C_q, C-5), 2×33.8, 31.8, 31.7, 2×21.1 (CH_2, C-9 to C-7 and C-4 to C-2), 18.0 (CH_3, C-13); Mass spectrum 328 (4, $M^{+\cdot}$), 243 (8, $[M\text{-}O_2CCH{=}CHMe]^+$), 121 (94, $[C_9H_{13}]^+$), 120 (94, $[C_9H_{12}]^+$), 105 (100, $[PhCO]^+$), 69 (91, $[O{=}CCMe{=}CH_2]^+$); Exact mass calc'd for $C_{20}H_{24}O_4$: 328.1675. Found: 328.1671.

(1*RS*,5*RS*,6*RS*)- and (1*R*,5*R*,6*R*)-1-Phenylcarbonyloxy-6-(crotonoxy)spiro[4.4]nonane ((±)-266)



(±)-**266**

Esterification of (±)-**245** (0.0539 g, 0.207 mmol) was done using general procedure 4 with crotonyl chloride (0.040 mL, 0.41 mmol), however $NaHCO_3$ (0.0696 g, 0.828 mmol) was added instead of Et_3N to minimise double bond isomerisation. The product was purified by radial plate chromatography ($CHCl_3$, 9:1) providing compound (±)-**266** (0.0515 g, 0.157 mmol) as a colourless oil, in 76% yield, which solidified on standing. mp 47 - 48°C; IR 2967 (H-C(sp^3)), 1718 (C=O) cm^{-1}; ^{1}H-NMR 7.92 (d, 2H, $J_{20,19}$ and $J_{16,15}$ = 7.0 Hz, H-20 and H-16), 7.52 (t, 1H, $J_{18,19}$ and $J_{18,17}$ = 7.0 Hz, H-18), 7.40 (t, 2H, $J_{19,20}$ and $J_{19,18}$ and $J_{17,18}$ and $J_{17,16}$ = 7.0 Hz, H-19 and H-17), 6.67 (dq, 1H, $J_{12,11}$ = 15.5 Hz and $J_{12,13}$ = 6.9 Hz, H-12), 5.61 (d, 1H, $J_{11,12}$ = 15.5 Hz, H-11), 5.32 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 3.8 Hz, H-6 or H-1), 5.23 (d, 1H, $J_{6,7}$ or $J_{1,2}$ = 4.0 Hz, H-6 or H-1), 2.09 - 1.75 (m, 10H), 1.63 - 1.48 (m, 2H) and 1.71 (d, 3H, $J_{13,12}$ = 6.9 Hz, H-13); ^{13}C-NMR 165.8, 165.7 (C_q, C-14 and C-10), 130.6 (C_q, C-15), 144.0 (CH, C-12), 132.6, 129.3, 128.1, 122.7 (CH, C-20 to C-16 and C-11), 81.9, 81.0 (CH, C-6 and C-1), 58.0 (C_q, C-5), 2×33.8, 31.6, 31.7,

2×21.0 (CH_2, C-9 to C-7 and C-4 to C-2), 17.7 (CH_3, C-13); Mass spectrum 242 (1, [M-$HO_2CCH{=}CHMe$]$^+$), 120 (69, [C_9H_{12}]$^+$), 105 (100, [PhCO]+), 77 (70, [C_6H_5]$^+$), 69 (79, [$O{=}CCH{=}CHMe$]$^+$); Exact mass calc'd for $C_{20}H_{24}O_4$: 328.1675. Found: 328.1682.

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4. Some chemists (See reference 5a), p. 1197) believe that the term "dissymmetric" is archaic. These chemists, however, have not introduced a new term to replace "dissymmetric" and therefore this term will be used here.
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218. The same method was used for all the Diels-Alder reactions with the various "blocking groups".

219. An error of ±1% ee (or de, reference 202) is typical for a determination made on an NMR spectrometer. This value will depend on not only the tuning of the instrument, but will also depend on the signals (sharpness and number of H's) that are being integrated (*i.e.* Signal to Noise). For these Diels-Alder adducts the de's (*endo* isomers) were determined from a broad singlet and/or a doublet of doublets (both integrating to only 1H). Also the HPLC trace for adduct **261** was obtained with the UV detector set at 220 nm which produced a noisy baseline (see Figure 5.4). These two factors prompted us to decrease the numerical estimate of the selectivity for the reaction (*i.e.* from ≥99% de to ≥97% de).

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