Corrigendum

(i) Page *vii*: replace *N*-bromosuccinamide with *N*-bromosuccinimide;

(ii) Page 21 and 23: References 10, 11 and 21: replace there-in with therein;

(iii) Page 33, Line 12: ...which are capable of forming... (insert the word of);

(iv) Page 37, Line 5 of footnote: replace persued with pursued;

(v) Page 38, Line 5: replace *et al* with *et al.*;

(vi) Page 39, **Table 2.3**: at this point and throughout the thesis the degree sign associated with cited values for optical rotations should be deleted;

(vii) Page 78, Line 17: replace hydroylsis with hydrolysis;

(viii) Page 82, Line 19: replace methodolgy with methodology;

(ix) Page 84, Line 5: delete the word "a";

(x) Page 93, Line 15: replace (*J* Hz) with (*J* Hz, as measured from the spectra);

(xi) Page 104, Line 1: the name for compound (±)-**73** should be (1*R**,2*S**)-2,3-Dihydro-6-methoxy-1-methyl-1*H*-indene-1,2-diol;

(xii) Page 118, Line 5: replace **^{13}C NMR** (300 MHz) with **^{13}C NMR** (75.4 MHz);

(xiii) Page 119, Line 1: the name for compound **96** should be (1*S**,2*S**)-1-Hydroxy-6-methoxy 1-methylindan-2-yl 3'-Chlorobenzoate;

(xiv) Page 119, Line 10: delete the sentence "The optical purity of this material was not determined."

STRAINED ORGANIC MOLECULES AS BUILDING BLOCKS FOR THE SYNTHESIS OF TAXOID FRAMEWORKS

A thesis submitted for the degree of Doctor of Philosophy

of The Australian National University

by

Susanne Pallich

Research School of Chemistry
Canberra, Australia

September, 1998

Declaration

This is to declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by me during the period 1994 - 1998 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Susanne Pallich

7th September, 1998

Acknowledgments

Firstly, I would like to thank my supervisor, Dr. Martin Banwell, for his supervision of this work. His guidance, advice and professionalism has taught me more than just the skills one gains at the bench during the course of a PhD. The opportunity that he provided for me to study at the Australian National University, in order to carry out the work described in this thesis, is also much appreciated.

Thank you to all the members of the Banwell group, both past and present, who have made my time in the group a happy experience. A special thank you to my labmates, Chris De Savi, Scott Stewart, Rob Longmore, Brendan Burkett and Alison King, a unique combination of characters that created a working environment which was full of enthusiasm, comraderie and a load of laughs. Whenever chemistry got the better of me, those guys would lighten the moment by reminding me of the humorous side of it all. For that, I will always be grateful.

For technical support, I am indebted to Rob Longmore (GC), Tony Herlt (HPLC) and Tin Culnane (NMR). Their expertise was invaluable and helped to make things run a whole lot smoother. I am also grateful to Dr. David Hockless and Dr. George Clark for the speedy acquistion of X-ray crystallographic data. Thank you also to Dr. George Adamson, Penny Darmos and Joanne Harvey for giving up their time to proof-read this manuscript. The suggestions and critiscisms they made were much appreciated.

Most of all I would like to thank my family, especially my mum, dad and sister Michelle for their neverending encouragement, support and patience. They have helped me to never lose sight of the bigger picture when it seemed, at times, that everything was getting too much. I hear the trout are on the bite at Eucumbene, let's go ...

Abstract

The diterpene paclitaxel (**1**, Taxol®) was first isolated in 1966 from the bark of the rare and slow-growing Pacific Yew tree (*Taxus brevifolia*) and is now in clinical use for the treatment of ovarian and breast cancers. As a consequence of its powerful anti-mitotic properties, novel mode of biological action, limited supply and complex molecular architecture, paclitaxel (**1**) has been described as "one of the most challenging targets for synthesis chemists today".[1h]

This thesis begins with a commentary on the history, biological properties and biosynthesis of paclitaxel (**1**). Brief descriptions of each of the five existing total syntheses of paclitaxel (**1**) are also provided, which serves to highlight the challenges associated with the preparation of this compound, as well as the key strategic elements employed to achieve its synthesis.

In connection with our approach to compound **1**, which involves cyclohexannulated [5.3.1]propellanes as key intermediates, methods for the preparation of indanol (+)-**71** in enantiopure form are described. Ultimately, the most serviceable route to this key compound involved, *inter alia*, formation of diol (+)-**73** *via* Sharpless Asymmetric Dihydroxylation (AD) of olefin **77**. This was followed by a resolution step which raised the optical purity of diol (+)-**73** to acceptable levels. Indanol (+)-**71** served as a suitable starting material for the synthesis of the highly functionalised taxane derivative **122**, in which the A-ring substituents associated with **1** (*viz.* C12 methyl group and C13 oxygen substituent) have been acknowledged.

A novel approach for the assembly of the oxetane D-ring of paclitaxel (**1**), which involved the generation and Diels-Alder trapping of oxete (**69**), was also investigated. In the course of this study, the previously unreported oxetanes **125** and **126** were prepared. Whilst these compounds did not undergo cycloreversion to afford the desired heterocycle **69**, the chemistry associated with their synthesis represents a new and potentially useful means of generating other oxetanes.

Publications and Presentations Based Upon Work Carried Out During the Period of PhD Candidature

Publication:

Model Studies Directed Towards the Synthesis of the Oxetane D-ring of Paclitaxel: Assessment of the Oxy-Anion Assisted retro-Diels-Alder Reaction as a Means for Generating Oxete.

M. G. Banwell, G. R. Clark, D. C. Hockless and S. Pallich, submitted to *Aust. J. Chem.*

Presentation:

"The Cyclopropane Route to Enantiopure Taxoids."

Oral Presentation given at the Royal Australian Chemical Institute 15th National Organic Division Conference, 30th June - 5th July 1996.

Glossary

The following abbreviations have been used throughout this thesis:

Ac	acetyl
app	apparent (^{1}H NMR spectra)
APT	attached proton test
aq.	aqueous
atm.	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
c	concentration (g/100 mL)
ca.	*circa* (approximately)
cat.	catalyst
CDI	carbonyldiimidazole
CHDMS	cyclohexyldimethylsilyl
CI	chemical ionisation
conc.	concentrated
m-CPBA	*m*-chloroperbenzoic acid
CPTS	collidinium *p*-toluenesulfonate
CSA	camphorsulfonic acid
δ	chemical shift (parts per million)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL	diisobutylaluminium hydride
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents
Et	ethyl
etc.	et cetera (and so on)
eV	electron volt
FVP	flash vacuum pyrolysis
g	gaseous
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
L-Selectride®	lithium tri-*sec*-butylborohydride
LTMP	lithium 2,2,6,6-tetramethylpiperidide
$M^{+\cdot}$	molecular ion (mass spectra)
Me	methyl
MEM	2-methoxyethoxymethyl

mins	minutes
MOP	2-methoxypropyl
m.p.	melting point (°C)
Ms	methanesulfonyl or mesyl
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
m/z	mass-to-charge ratio
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinamide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ν_{max}	infrared absorption maxima (cm^{-1})
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
^{i}Pr	*iso*-propyl
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
pyr.	pyridine
R_f	retardation factor
R_t	retention time
Red-Al®	sodium dihydrobis(2-methoxyethoxy)aluminate
rt	room temperature
sh	shoulder (infrared spectra)
TASF	tris(dimethylamino)sulfonium(trimethylsilyl) difluoride
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide

TBDMS	*tert*-butyldimethylsilyl
TCDI	1,1'-thiocarbonyldiimidazole
TEBAC	triethylbenzylammonium chloride
TES	triethylsilyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate (VII)
TPS	*tert*-butyldiphenylsilyl
Tris	tris(hydroxymethyl)aminomethane
Troc	2,2,2-trichloroethyoxycarbonyl
Ts	*p*-toluenesulfonyl or tosyl
p-TsOH	*p*-toluenesulfonic acid
UV	ultraviolet
V	volts
viz.	*videlicit* (namely)
wt	weight
<	less than
>	greater than

TABLE OF CONTENTS

Chapter 3 Synthesis of Enantiopure Taxane Analogues from Indanol (+)-71

Chapter 4 Studies Directed Towards the Generation and Diels-Alder Trapping of Oxete

Chapter 5 Experimental Section

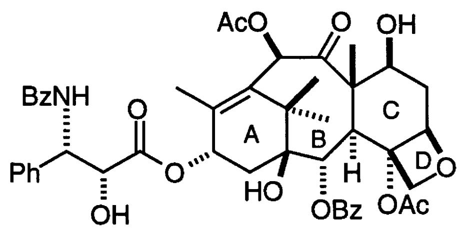
Appendices

CHAPTER 1

Introduction

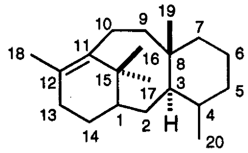
1.1 Overview

In 1960, the National Cancer Institute initiated an intensive screening program of plant samples in an effort to discover new drugs possessing antineoplastic activity.[1] In collaboration with the U.S. Department of Agriculture, samples were collected at random from the states of California, Washington and Oregon. These samples included bark, twig, leaf and fruit matter from the rare and slow-growing Pacific Yew Tree (*Taxus brevifolia*) found in Washington. Initial screening of the crude bark extract derived from *T. brevifolia* revealed exciting cytotoxic activity against murine leukemia cells and inhibitory action against a variety of tumors. Utilizing bioactivity-guided fractionation protocols, the active component of this bark extract, Taxol,[£] was isolated in pure form in June 1966. The structure and absolute stereochemistry associated with this natural product were established in 1971 by Wani and co-workers[2] on the basis of ^{1}H NMR spectroscopic and X-ray crystallographic studies. Thus, the diterpene paclitaxel (**1**) is composed of a phenylisoserine derived side-chain attached to a highly oxygenated tetracyclic nucleus which is defined by the so-called A-, B-, C- and D-rings.*



(-)-1

£ Taxol® is now a registered trademark of the Bristol-Myers Squibb Company and will be referred to by its generic name, paclitaxel (compound with the structure **1**) throughout the remainder of this thesis.
* The taxoid numbering system, as depicted in structure **1a**, will be used (where appropriate) throughout the remainder of this thesis.



1a

1.2 Biological Properties of Paclitaxel

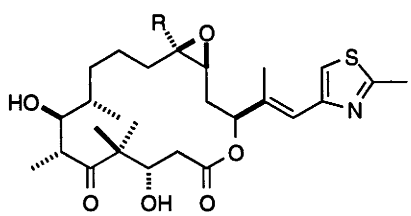
After its structural elucidation in 1971, interest in paclitaxel (**1**) languished for almost a decade primarily due to (i) difficulties associated with securing sufficient quantities of the compound for further investigation[¥] (ii) problems with the murine screening system and (iii) the belief that **1** was just another spindle poison like colchicine and the vinca alkaloids, which act as microtubule-destabilizing agents.[6] However, interest in paclitaxel (**1**) rose dramatically when detailed investigations by the Horowitz group revealed its unique mode of action. Thus, these workers discovered that paclitaxel (**1**) acts as a potent inhibitor of eukaryotic cell replication by promoting the formation of discrete bundles of stable microtubules and inhibiting their depolymerization back to tubulin.[7,∞]

By virtue of its unusual mechanism of action, paclitaxel (**1**) has emerged as an important new cancer chemotherapeutic agent and is now in clinical use[1b,9] for the treatment of breast and ovarian cancer. The drug has also demonstrated promising anti-tumor activity against other types of cancers, including those associated with the lung, head and neck, skin and gastrointestinal tract. Despite paclitaxel's impressive biological profile, there are some problems associated with its use. For example, there are formulation difficulties (due to paclitaxel's low water solubility), unpleasant side

---

¥ To obtain one kilogram of paclitaxel (**1**) from the Pacific Yew tree, ten tonnes of bark are required which, in turn, involves the sacrifice of about three thousand mature trees. Today, clinical supplies of paclitaxel (**1**) are obtained by semisynthesis.[3] Other methods of drug supply currently under investigation include plant cell culture[4] and plantation farming.[5]

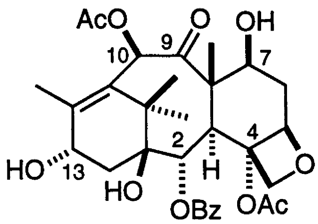
∞ The epothilones,[8] a new family of natural products isolated from the myoxobacteria *Sorangium cellulosum*, also elicit their powerful anti-mitotic activity *via* the same unusual mechanism of action as shown by paclitaxel (**1**). Of particular interest are epothilones A (**2**) and B (**3**). These macrocyclic compounds not only exhibit superior cytotoxic properties when compared with paclitaxel (**1**) but have also shown, when tested *in vitro*, to be 2000-5000 times more active than compound **1** in combating multiple drug-resistant cells.



2 : R = H
3 : R = CH_3

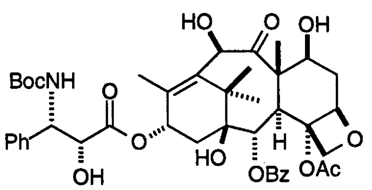
effects (both drug and formulation related) and its ineffectiveness against a variety of multiple drug-resistant tumors. This situation has provided the stimulus for the development of structurally simpler but clinically superior analogues of paclitaxel (**1**).‡ Thus, an understanding of the structural modifications which influence the biological properties of **1** would greatly benefit the advance of such compounds.

It is beyond the scope of this thesis to provide a detailed analysis of the structure-activity relationships associated with paclitaxel (**1**) and there are many reviews[1] which deal with this subject in a comprehensive manner. Consequently, only a summary of the structural modifications which influence the activity of **1** is presented here (Figure 1.1). It is known that baccatin III (**5**)§ (a biosynthetic precursor of **1**) and derivatives thereof which lack the *N*-benzoylphenylisoserine side-chain at C13 are neither active in tubulin binding assays nor cytotoxic. Thus, the presence of the side-chain is crucial for biological activity. In general, analogues of paclitaxel (**1**) derived by modification of substituents in the southern sector of the taxoid framework (i.e. C2, C4 and the oxetane D-ring) are, for all practical purposes, inactive. In contrast, substituent modification at C7, C9 and C10 (northern sector) has little effect on the activity of analogues so-derived.



5

‡ Taxotere® (**4**) (the name is a registered trademark of Rhône-Poulenc) is an example of a semi-synthetic analogue of paclitaxel (**1**) that is approximately twice as potent as the natural product.



4

§ Baccatin III (**5**) is isolated in large quantities from renewable parts (i.e. needles) of various *Taxus* species. Semi-synthesis of paclitaxel (**1**) from **5** is well documented[3] and represents an alternate means of drug supply.

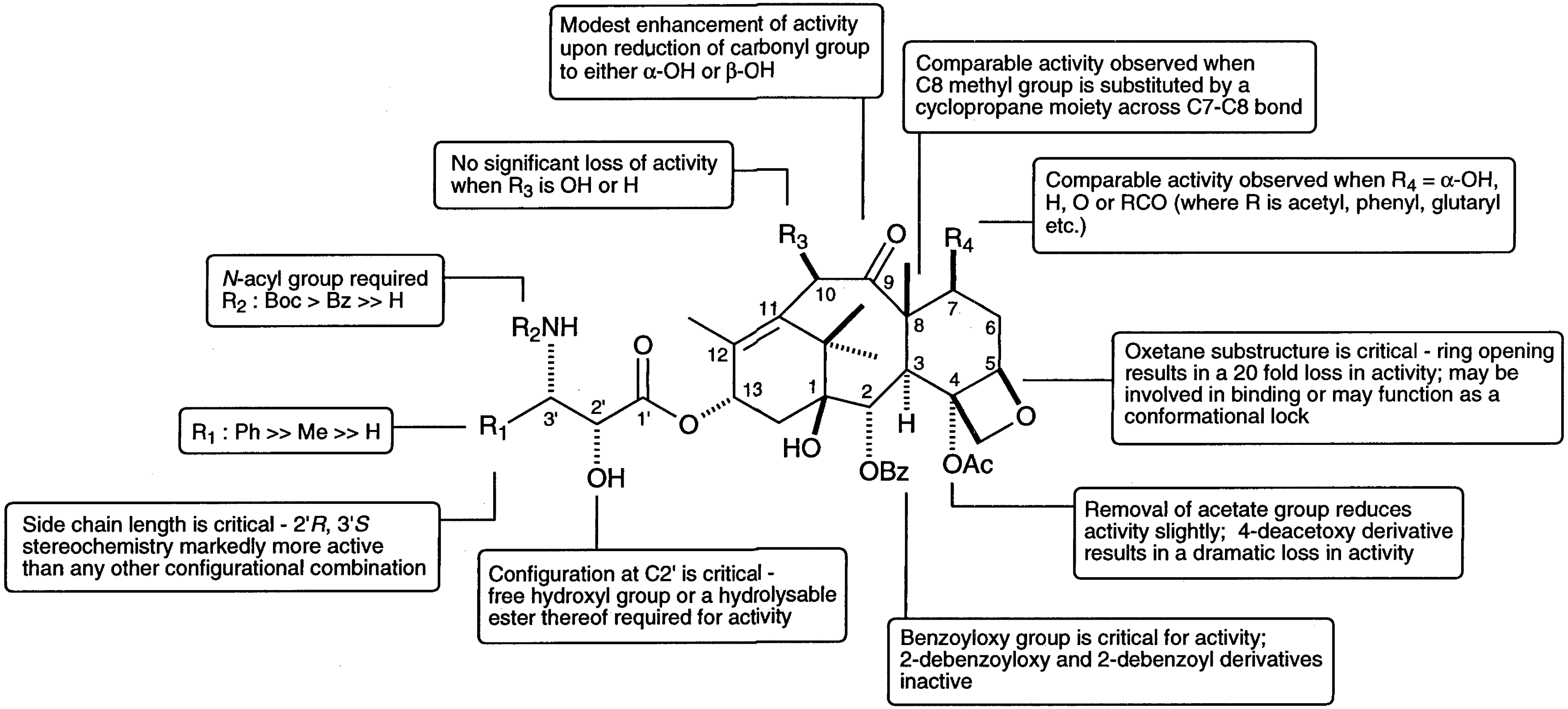
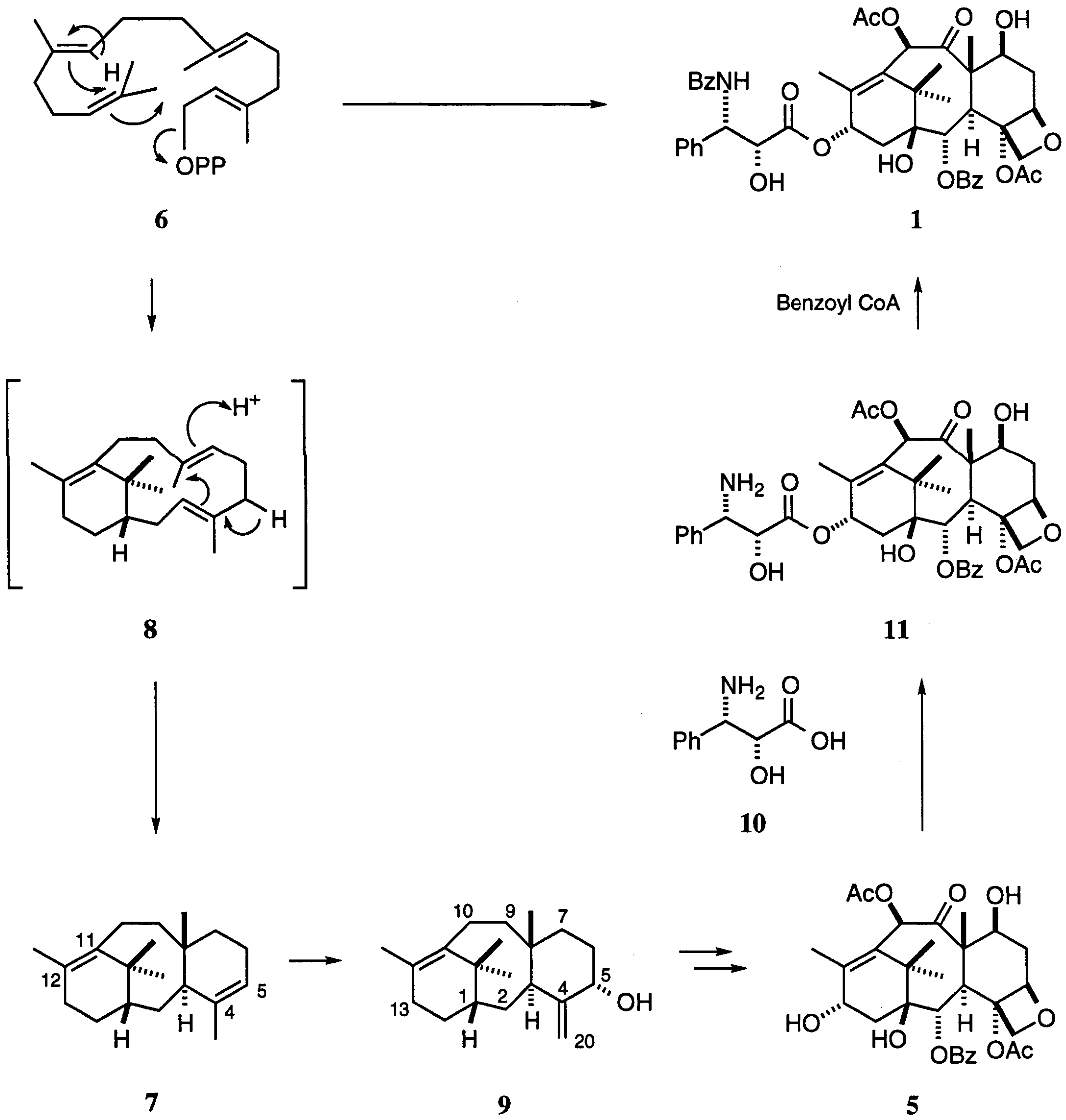


Figure 1.1: Structure-Activity Relationships of Paclitaxel (**1**) (R_1=Ph, R_2=Bz, R_3=OAc, R_4=OH)

1.3 Biosynthesis of Paclitaxel

Relatively little is known about the biosynthetic pathway leading to paclitaxel (**1**) and related taxoids in yew (*Taxus*) species. However, exhaustive radiolabelling studies and feeding experiments conducted by Croteau,[10] (in collaboration with Floss and Williams) have established many of the details concerning the early stages of paclitaxel's biosynthesis, the key elements of which are shown in Scheme 1.1.

It is believed that the first dedicated step in the biosynthesis of paclitaxel



Scheme 1.1

(**1**) involves cyclisation of the common isoprenoid precursor geranylgeranyl diphosphate (**6**) to taxa-4(5),11(12)-diene (**7**). This conversion is mediated by an enzyme, taxadiene synthase, in which 1*S*-verticillene (**8**) is considered a likely intermediate. Oxidative modification of tricycle **7** by the enzyme taxadiene-5-hydroxylase delivers the known biosynthetic intermediate, allylic alcohol **9**. Subsequent to this key event, a succession of oxidations and acylations of the taxane nucleus is presumed to occur. Whilst the order of these oxygenation steps is still the subject of some speculation, it has been suggested that oxygen is first introduced at C10 in compound **9**, followed by oxygenation at C2, C9 and then at C13. Assembly of the oxetane substructure is believed to occur next, presumably *via* initial epoxidation of the C4-C20 double bond and subsequent ring-expansion. Functionalisation at C1 and C7 is thought to occur late in the oxidative sequence. Baccatin III (**5**) so-derived from these oxidation/acylation processes is then coupled with phenylisoserine (**10**), the side-chain pregenitor derived from phenylalanine. Debenzoyltaxol **11** so-derived in this manner is *N*-benzoylated to deliver the natural product **1**.

1.4 Challenges Involved in Assembling the Taxoid Framework

As a consequence of its powerful anti-mitotic properties, novel mode of biological action, limited supply and complex molecular architecture, paclitaxel (**1**) has been described as "one of the most challenging targets for synthesis chemists today".[1h] Whilst methodologies for the preparation of the *N*-benzoylphenylisoserine side chain are now well-established,[11] the development of protocols for the assembly of the taxoid carbon framework have proven much more demanding.

From a synthetic viewpoint, paclitaxel (**1**) presents a multitude of challenges. Firstly, construction of the eight-membered carbocycle associated with the B-ring of **1** is a formidable task in its own right. Such carbocycles are notoriously difficult to construct in a diastereoselective manner due to unfavourable enthalpic and entropic factors. The presence of a bridgehead alkene within the A-ring (formally an *anti*-Bredt olefin), as well as *trans*-ring fusion at the BC-ring junction, augments the difficulties inherent in constructing the carbon framework of **1**.

Adding to the structural complexity of paclitaxel (**1**) is the high degree of oxygenation present as well as the nine stereogenic centres embedded within the carbon backbone. Furthermore, some of the functionality within compound **1** is known to be quite sensitive. For example, the C7 hydroxyl group which, if left unprotected, will epimerise, *via* a retro-aldol/aldol sequence, under basic conditions. The oxetane ring too, is a labile entity and is known to open readily under acidic conditions.

1.5 Previously Reported Total Syntheses of Paclitaxel

To date (September, 1998), five total syntheses of paclitaxel (**1**) have been reported.[12-16] This section serves to summarise these syntheses by highlighting the key strategic elements employed to construct the carbocyclic framework associated with **1**.

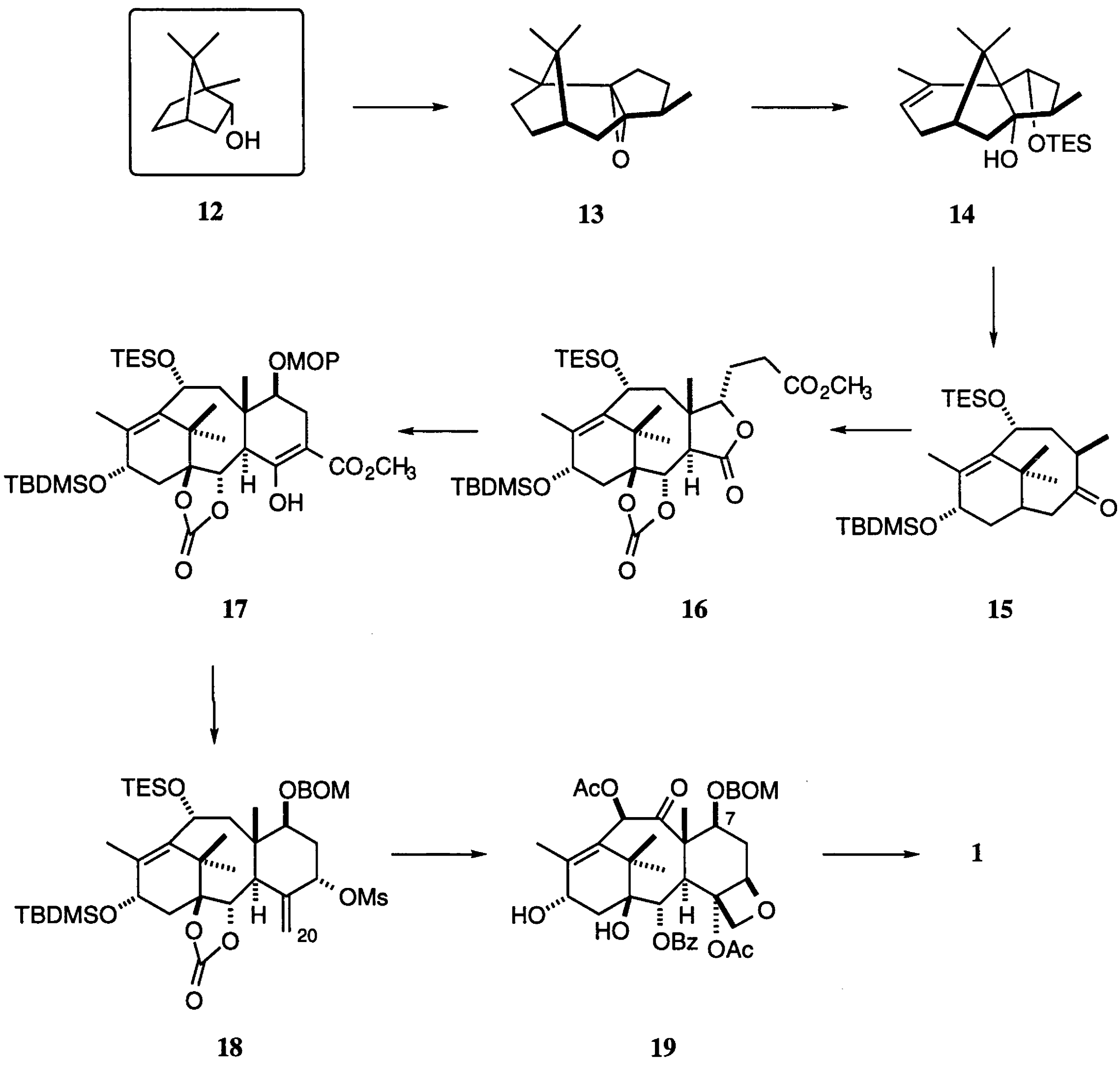
Holton Synthesis - 1994

A linear approach was adopted by the Holton group[12] for the preparation of paclitaxel (**1**) and involved initial assembly of the AB-ring system of **1**, followed by annelation of the C- and D-rings onto this carbocyclic framework.

Beginning from (-)-borneol (**12**) (Scheme 1.2),† the preparation of (+)-β-patchoulene oxide (**13**) was accomplished in 12 steps following known protocols.[17] This material was converted through standard chemistry, which included a Wagner-Meerwein-type rearrangement, to olefin **14**. Facially selective epoxidation of the double bond within compound **14**, followed by Grob-type fragmentation of the resulting intermediate hydroxy-epoxide, then afforded bicycle **15**. In this manner, assembly of the carbon framework associated with the AB-ring system of **1** was achieved. Aldol reaction

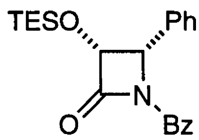
† For convenience, schemes marked thus reappear (in full or abbreviated form) in Appendix 1.

of 4-pentenal (the source of the remaining C-ring carbons) with the magnesium enolate of ketone **15**, followed by functional group manipulation, fashioned the lactone **16**. Base-mediated Dieckmann cyclisation of this latter species delivered the ABC-ring analogue **17**, which was subsequently elaborated to diene **18**. Following protocols similar



Scheme 1.2†

to those reported by Potier,[18] the oxetane D-ring was constructed from the allylic mesyloxy substructure within species **18**. Thus, a key step in the assembly of the heterocyclic D-ring involved dihydroxylation of the exocyclic double bond within compound **18**, followed by nucleophilic attack of the newly introduced C20 hydroxy group onto the carbon bearing the mesyloxy substituent. Further derivatisation afforded 7-BOM baccatin III **19**. The final steps associated with the Holton synthesis of **1** involved coupling, following known protocols,[3a,19] of compound **19** with the side-chain pregenitor **20** (the so-called Ojima lactam).[19d,e]

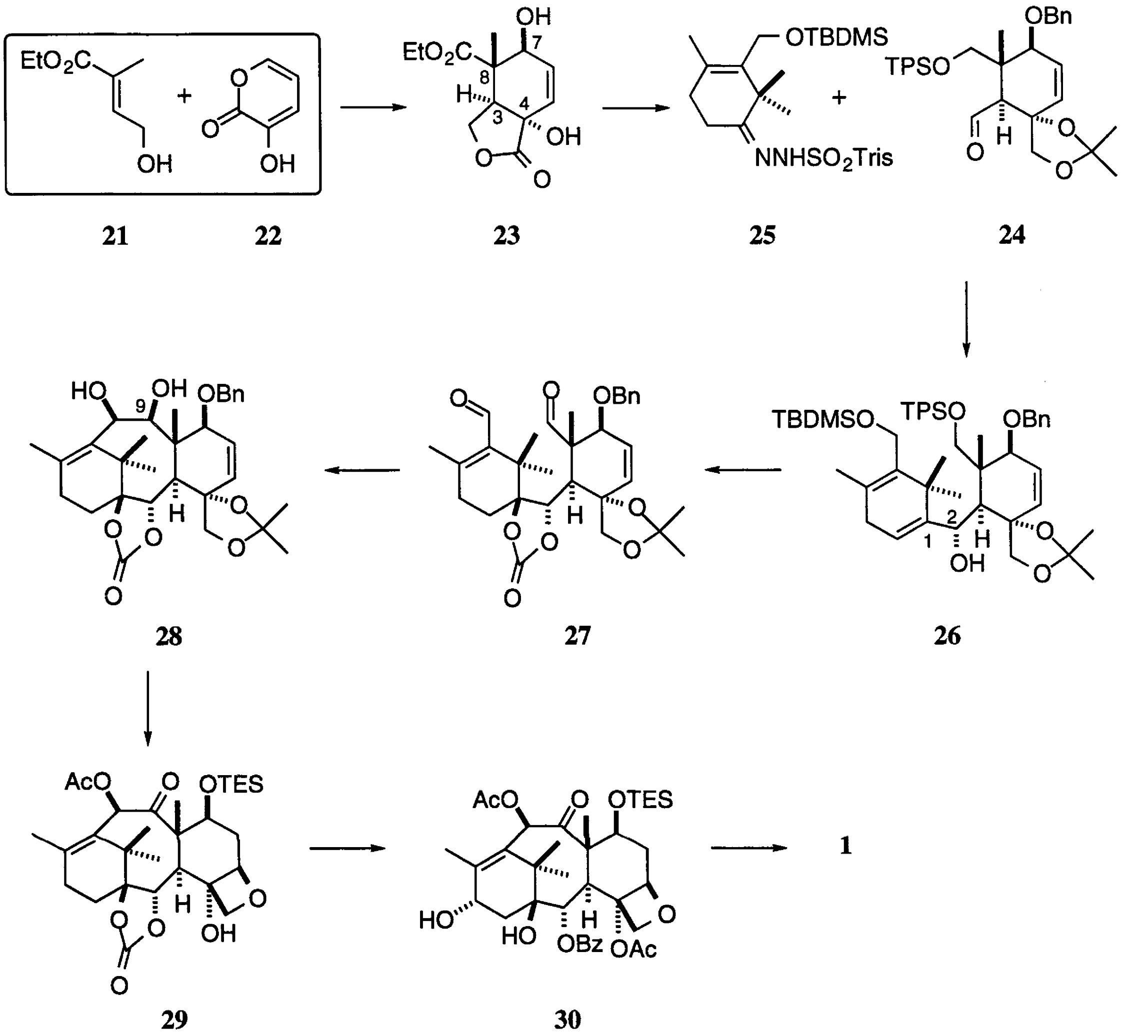


20

Nicolaou Synthesis - 1994

The key element associated with Nicolaou's[13] convergent approach to the synthesis of paclitaxel (**1**) was the intramolecular cyclisation of a highly functionalised AC-ring substructure so as to form the central eight-membered B-ring of **1**.

The stereocontrolled installation of four important structural elements associated with the C-ring of paclitaxel (**1**) (*viz.* α-hydrogen at C3, methyl group at C8 and oxygenation at C4 and C7) was achieved by rearrangement of the Diels-Alder adduct obtained from compounds **21** and **22** (Scheme 1.3). Lactone **23** so-derived was converted to aldehyde **24** through conventional chemical operations. Shapiro reaction between this latter compound and the alkenyllithium species generated from A-ring pregenitor **25** gave alcohol **26**. Having established the important C1-C2 bond connection, compound **26** was elaborated to the highly functionalised dialdehyde **27** which then participated in an intramolecular M^{c}Murray coupling reaction to form the ABC-ring analogue **28**. The synthetic sequence to this point had generated compounds in racemic form, however, access to the correct enantiomer of paclitaxel (**1**) was accomplished *via* a resolution procedure involving chromatographic separation of the C9-camphanyl derivatives formed from the racemic diol **28**. Having established the correct oxygenation pattern associated with the B-ring of **1**, the next objective was to construct the oxetane D-ring. As was the case in the Holton synthesis, a modification of the Potier protocol[18] was employed to this end and, after protective group tuning, pentacycle **29** was obtained. Further oxidation and deprotection steps delivered 7-TES baccatin III **30** which was converted into paclitaxel (**1**) *via* known protocols.[3a,19]

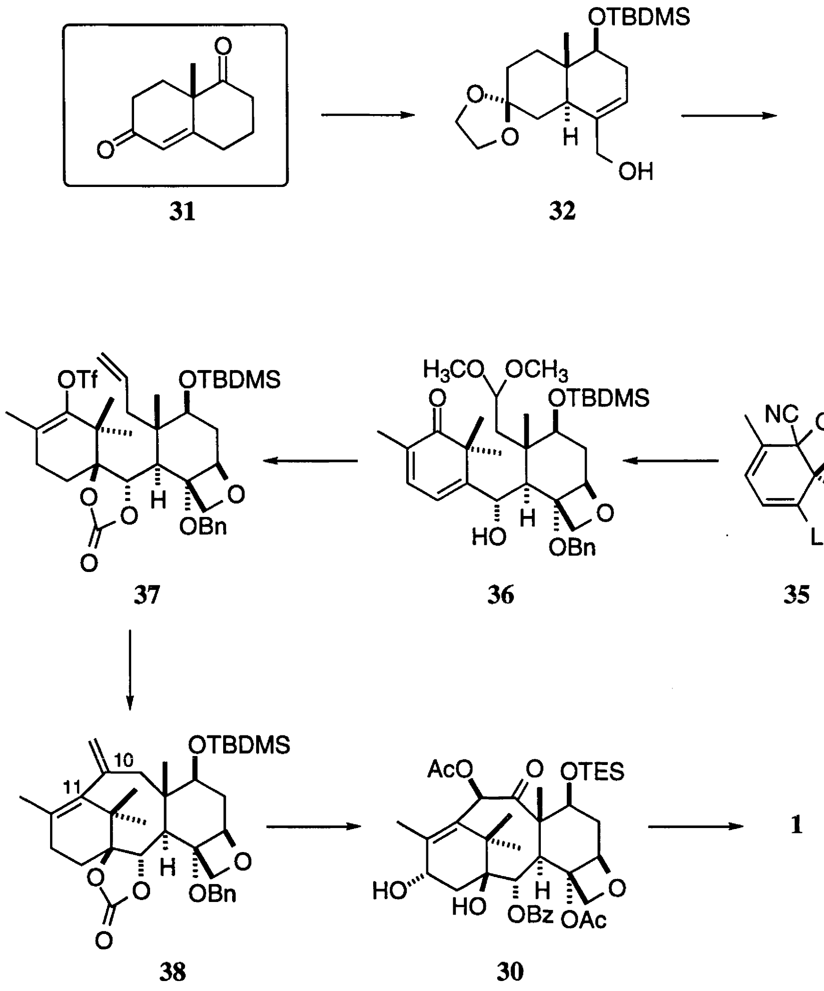


Scheme 1.3†

Danishefsky Synthesis - 1996

In a conceptually different approach to the preparation of paclitaxel (**1**), Danishefsky[14] demonstrated that the sensitive oxetane D-ring could be introduced early on in the synthesis and carried through a multistep sequence (Scheme 1.4).

The Wieland-Miescher ketone (**31**) served as a suitable starting material for this synthesis of paclitaxel (**1**). Its conversion into allylic alcohol **32** was achieved in

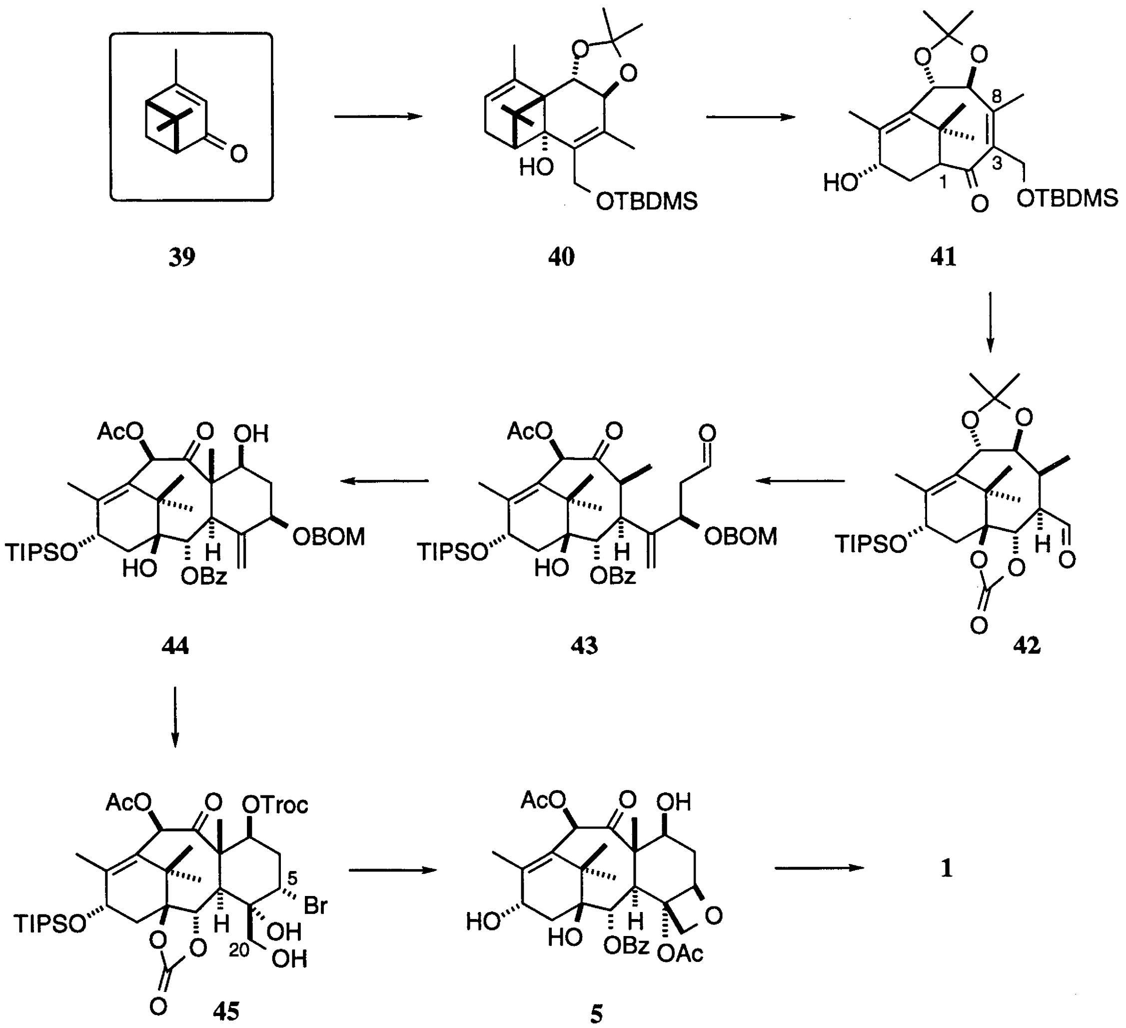


Scheme 1.4†

nine steps utilising standard functional group transformations. Assembly of the heterocyclic D-ring was accomplished *via* initial dihydroxylation of the alkene moiety within compound **32**, followed by cyclisation of an activated triol intermediate. Having thus obtained the fully functionalised CD-ring fragment **33**, this material was readily converted to aldehyde **34**. Coupling of this latter species with A-ring pregenitor **35** formed the intermediate alcohol **36**, which was then appropriately modified to afford the cyclisation precursor **37**. The last major challenge in the preparation of **1** was the construction of the central B-ring. To this end, an intramolecular Heck reaction was employed to establish the required C10-C11 bond connection, thereby affording pentacycle **38**. Further oxidation and deprotection steps gave 7-TES baccatin III **30** which was converted into paclitaxel (**1**) *via* established methods.[3a,19]

Wender Synthesis - 1997

Wender, having recognised that α-pinene could, in principle, supply 10 of the 20 carbons and the chirality of the taxane core, began his synthetic programme[15] (Scheme 1.5) for the total synthesis of paclitaxel (**1**) from verbenone (**39**), the air oxidation product of α-pinene.



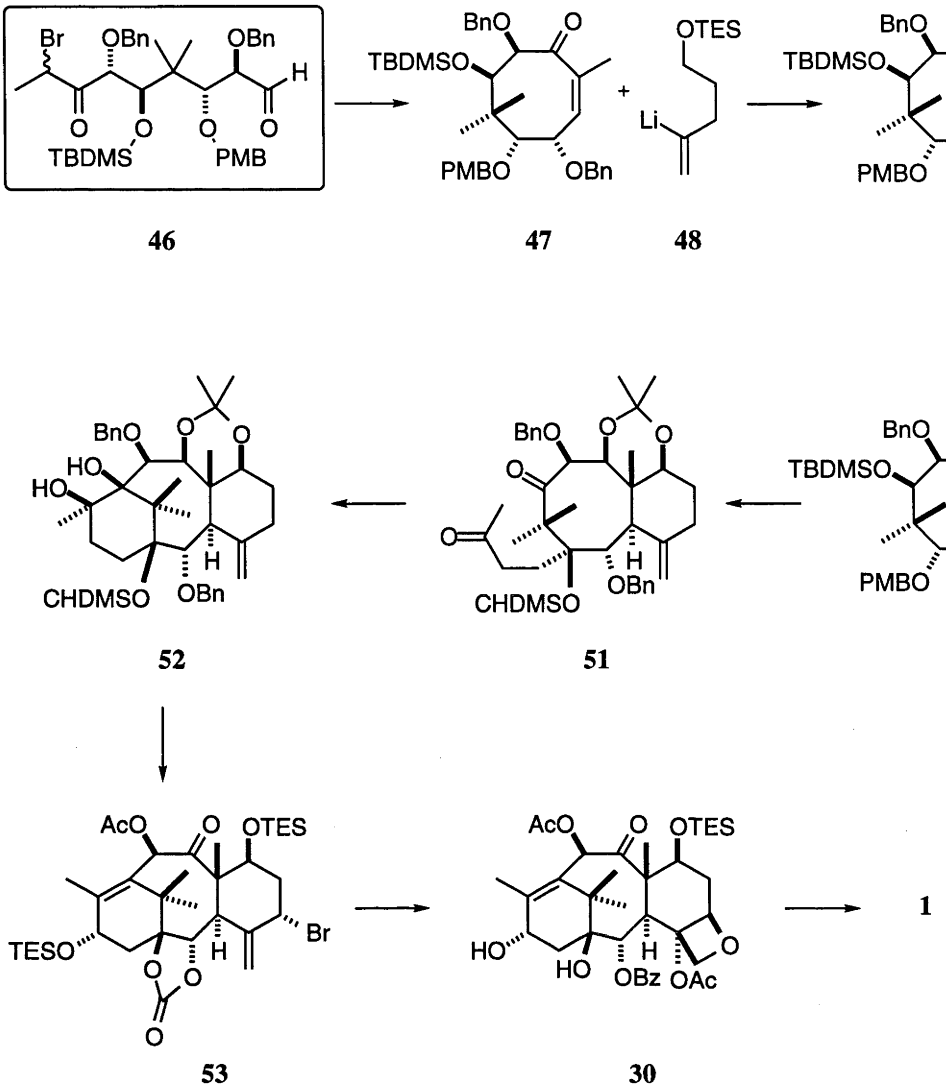
Scheme 1.5†

The conversion of verbenone (**39**) to diene **40** was accomplished through conventional chemical transformations in nine steps. Regioselective epoxidation of the trisubstituted olefin within compound **40** from the sterically less encumbered α-face, followed by base-promoted fragmentation of the resulting hydroxy-epoxide, afforded bicycle **41**. The conformational influence exerted by the acetonide moiety within this latter species allowed for the stereocontrolled introduction of an oxygen substituent at C1 and for the stereoselective reduction of both the ketone and C3-C8 double bond functions within compound **41**. Such operations afforded derivative **42** which possesses the complete carbon framework and oxygenation pattern associated with the AB-ring system of paclitaxel (**1**). Elaboration of **42** to aldehyde **43**, followed by aldol cyclisation, provided the ABC-ring derivative **44**. The final task *en route* to the ABCD-ring system of **1** was the formation of the oxetane ring. To this end, an analogous cyclisation strategy to that used by Holton, Nicolaou and Danishefsky (*viz.* nucleophilic C20 hydroxy, C5 leaving group) was employed, in which bromide **45** is a key intermediate. The preparation of baccatin III (**5**) was then achieved *via* standard deprotection/protection chemistry and its conversion into paclitaxel (**1**) was realised by known methods.[3a,19]

Mukaiyama Synthesis - 1997

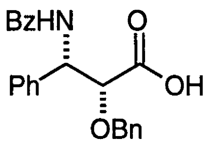
The synthetic strategy employed by Mukaiyama[16] for the preparation of paclitaxel (**1**) was based upon initial construction of the eight-membered B-ring, followed by annelation of the C- and A-rings onto this carbocyclic framework (Scheme 1.6).

Thus, optically pure ketoaldehyde **46** was accessed *via* a nineteen step sequence beginning with *L*-serine.[16a] Treatment of the polyoxygenated compound **46** with excess samarium diiodide promoted an intramolecular aldol cyclisation reaction which, after an elimination process, afforded the B-ring derivative **47**. Michael addition of the cuprate reagent derived from vinyllithium species **48** to enone **47** proceeded in a highly diastereoselective fashion, thereby establishing the required *trans*-stereochemical relationship between the C3 hydrogen and the C8 methyl group (paclitaxel numbering). Minor chemical manipulation of the initial Michael adduct provided ketoaldehyde **49** which underwent an intramolecular aldol reaction upon treatment with base to furnish the BC-ring fragment **50**. Elaboration of this latter species afforded the diketone **51** which, upon exposure to a low-valent titanium reagent, participated in an intramolecular pinacolic



Scheme 1.6†

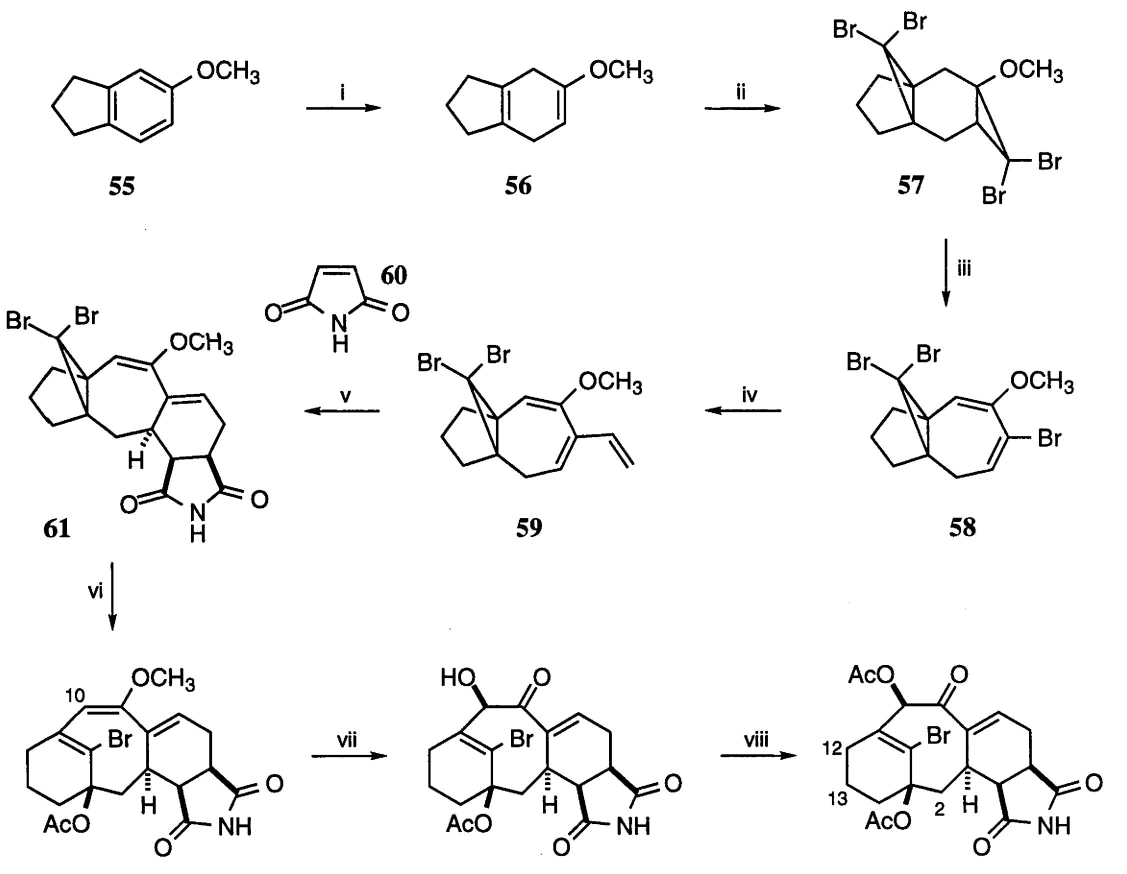
coupling reaction to effect A-ring closure, thereby giving diol **52**. A series of functional group interconversions generated tetracycle **53** which possessed an allylic bromide subunit from which the oxetane D-ring was constructed (*c.f.* Wender synthesis). Finally, 7-TES baccatin III **30** was acylated with the side chain pregenitor **54** to deliver the target **1**.



54

1.6 The Cyclopropane Approach to Assembling the Taxoid Framework

Previous workers in these laboratories[20] have developed a new, simple and efficient method for the assembly of the ABC-ring system of paclitaxel (**1**) which involves cyclohexannulated [5.3.1]propellanes as key intermediates (Scheme 1.7). Thus, initial reduction of commercially available 5-methoxyindane (**55**), under standard Birch conditions, afforded the dihydro-derivative **56**. *bis*-Cyclopropanation of this species with dibromocarbene (generated under phase transfer conditions from bromoform and sodium hydroxide) then gave tetracycle **57**. The *anti*-relationship between the two *gem*-dibromocyclopropyl moieties within compound **57** has been assigned by analogy



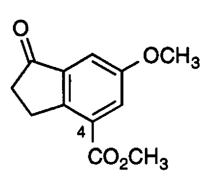
Scheme 1.7

Reagents and Conditions: (i) Li, NH_3, DME, 0.5 h then EtOH; (ii) $CHBr_3$, NaOH, TEBAC, 18 °C, 40 h; (iii) toluene/pyr., 110 °C, 15 h; (iv) (H_2C=CH)$SnBu_3$, $(Ph_3P)_4Pd$, 1,4-dioxane, 18 °C, 40 h; (v) maleimide (**60**), C_6H_6, 18 °C, 15 h; (vi) AgOAc (10 equiv.), CH_2Cl_2, 40 °C, 15 h; (vii) *m*-CPBA, MeOH, 65 °C, 15 h then THF, 5% HCl (aq.); (viii) Ac_2O, C_6H_5N, 18 °C, 15 h.

with the stereochemical outcomes observed in numerous *bis*-dihalocarbene additions to cyclohexa-1,4-diene and its derivatives.[21] Thermolysis of compound **57** in refluxing toluene-pyridine resulted in smooth electrocyclic ring-opening of the oxygenated (and therefore more activated) cyclopropane ring, thus delivering the [5.3.1]propelladiene **58**. Stille cross-coupling of bromodiene **58** with vinyltributylstannane in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst provided triene **59** which readily engaged in a regio- and diastereoselective Diels-Alder reaction with maleimide (**60**), thereby producing the cyclohexannulated [5.3.1]propellane **61**. Treatment of this pentacyclic adduct with silver acetate induced electrocyclic ring-opening and trapping of the resulting π-allyl cation thus provided the ABCD-ring analogue, **62**, of paclitaxel (**1**). Epoxidation of enol ether **62** with *m*-CPBA in methanol, followed by acid hydrolysis of the acetal intermediate, afforded acyloin **63**. Acetylation of the free hydroxy group associated with the latter compound then gave *bis*-acetate **64**.

Whilst this synthetic sequence provides access to usefully functionalised ABCD-ring analogues of paclitaxel (**1**) in a concise and facile manner, the compounds so obtained are generated in racemic form. Another deficiency of the synthetic pathway just described is that there is no opportunity in which to introduce C2 oxygenation√ or substituents onto the A-ring, *viz.* the C12 methyl group and oxygenation at C13. Functionalisation at C13 is especially important, since it is the site of side-chain attachment.

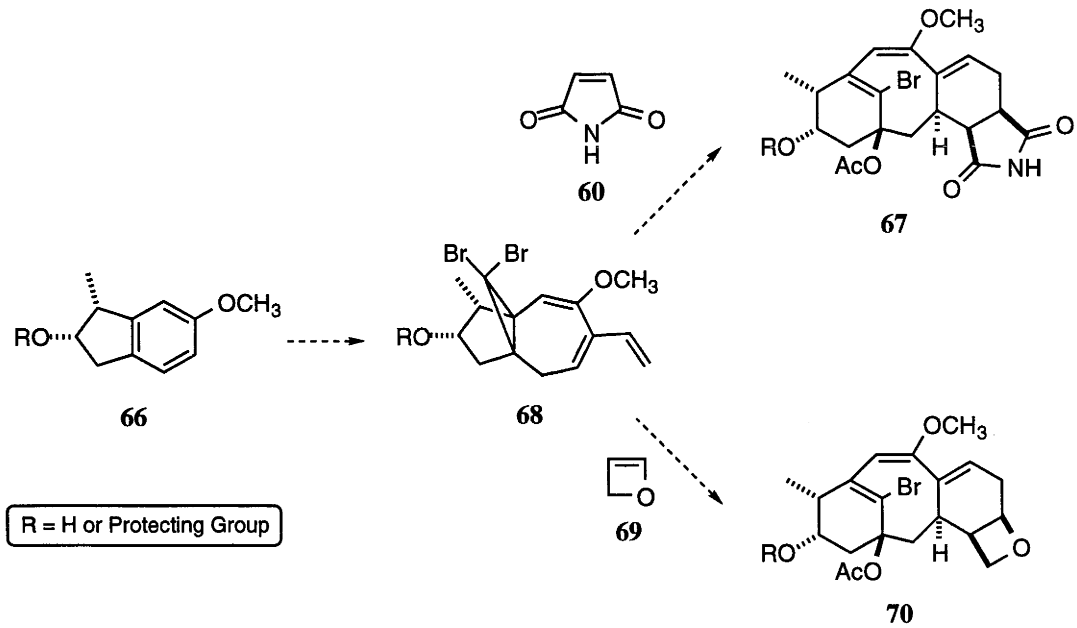
√ Methods for the incorporation of an oxygen substituent at C2 are currently under investigation by another worker in these laboratories. The most promising of the approaches studied thus far involves the preparation of the previously unknown indanone **65** (S. G. Stewart, unpublished observations). It is envisaged that Baeyer-Villiger oxidation of the C4 carbomethoxy substituent [equivalent to C2 in paclitaxel (**1**)] will allow for the introduction of oxygen at C2, as required in biologically active taxanes.



65

1.7 Aims of this Work

The aim of the research work presented in this thesis was to generate more highly substituted analogues of compound **64** and to obtain such materials in optically pure form. To this end, it was envisaged that chiral indanols of the type **66** (Scheme 1.8) could serve as suitable starting materials for the synthesis of enantiopure ABCD-ring analogues of paclitaxel (**1**). The lack of synthetic protocols for the generation of such indanols required that an appropriate examination of methods for their preparation be undertaken. The results of this study are outlined in Chapter 2.



Scheme 1.8

Chapter 3 describes the synthesis of enantiopure taxoids of the type **67**, based upon the methodology described in Section 1.6 (page 16). Compounds such as **67** are derived from a Diels-Alder reaction between the key intermediate triene **68** and maleimide (**60**), which functions as a D-ring surrogate.

Chapter 4 details efforts to develop new methods for the synthesis of oxete (**69**), required for the purpose of investigating its ability to participate in a Diels-Alder cycloaddition reaction with diene **68**. The success of such an operation would, in principle, provide a novel and concise route to analogues of paclitaxel (**1**), such as compound **70**, which possess the complete ABCD-ring system associated with this natural product.

1.8 References

1. For some excellent reviews concerned with the history, chemistry and/or biology of paclitaxel and taxoids, see: (a) M. E. Wall and M. C. Wani in *Alkaloids: Chemical and Biological Perspectives*, S. W. Pelletier, Ed.; Pergamon Press, 1995, Vol. 9, Chapter 1, p. 1; (b) Taxane Anticancer Agents: Basic Science and Current Status, *ACS Symposium Series* **583**, G. I. Georg, T. T. Chen, I. Ojima and D. M. Vyas, Eds.; 1995; (c) K. C. Nicolaou, W-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; (d) A. N. Boa, P. R. Jenkins and N. J. Lawrence, *Contemp. Org. Synth.*, 1994, **1**, 47; (e) D. G. I. Kingston, A. A. Molinero and J. M. Rimoldi, *Prog. Chem. Nat. Prod.*, 1993, **61**, 1; (f) D. Guénard, F. Guéritte-Voegelein and P. Potier, *Acc. Chem. Res.*, 1993, **26**, 160; (g) M. Suffness, *Annual Reports in Medicinal Chemistry*, Academic Press, New York, 1993, Vol. 28, Chapter 32; (h) C. S. Swindell, *Org. Prep. Proc. Int.*, 1991, **23**, 465; (i) G. I. Georg, S. M. Ali, J. Zygmunt and L. R. Jayasinghe, *Exp. Opin. Ther. Patents*, 1994, **4**, 109.
2. M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.
3. (a) R. A. Holton, Eur. Pat. Appl. EP 400,971, 1990 (*Chem. Abstr.*, 1991, **114**, 164568q); (b) R. A. Holton, *Workshop on Taxol and Taxus: Current and Future Perspectives*, National Cancer Institute, Bethesda, MD, USA, 26 June 1990.
4. (a) A. A. Christen, D. M. Gibson and J. Bland, US-A 5019504, 1992; (b) E. Blume, *J. Natl. Cancer. Inst.*, 1991, **83**, 1054.
5. S. Bormann, *Chem. Eng. News*, 1992, **70** (41), 30.
6. D. A. Fuchs and R. K. Johnson, *Cancer Treat. Rep.*, 1978, **62**, 1219.
7. P. B. Schiff, J. Fant and S. B. Horowitz, *Nature*, 1979, **277**, 665.
8. R. Finlay, *Chem. Ind.*, 1997, 991.
9. The clinical use of paclitaxel has been reviewed, see: (a) E. K. Rowinsky, L. A. Cazenave and R. C. Donehower, *J. Natl. Cancer Inst.*, 1990, **82**, 1247; (b)

E. K. Rowinsky and R. C. Donehower, *J. Natl. Cancer Inst.,* 1991, **83**, 1778; (c) E. K. Rowinsky, N. Onetto, R. M. Canetta and S. G. Arbuck, *Semin. Oncol.*, 1992, **19**, 646.

10. For reviews on the biosynthesis of paclitaxel and taxoids, see: (a) J. Rohr, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2190; (b) Taxane Anticancer Agents: Basic Science and Current Status, *ACS Symposium Series* **583**, G. I. Georg, T. T. Chen, I. Ojima and D. M. Vyas, Eds.; 1995, Chapter 5, p. 72 and references cited there-in.

11. (a) J. Rohr, *Nachr. Chem. Tech. Lab.*, 1993, **41**, 559; (b) K. C. Nicolaou, W-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; (c) J-N. Denis, A. Correa and A. E. Greene, *J. Org. Chem.*, 1990, **55**, 1957; (d) G. Li, H-T. Chang, K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451; (e) C. Gennari, A. Vulpetti, M. Donghi, N. Mongelli, E. Vanotti, *Angew. Chem., Int. Ed. Engl.,* 1996, **35**, 1723 and references cited there-in.

12. (a) R. A. Holton, C. Somoza, H-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1597; (b) R. A. Holton, H-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1599.

13. (a) K. C. Nicolaou, Z. Yang, J.-J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan and E. J. Sorensen, *Nature*, 1994, **367**, 630; (b) K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros and E. J. Sorensen, *J. Am. Chem. Soc.*, 1995, **117**, 624; (c) K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada and P. G. Nantermet, *J. Am. Chem. Soc.*, 1995, **117**, 634; (d) K. C. Nicolaou, Z. Yang, J.-J. Liu, P. G. Nantermet, C. F. Claiborne, J. Renaud, R. K. Guy and K.

Shibayama, *J. Am. Chem. Soc.*, 1995, **117**, 645; (e) K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan and R. Chadha, *J. Am. Chem. Soc.*, 1995, **117**, 653.

14. S. J. Danishefsky, J. M. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn and M. J. Di Grandi, *J. Am. Chem. Soc.,* 1996, **118**, 2843.

15. (a) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Gränicher, J. B. Houze, J. Jänichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Mühlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor and K. Tomooka, *J. Am. Chem. Soc.*, 1997, **119**, 2755; (b) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton and R. E. Taylor, *J. Am. Chem. Soc.*, 1997, **119**, 2757.

16. (a) T. Mukaiyama, I. Shiina, H. Iwadare, H. Sakoh, Y. Tani, M. Hasegawa and K. Saitoh, *Proc. Japan Acad.*, 1997, **73**, Ser. B, 95; (b) I. Shiina, H. Iwadare, H. Sakoh, M. Hasegawa, Y. Tani and T. Mukaiyama, *Chem. Lett.*, 1998, 1; (c) I. Shiina, K. Saitoh, I. Fréchard-Ortuno and T. Mukaiyama, *Chem. Lett.*, 1998, 3.

17. (a) G. Büchi, W. D. MacLeod Jr. and J. Padilla, *J. Am. Chem. Soc.*, 1964, **86**, 4438; (b) R. V. Stevens and F. C. A. Gaeta, *J. Am. Chem. Soc.*, 1977, **99**, 6105.

18. L. Ettouati, A. Ahond, C. Poupat and P. Potier, *Tetrahedron*, 1991, **47**, 9823.

19. For procedures using a C13 alkoxide/β-lactam coupling to attach the paclitaxel side-chain, see: (a) R. A. Holton, US Patent 5,015,744, 1991; (b) R. A. Holton, US Patent 5,136,060, 1992; (c) R. A. Holton, US Patent 5,175,315, 1992; (d) I. Ojima, I. Habus, M. Zhao, G. I. Georg and L. R. Jayasinghe, *J. Org. Chem.*, 1991, **56**, 1681; (e) I. Ojima, I. Habus, M. Zhao, M. Zucco, Y. H. Park, C. M. Sun and T. Brigaud, *Tetrahedron*, 1992, **48**, 6985; (f) I. Ojima, C. M. Sun, M.

Zucco, Y. M. Park, O. Duclos and S. Kuduk, *Tetrahedron Lett.*, 1993, **34**, 4149.

20. M. G. Banwell, R. W. Gable, S. C. Peters and J. R. Phyland, *J. Chem. Soc., Chem. Commun.*, 1995, 1395.

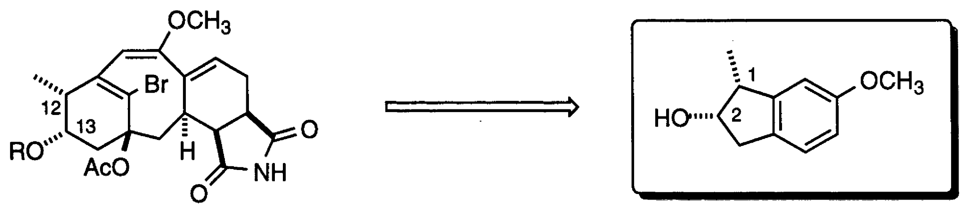
21. M. G. Banwell and B. Halton, *Aust. J. Chem.*, 1979, **32**, 849 and references cited there-in.

CHAPTER 2

Synthesis of Chiral Indanols

2.1 Overview

This chapter describes efforts to obtain indanol **71** (Scheme 2.1) in optically pure form.* As noted (Scheme 1.8) in the preceeding chapter, it was envisaged that this compound would serve as a suitable starting material for the preparation of enantiopure taxane derivatives, such as tetracycle **67**, in which the A-ring substituents, *viz.* C13 oxygenation and the C12 methyl group (paclitaxel numbering), have been acknowledged.



67 **71**

R = H or Protecting Group

Scheme 2.1

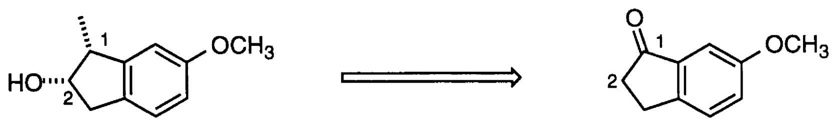
2.2 Asymmetric Oxidation Strategies

Commercially available 6-methoxyindan-1-one (**72**)[1] (Scheme 2.2) was identified as an appropriate starting material for the preparation of indanol **71**.‡ In the first instance, efforts were focussed on the challenging task of introducing, in a highly enantioselective manner, an oxygen substituent at C2 of indanone **72** (or derivatives

---

* Indanol **71** was targeted for two reasons - (i) the configuration at C2 [equivalent to C13 in paclitaxel (**1**)] is as observed in the natural product and (ii) it was believed that a *cis*-relationship between the C1 methyl group and the C2 oxygen substituent may be important in directing the diastereoselectivity of the pivotal carbene addition reaction associated with the present approach to the taxane carbocyclic framework (see Chapter 3).

‡ Literature methods for the preparation of chiral indanols (in which the C1 position and the aromatic ring may or may not be substituted) include enzymatic kinetic resolution of racemic materials,[2] microbial oxidation of aromatic substrates,[3] and intramolecular Friedel-Crafts acylation involving phenylalanine derivatives as substrates.[4]



71 **72**

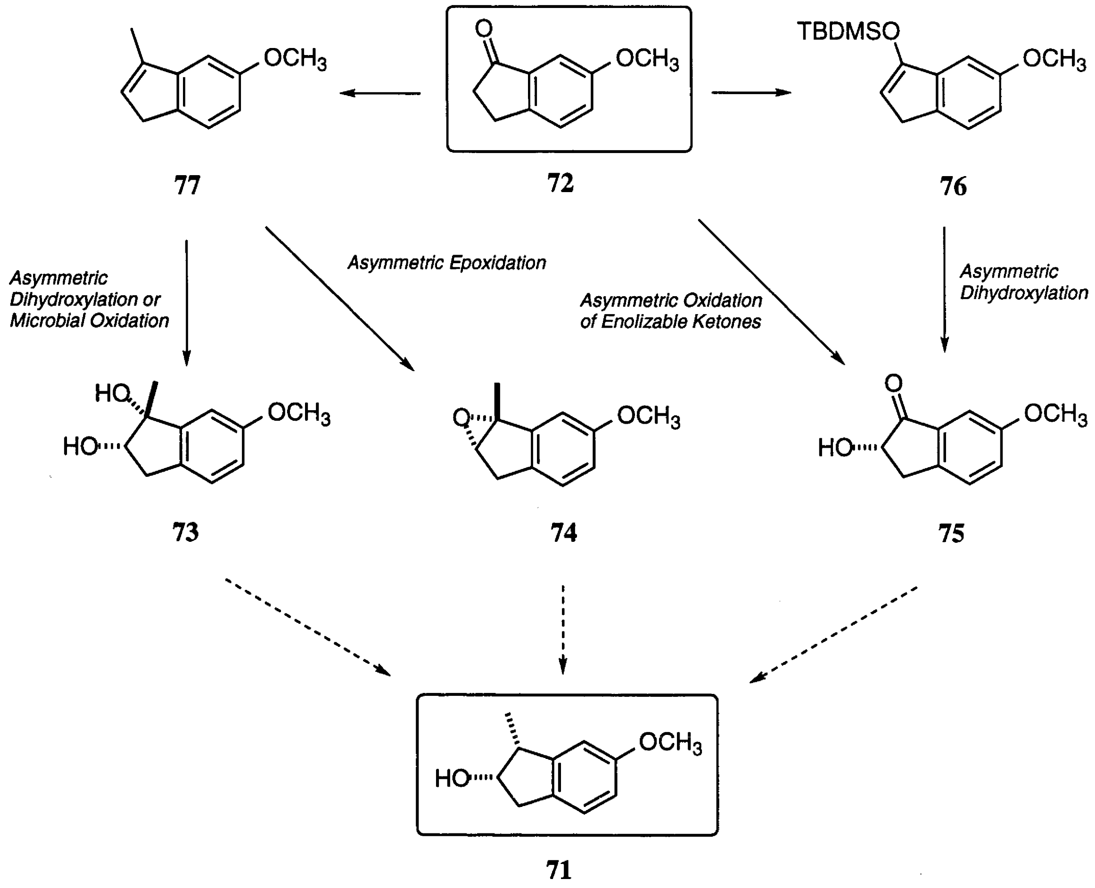
Scheme 2.2

thereof).

There are many well-established methodologies available to the synthesis chemist for the asymmetric oxidation of organic molecules. A number of these were investigated in order to generate a variety of C2 oxygenated indanes, such as compounds **73**, **74** and/or **75** (Scheme 2.3)[π] which could, in principle, be elaborated to the target indanol **71**.[¶] Oxidation of enolizable ketones using optically pure (camphorylsulfonyl)oxaziridine reagents[7] (the Davis-type reagents) offers a direct method for enantioselective functionalisation adjacent (α) to a carbonyl group.[8] Consequently, it was anticipated that subjection of indanone **72** to this protocol would deliver α-hydroxyketone **75**, which might also be accessed *via* asymmetric dihydroxylation[9] of silyl enol ether **76**. Another simple derivative of ketone **72**, *viz.* 6-methoxy-1-methyl-3*H*-indene (**77**), was considered to be a particularly useful substrate for asymmetric oxidation because the products so-derived would possess the methyl group as ultimately required in the target indanol **71**. Thus, chemically or microbiologically-mediated enzymatic dihydroxylation[3] of olefin **77** should furnish diol **73**. Asymmetric epoxidation[10] of the same substrate should form epoxide **74**. Efforts to implement these types of oxidation strategies are described below.

π For the sake of simplicity, only the desired enantiomeric compounds are shown.

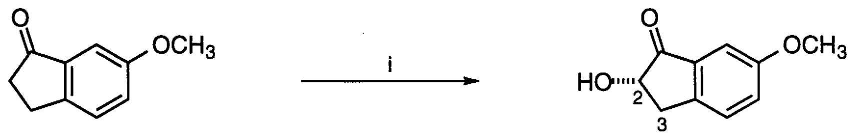
¶ We envisaged that indanol **71** may be generated from compounds **73**, **74** and/or **75** in the following ways: (i) **73** → **71** *via* hydrogenolytic cleavage of the benzylic hydroxy group with inversion of C1 stereochemistry;[5] (ii) **74** → **71** *via* epoxide ring-opening with concomitant inversion of the C1 methyl group stereochemistry using $NaCNBH_4$;[6] (iii) **75** → **71** *via* Grignard addition of MeMgCl followed by hydrogenolytic cleavage or, Wittig olefination followed by hydrogenation.



Scheme 2.3

(i) Asymmetric Oxidation of Enolizable Ketones

Employing the method of Davis,[11] the sodium enolate derived from 6-methoxyindan-1-one (**72**) was treated, at -70 °C, with a solution of (+)-(camphorylsulfonyl)oxaziridine (**78**) in THF (Scheme 2.4). As a result, α-hydroxyketone **75** was obtained as a colourless solid and in 60-70% enantiomeric excess (ee), as determined by chiral HPLC analysis. Despite the potentially useful enantioselectivities observed in this reaction, the chemical yields of the desired product were poor (5-35%) which can, in part, be attributed to the difficulties associated with separation of the oxaziridine-derived by-product, camphorsulfonimine **79**, from the target acyloin **75**. An optically pure sample of the major enantiomeric acyloin derived from this reaction, *viz.* (+)-**75**, was obtained by fractional recrystallisation of the chromatographed product.

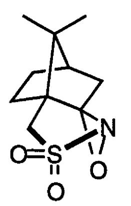


72 **75**

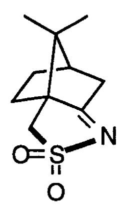
Scheme 2.4

Reagents and Conditions: (i) NaHMDS, (+)-(camphorylsulfonyl)oxaziridine (**78**), THF, -70 °C, 25 mins then NH_4I (aq.).

All physical and spectroscopic data obtained for compound (+)-**75** were in full accord with the assigned structure. Thus, the 70 eV EI mass spectrum displayed the molecular ion (*m/z* 178) as the base peak and the elemental composition of this species was determined to be $C_{10}H_{10}O_3$ by accurate mass measurement. Satisfactory microanalytical data were also obtained on this compound. The infrared spectrum displayed an intense absorption maximum at 3473 cm^{-1}, diagnostic for the newly introduced hydroxy group. As expected, ten carbon resonances were observed in the APT ^{13}C NMR¢ spectrum of alcohol (+)-**75**, the signal at δ 74.8 corresponding to the oxygenated carbon at C2. The ^1H NMR spectrum displayed a broad doublet of doublets (*J* 7.6 and 5.0 Hz) at δ 4.55 which was assigned to the methine proton at C2. Two mutually coupled doublet of doublets appearing at δ 3.52 (*J* 16.3 and 7.7 Hz) and 2.94



(+)-**78**

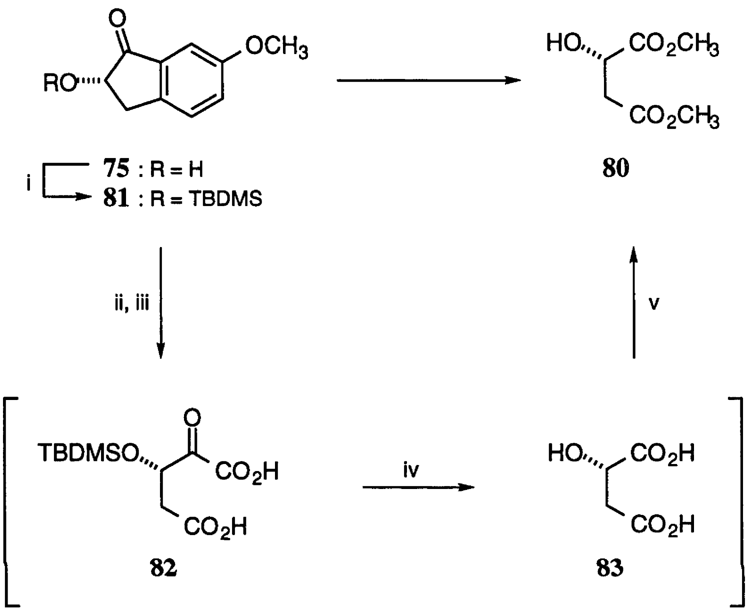


(-)-**79**

¢ Unless otherwise noted, all APT ^{13}C NMR and ^1H NMR spectra described in this thesis were recorded at 75.4 and 300 MHz, respectively.

(J 16.3 and 4.2 Hz) were assigned to the diastereotopic methylene protons associated with C3. A three-proton singlet, corresponding to the methoxy methyl group protons, was observed at δ 3.84 whilst the aromatic protons appeared in the region δ 7.40-7.20.

The absolute configuration of the major enantiomeric α-hydroxyketone, (+)-**75**, produced in the forementioned reaction was established by oxidative degradation[12] to the known compound, dimethyl (*S*)-(-)-malate (**80**) (Scheme 2.5). In



Scheme 2.5

Reagents and Conditions: (i) TBDMSCl, imidazole, DMF, 0 °C - rt, 16 h; (ii) O_3, CH_2Cl_2, -70 °C, 2 h; (iii) H_2O_2; (iv) AcOH, 70 °C, 1 h; (v) CH_2N_2, ether, 0 °C - rt, 20 h.

order to prevent possible oxidation of the secondary hydroxy group associated with acyloin (+)-**75** during the degradation sequence (and thus loss of all stereochemical information), an enantiomerically enriched sample (60% ee) of this material was first converted to the *tert*-butyldimethylsilyl derivative **81** using well-established protocols.[13] Then, a solution of compound **81** in dichloromethane, maintained at -70 °C, was treated with ozone gas for 2 hours. Oxidative work-up of the crude reaction mixture using hydrogen peroxide afforded diacid **82**.∂ This compound was heated at 70 °C for 1 hour in the presence of acetic acid to form, after a decarboxylation/oxidation sequence, malic acid (**83**).∂ Esterification of this intermediate using diazomethane afforded diester **80** as a colourless oil. Analysis of this material by chiral gas chromatography revealed a 1:4 integral ratio of peaks at retention times corresponding to dimethyl (*R*)- and dimethyl (*S*)-malate, respectively.£ Thus, the absolute configuration of the major enantiomeric α-hydroxyketone (+)-**75** (Scheme 2.4) was assigned as (*S*).

(ii) Sharpless Asymmetric Dihydroxylation (AD)

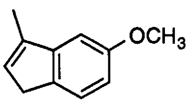
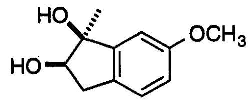
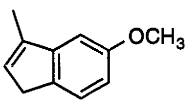
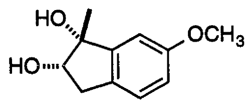
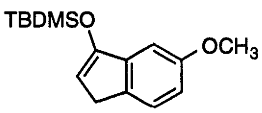
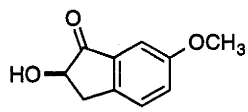
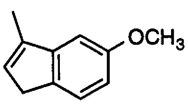
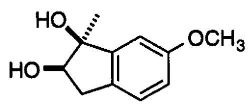
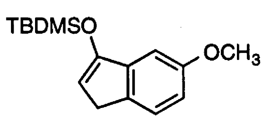
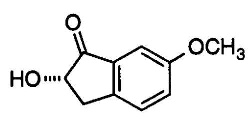
The Sharpless Asymmetric Dihydroxylation (AD) reaction[14] is an extremely general and reliable method for the oxidation of organic compounds. The chemistry associated with the AD reaction is sufficiently well-established such that there is a defined ligand preference (as a function of olefin substitution pattern) for achieving optimal enantioselectivities. In the case of trisubstituted double bonds (including enol ethers),[9] the ligands of choice are those based on a phthalazine (PHAL) unit, *viz.* PHAL(DHQ)$_2$◊ and PHAL(DHQD)$_2$, which often deliver enantioselectivities in the range of 90-99% ee.

As was mentioned earlier (page 26), compounds **76** and **77** were deemed to be suitable substrates for asymmetric dihydroxylation and the chemistry associated with their preparation was straightforward. Thus, trapping of the enolate anion derived from indanone **72** with *tert*-butyldimethylsilyl triflate afforded silyl enol ether **76**, whilst olefin **77** was prepared in multigram quantities *via* Grignard addition of methylmagnesium chloride to indanone **72**, followed by acid-catalysed dehydration of the resulting tertiary alcohol. With these substrates in hand, compounds **76** and

∂ The degradation experiment was carried out in the 'one pot' and so, compounds thus marked were not isolated but are the expected intermediates in the reaction sequence.
£ The integral ratio observed provided a useful cross-check for the enantiopurity of the starting acyloin **75**.
◊ The PHAL(DHQ)$_2$ and PHAL(DHQD)$_2$ ligands are commercially available in convenient, ready-to-use mixes (*viz.* AD-mix-α and AD-mix-β, respectively) from the ALDRICH Chemical Company. DHQ and DHQD refer to the alkaloids dihydroquinine and dihydroquinidine, respectively.

77 were oxidized according to the method of Sharpless *et al.*[9] and the optical purities of the products so-derived are summarised in Table 2.1. Dihydroxylation of methylindene **77** using PHAL(DHQ)$_2$ (Table 2.1, entry 1) afforded diol (-)-**73** as a colourless solid in

Table 2.1: Enantiopurity of Products Derived from Asymmetric Dihydroxylation of Substrates **76** and **77**.

Entry	Substrate	Ligand[a]	Product[b,c]	Yield[d] (%)	ee[e] (%)
1	 **77**	PHAL(DHQ)$_2$	 (-)-**73**	91	69
2	 **77**	PHAL(DHQD)$_2$	 (+)-**73**	88	52
3	 **76**	PHAL(DHQ)$_2$	 (-)-**75**	43 (at 92% conv.)	55
4	 **77**	AQN(DHQD)$_2$	 (-)-**73**	85	25
5	 **76**	AQN(DHQD)$_2$	 (+)-**75**	52	44

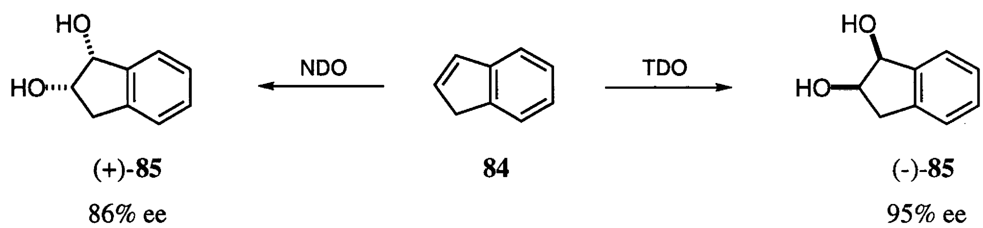
[a] Commercially available AD-mix-α and AD-mix-β were used as the source of the ligands PHAL(DHQ)$_2$ and PHAL(DHQD)$_2$, respectively. See Experimental Section for the preparation of the ligand AQN(DHQD)$_2$. [b] The absolute configuration of the products shown in this table have been determined (see Sections 2.2 and 2.4). [c] The ^{1}H NMR and APT ^{13}C NMR spectroscopic data associated with compounds (+)-**75** and (-)-**75** were identical, in all respects, with a sample obtained previously (Scheme 2.4). [d] Refers to yield after chromatography. [e] Enantiomeric excesses (ee's) were determined by chiral HPLC analysis. See Experimental Section for details.

69% ee. Its enantiomer, diol (+)-**73**, was obtained in 42-52% ee when the ligand PHAL(DHQD)$_2$ was employed (Table 2.1, entry 2). Oxidation of silyl enol ether **76** using PHAL(DHQ)$_2$ (Table 2.1, entry 3) afforded α-hydroxyketone (-)-**75** with comparable enantioselectivity (55% ee) but in substantially lower yield. A new class of AD ligand, *viz.* the anthraquinone (AQN) based ligands,[15] have recently been developed by Sharpless and, in many cases, show improved enantioselectivities over the phthalazine based ligands. Consequently, the former ligands were examined in the hope of improving the enantioselectivities seen thus far. In the event, however, dihydroxylation of olefin **77** using AQN(DHQD)$_2$ (Table 2.1, entry 4) afforded diol (-)-**73** with a dramatic reduction in enantioselectivity (25% ee). The same trend was observed in the case of oxidation of enol ether **76** (Table 2.1, entry 5), in that acyloin (+)-**75** was obtained in only 44% ee.

Despite the modest stereoselectivities obtained, the optical purity of the products generated in the AD reaction could be enhanced by fractional recrystallisation. For example, the enantiopurity of diol (+)-**73** was improved from 52% ee to >96% ee after one recrystallisation.

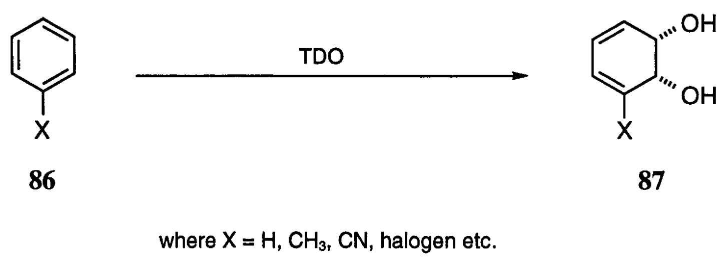
(iii) Microbial Oxidation

Microbial oxidation of organic substrates is emerging as an increasingly popular method for the large scale preparation of new and novel optically active materials.[3] Of particular relevance to the present discussion is the known microbial oxidation of indene (**84**)[16] (Scheme 2.6). Depending upon the nature of the enzyme



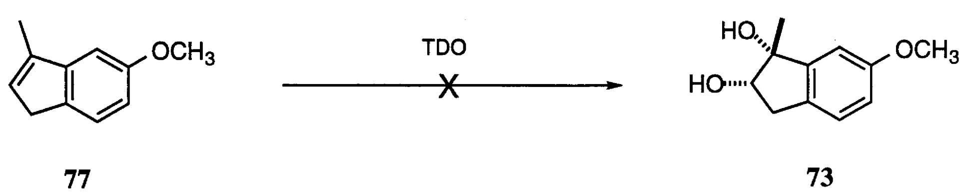
Scheme 2.6

used in the biotransformation process, diol (+)-**85** or its enantiomer (-)-**85**, can be obtained with high levels of enantioselectivity. The enzymes used in the forementioned biotransformation, *viz.* toluene dioxygenase (TDO) and naphthalene dioxygenase (NDO), display remarkably broad substrate tolerances.[3] For example, TDO is used in the microbial oxidation of a variety of substituted arenes **86** to the corresponding *cis*-1,2-dihydrocatechols **87**[17] (Scheme 2.7).



Scheme 2.7

Our experience in carrying out the latter biotransformation, coupled with a desire to extend our knowledge as to what type of substrates can be oxidized by TDO, prompted us to subject olefin **77** to the appropriate biotransformation conditions. In the event, however, no reaction was observed (Scheme 2.8). Despite this outcome, microbial degradation of methylindene **77** warrants further investigation. Exposure of this substrate to the increasing library of enzymes which are capable forming *cis*-dihydrodiols from arene substrates may uncover a suitable enzyme system capable of bringing about the desired transformation (i.e. Scheme 2.8).

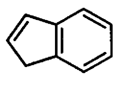
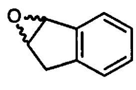
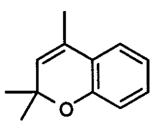
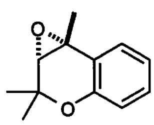
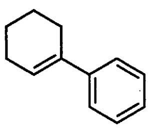
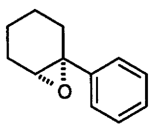


Scheme 2.8

(iv) Asymmetric Epoxidation

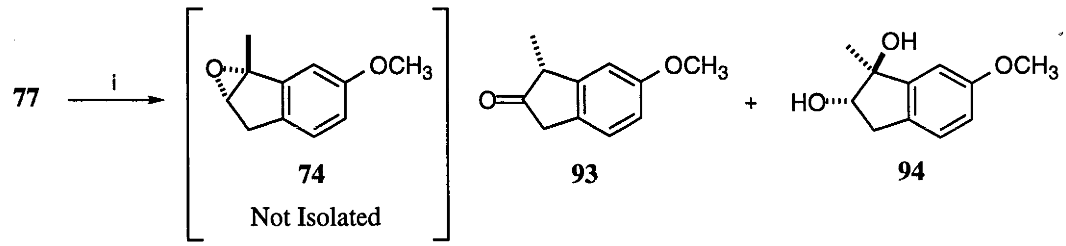
Enantioselective epoxidation of alkenes is an appealing strategy for the synthesis of optically active organic molecules. Complementary to the titanium (IV) tartrate catalysed epoxidation of allylic alcohols[18] is the epoxidation of unfunctionalised alkenes using chiral (salen)manganese(III) complexes.[10] Jacobsen *et al.* have shown that the highest enantioselectivities observed to date involve substrates which possess a conjugated double bond and some representative literature examples are shown in Table 2.2. Epoxidation of indene (**84**) (Table 2.2, entry 1) afforded oxide **88** in 88% ee and in high chemical yield (80%). More impressively, trisubstituted olefins **89** and **90** (Table 2.2, entries 2 and 3) were converted to their respective oxirane derivatives **91** and **92** with excellent enantioselectivities (97% and 93% ee, respectively).

Table 2.2: Selected Literature Examples of the Jacobsen Epoxidation Reaction.[a]

Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)	Ref.
1	 **84**	 **88**	80	88	19
2	 **89**	 **91**	51	97	20
3	 **90**	 **92**	69	93	21

[a] (*R,R*)-(-)-*N,N'*-bis(3,5-Di-*tert*-butylsalicyclidene)-1,2-cyclohexane-diamino-manganese chloride, also known as (*R,R*)-Jacobsen's catalyst, was used in all cases. [b] Refers to isolated yield. [c] Absolute configuration of major enantiomeric epoxide **88** not determined.

Encouraged by such observations, methylindene **77** was subjected to Jacobsen epoxidation conditions (Scheme 2.9). Thus, a dichloromethane solution of olefin **77**, (*R,R*)-Jacobsen's catalyst and 4-phenylpyridine *N*-oxide was treated with a phosphate buffered (pH 11.4) bleach solution (NaOCl is the stoichiometric oxidant in this reaction). After stirring at 4 °C for 17 hours, TLC analysis of the crude reaction mixture revealed complete consumption of the substrate and the presence of >12 products. None of the desired epoxide **74** was isolated from the complex reaction mixture. The major product isolated was identified as ketone **93** which was obtained in 36% yield.[ʃ] Trace quantities of *trans*-diol **94**[ʃ,∞] were also isolated. A mechanistic rationale for the formation of the



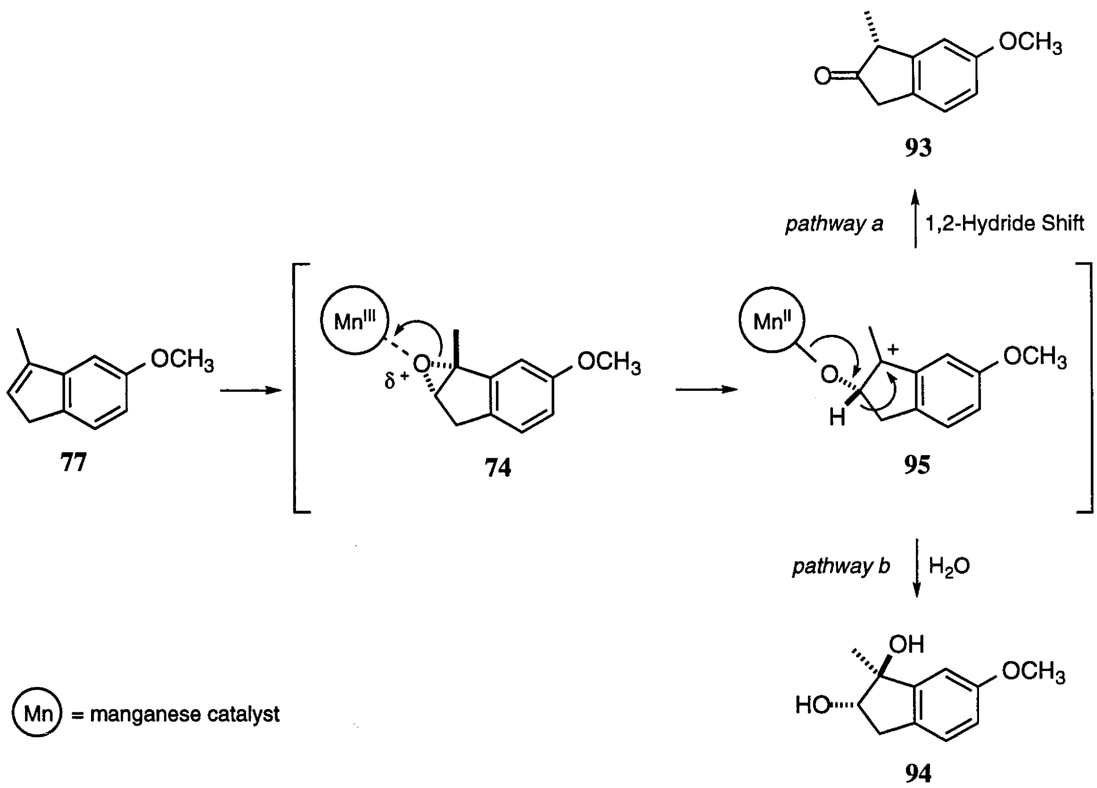
Scheme 2.9

Reagents and Conditions: (i) (*R,R*)-Jacobsen's catalyst, 4-phenylpyridine *N*-oxide, CH_2Cl_2, buffered bleach solution (pH 11.4), 4 °C, 17 h.

observed products is presented in Scheme 2.10. Thus, initial epoxidation of olefin **77** would form the target epoxide **74**. Subsequent Lewis acid-mediated cleavage of the benzylic C-O bond within the latter compound would be expected to occur readily (by virtue of the electron-rich aromatic ring) and lead to carbocation **95**. Species **95** may then undergo a 1,2-hydride shift (pathway a) to generate ketone **93** or, alternatively,

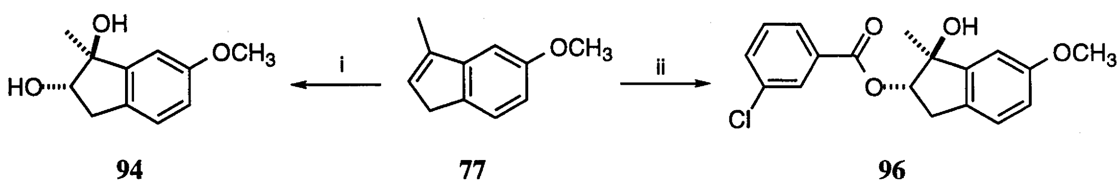
ʃ The absolute stereochemistry and optical purity of compounds thus marked was not determined. For the sake of simplicity, however, only the desired enantiomeric products or those derived from such compounds have been illustrated.

∞ Our assignment of the relative stereochemistry of compound **94** is tentative and is based upon the mechanistic proposal presented (see Scheme 2.10) to account for its formation. It should be noted, however, that the ^{1}H NMR and APT ^{13}C NMR spectral data associated with this compound shows no discernable differences from the ^{1}H NMR and APT ^{13}C NMR spectral data acquired for authentic samples of the *cis*-isomer, either (+)-**73** or (-)-**73**.



Scheme 2.10

may be trapped by water (pathway b; nucleophilic attack from the opposite face of the oxygenated moiety) to form *trans*-diol **94**. Interestingly, attempts to prepare racemic samples of epoxide **74** also failed. Thus, reaction of olefin **77** using dimethyldioxirane[22] (Scheme 2.11) afforded the *trans*-diol **94**, whilst the use of *m*-CPBA furnished exclusively the *m*-chlorobenzoyl ester **96**.[23] Once again, production of compounds **94** and **96** can be rationalised (based on a similar argument to that presented earlier) in terms of initial epoxide formation.



Scheme 2.11

Reagents and Conditions: (i) *ca.* 0.10 M solution of dimethyldioxirane in acetone, rt, 40 mins; (ii) *m*-CPBA (with or without $NaHCO_3$ present), ether, 0 °C - rt, 26 h.

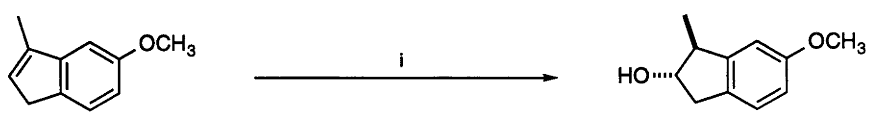
Having examined a variety of oxygenation strategies, it was decided that the AD reaction of methylindene **77** was the most appropriate method for generating C2 oxygenated indanes which may then be elaborated to the target molecule **71**. Despite the moderate optical purity of the diol products generated *via* this approach, the attractive features were the ease of reaction, ease of product isolation and purification and the high chemical yields of product obtained.Σ

2.3 Preparation of Enantiopure Diol (+)-73

Fractional recrystallisation of enantiomerically enriched samples of diol (+)-**73** was not an efficient technique for the large scale preparation of this compound in optically pure form. This method was both time consuming and, more importantly, did not return large quantities of enantiopure material as was required for further chemical manipulations. Efforts to circumvent this problem focussed on generating derivatives of diol (+)-**73** which would be suitable for chemical resolution purposes.

Initial attempts to convert optically enriched (42% ee) diol (+)-**73** to the diastereomeric (-)-menthone-derived acetals **98** and **99** (Scheme 2.13) under standard

Σ Hydrocarbonboration of methylindene **77** (Scheme 2.12) was also considered as a means of introducing oxygen functionality at C2. Indeed, this reaction has been performed by a previous worker in these laboratories (J. R. Phyland, unpublished results) and provided, due to the stereospecificity of the reaction, an authentic sample of racemic *trans*-indanol **97**. Application of this methodology (including asymmetric versions thereof) was not persued any further because, as was stated earlier in this chapter (page 25), the *cis*-isomer was targeted because it was expected to influence the stereochemical outcome in the pivotal carbene addition reaction (see Chapter 3).

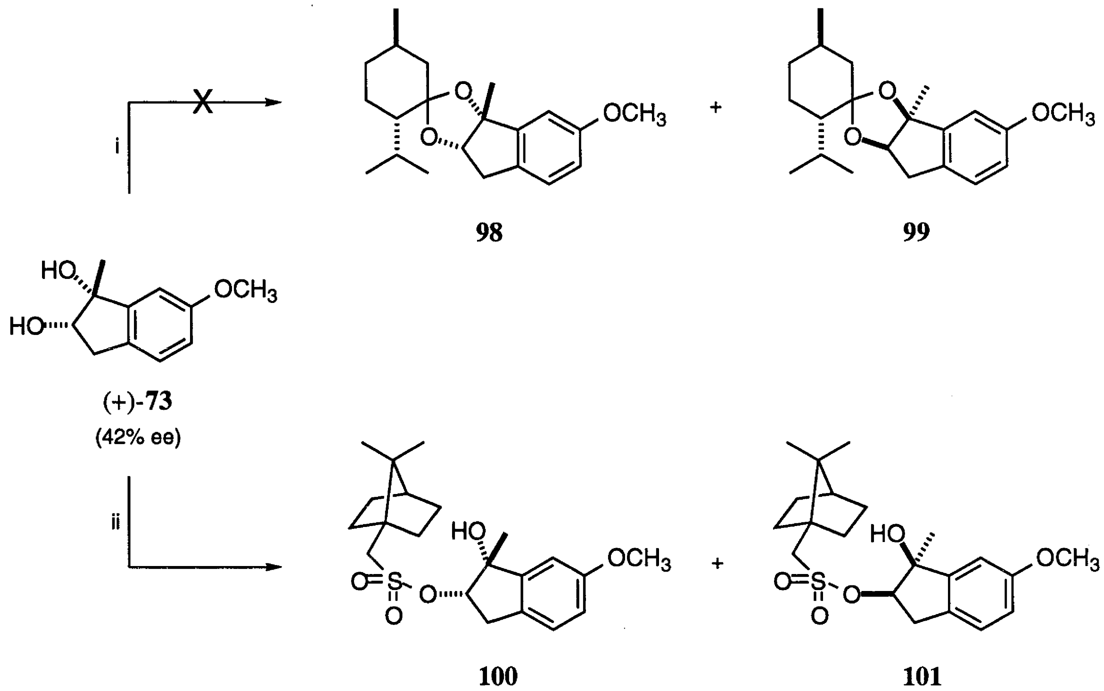


77 **97**

Scheme 2.12

Reagents and Conditions: (i) BH_3.THF, rt, 4 h then NaOH (aq.), H_2O_2, 0 °C - reflux, 2 h (95% yield).

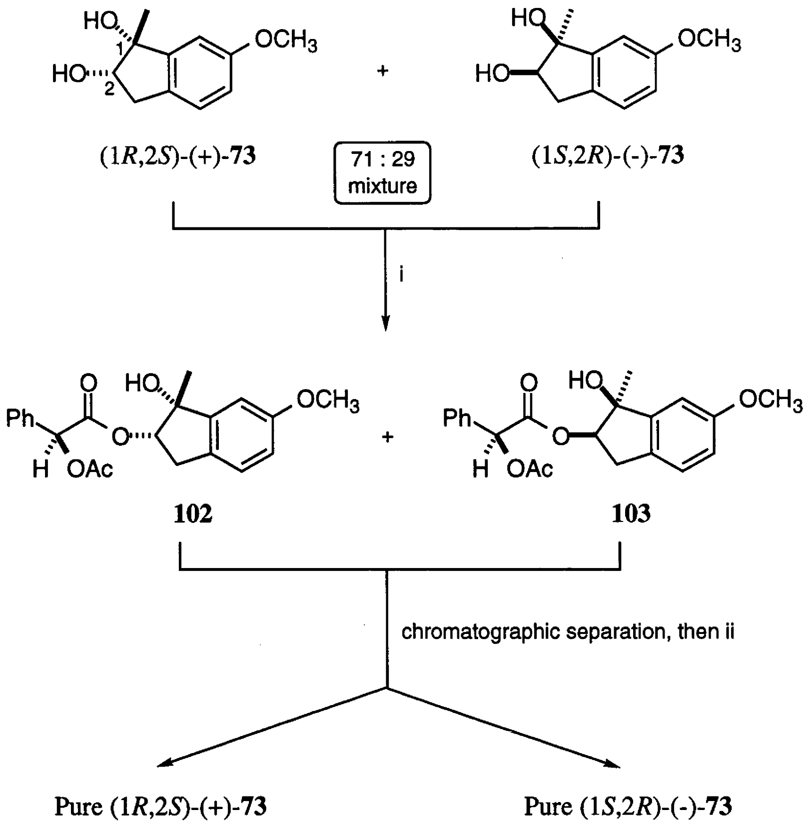
Dean-Stark conditions failed to deliver any products. In contrast, reaction of diol (+)-**73** with (+)-camphorsulfonyl chloride (Scheme 2.13) furnished esters **100** and **101** but unfortunately, these compounds were chromatographically inseparable.



Scheme 2.13

Reagents and Conditions: (i) (-)-menthone, *p*-TsOH, pentane, 35 °C, 2 h; (ii) (+)-camphorsulfonyl chloride, DMAP, CH_2Cl_2, rt, 18 h.

The chiral derivatising agent (*S*)-(+)-*O*-acetylmandelic acid was also successfully coupled with enantioenriched diol (+)-**73** (Scheme 2.14) according to the method of Parker *et al*[24] and the resulting diastereomeric esters **102** and **103** were easily separated by flash chromatography. Saponification (KOH/methanol) of each ester delivered, with extremely high optical purities, diols (+)-**73** and (-)-**73**, both of which were obtained as colourless solids.



Scheme 2.14

Reagents and Conditions: (i) (*S*)-(+)-*O*-Acetylmandelic acid, DCC, DMAP, CH_2Cl_2, 0 °C - rt, 2 h; (ii) KOH (aq.), MeOH, rt, 16 h.

The optical rotations and melting points of these compounds were measured and found to be internally consistent (Table 2.3). Accurate mass measurement of the molecular ion (*m/z* 194) observed in the 70 eV EI mass spectrum of diol (+)-**73** confirmed the molecular formula as $C_{11}H_{14}O_3$. The APT ^{13}C NMR spectrum (Figure 2.1) of this

Table 2.3: Comparison of the Optical Rotations and Melting Points of Diols (+)- and (-)-**73**.

Compound	Configuration[a]	ee[b]	Optical Rotation	Melting Point
(+)-**73**	(1*R*, 2*S*)	>99.5%	+ 69.3°	100 - 101 °C
(-)-**73**	(1*S*, 2*R*)	98.5%	- 73.2°	101 - 102 °C

[a] The absolute configuration has been determined, see Section 2.4. [b] The enantiomeric excesses of diols (+)-**73** and (-)-**73** were determined by chiral HPLC analysis. See Experimental Section for details.

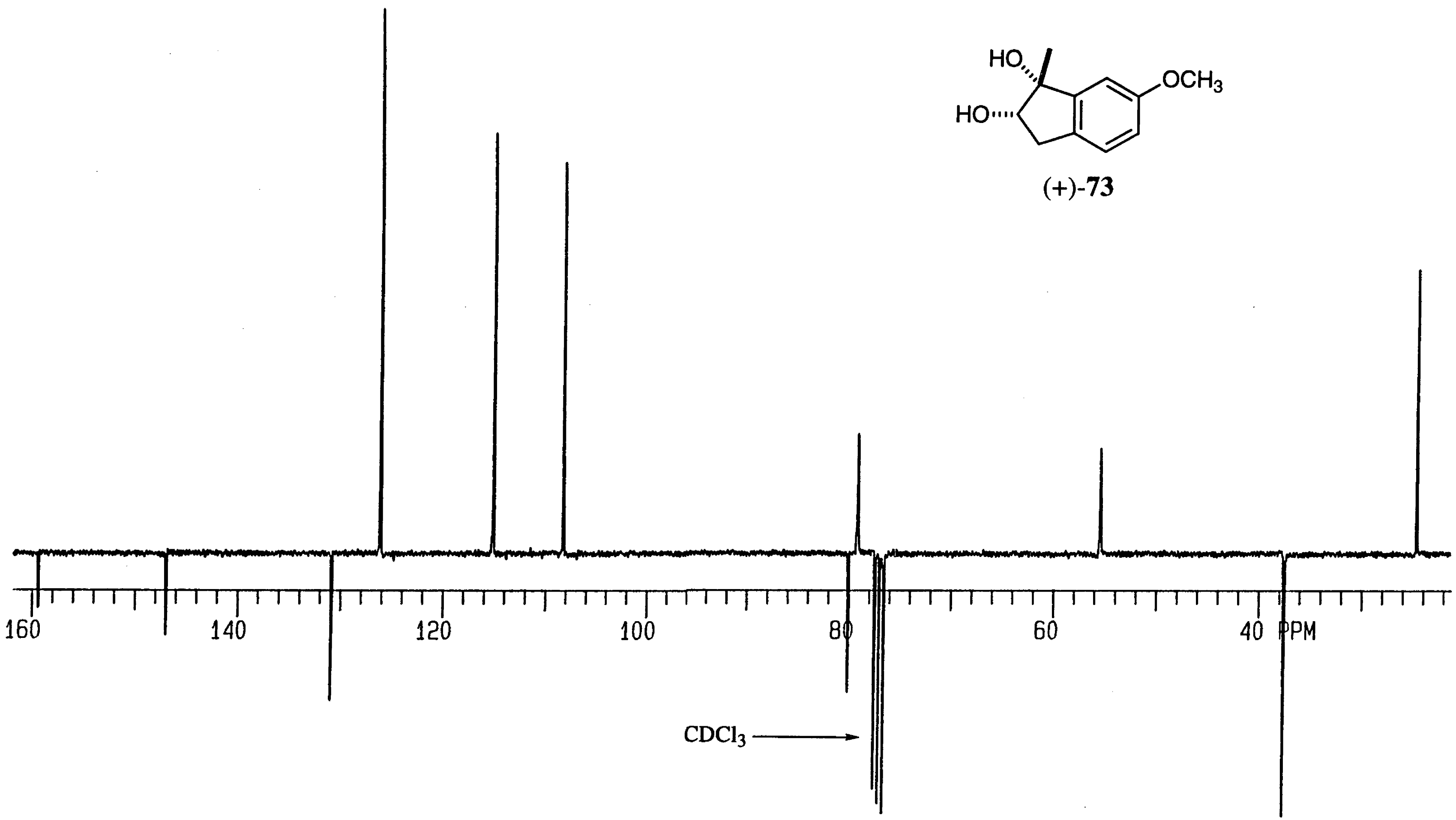


Figure 2.1: 75.4 MHz APT ^{13}C NMR Spectrum of Diol (+)-**73**.

(Spectrum recorded in $CDCl_3$ solution)

material displayed the expected eleven signals. The three quaternary and sp^2-hybridised carbons resonated at δ 159.4, 146.9 and 130.8, whilst the protonated aromatic carbons were observed in the region δ 126-108. The signal at δ 80.1 was assigned to the oxygenated benzylic carbon, whilst that at δ 79.2 was assigned to C2. The resonances associated with the methoxy, methylene and methyl groups were easily distinguished, appearing at δ 55.5, 37.5 and 24.7, respectively. The ^{1}H NMR spectrum was consistent with the assigned structure and could be completely assigned (Figure 2.2). The enantiomeric diol (-)-**73** was also fully characterised and showed the same NMR spectroscopic and mass spectrometric characteristics as its optical antipode.

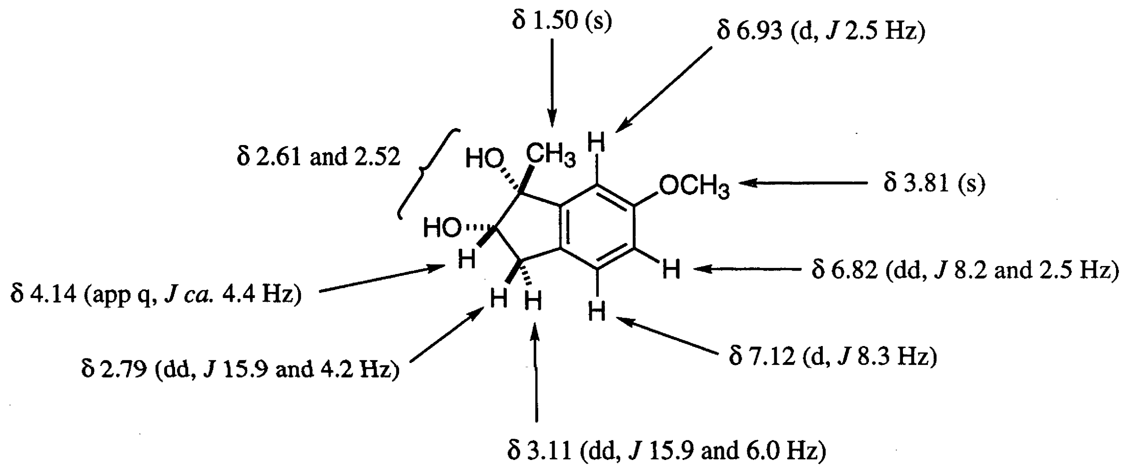
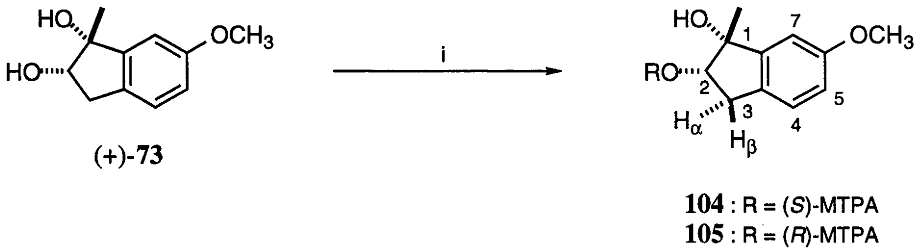


Figure 2.2: ^{1}H NMR Spectroscopic Assignments for Compound (+)-**73**.
(Data acquired in $CDCl_3$ solution)

2.4 Determination of the Absolute Stereochemistry of Diol (+)-73

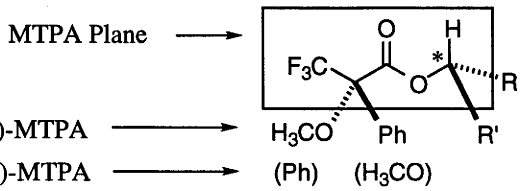
The absolute stereochemistry of diol (+)-**73** was determined *via* application of a modified Mosher method.[25] In the first instance, optically pure diol (+)-**73** was converted into the corresponding (*S*)- and (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) ester derivatives, **104** and **105** respectively, (Scheme 2.15) upon treatment with MTPA-chloride which was prepared *in situ* according to the method of Ward and Rhee.[26] Compounds **104** and **105** were obtained, both as colourless oils, in moderate to good yield (60% and 80%, respectively).



Scheme 2.15

Reagents and Conditions: (i) (*S*)- or (*R*)-MTPA, $(COCl)_2$, DMF, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C - rt, 1.5 h - 16 h.

Mosher has proposed[25c,d] that the preferred conformation of MTPA ester derivatives of secondary alcohols in solution is one in which the methine proton, ester carbonyl and trifluoromethyl groups lie in the same plane (referred to as the MTPA plane) (Figure 2.3). Such a proposal has been supported by both X-ray crystallographic and IR



where R and R' = substituents α to the carbinyl (*) carbon

Figure 2.3: Schematic Representation of the MTPA Plane.

spectroscopic data.[25a] In this preferred conformation, substituents which lie *on the same face* of the MTPA plane as the phenyl group of the ester moiety (i.e. R') are anisotropically shielded. This effect is manifested in the ^1H NMR spectra by the *upfield* shift of signals of one MTPA ester derivative relative to the other. Such spectral differences allow for the determination of absolute configuration. To this end, the ^{1}H NMR spectra of esters **104** and **105** were assigned and the relative shielding effects [Δ(δ(*S*)-δ(*R*)] calculated (Table 2.4). Inspection of these data strongly suggests that the

Table 2.4: Relative Shielding Effects, Δ[δ(*S*)-δ(*R*)], for MTPA Esters **104** and **105**.

Assignment	δ(*S*)-MTPA (**104**)	δ(*R*)-MTPA (**105**)	Δ[δ(*S*)-δ(*R*)]
CH_3	1.55	1.50	+ 0.05
OH	2.23	2.14	+ 0.09
H2	5.38	5.39	- 0.01
$H3_\alpha$	3.26	3.29	-0.03
$H3_\beta$	2.90	3.00	- 0.10
H4	7.07	7.11	- 0.05
H5	6.81	6.83	- 0.03
H7	6.90	6.89	+ 0.01

stereochemistry of esters **104** and **105** is as depicted in Figure 2.4, in order for the methylene protons (H_α and H_β) associated with (*S*)-MTPA ester **104** to be shielded relative to those in the (*R*)-MTPA diastereomer **105**. Thus, the absolute configuration of the major enantiomeric diol (+)-**73**, formed in the AD reaction of methylindene **77** using AD-mix-β, was assigned as (1*R*,2*S*).

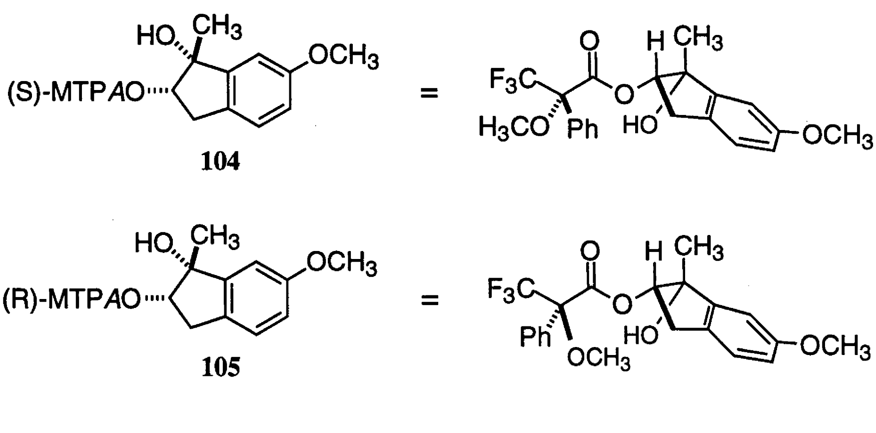
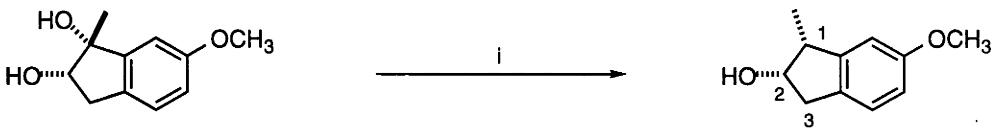


Figure 2.4: Stereochemistry of MTPA Esters **104** and **105** Derived from Diol (+)-**73**.

2.5 Synthesis of Indanol (+)-71

With multigram quantities of enantiopure diol (+)-**73** in hand (see Section 2.3), the next task was to convert this material into the desired indanol **71**. To this end, diol (+)-**73** (Scheme 2.16) was subjected to palladium-catalysed hydrogenolysis, which resulted in removal of the benzylic hydroxy group with concomitant inversion of stereochemistry[5] of the C1 methyl group.[Ô] As a result, the long sought after alcohol (+)-**71** was obtained as a clear, colourless oil in 70% yield after column chromatography. Full characterisation of this material allowed for confident assignment



(+)-**73** (+)-**71**

Scheme 2.16

Reagents and conditions: (i) 10% Pd on C, *p*-TsOH (cat.), MeOH, H_2, 1 atm., rt, 16 h.

of its structure. Thus, the 70 eV EI mass spectrum of indanol (+)-**71** displayed a strong peak at *m/z* 178, corresponding to the molecular ion. An accurate mass measurement on this species confirmed the molecular formula $C_{11}H_{14}O_2$. All of the expected eleven carbon resonances were observed in the APT ^{13}C NMR spectrum, the most diagnostic signal being that at δ 44.4, which is assigned to C1. In the ^1H NMR spectrum (Figure 2.5), the three-proton doublet (*J* 7.1 Hz) at δ 1.32 was assigned to the methyl group at

Ô The *cis*-relative stereochemical relationship between the C1 methyl group and the C2 hydroxy group of indanol (+)-**71** was subsequently confirmed by an X-ray crystal structure obtained on a derivative of this compound (see Section 3.3). As was mentioned earlier (page 37), racemic samples of *trans*-indanol **97** have been prepared by another worker in this group. The ^1H NMR and ^{13}C NMR spectral data (see below) of compound **97** were compared with those obtained for *cis*-indanol (+)-**71** and aided the stereochemical assignment of the latter compound. **^{1}H NMR** (400 MHz) δ 7.11-7.08 (m, 1H), 6.75-6.71 (m, 2H), 4.18-4.13 (m, 1H), 3.79 (s, 3H, -OCH_3), 3.19 (dd, *J* 15.4 and 6.7 Hz, 1H), 3.06-2.97 (m, 1H), 2.76 (dd, *J* 15.4 and 6.1 Hz, 1H), 1.78 (br s, 1H, -OH), 1.30 (d, *J* 7.1 Hz, 3H, -CH_3). **^{13}C NMR** (400 MHz) δ 159.1, 147.0, 131.4, 125.3, 112.4, 109.4, 81.1, 55.4, 48.2, 39.7, 17.0.

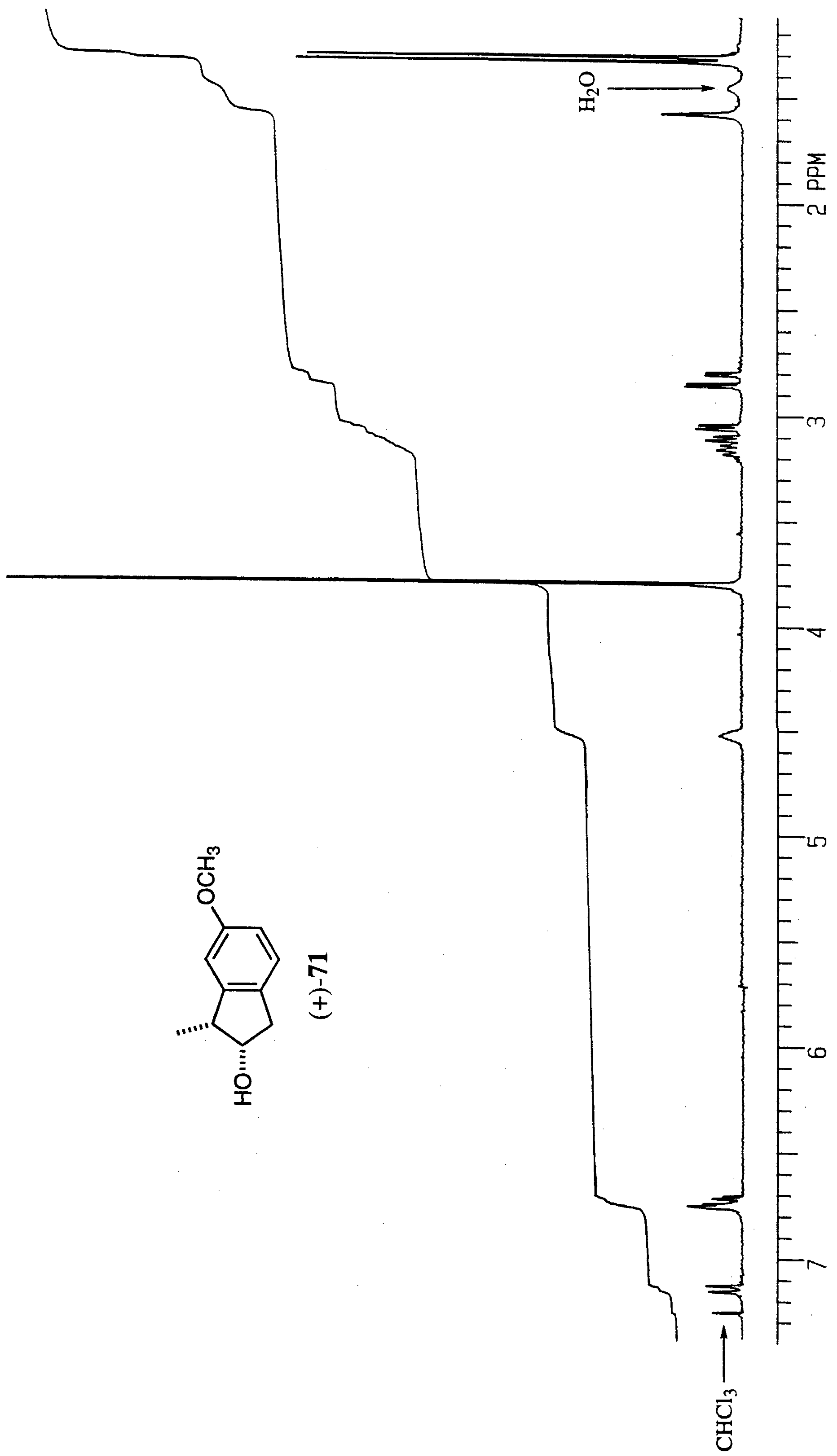


Figure 2.5: 300 MHz ^{1}H NMR Spectrum of Indanol (+)-**71**.

(Spectrum recorded in $CDCl_3$ solution)

C1 which is vicinally coupled to H1. The two mutually coupled doublet of doublets observed at δ 2.83 (*J* 15.9 and 2.5 Hz) and 3.08 (*J* 15.9 and 5.5 Hz) have been assigned to the diastereotopic methylene protons associated with C3. The one-proton multiplet observed in the region δ 3.12-3.20 was assigned to H1. The three-proton singlet at δ 3.80 corresponded to the protons of the methoxy methyl group whilst the broad, one-proton multiplet at *ca.* δ 4.52 was assigned to the methine proton attached to C2. The three remaining protons, *viz.* those associated with the aromatic ring, resonated in the region δ 6.70-7.15. The enantiomeric diol, compound (-)-**73**, was also converted to the corresponding indanol (-)-**71**, this time using palladium black in stoichiometric amounts. Reaction times were found to be much shorter (4 h) and yields were significantly higher (97%). The optical rotation of indanol (-)-**71** was recorded as - 21.8° (*c* 1.2, $CHCl_3$) and compares favourably with that recorded for its optical antipode (+)-**71** [$[\alpha]_D$ + 19.9° (*c* 1.7, $CHCl_3$)].

Having established protocols for the preparation of indanol (+)-**71** in multigram quantities, the next objective was to convert this material into the taxane carbon framework employing methods previously established by others (see Chapter 1, Section 1.6). Efforts directed towards this end are discussed in the following chapter.

2.6 References

1. H. O. House and C. B. Hudson, *J. Org. Chem.*, 1970, **35**, 647.
2. H. Kajiro, S. Mitamura, A. Mori and T. Hiyama, *Tetrahedron: Asymmetry*, 1998, 907.
3. D. R. Boyd and G. N. Sheldrake, *Natural Product Reports*, 1998, **15**, 309.
4. H. Kajiro, S. Mitamura, A. Mori and T. Hiyama, *Synlett*, 1998, 51.
5. S. Mitsui, S. Imaizumi and Y. Esashi, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 2143.
6. D. F. Taber and J. B. Houze, *J. Org. Chem.*, 1994, **59**, 4004.
7. F. A. Davis and B-C. Chen, *Chem. Rev.*, 1992, **92**, 919.
8. For a review on methods for functionalisation adjacent to a carbonyl group, see: A. B. Jones, Oxidation Adjacent to C=X Bonds by Hydroxylation Methods in *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds.; Pergamon Press, 1991, Vol. 7, Chapter 2.3, p. 151.
9. T. Hashiyama, K. Morikawa and K. B. Sharpless, *J. Org. Chem.*, 1992, **57**, 5067.
10. E. N. Jacobsen in *Catalytic Asymmetric Synthesis*, I. Ojima, Ed.; VCH Publishers, 1993, Chapter 4.2, p. 159.
11. F. A. Davis, A. C. Sheppard, B-C. Chen and M. S. Haque, *J. Am. Chem. Soc.*, 1990, **112**, 6679.
12. A. Guerriero, M. D'Ambrosio and F. Pietra, *Helv. Chim. Acta*, 1988, **71**, 1094.
13. S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99.
14. H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
15. H. Becker and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 448.
16. (a) D. R. Boyd, N. D. Sharma, M. V. Hand, M. R. Groocock, N. A. Kerley, H. Dalton, J. Chima and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1993, 974; (b) L. P. Wackett, L. D. Kwart and D. T. Gibson, *Biochemistry*, 1988, **27**,

1360; (c) G. M. Whited, J. C. Downie, T. Hudlicky, S. P. Fearnley, J. C. Dudding, H. F. Olivo and D. Parker, *Bioorg. Med. Chem.*, 1994, **2**, 727; (d) D. T. Gibson, S. M. Resnick, K. Lee, J. M. Brand, D. S. Torok, L. P. Wackett, M. J. Schocken and B. E. Haigler, *J. Bacteriol.*, 1995, **177**, 2615; (e) C. C. R. Allen, D. R. Boyd, H. Dalton, N. D. Sharma, I. Brannigan, N. A. Kerley, G. N. Sheldrake and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 117; (f) I. Brannigan, PhD Thesis, The Queen's University of Belfast, 1997.

17. For some detailed reviews on the production and chemistry of *cis*-1,2-dihydrocatechols, see: (a) T. Hudlicky and A. J. Thorpe, *Chem. Commun.*, 1996, 1993; (b) T. Hudlicky and J. W. Reed in *Advances in Asymmetric Synthesis*, A. Hassner, Ed.; JAI Press, Greenwich, CT, 1995, Vol. 1, p. 271; (c) T. Hudlicky and S. M. Brown in *Organic Synthesis: Advances and Applications*, T. Hudlicky, Ed.; JAI Press, Greenwich, CT, 1993, Vol. 2, p. 113; (d) G. N. Sheldrake in *Chirality in Industry*, A. N. Collins, G. N. Sheldrake and J. Crosby, Eds.; John Wiley & Sons Ltd., Chichester, West Sussex, 1992, Chapter 6, p. 127; (e) H. A. J. Carless, *Tetrahedron: Asymmetry*, 1992, **3**, 795.

18. R. A. Johnson and K. B. Sharpless in *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds.; Pergamon Press, 1991, Vol. 7, Chapter 3.2, p. 389.

19. E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063.

20. N. H. Lee, A. R. Muci and E. N. Jacobsen, *Tetrahedron Lett.*, 1991, **32**, 5055.

21. B. D. Brandes and E. N. Jacobsen, *J. Org. Chem.*, 1994, **59**, 4378.

22. (a) W. Adam, J. Bialas and L. Hadjiarapoglou, *Chem. Ber.*, 1991, **124**, 2377; (b) R. W. Murray, *Chem. Rev.*, 1989, **89**, 1187; (c) *Encyclopedia of Reagents for Organic Synthesis*, L. A. Paquette, Ed.; John Wiley & Sons, 1995, Vol. 3, p. 2061.

23. Ring-opening of epoxides by carboxylic acids is well-known, see: H. O. House, *Modern Synthetic Reactions*, 2nd Edition, W. A. Benjamin Inc., 1972, Chapter 6, p. 297 and references cited there-in.

24. D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 1983, 83.

25. (a) I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092; (b) T. Kusumi, T. Hamada, M. O. Ishitsuka, I. Ohtani and H. Kakisawa, *J. Org. Chem.*, 1992, **57**, 1033; (c) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; (d) G. R. Sullivan, J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 2143.

26. D. E. Ward and C. K. Rhee, *Tetrahedron Lett.*, 1991, **32**, 7165.

CHAPTER 3

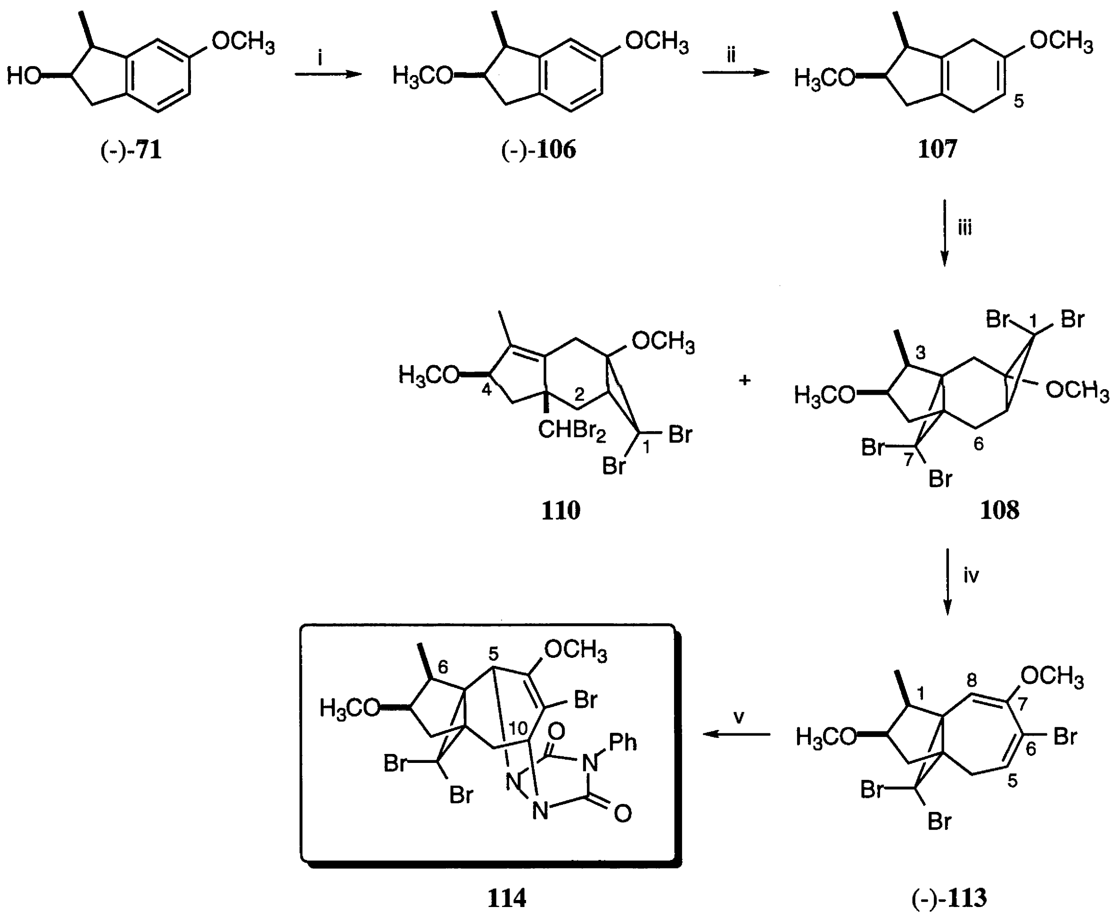
Synthesis of Enantiopure Taxane Analogues from Indanol (+)-71

3.1 Overview

This chapter describes efforts to prepare, in optically pure form, compounds embodying the carbocyclic framework associated with the ABC-ring system of taxoids in which the A-ring substituents (*viz.* C12 methyl and C13 oxygen substituents) have been acknowledged. It should be noted that the chemistry to be described in the following section (Section 3.2) was performed in the *ent*-taxane series. At the time this work was being carried out, it was presumed (based on the Sharpless mnemonic[1]) that the configuration of diol **73**, obtained *via* Sharpless asymmetric dihydroxylation of methylindene **77** using AD-mix-α, was (1*R*,2*S*). It is now known, of course (Section 2.4), that the absolute stereochemistry of this material is, in fact, (1*S*,2*R*). As a consequence of this original stereochemical misassignment, it was assumed that the configuration of indanol (-)-**71** was (1*R*,2*S*). All compounds described in Section 3.2 are, however, depicted with the correct (as it is now known to be) absolute stereochemistry.

3.2 A False Start

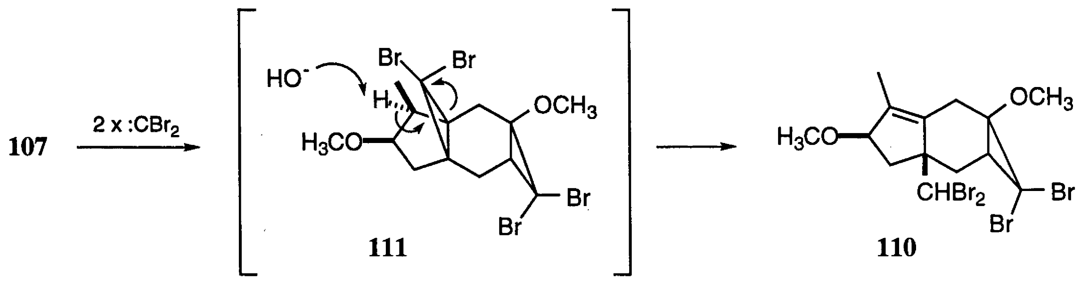
The synthetic pathway *en route* to enantiopure taxoids is shown in Scheme 3.1. Beginning from indanol (-)-**71**, the hydroxy group associated with this compound was protected, under standard conditions,[2] as the corresponding methyl ether derivative **106** because of the need to have a protecting group which was small, chemically robust and which could also act as a simple spectroscopic marker by which the diastereoselectivities of certain key reactions could be readily assessed. Dimethyl ether **106** was obtained as a clear, colourless oil in 88% yield and all of the expected twelve carbon resonances were observed in the APT ^{13}C NMR spectrum of this compound. The ^{1}H NMR spectrum displayed two three-proton singlets at δ 3.78 and 3.39 which correspond to the protons of the two methoxy methyl groups. The absence of any stretching bands in the region 3200-3600 cm^{-1} in the infrared spectrum of compound **106** also implied that there were no free hydroxy groups remaining in this product. Subsequent reduction of ether **106** under standard Birch conditions[3] afforded the unstable dihydro-derivative **107** in excellent yield (97%). In the ^{1}H NMR spectrum of this compound, the presence of only one signal in the olefinic region (a broad multiplet at δ 4.65, assigned to H5) provided convincing evidence that reduction had occured to form, in an exclusive manner, the illustrated 1,4-diene **107**. The infrared spectrum displayed absorption maxima at 1700 and 1661 cm^{-1}, characteristic C=C stretching bands for an enol ether and a double bond, respectively. *bis*-Cyclopropanation of diene **107**



Scheme 3.1

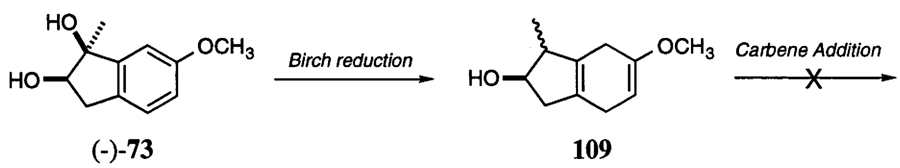
Reagents and Conditions: (i) NaH, MeI, THF, 0 °C - rt, 17 h; (ii) Li, NH_3, THF, -70 °C, 40 mins then EtOH; (iii) $CHBr_3$, NaOH, TEBAC, C_6H_6, rt, 17 h; (iv) toluene/pyr. (9:1), 110 °C, 23 h; (v) PTAD, CH_2Cl_2, rt, 19 h.

using dibromocarbene§ afforded a tetracyclic adduct, the structure of which was tentatively assigned as **108**. The 70 eV EI mass spectrum of this compound displayed the expected ratio of molecular ions (1, 3, 5, 4 and 1% of base peak) characteristic of a tetrabromo-containing compound. An accurate mass measurement on the ion at *m/z* 534 confirmed the molecular formula as $C_{14}H_{18}{}^{79}Br_4O_2$. The APT ^{13}C NMR spectrum displayed fourteen carbon resonances and the absence of signals in the olefinic region, δ 150-110, further indicated that the desired *bis*-cyclopropanation reaction had been successful.¤ Whilst there is ample literature precedent[4] to support the proposal that there is an *anti*-stereochemical relationship between the two cyclopropyl moieties in adduct **108**, the relative stereochemical relationship between the tetra-substituted cyclopropyl ring and the substituents on the cyclopentyl ring was unclear. Clarification of this stereochemical issue was assisted by the identification of a second, minor product from the carbene addition reaction, *viz.* compound **110**. Formation of this species (Scheme 3.3) can be rationalised in terms of the alternate diastereomeric adduct **111**, in which the tetra-substituted cyclopropyl ring and the substituents on the cyclopentyl ring are



Scheme 3.3

§ Generated under phase transfer conditions from bromoform and sodium hydroxide.
¤ Initial attempts to generate carbene addition adducts involved reduction of diol (-)-**73** (Scheme 3.2) to the dihydro-analogue **110**, followed by *bis*-cyclopropanation with dibromocarbene (generated from either ethyl tribromoacetate/sodium methoxide or from bromoform/sodium hydroxide). However, no characterisable products were isolated from the crude reaction mixture.



Scheme 3.2

syn-related to each other. Presumably, relief of the severe steric interactions imposed by this stereochemical arrangement would provide a powerful driving force for cyclopropane ring-cleavage in an E2 fashion, thereby resulting in formation of olefin **110**.† On this basis, an *anti*-relationship was assigned between the internal cyclopropyl ring and the substituents on the cyclopentyl ring of adduct **108**. This stereochemical outcome is extremely significant since it establishes the required *anti*-disposition between the *gem*-dibrominated methylene bridge (analogous to the *gem*-dimethylated methylene bridge (C1-C15-C11) in the taxoid carbon framework) and the C13 (paclitaxel numbering) oxygen moiety. The origin of the observed diastereoselectivity in the carbene addition reaction leading to adduct **108** remains unclear. It has been postulated (Figure 3.1) that

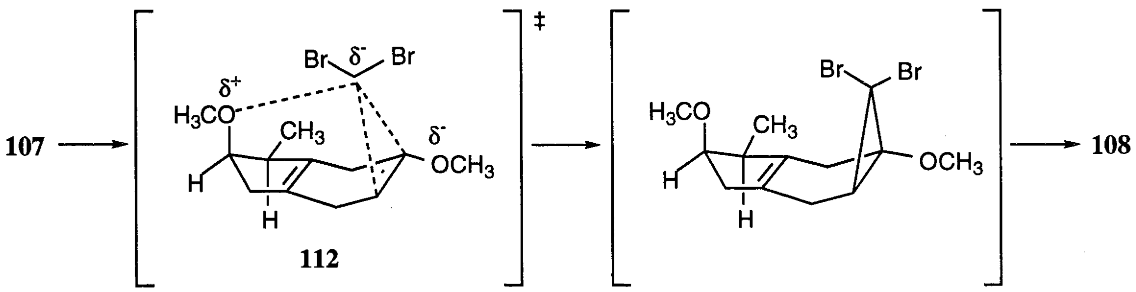


Figure 3.1: Possible Transition State Structure, **112**, Associated with the Addition of Dibromocarbene to Diene **107**.

the methoxy substituent on the cyclopentyl ring may direct (through co-ordinative effects) the addition of the first carbenoid moiety to the top face (as drawn) of the more electron-rich (methoxy-substituted) double bond within diene **107**. Addition of the second molecule of dibromocarbene is then pre-disposed, by virtue of steric effects, to add to the tetra-substituted double bond from the opposite face to that which the first carbene species added.

The synthetic pathway *en route* to the taxoid carbon skeleton continued with the thermolysis of tetracycle **108** in refluxing toluene-pyridine (9:1 mixture). This

† The preferred geometry for an elimination reaction *via* an E2 pathway is one in which the proton being abstracted and the leaving group are *anti*-periplanar to each other. This geometric requirement is satisfied in the proposed intermediate **111**.

resulted in electrocyclic ring-opening[5] of the oxygenated (and hence more activated) cyclopropyl ring to furnish the [5.3.1]propelladiene **113** in good yield (87% at 76% conversion). Full characterisation of this compound, including the acquisition of satisfactory microanalytical data, supported the assigned structure. Thus, the ^{1}H NMR spectrum showed a doublet of doublets (*J* 8.4 and 5.8 Hz) at δ 6.77 and a singlet at δ 5.19, which are assigned to H5 and H8, respectively. The resonances at δ 152.9, 135.4, 118.8 and 103.6 in the APT ^{13}C NMR spectrum of this compound are assigned to the four sp^2-hybridised carbons C7, C8, C6 and C5, respectively. The infrared spectrum of this material displayed absorption maxima at 1637 and 1622 cm^{-1}, characteristic C=C stretching bands for conjugated double bonds.

At this point it was deemed prudent to attempt to prepare a crystalline derivative of diene **113** which would be suitable for X-ray analysis, in order to confirm the stereochemical assignments made thus far. The presence of a heavy atom(s) (i.e. bromine) within such a derivative should also allow for the determination of its absolute configuration and, in turn, those of all its precursors. To this end, compound **113** was subjected to a Diels-Alder cycloaddition reaction with the highly electron-deficient dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). Adduct **114** so-derived was obtained as colourless, crystalline prisms after recrystallisation from ether/hexane. The 70 eV EI mass spectrum of this material displayed the expected ratio of molecular ions (2, 7, 7 and 2% of base peak) for a tribromo-containing compound. An accurate mass measurement on the species at *m/z* 629 confirmed the molecular formula as $C_{22}H_{22}{}^{79}Br_3N_3O_4$. Nineteen resonances were observed in the APT ^{13}C NMR spectrum while the ^{1}H NMR spectrum displayed all the expected features, with the triplet (*J* 3.4 Hz) at δ 5.14 and the singlet at δ 5.47 being assigned to H10 and H5, respectively. Final structure confirmation followed from a single-crystal X-ray analysis (Figure 3.2) which confirmed - (i) the *cis*-relative stereochemical relationship between the methyl and methoxy substituents on the cyclopentyl ring and (ii) the *anti*-relative stereochemical relationship between the tetra-substituted cyclopropyl ring and the cyclopentyl ring

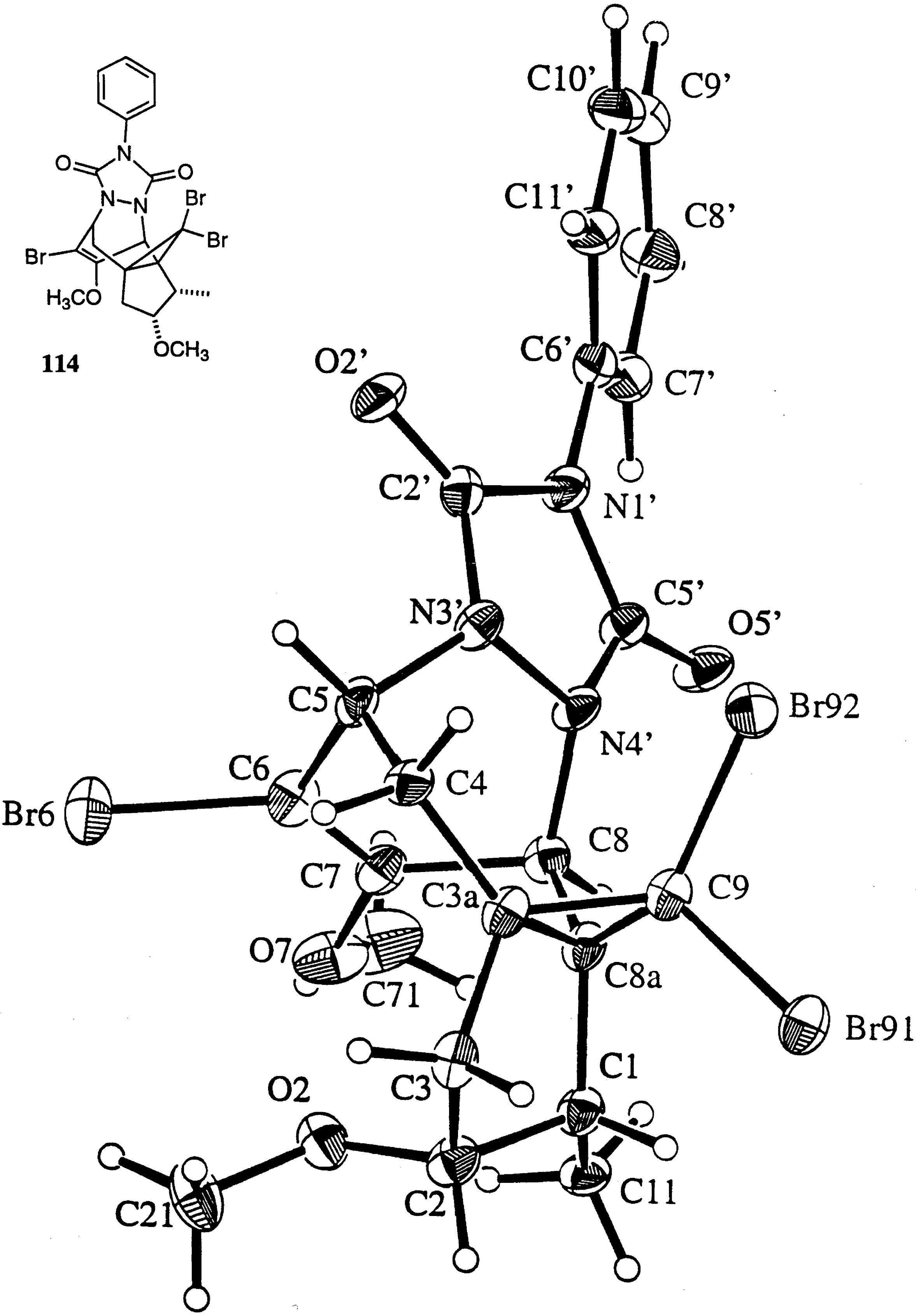


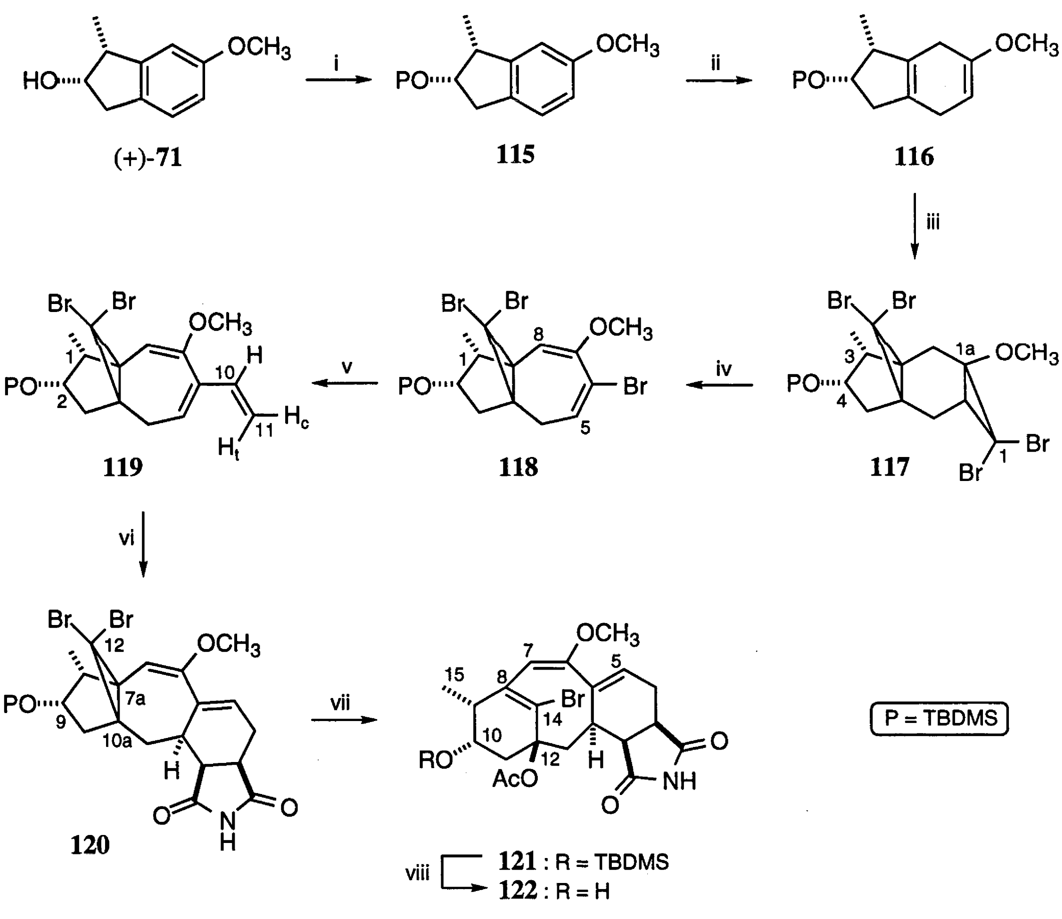
Figure 3.2: ORTEP Derived from Single-Crystal X-ray Analysis of Adduct **114**.

(This analysis was conducted by Dr. D. C. R. Hockless, The Australian National University)

substituents. This study also established that the absolute stereochemistry of diol (-)-**73**, from which adduct **114** was ultimately derived, must be (1*S*,2*R*) and not (1*R*,2*S*) as previously assumed.

3.3 Formation of Enantiopure Taxane Analogues

On the basis of the results described in the preceeding section, the preparation of optically pure taxoids in the correct enantiomeric series (Scheme 3.4) began with indanol (+)-**71**. The hydroxy group of this compound was protected,



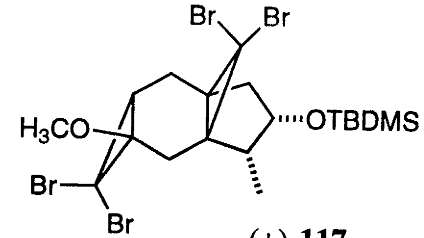
Scheme 3.4

Reagents and Conditions: (i) TBDMSCl, imidazole, DMF, 0 °C - rt, 11 h; (ii) Li, NH_3, THF, -70 °C, 45 mins then EtOH; (iii) $CHBr_3$, NaOH, TEBAC, C_6H_6, rt, 16 h; (iv) toluene/pyr. (9:1), 110 °C, 18 h; (v) $(H_2C{=}CH)SnBu_3$, $(Ph_3P)_4Pd$, 1,4-dioxane, 45 °C, 36 h; (vi) **60**, C_6H_6, rt, 18 h; (vii) AgOAc (10 equiv.), CH_2Cl_2, 40 °C, 20 h; (viii) TBAF, THF, 0 °C, 18 h.

this time as the *tert*-butyldimethylsilyl ether **115** because of the need to have a protecting group which could be chemoselectively removed under mild conditions towards the end of the synthesis. Reduction of silyl ether **115** was achieved under standard Birch conditions and furnished the dihydro-analogue **116** in near quantitative yield as an unstable, straw-coloured oil. *bis*-Cyclopropanation of this material with dibromocarbene§ resulted in the diastereoselective formation of the key intermediate **117** (71% yield). This material was obtained as a crystalline solid after purification by silica gel flash chromatography. No other carbene adducts were isolated from this reaction.

All physical, analytical and spectroscopic data acquired for this compound were in full accord with the assigned structure. The 70 eV EI mass spectrum of adduct **117** showed the molecular ion ratios (<1, <2, 2, <2, <1% of base peak) characteristic of a tetrabromo-containing compound and an accurate mass measurement on the species at *m/z* 634 established that it had the molecular formula $C_{19}H_{30}{}^{79}Br_4O_2Si$. In the APT ^{13}C NMR spectrum, seventeen of the expected nineteen carbon resonances were observed. The signal assigned to the oxygenated methine carbon (C4) appeared furthest downfield at δ 77.9, whilst the two apical carbons associated with the *gem*-dibromosubstituted cyclopropyl rings appeared as low intensity resonances at δ 57.6 and 39.7. The two quaternary carbons associated with the propellane bond appeared at δ 38.5 and 36.7, whilst the oxygenated and tertiary carbons of the alternate cyclopropyl ring resonated at δ 63.1 and 47.4, respectively. The three methylene carbons appeared at δ 22.5, 26.3 and 50.6 and the methine carbon (C3) associated with the cyclopentyl ring was observed at δ 35.2. The resonances corresponding to the methyl and methoxy methyl substituents appeared at δ 13.8 and 54.2, respectively. The signals associated with the *tert*-butyldimethylsilyl moiety were observed at δ 25.8, 18.0, -4.7 and -5.2 (the latter two resonances are assigned to the two diastereotopic methyl groups). Single-crystal X-ray analysis of adduct **117** (Figure 3.3) unequivocally established the absolute stereochemistry of this compound. The results of this study also confirmed the stereochemical assignment made for the enantiomeric derivative **108**.

§ Generated under phase transfer conditions from bromoform and sodium hydroxide.



(+)-**117**

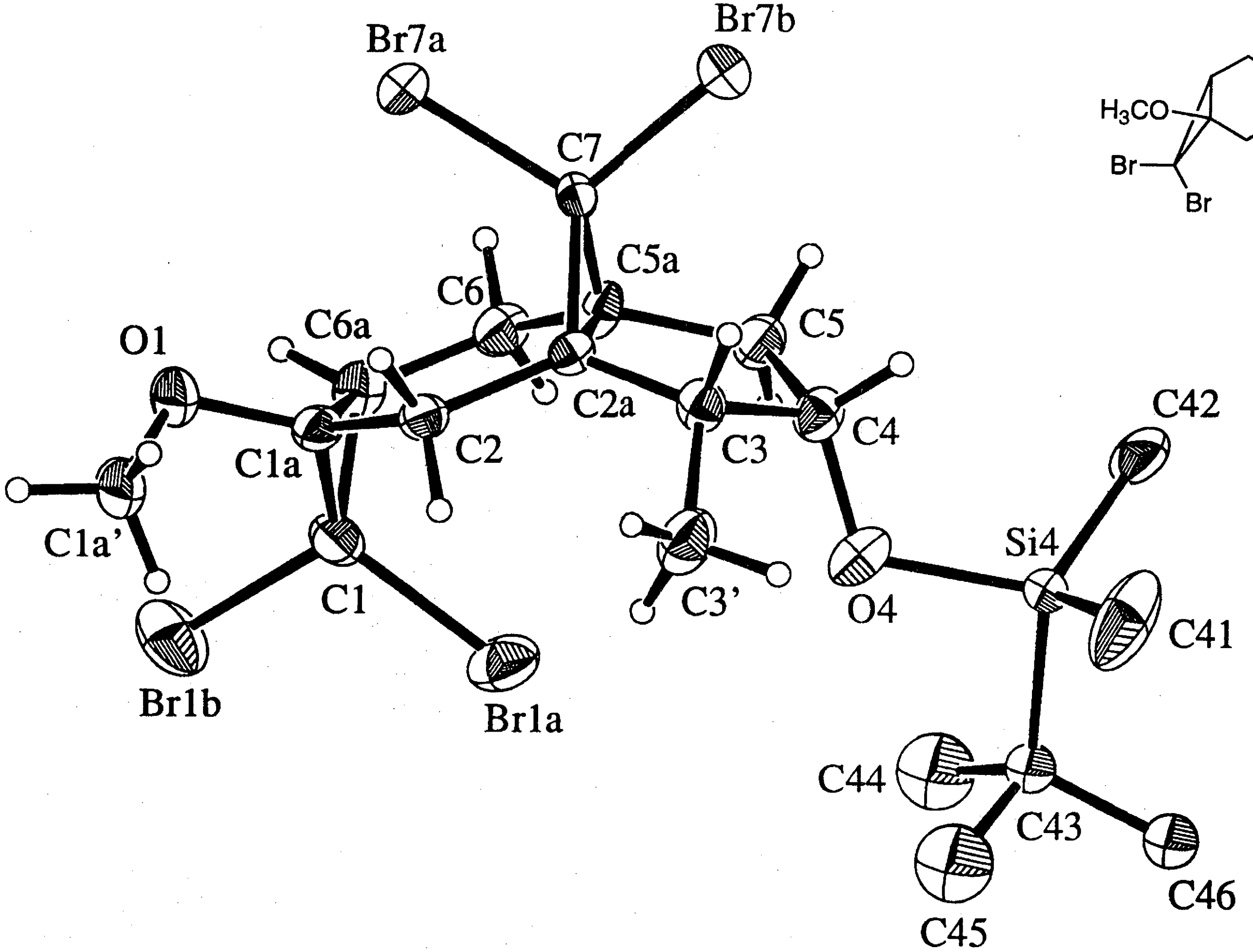


Figure 3.3: ORTEP Derived from Single-Crystal X-ray Analysis of Adduct **117**.

(This analysis was conducted by Dr. D. C. R. Hockless, The Australian National University)

Thermolysis of tetracycle **117**, using protocols previously described, furnished the [5.3.1]propelladiene **118** in 38% yield (at 81% conversion). Not surprisingly, the spectroscopic data acquired for this compound were similar to those observed for the related diene **113** prepared earlier. Thus, the doublet of doublets (*J* 8.5 and 5.8 Hz) at δ 6.76 and the singlet at δ 5.17 observed in the ^{1}H NMR spectrum were assigned to H5 and H8, respectively. The infrared spectrum of compound **118** displayed absorption maxima at 1634 and 1620 cm^{-1}, characteristic C=C stretching frequencies for conjugated double bonds. Furthermore, the composition of the molecular ion observed at *m/z* 554 in the 70 eV EI mass spectrum was confirmed as $C_{19}H_{29}{}^{79}Br_3O_2Si$ by accurate mass measurement. All other physical and spectroscopic data were in accord with the assigned structure.

Elaboration of compound **118** to triene **119** was accomplished *via* the method of Stille *et al.*[6] Thus, heating a mixture of diene **118** and vinyltributylstannane in the presence of catalytic $Pd(Ph_3)_4$ for 36 hours afforded, after purification by flash chromatography, triene **119** (64% yield) as a sharp-melting, crystalline solid. In the ^{1}H NMR spectrum of this material (Figure 3.4), the three new signals at δ 6.23 (dd, *J* 17.5 and 10.9 Hz), 5.28 (dd, *J* 17.4 and 1.5 Hz) and 5.04 (dd, *J* 11.0 and 1.5 Hz) were assigned to the olefinic protons associated with the newly introduced vinyl moiety, *viz.* H10, $H11_t$ and $H11_c$, respectively. The most salient features in the APT ^{13}C NMR of triene **119** were the two new olefinic resonances at δ 131.8 (C10) and 114.8 (C11). The composition of the molecular ion observed at *m/z* 502 in the 70 eV EI mass spectrum was confirmed as $C_{21}H_{32}{}^{79}Br_2O_2Si$ by accurate mass measurement. Satisfactory microanalytical data were also obtained on this material.

With triene **119** in hand, the next task was to assemble the carbon framework associated with the C-ring of taxoids. This objective was realised *via* the regio- and diastereoselective Diels-Alder reaction[7] between triene **119** and maleimide (**60**), which serves as a surrogate D-ring. Formation of the desired pentacyclic adduct **120** was inferred by the observation, in the 70 eV EI mass spectrum, of a weak

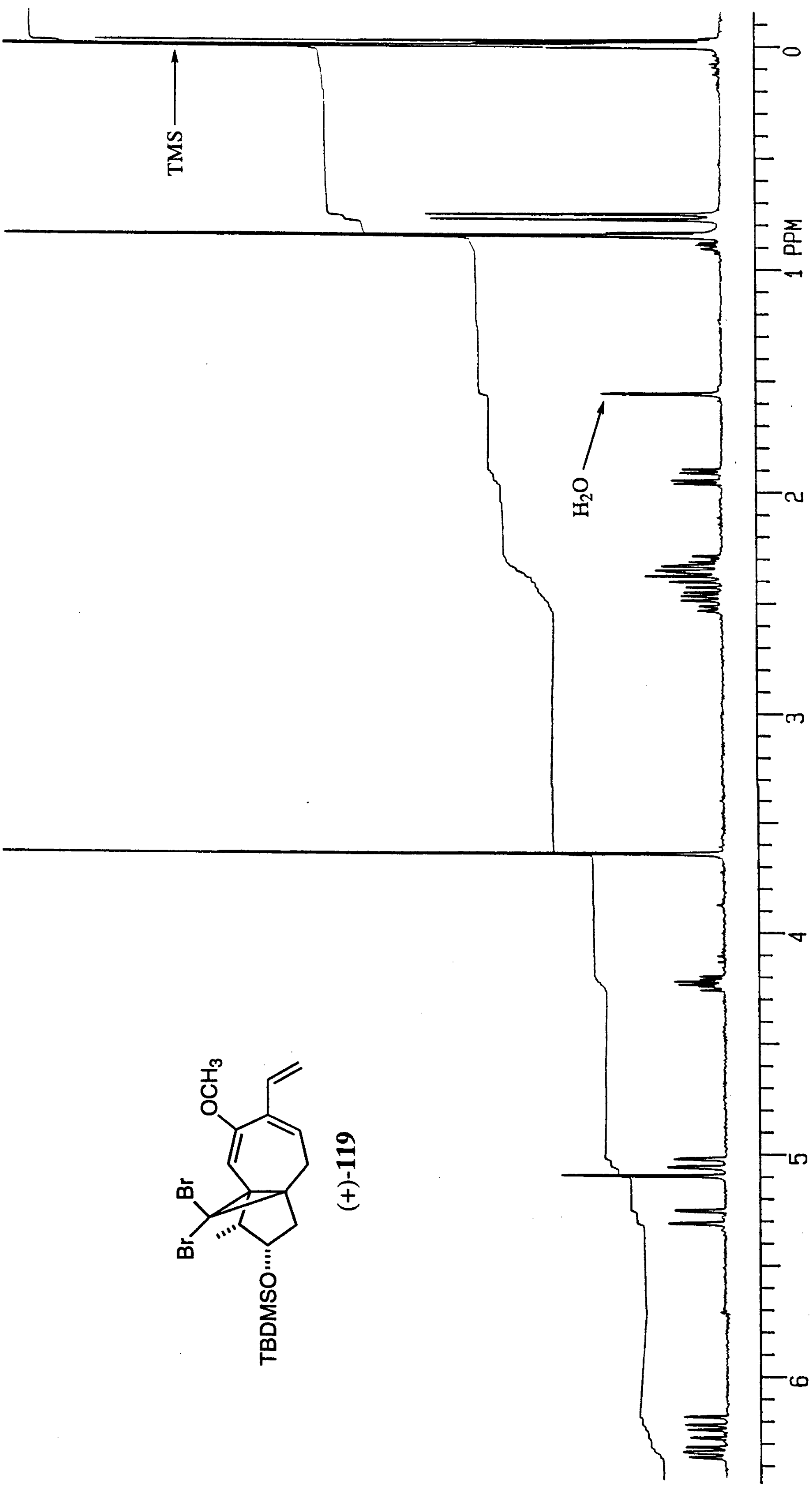
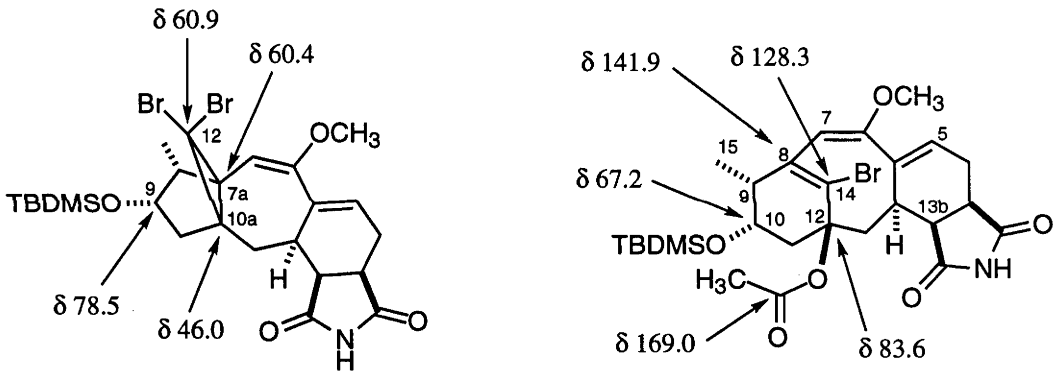


Figure 3.4: 300 MHz ^{1}H NMR Spectrum of Triene (+)-**119**.

(Spectrum recorded in $CDCl_3$ solution)

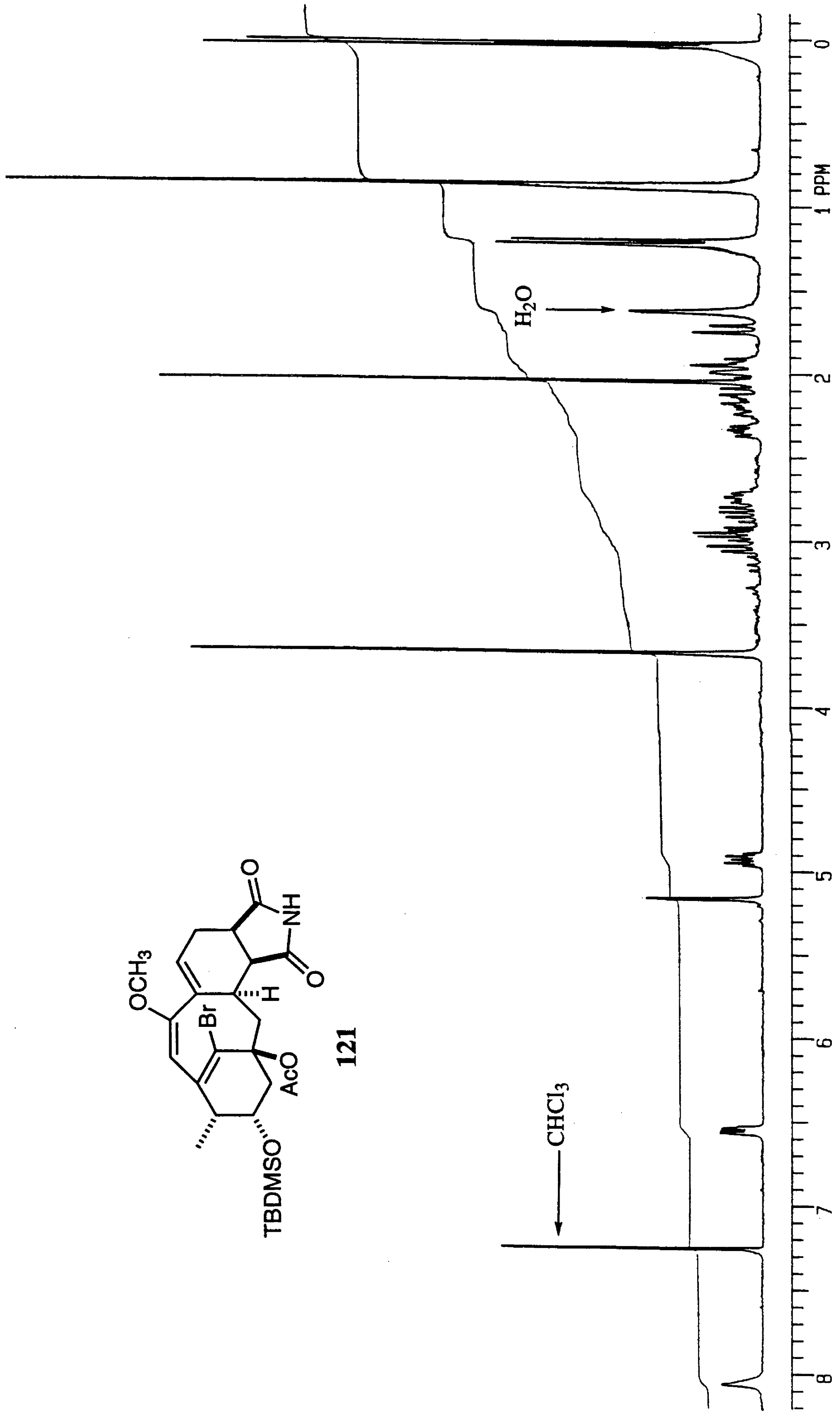
molecular ion at *m/z* 599. Accurate mass measurement of this species established the molecular formula as $C_{25}H_{35}{}^{79}Br_2NO_4Si$. Adduct **120** was found to be quite unstable and was immediately subjected to the next step of the reaction sequence. Thus, a mixture of adduct **120** and silver acetate (ten molar equivalents) in dichloromethane was heated at reflux for 20 hours. After work-up and HPLC purification of the major reaction product, tetracycle **121** (18% yield) was obtained as a colourless foam. The diagnostic isotope pattern (<1 and <1% of base peak) associated with the molecular ions of a monobromo-containing species was observed in the 70 eV EI mass spectrum of compound **121**. Confirmation of the molecular formula, $C_{27}H_{38}{}^{79}BrNO_6Si$, was realised *via* accurate mass measurement on the ion at *m/z* 579. Twenty five resonances were observed in the APT ^{13}C NMR spectrum of adduct **121**, the most pertinent features of which are summarised in Figure 3.5. Comparison of the chemical shifts associated with C12, C14



120 **121**

Figure 3.5: Selected APT ^{13}C NMR Spectroscopic Data for Adducts **120** and **121**.
(Data acquired in $CDCl_3$ solution)

and C8 of compound **121** and C10a, C12 and C7a of pregenitor **120** provided convincing evidence that the propellane bond associated with the latter species had been cleaved. Interestingly, the chemical shift associated with C9 in compound **120** appeared at δ 78.5, whilst in the ring-expanded derivative **121**, the analogous carbon (C10) resonated at δ 67.2. In the ^{1}H NMR spectrum of compound **121** (Figure 3.6), the C10 methine proton was observed as a one-proton multiplet at *ca.* δ 4.94, whereas in the



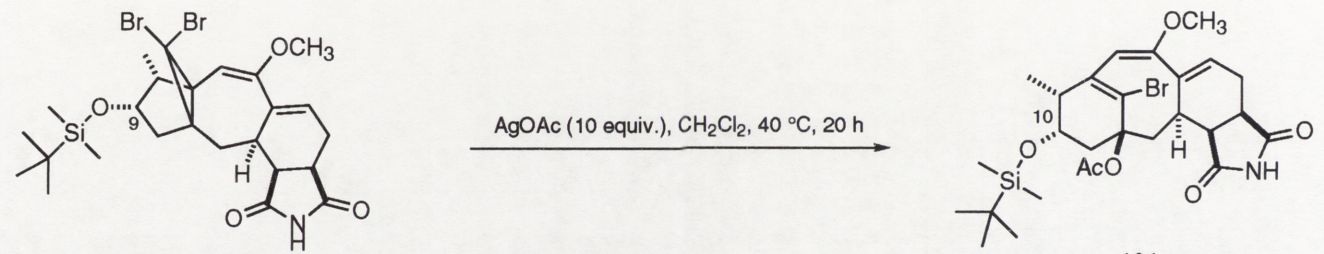
121

Figure 3.6: 300 MHz ^{1}H NMR Spectrum of Compound **121**.

(Spectrum recorded in $CDCl_3$ solution)

precursor pentacycle **120**, the analogous proton (H9) appeared further upfield at δ 4.16 as a triplet of doublets (*J* 6.5 and 1.7 Hz). Presumably, the observed difference in chemical shift is a manifestation of the change in molecular conformation accompanying propellane bond cleavage (Figure 3.7), the effect of which is to bring the proton associated with C10 of compound **121** into close proximity to the newly introduced acetate group at C12. The two olefinic protons, H5 and H7 within this same species, resonated at δ 6.56 and 5.17, respectively. The methyl groups associated with the methoxy and acetate moieties were also easily recognised, appearing as three-proton singlets at δ 3.68 and 2.05, respectively. The C15 methyl group, which is vicinally coupled to the methine proton at C9, appeared as a three-proton doublet (*J* 7.3 Hz) at δ 1.22. The two complex envelopes of signals between δ 3.08-2.70 and 2.25-1.90, as well as the doublet (*J* 12.2 Hz) at δ 1.74, accounted for the remaining ten aliphatic protons associated with C4, C5, C9, C11, C13, C13a and C13b. The protons associated with the *tert*-butyldimethylsilyl group appeared at δ 0.88, 0.05 and 0.03, whilst the broad singlet at δ 8.07 was assigned to the proton attached to the imide nitrogen.

As anticipated, the *tert*-butyldimethylsilyl protecting group associated with compound **121** was chemoselectively removed upon treatment with tetra-*n*-butylammonium fluoride (TBAF). Alcohol **122** so-formed was obtained, after silica gel flash chromatography, as a pale-yellow oil and in 68% yield. This material was found to be quite unstable and as a consequence, full characterisation of **122** could not be carried out. Nevertheless, both the mass spectrometric and ^{1}H NMR spectroscopic data obtained for alcohol **122** supported the proposed structure. For example, the 70 eV EI mass spectrum displayed a fragment ion at *m/z* 386 corresponding to the loss of a bromine radical from the molecular ion. A second fragment ion corresponding to the loss (from the molecular ion) of both a bromine radical and a molecule of acetic acid was clearly visible at *m/z* 326. In the ^{1}H NMR spectrum of alcohol **122**, the most distinctive feature was the absence of signals due to the *tert*-butyldimethylsilyl protecting group. Not surprisingly, the ^{1}H NMR spectrum of this compound was otherwise very similar to that of its precursor, compound **121**. Thus, a broad singlet observed at δ 8.05 was assigned



120 **121**

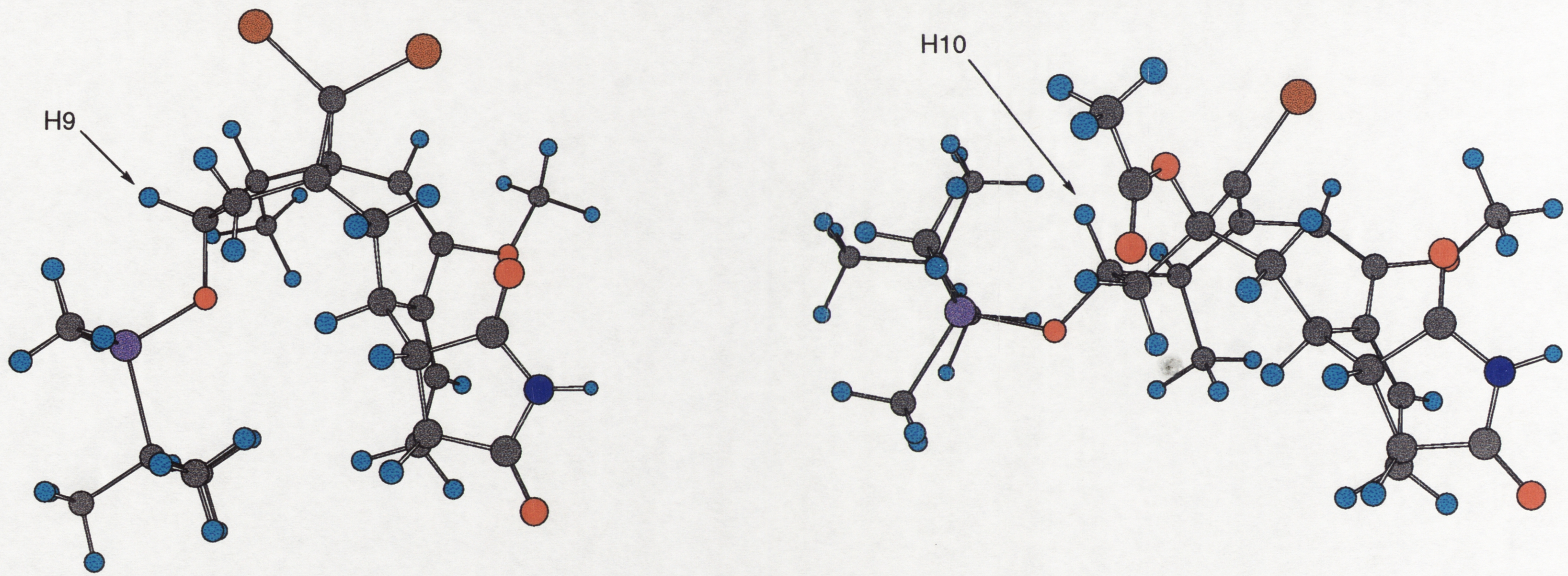


Figure 3.7: Conformational Change Accompanying Propellane Bond-Cleavage in the Conversion of Compound **120** to **121**.
(The illustrated and presumably near ground state conformers were obtained *via* semi-empirical AM1 calculations using Spartan™ SGI Version 5.03 software.)

to the imide proton, while the doublet of doublets (*J* 8.0 and 3.0 Hz) at δ 6.56, the singlet at δ 5.19 and the broad multiplet at *ca.* δ 4.95 were assigned to the protons attached to C5, C7 and C10, respectively. The protons associated with the methoxy group were clearly recognised as a three-proton singlet at δ 3.69, whilst the doublet (*J* 7.3 Hz) at δ 1.26 was assigned to the methyl substituent at C9. The methyl group associated with the acetate function appeared as a three-proton singlet at δ 2.06 and the remaining aliphatic protons were observed in the region δ 3.10-1.80.

In summary, compound **122** has been prepared in eight steps and in optically form from the readily available indanol (+)-**71**. The presence of an oxygen substituent at C10 in compound **122** [(equivalent to C13 in paclitaxel (**1**)] provides the opportunity to prepare paclitaxel analogues *via* coupling of the phenylisoserine side-chain. Such coupling procedures are well-established[8] and, rather than carry out the formality of attaching the paclitaxel side-chain to alcohol **122**, it was decided to focus attention on developing new and novel methods for the assembly of the oxetane D-ring. One approach could involve the Diels-Alder cycloaddition of compound **119** with oxete (**69**) (Chapter 1, Scheme 1.8, page 18). Studies directed toward the generation and Diels-Alder trapping of oxete (**69**) are described in the following chapter.

3.4 References

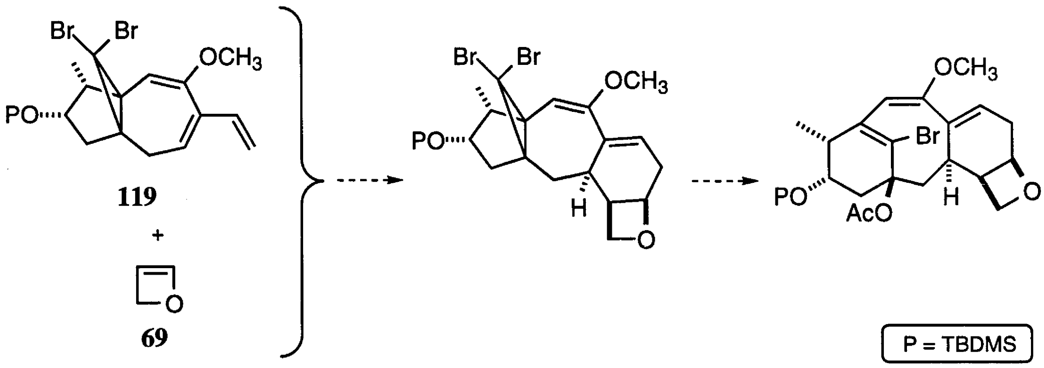
1. H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
2. M. E. Jung and S. M. Kaas, *Tetrahedron Lett.*, 1989, **30**, 641.
3. H. O. House and C. J. Blankley, *J. Org. Chem.*, 1968, **33**, 53.
4. M. G. Banwell and B. Halton, *Aust. J. Chem.*, 1979, **32**, 849 and references cited there-in.
5. For related ring-cleavage reactions of [n.m.1] propellanes, see: (a) P. M. Warner, *Chem. Rev.*, 1989, **89**, 1067 and references cited there-in; (b) G. W. Wijsman, W. H. de Wolf, F. Bickelhaupt, H. Kooijman and A. L. Spek, *J. Am. Chem. Soc.*, 1992, **114**, 9191.
6. M. E. Krolski, A. F. Renaldo, D. E. Rudisill and J. K. Stille, *J. Org. Chem.*, 1988, **53**, 1170.
7. A. G. Fallis and Y-F. Lu in *Advances in Cycloaddition*, D. Curran, Ed.; JAI Press, Greenwich, CT, 1993, Vol. 3, p.1. Similar cycloaddition reactions have been employed by others in the paclitaxel area, see: J. Oh and J. K. Cha, *Synlett*, 1994, 967.
8. For procedures using a C13 alkoxide/β-lactam coupling to attach the paclitaxel side-chain, see: (a) R. A. Holton, US Patent 5,015,744, 1991; (b) R. A. Holton, US Patent 5,136,060, 1992; (c) R. A. Holton, US Patent 5,175,315, 1992; (d) I. Ojima, I. Habus, M. Zhao, G. I. Georg and L. R. Jayasinghe, *J. Org. Chem.*, 1991, **56**, 1681; (e) I. Ojima, I. Habus, M. Zhao, M. Zucco, Y. H. Park, C. M. Sun and T. Brigaud, *Tetrahedron*, 1992, **48**, 6985; (f) I. Ojima, C. M. Sun, M. Zucco, Y. M. Park, O. Duclos and S. Kuduk, *Tetrahedron Lett.*, 1993, **34**, 4149.

CHAPTER 4

Studies Directed Towards the Generation and Diels-Alder Trapping of Oxete

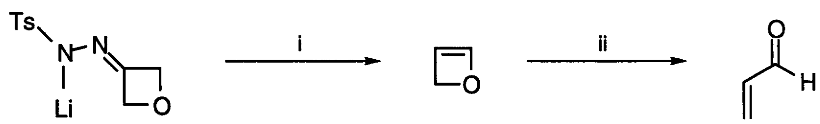
4.1 Overview

This chapter describes efforts directed toward the development of new methodologies for the generation and Diels-Alder trapping of oxete (**69**). Such efforts were driven by the expectation that Diels-Alder cycloaddition between the highly functionalised triene **119** and oxete (**69**) (Scheme 4.1) would offer a novel and concise route to the complete tetracyclic framework associated with the ABCD-ring system of taxoids.ø



Scheme 4.1

Oxete (**69**) was first prepared by Martino and Shevlin[1] in 1980 *via* flash vacuum pyrolysis (FVP) of the tosylhydrazone lithium salt **123** (Scheme 4.2). The unique heterocycle, **69**, has been characterised by both ^{1}H NMR and IR spectroscopy and undergoes thermally-induced ring-opening to give acrolein (**124**) with a half-life of



Scheme 4.2

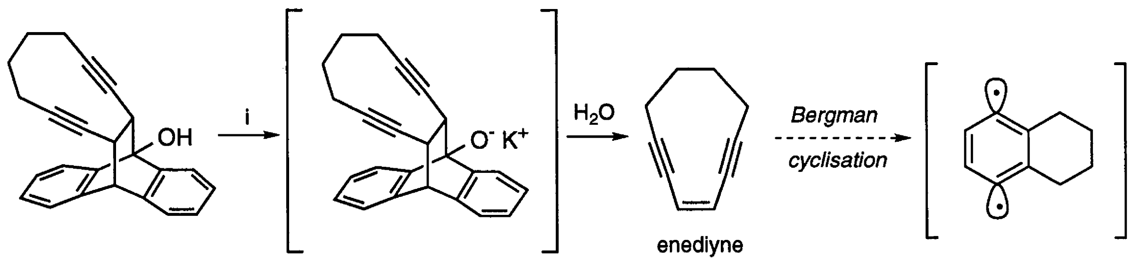
Reagents and Conditions: (i) FVP, 180-190 °C (11%); (ii) heat or acid.

ø Hückel molecular orbital calculations (HMO) suggest that a cycloaddition reaction involving addends **119** and **69** should proceed with the desired regioselectivity, as illustrated in Scheme 4.1.

ca. 8.4 hours in deuterochloroform solution at 25 °C.[2] This conversion is also catalysed by protic acids. A variety of methyl-, phenyl- and fluoro-substituted oxetes are also known[2] and have been prepared photochemically, but only in low yields. The difficulty in obtaining workable quantities of oxete (**69**) using existing protocols prompted us to investigate alternative methods for the preparation of this compound.

4.2 A New Strategy for the Synthesis of Oxete - The Oxy-Anion Assisted retro-Diels-Alder Reaction

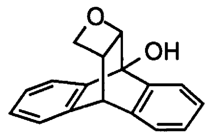
The remarkable ability of the oxy-anion to accelerate pericyclic reactions (with rate enhancement factors approaching up to 10^{17}) is well known.[3a] In particular, the oxy-anion assisted retro-Diels-Alder reaction[3b] is now finding some application as a method for the synthesis of sensitive alkenes[4,5] largely because of the mild reaction conditions often employed. For example, Nicolaou *et al.*[6] have recently utilised such a process for the generation of enediynes (Scheme 4.3), compounds known to undergo facile Bergman cycloaromatisation to give *p*-benzyne derivatives.



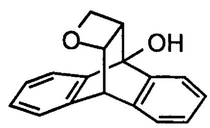
Scheme 4.3

Reagents and Conditions: (i) KH, THF, 25 °C, 30 mins.

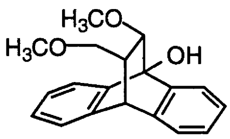
Such observations encouraged us to consider the oxy-anion assisted retro-Diels-Alder reaction as possible means for the generation of oxete (**69**). It was envisaged that oxetanes **125** and **126** would each be capable of generating the desired heterocycle **69**, *via* the aforementioned cycloreversion process. There was some expectation though, given the high degree of ring strain associated with oxete (**69**), that the activation barriers for such reactions may be higher than "normal". Consequently, we believed that there might be some value in preparing the corresponding open-chain analogues, *viz.* compounds **127** and **128**, and comparing their cycloreversion capabilities.



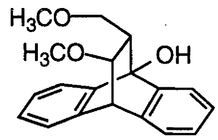
125



126



127



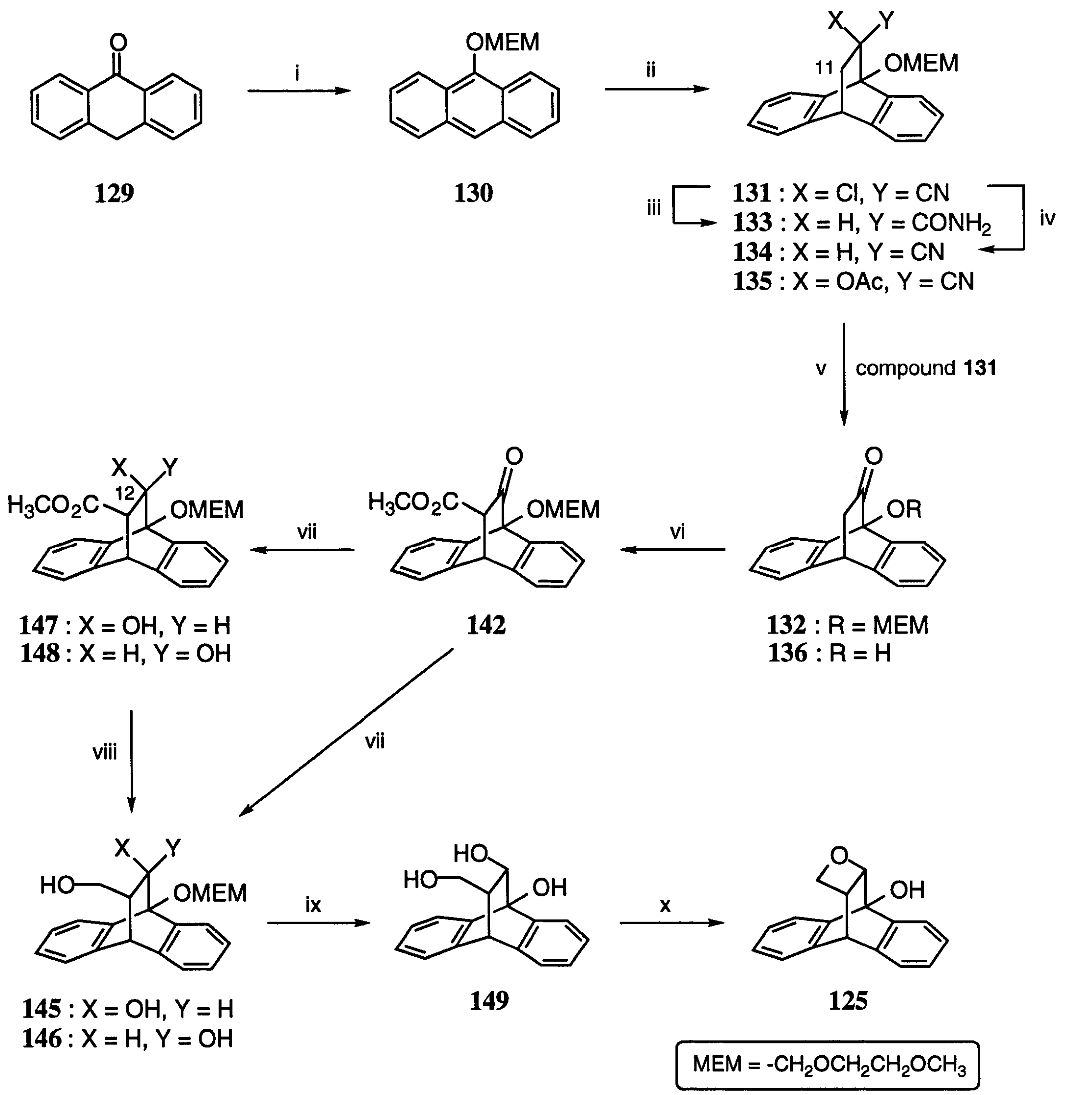
128

4.3 Synthesis of Oxetane 125

The only previously reported example of a molecule embodying the pentacyclic framework associated with target compounds **125** or **126** is the Paterno-Büchi photo-adduct derived from benzophenone and dibenzobarrallene.[7] Whilst bridgehead-oxygenated dibenzobarrallenes are known,[8] formaldehyde does not participate effectively in Paterno-Büchi reactions and so this approach to oxetanes **125** and **126** was not considered appropriate.

The synthesis of oxetane **125** is outlined in Scheme 4.4. Thus, the enolate anion derived from commercially available anthrone (**129**) was treated with 2-methoxyethoxymethyl chloride (MEM-chloride) to afford, in high yield (93%), the 9-oxygenated anthracenyl derivative **130** as light-yellow needles. Reaction of this material with 2-chloroacrylonitrile in benzene solution at *ca.* 125 °C, contained in an ACE™ pressure tube, furnished the Diels-Alder adduct **131** in near quantitative yield (98%). All physical, spectroscopic and analytical data were in full accord with the assigned structure.

For example, the APT ^{13}C NMR spectrum displayed the expected twenty one signals. In particular, the resonances associated with the carbons of the ethano-bridge appeared at δ 118.4 (CN), 60.8 (C12) and 49.0 (C11). The infrared spectrum of adduct **131** showed a nitrile stretching band at 2240 cm^{-1}. The ^1H NMR spectrum displayed all the expected features, the most diagnostic being the two mutually coupled doublet of doublets at



Scheme 4.4

Reagents and Conditions: (i) NaH, THF, 0 °C, 1 h then MEMCl; (ii) 2-chloroacrylonitrile, C_6H_6, ACE™ pressure tube, 125 °C, 16 h; (iii) KOH (aq.), 100 °C, 18 h; (iv) $Na_2S.xH_2O$, EtOH, reflux, 24 h; (v) *n*-BuLi, THF, -70 °C, O_2, $SnCl_2$ in HCl (aq.), NaOH (aq.); (vi) LDA, THF, -70 °C, 1 h then HMPA, $NCCO_2CH_3$; (vii) See Table 4.1; (viii) $LiBH_4$, THF, reflux, 13 h; (ix) 2 M HCl, THF, rt, 22 h; (x) Tf_2O, 2,6-lutidine, 0 °C - rt, 1.5 h.

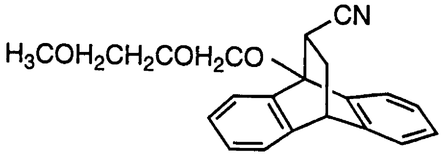
δ 2.40 (*J* 13.8 and 2.7 Hz) and 2.85 (*J* 13.9 and 2.7 Hz), which were assigned to the diastereotopic methylene protons attached to C11. Hydrolysis of adduct **131** to the target ketone **132** was not straightforward. No reaction was observed when the substrate was treated with potassium hydroxide in DMSO at room temperature.[9] Under more forcing conditions (aqueous KOH, 100 °C),[10] the dechlorinated amide **133** was formed on one occasion and all attempts to reproduce this outcome failed. In contrast, reaction of adduct **131** with hydrated sodium sulfide in refluxing ethanol,[11] conditions reported to effect hydrolysis of α-chloronitriles to ketones, only afforded compounds **134** and **130**.[Δ] The structure of the former product was confirmed by single-crystal X-ray analysis (Figure 4.1).

A comprehensive inspection of the chemical literature revealed that secondary nitriles can be converted into the corresponding ketone *via* oxidative decyanation protocols.[13] To this end, adduct **131** was treated with *n*-butyllithium and the ensuing lithio-species was trapped with oxygen gas. The resulting peroxyanion was then reduced, *in situ,* with tin(II) chloride (in aqueous HCl) to afford an intermediate cyanohydrin which was rapidly hydrolysed upon basic work-up to afford the long sought after ketone **132** (58%).[≠] All physical and spectroscopic data obtained for this compound were consistent with the assigned structure. Satisfactory microanalytical data were also acquired on this key compound. The 70 eV EI mass spectrum displayed the expected molecular ion at *m/z* 324, the composition of which ($C_{20}H_{20}O_4$) was confirmed by an accurate mass measurement. A fragment ion at *m/z* 296, corresponding to the loss of CO from the molecular ion, was also observed. The intense absorption maximum at 1731 cm^{-1} in the infrared spectrum and the signal at δ 204.8 in the APT ^{13}C NMR spectrum clearly established the presence of a ketone moiety. The ^{1}H NMR spectrum of compound **132** (Figure 4.2) displayed a two-proton doublet (*J* 2.7 Hz) at δ 2.45,

---

Δ The difficulties experienced in trying to generate ketone **132** *via* established hydrolytic procedures is in keeping with observations made on other α-chloronitrile species.[12] All attempts to prepare adduct **135** (which was expected to be more hydrolytically labile than species **131**) *via* Diels-Alder cycloaddition between **130** and 2-acetoxyacrylonitrile failed.

≠ Compound **132** was always accompanied by small amounts (≤5%) of the corresponding acyloin **136**, which results from loss of the MEM-protecting group.



134

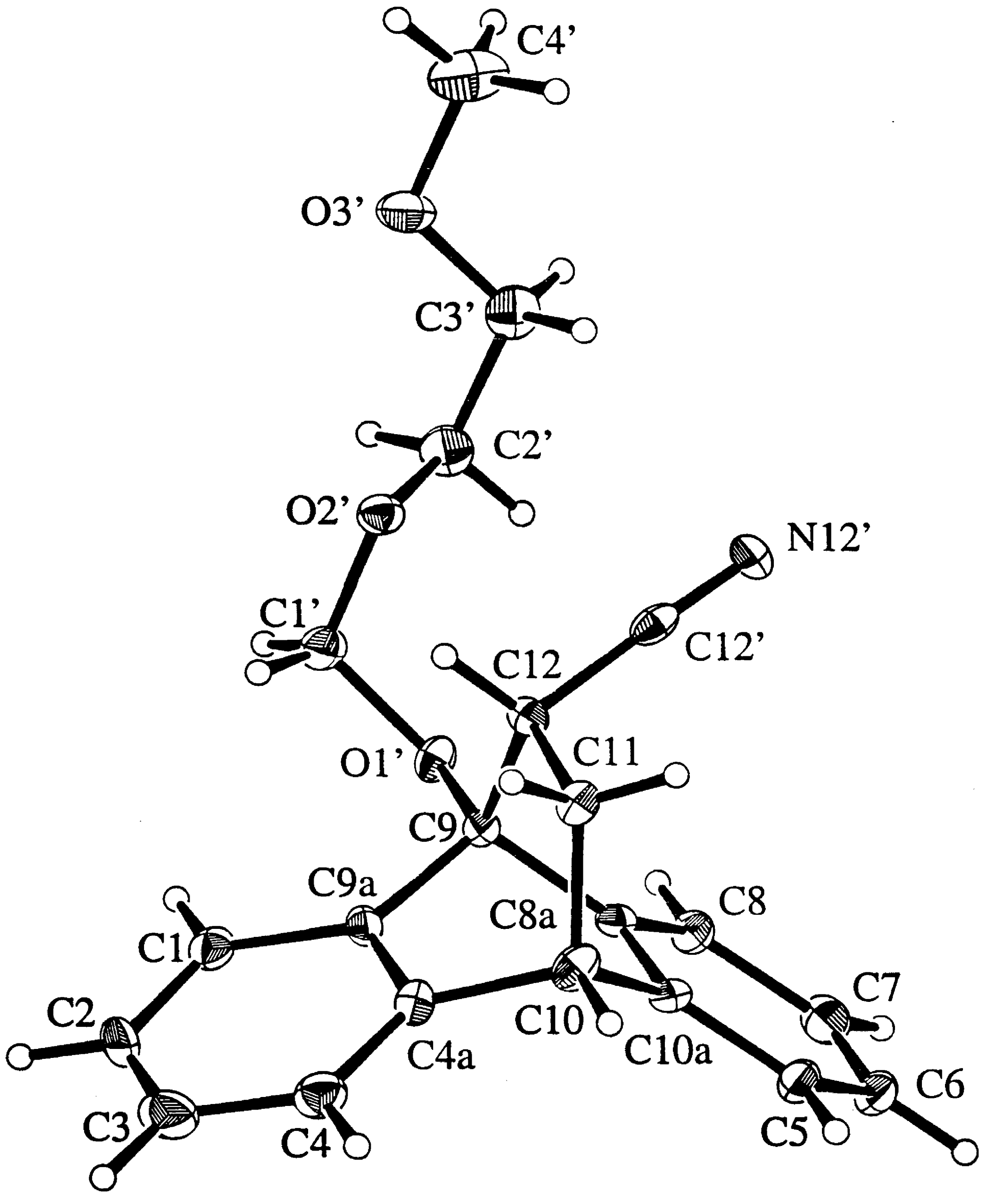


Figure 4.1: ORTEP Derived from Single-Crystal X-ray Analysis of Nitrile **134**.

(This analysis was conducted by Dr. D. C. R. Hockless, The Australian National University)

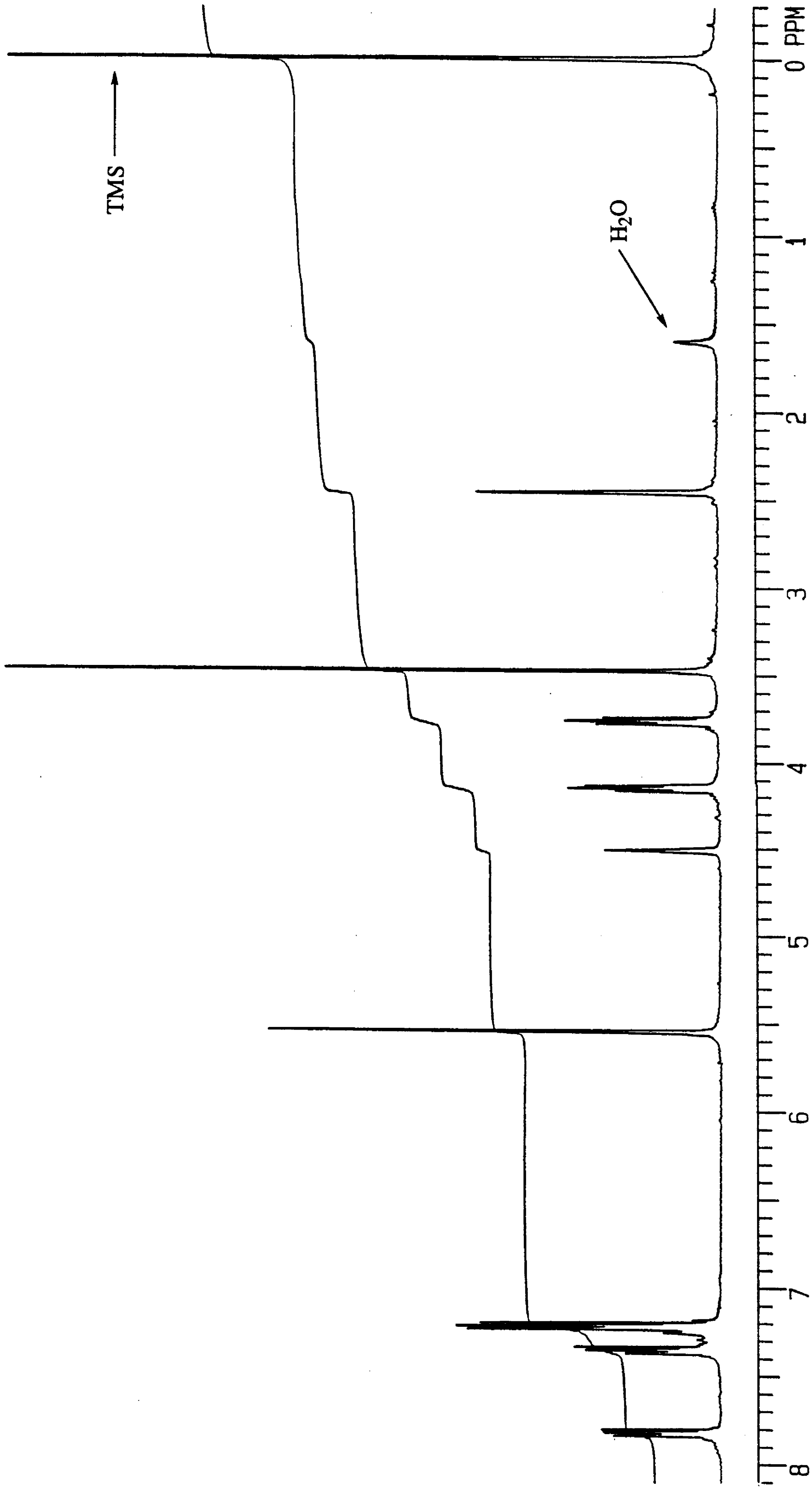
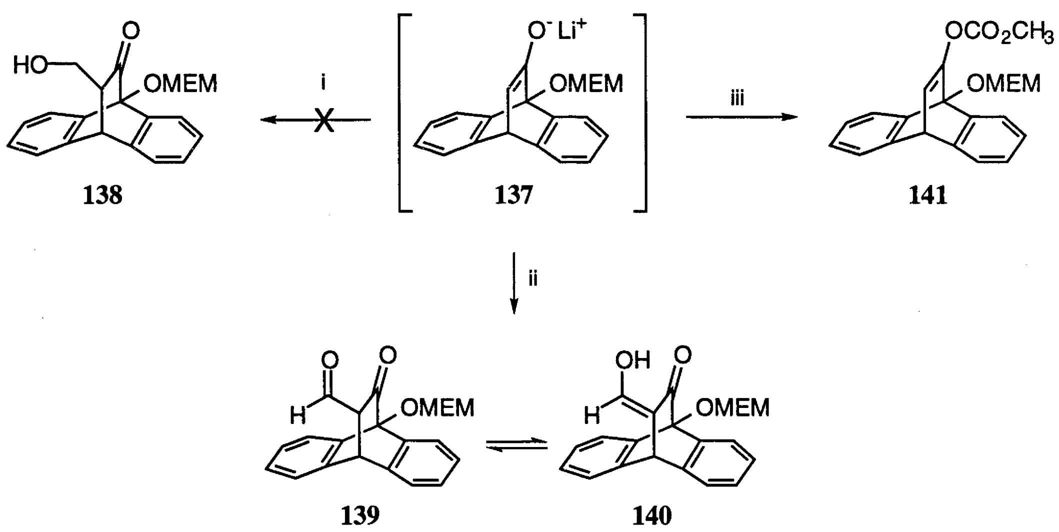


Figure 4.2: 300 MHz ^{1}H NMR Spectrum of Ketone **132**.

(Spectrum recorded in $CDCl_3$ solution)

which is assigned to the chemically equivalent methylene protons at C11. The one-proton triplet (J 2.7 Hz) observed at δ 4.50 was indicative of the bridgehead methine proton (C10), whilst the eight aromatic protons appeared in the region δ 7.20-7.90. The signals observed at δ 5.55 (singlet, 2H), 4.15 (multiplet, 2H), 3.76 (multiplet, 2H) and 3.47 (singlet, 3H) are all associated with the MEM-protecting group.

With workable quantities of the pivotal ketone **132** in hand, the next task *en route* to oxetane **125** involved installation of a one carbon unit adjacent (α) to the carbonyl moiety. To this end, ketone **132** was treated with lithium diisopropylamide (LDA) at -70 °C in THF solution and the resulting enolate anion **137** was reacted with various electrophiles (Scheme 4.5). Reaction of anion **137** with gaseous formaldehyde



Scheme 4.5

Reagents and Conditions: (i) formaldehyde (g); (ii) ethyl formate, THF, -70 °C; (iii) methyl chloroformate, THF, -70 °C - rt, 18 h.

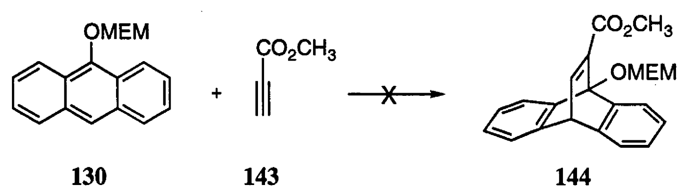
did not produce any of the anticipated alcohol **138** and only the starting material was returned. In contrast, trapping of enolate **137** with ethyl formate[14] was successful and generated an inseparable mixture of readily interconvertible tautomers, **139** and **140**. The difficulties associated with reproducing this reaction, coupled with the low yield of products (32% combined yield), made this process non-viable from a preparative point-of-view. When methyl chloroformate was employed as the electrophilic species, exclusive formation of the *O*-carbomethoxylated product, *viz.* carbonate **141**, was observed. Trapping of enolate **137** using the softer electrophile methyl cyanoformate (Mander's reagent[15]) resulted in exclusive formation of the desired *C*-alkylated product, ester **142**, which contains all of the carbon atoms required for the assembly of oxetane **125**.»

Complete and stereoselective reduction of compound **142** to the *cis*-diol **145** proved to be somewhat problematic (Table 4.1). For example, treatment of β-ketoester **142** with lithium aluminium hydride in THF at 0 °C (Table 4.1, entry 1) afforded a 4:1 mixture of the *cis*- and *trans*-diols, **145** and **146**, respectively. Use of the more bulky aluminium based reagent, diisobutylaluminium hydride (DIBAL), in THF at 0 °C (Table 4.1, entry 2), resulted in exclusive formation of the *trans*-diol **146**. Lithium

Table 4.1: Stereoselective Reduction of Ester **142** to *cis*-Diol **145**.

Entry	Reducing Agent	Reaction Conditions		Product Ratio			
		Solvent	Temp.	**145**	**146**	**147**	**148**
1	$LiAlH_4$	THF	0 °C - rt	4	1	-	-
2	DIBAL	THF	0 °C - rt	-	1	-	-
3	$LiBH_4$	THF	-70 °C	-	-	1	1
4	$NaBH_4$	MeOH	0 °C	-	-	7	1
5	$NaBH_4$, $CeCl_3.7H_2O$	^{i}PrOH	0 °C - rt	1	-	>30	-

» A more direct approach to compounds possessing the correct number of carbon atoms for the synthesis of oxetane **125** was investigated (Scheme 4.6) and involved Diels-Alder cycloaddition between compound **130** and methyl propiolate (**143**). All attempts, however, to form adduct **144**, including the use of high pressure (19 kbar), failed.



Scheme 4.6

borohydride-mediated reduction of ester **142** (Table 4.1, entry 3) resulted in the formation of a 1:1 mixture of *cis*- and *trans*-β-hydroxyesters, **147** and **148**, respectively. Spectroscopic differentiation between these two epimeric hydroxyesters was readily achieved by comparison of the vicinal couplings associated with the resonances due to H12 in each system (Figure 4.3). The magnitude of the observed coupling ($J_{12,11}$ 9.1 Hz) associated with H12 in the ^{1}H NMR spectrum of compound **147**, relative to that ($J_{12,11}$ 2.6 Hz) for the alternate epimer **148**, is consistent with a *cis*-relationship between H11 and H12 in the former system. High *cis*-selectivity (7:1) was

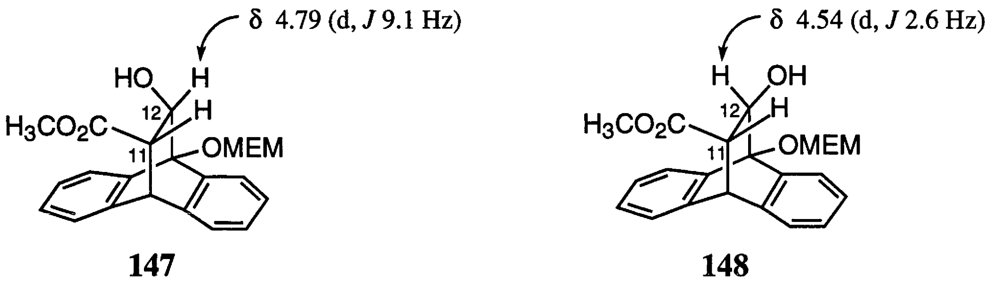


Figure 4.3: Comparison of Vicinal Couplings Associated with H12 of Compounds **147** and **148**.

observed when ester **142** was reduced with sodium borohydride in methanol at 0 °C (Table 4.1, entry 4) and exclusive formation of the *cis*-hydroxyester **147** was achieved using the Luche reagent[16] ($NaBH_4$ and $CeCl_3.7H_2O$) in *iso*-propanol (Table 4.1, entry 5). Trace quantities of *cis*-diol **145** were also isolated from the latter reaction. Completion of the reduction sequence leading to the target diol **145** was effected by reaction of ester **147** with lithium borohydride in refluxing THF. In this manner, *cis*-diol **145** was obtained in 80% yield.

Completion of the synthesis of oxetane **125** was straightforward. Hydroylsis of diol **145** with 2 M aqueous HCl in THF afforded triol **149** which, when treated with trifluoromethanesulfonic anhydride (Tf_2O) in 2,6-lutidine, furnished the oxetane **125** in 67% yield. Presumably, this last step involves initial formation of the triflate derived from the primary hydroxy function within triol **149**, followed by *in situ* cyclisation to provide the observed product. Attempts to increase the yield of this reaction by modifying (i) the amount of Tf_2O used, (ii) the reaction temperature and/or (iii) the reaction time were unsuccessful. Nevertheless, the 'one-pot 'formation of oxetane **125** from triol **149** just described represents a new and potentially useful reaction that warrants consideration as a means for generating other oxetanes.[17]

All physical and spectroscopic data acquired for compound **125** were fully consistent with the assigned structure. The APT ^{13}C NMR spectrum displayed the expected seventeen resonances and the molecular ion (*m/z* 250) was detected in the 70 eV EI mass spectrum. Accurate mass measurement on this species confirmed the molecular formula as $C_{17}H_{14}O_2$. Interestingly, the base peak appeared at *m/z* 194 which corresponds to the loss of the elements of oxete (**69**) (C_3H_4O) from the molecular ion, presumably *via* a retro-Diels-Alder reaction. The ^1H NMR spectrum of oxetane **125** displayed all of the expected features, the most pertinent of which are summarised in Figure 4.4. The methylene protons attached to C13 appeared as two distinct triplets

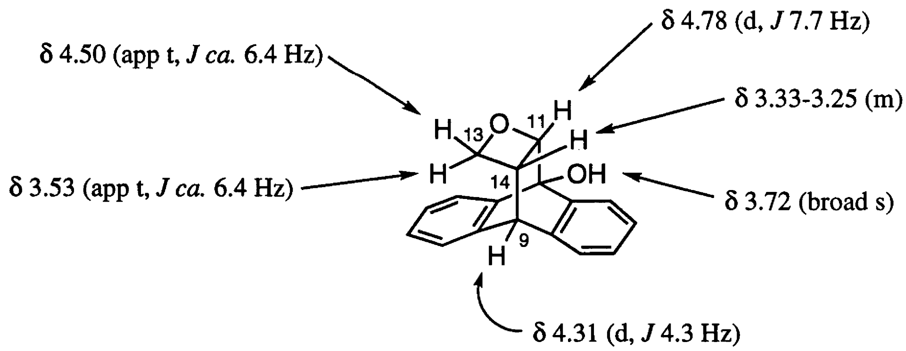
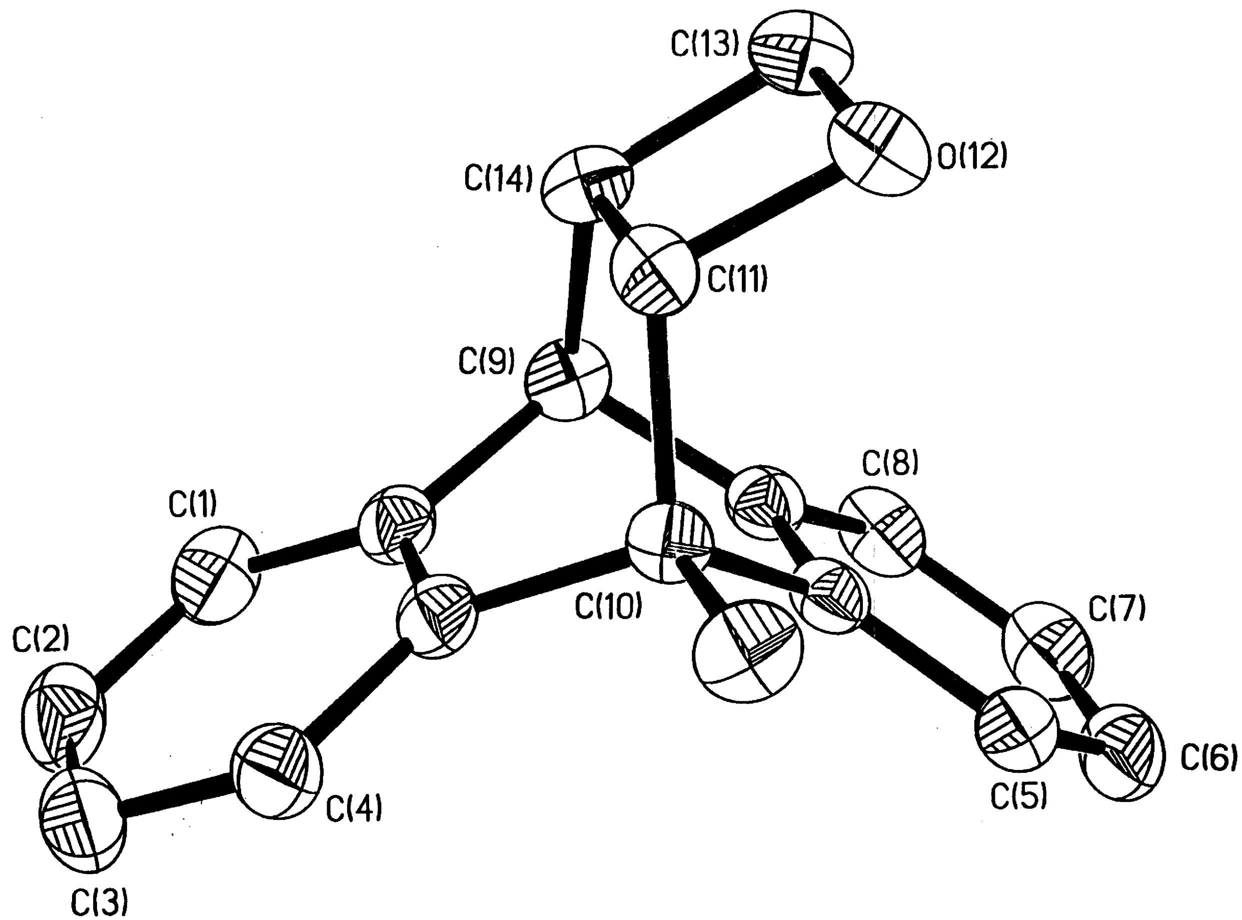
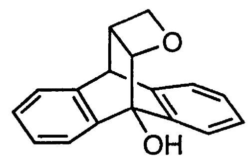


Figure 4.4: Selected ^1H NMR Spectroscopic Data for Compound **125**.
(Data acquired in $CDCl_3$ solution)

(*J ca.* 6.4 Hz) at δ 4.50 and 3.53, the chemical shift of the latter probably being due to that hydrogen projecting into the shielding zone of the nearby aromatic ring. The signal due to the oxymethine proton at C11 appeared as a doublet (*J* 7.7 Hz) at δ 4.78, whilst the multiplet at *ca.* δ 3.31 was assigned to H14. Final confirmation of the structure of compound **125** followed from a single-crystal X-ray analysis (Figure 4.5).





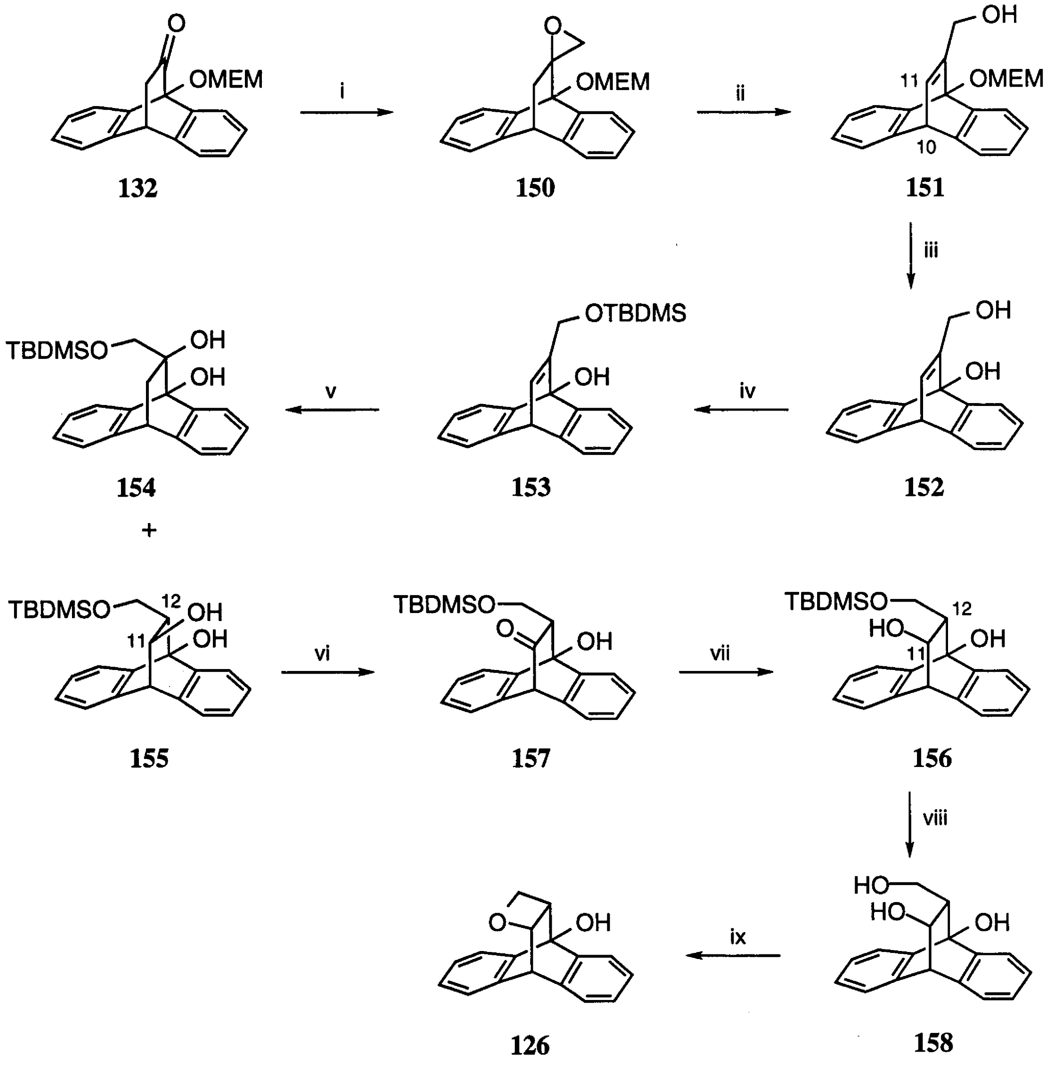
125

Figure 4.5: ORTEP Derived from Single-Crystal X-ray Analysis of Oxetane **125**.

(This analysis was conducted by Dr. G. R. Clark, The University of Auckland)

4.4 Synthesis of Oxetane 126

The synthesis of the regioisomeric oxetane, compound **126**, is outlined in Scheme 4.7. Thus, treatment of ketone **132** with dimethylsulfonium methylide[18] afforded the unstable spiro-epoxide **150** in 78% yield after purification by flash chromatography. The infrared stretching band associated with the epoxide function of **150** was clearly visible at 1248 cm^{-1}. The composition of the molecular ion (m/z 338)



Scheme 4.7

Reagents and Conditions: (i) KHMDS, THF, $(H_3C)_3SI$, 0 °C - rt, 1 h; (ii) $LiNEt_2$, THF, -70 °C - rt, 4 h; (iii) 2 M HCl (aq.), THF, rt, 16 h; (iv) TBDSMCl, imidazole, DMF, 0 °C - rt, 13 h; (v) BH_3.THF, rt, 1 h then NaOH (aq.), H_2O_2, rt, 1 h; (vi) Swern oxidation; (vii) L-Selectride, -70 °C - rt, 5 h; (viii) TBAF, THF, rt, 5 mins; (ix) Tf_2O, 2,6-lutidine, 0 °C - rt, 2 h.

observed in the 70 eV EI mass spectrum was confirmed as $C_{21}H_{22}O_4$ by accurate mass measurement. The APT ^{13}C NMR spectrum displayed nineteen resonances while the ^1H NMR spectrum of epoxide **150** (Figure 4.6) possessed all the required features. In particular, the two diastereotopic methylene protons associated with the oxirane ring appear as one-proton doublets (*J* 5.2 Hz) at δ 3.25 and 2.58. Base-induced epoxide ring-opening of compound **150** was effected with lithium diethylamide[19] and afforded the allylic alcohol **151** as a viscous oil. The ^1H NMR spectrum of this material revealed two mutually coupled doublets (*J* 6.0 Hz) at δ 6.78 and 4.98, which have been assigned to the olefinic (H11) and bridgehead methine protons (H10), respectively. The intense absorption maximum at 3420 cm^{-1} in the infrared spectrum, indicative of a free hydroxy group, supported the proposed structure. Hydrolytic cleavage of the MEM-protecting group then afforded diol **152** in near quantitative yield (98%), the primary hydroxy function of which was selectively protected, under standard conditions,[20] as the *tert*-butyldimethylsilyl ether **153**. Subsequent hydroboration/oxidation[21] of this latter compound furnished a *ca.* 1:8 mixture of regioisomers, **154** and **155**, which could be easily separated by flash chromatography. Full characterisation of both compounds secured their illustrated structures.

In connection with efforts to apply the same triflation/cyclisation methodolgy developed previously for the preparation of oxetane **126** (see Section 4.3), diol **156** was required. To this end, compound **155** was oxidised, under standard Swern[22] conditions, to afford ketone **157** as a clear, colourless oil. Stereoselective reduction of this latter species using L-Selectride in THF solution at -70 °C delivered, in an exclusive fashion, the desired alcohol **156** in moderate yield (43%).[Π] Spectroscopic differentiation between the two epimeric hydroxyesters **155** and **156** was readily achieved by comparison of the three-bond couplings associated with the resonances due to H11. The magnitude of the observed coupling associated with H11 in the ^1H NMR spectrum of compound **156** ($J_{11,12}$ 8.5 Hz), relative to that for epimer **155**

Π Interestingly, reduction of compound **157** using $NaBH_4$ and $CeCl_3.7H_2O$ in *iso*-propanol at 0 °C, afforded a 2:1 mixture of *cis*- and *trans*-alcohols, **156** and **155**, respectively.

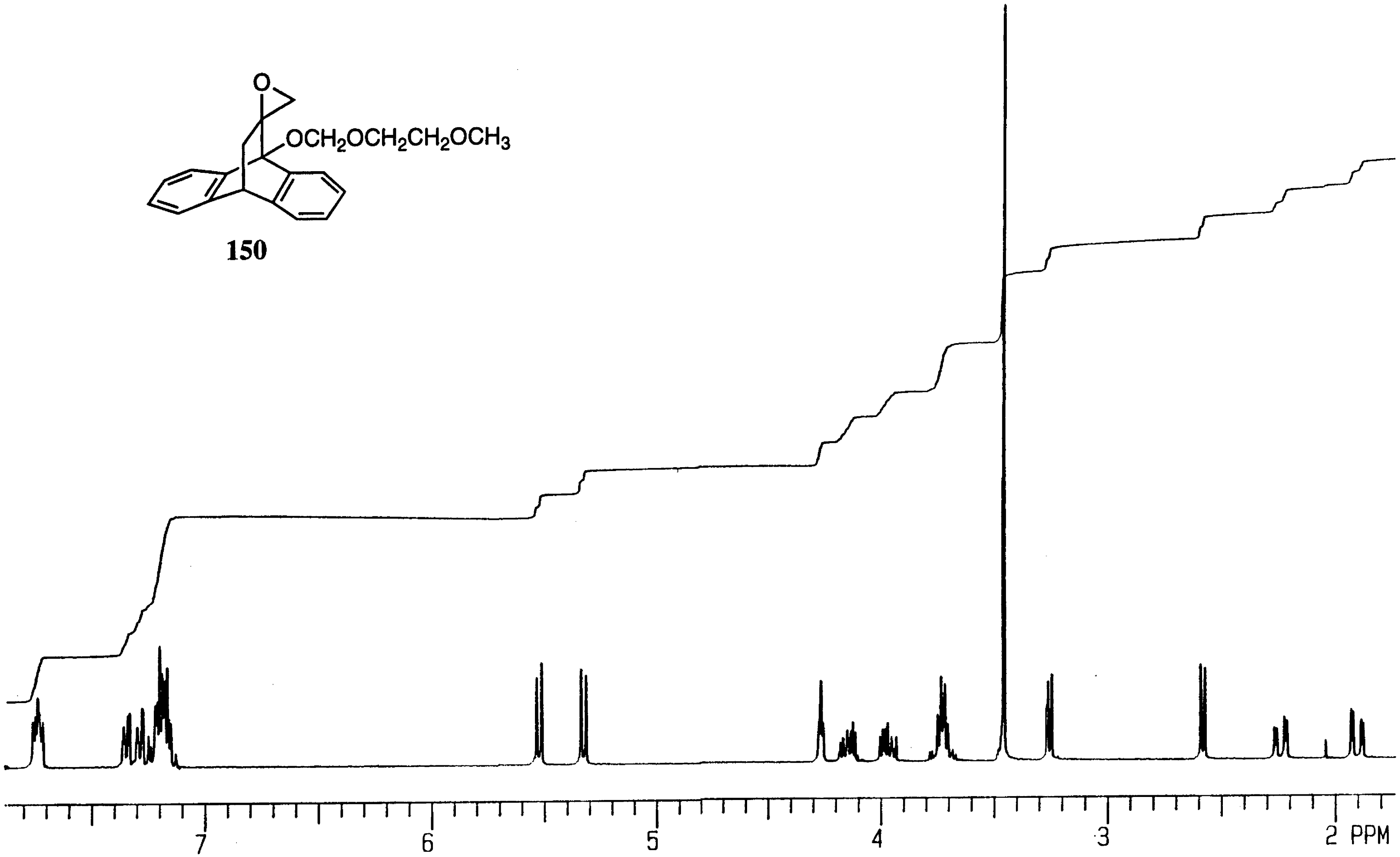
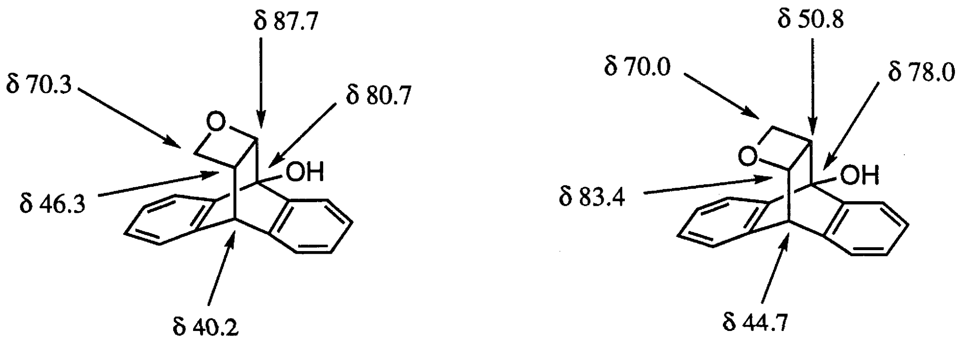


Figure 4.6: 300 MHz ^{1}H NMR Spectrum of Spiro-Epoxide **150**.

(Spectrum recorded in $CDCl_3$ solution)

($J_{11,12}$ 3.0 Hz), is consistent with a *cis*-relationship between H11 and H12 in the former compound. Desilylation of ether **156** was effected with tetra-*n*-butylammonium fluoride (TBAF) and the resulting triol **158** was then cyclised (Tf_2O/2,6-lutidine) under conditions previously described (see page 78). Oxetane **126** so-formed was obtained in good yield (75% at 57% conversion) as a colourless, crystalline needles. The composition of the molecular ion (*m/z* 250) observed in the 70 eV EI mass spectrum of this compound was confirmed as $C_{17}H_{14}O_2$ by accurate mass measurement. As with regioisomer **125**, the base peak was observed at *m/z* 194. The expected seventeen resonances were observed in the APT ^{13}C NMR spectrum of compound **126**, a selection of which are presented in Figure 4.7.

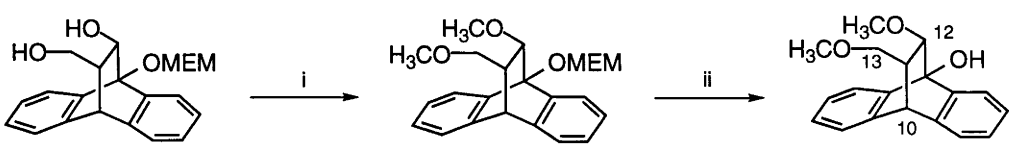


125 **126**

Figure 4.7: Selected APT ^{13}C NMR Spectroscopic Data for Oxetanes **125** and **126**.
(Data acquired in $CDCl_3$ solution)

4.5 Synthesis of Open-Chain Analogue 127

The synthesis of compound **127** was accomplished in two steps (Scheme 4.8) from *cis*-diol **145** and simply involved *O*-methylation of the latter species using potassium hydride and methyl iodide.[23] The MEM-protecting group associated with the resulting *bis-O*-methyl ether **159** was then removed with aqueous HCl and provided the desired model compound **127** as a colourless oil in high yield (91%). Full characterisation of this material supported the assigned structure.



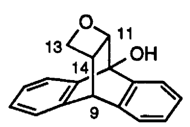
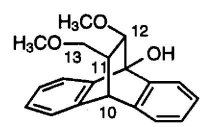
145 **159** **127**

Scheme 4.8

Reagents and Conditions: (i) KH, THF, rt, 1 h then MeI; (ii) 2 M HCl (aq.), THF, rt, 16 h.

Interestingly, the signals associated with H11, H12 and H13 in the ^{1}H NMR spectrum of compound **127** appeared significantly further upfield (up to $\Delta\delta$ 1.8 ppm) (Table 4.2) with respect to their counterparts (H14, H11 and H13) in oxetane **125**, presumably reflecting the strain associated with the four-membered ring of heterocycle **125**.

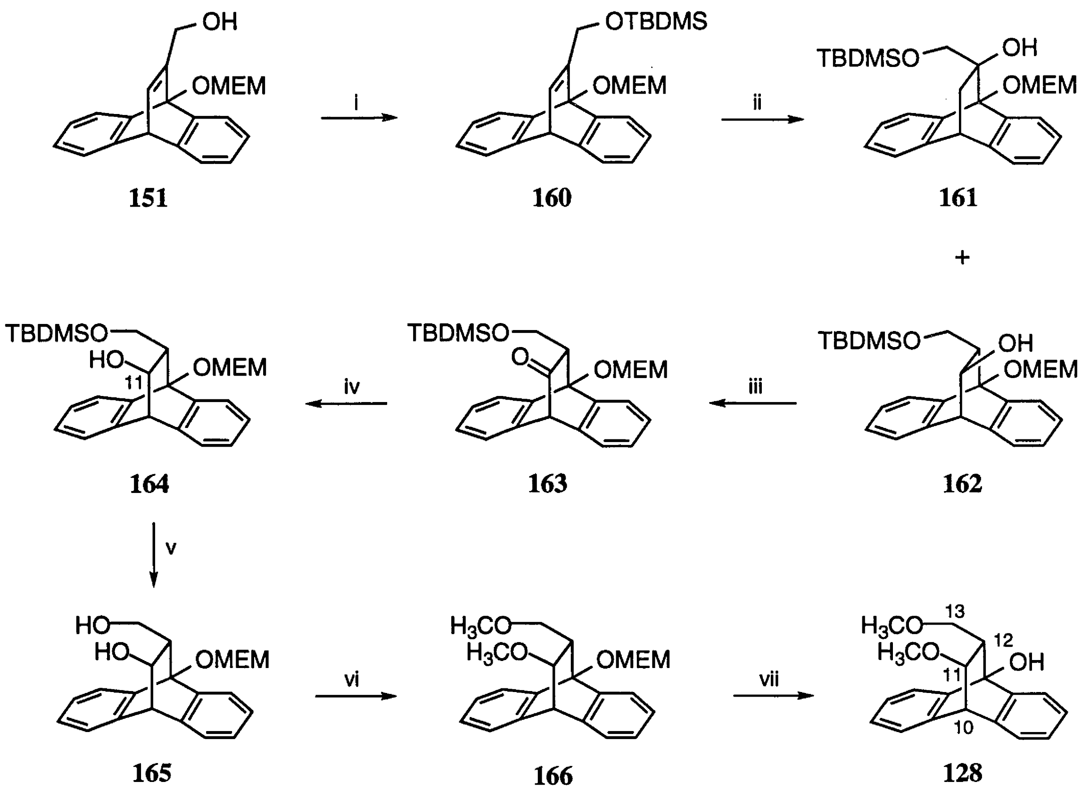
Table 4.2: Selected ^{1}H NMR Spectroscopic Data[a] for Compounds **125** and **127**.

 **125**		 **127**	
δ 4.31 (d, *J* 4.3 Hz)	H9	H10	δ 4.28 (d, *J* 2.5 Hz)
δ 3.33-3.25 (complex m)	H14	H11	δ 2.11-2.03 (m)
δ 4.78 (d, *J* 7.7 Hz)	H11	H12	δ 2.97 (d, *J* 2.8 Hz)
δ 4.50 (app t, *J ca.* 6.4 Hz)	H13	H13	δ 3.13 (dd, *J* 9.3 and 6.5 Hz)
δ 3.53 (app t, *J ca.* 6.4 Hz)	H13'	H13'	δ 2.90 (t, *J* 9.3 Hz)

[a] Data acquired in $CDCl_3$ solution.

4.6 Synthesis of Open-Chain Analogue 128

The preparation of compound **128** (Scheme 4.9) was more involved than that associated with regioisomer **127**, largely because of the need to retain the MEM-protecting group until after the relevant *bis-O*-methylation step. Thus, alcohol **151** was converted to the corresponding silyl ether derivative **160** in good yield (71%) by following known protocols. Hydroboration/oxidation of the latter material afforded a *ca.* 1:3 mixture of regioisomeric alcohols **161** and **162**, which were easily separated by flash chromatography. Swern oxidation of alcohol **162** afforded ketone **163** in high yield (84%), which was subsequently reduced with L-Selectride at -70 °C to give, in an exclusive manner, the C11 epimeric alcohol, compound **164**. Removal of the

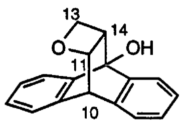
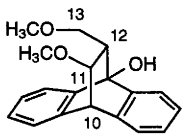


Scheme 4.9

Reagents and Conditions: (i) TDBMSCl, imidazole, DMF, 0 °C - rt, 10 h; (ii) BH_3.THF, rt, 2 h then NaOH (aq.), H_2O_2,, rt, 1 h; (iii) Swern oxidation; (iv) L-Selectride, THF, -70 °C - rt, 6 h; (v) TBAF, THF, rt, 15 mins; (vi) KH, THF, 0 °C, 1 h then MeI; (vii) 2 M HCl (aq.), THF, rt, 18 h.

tert-butyldimethylsilyl protecting group with TBAF, followed by *bis-O*-methylation of the resulting diol **165**, afforded compound **166**. Acidic hydrolysis to remove the MEM-protecting group within the latter compound then furnished the target alcohol **128** as a crystalline solid. All physical, microanalytical and spectroscopic data acquired for this compound were consistent with the proposed structure. The ^{1}H NMR spectroscopic variations between compounds **126** and **128** (Table 4.3) were similar to those noted for the regioisomeric pair, **125** and **127**. Interestingly, the APT ^{13}C NMR resonances assigned to C14 in compound **126** (δ 50.8) and C12 in compound **128** (δ 46.6) displayed a larger chemical shift difference with respect to the equivalent carbons of the alternate regioisomeric pair, compounds **125** and **127** (δ 87.7 and 86.3, respectively).

Table 4.3: Selected ^{1}H NMR Spectroscopic Data[a] for Compounds **126** and **128**.

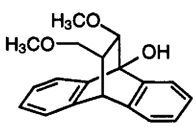
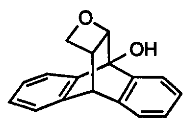
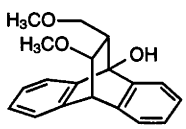
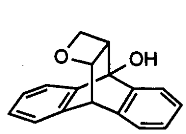
 **126**			 **128**
δ 4.54 (d, *J* 4.6 Hz)	H10	H10	δ 4.49 (d, *J* 2.9 Hz)
δ 5.02 (dd, *J* 7.7 and 4.5 Hz)	H11	H11	δ 2.56-2.47 (m)
δ 3.12-3.05 (m)	H14	H12	δ 3.82 (dd. *J* 9.3 and 3.0 Hz)
δ 4.45 (t, *J* 6.8 Hz)	H13	H13	δ 3.53 (dd, *J* 10.3 and 3.7 Hz)
δ 3.58 (dd, *J* 6.5 and 5.0 Hz)	H13'	H13'	δ 2.88 (dd, *J* 10.4 and 0.9 Hz)

[a] Data acquired in $CDCl_3$ solution.

4.7 Cycloreversion Studies

The foreshadowed cycloreversion reactions were performed in the following manner: separate solutions of the substrates **125**, **126**, **127** and **128** in 1,4-dioxane, each containing 3 molar equivalents of 18-crown-6, were treated with 7 molar equivalents of potassium hydride. After stirring for 1 hour at 18 °C, an aliquot was withdrawn from each of the reaction mixtures and quenched in methanol. The quenched reaction aliquot was then analysed by GC (see Experimental Section for details). The appearance of anthrone (**129**) (and/or the disappearance of the substrate) in the GC trace was taken as evidence that the desired cycloreversion reaction was occuring. If and when anthrone (**129**) production was detected, the bulk reaction mixture was analysed, after work-up, by ^{1}H NMR spectroscopy. If, however, after 1 hour at a given temperature anthrone (**129**) formation had not been detected, the temperature of the reaction mixture was raised (to 50, 80 and/or 100 °C), heated at that temperature for 1 hour and then analysed in the manner described above. The results of conducting such experiments are summarised in Table 4.4. It can be seen that neither of the oxetanes **125** or **126** engaged in the desired oxy-anion assisted retro-Diels-Alder reaction, even at temperatures as high as 100 °C. The same outcome was observed for the open-chain analogue **127**.

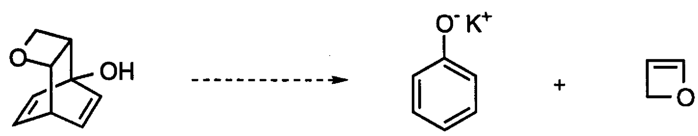
Table 4.4: Cycloreversion Studies: - Subjection of substrates **125, 126, 127** and **128** to reaction with potassium hydride and 18-crown-6 at various temperatures.

Substrate	Reaction Temperature			
	18 °C	50 °C	80 °C	100 °C
 **127**	no reaction	no reaction	no reaction	no reaction[a]
 **125**	no reaction	no reaction	no reaction	no reaction[a]
 **128**	anthrone[b] (**129**)	not attempted	not attempted	not attempted
 **126**	no reaction	no reaction	no reaction	no reaction[a]

[a] The substrate was returned in near quantitative yield after work-up. [b] All of the substrate was consumed in this reaction and anthrone (**129**) was the only compound detected by GC and ^{1}H NMR spectroscopy.

In stark contrast, regioisomer **128** underwent smooth cycloreversion at room temperature to afford anthrone (**129**) in near quantitative yield.

Since the half-life of oxete (**69**) is reported[2] to be *ca.* 8.4 h at 25 °C, it can be estimated, using the Arrhenius equation, that this molecule would only exist for a matter of seconds at 100 °C or higher. Consequently, it is unlikely that a cycloreversion process requiring temperatures of this order is going to provide a useful means for generating oxete (**69**). The different behaviours observed for the open-chain compounds **127** and **128** suggests that electronic factors are important in anionically assisted cycloreversion processes. In addition, strain effects also seem to be of some importance given the divergent behaviours of compounds **126** and **128**. On this basis, it would seem worthwhile investigating the response of tricycle **167** to treatment with potassium hydride/18-crown-6, since the cycloreversion reaction leading to potassium phenolate (**168**) and oxete (**69**) (Scheme 4.10) would result in a much greater gain in resonance stabilisation energy than that accompanying the analogous process involving compounds **125** or **126**. Such studies are currently being undertaken in these laboratories.



167 **168** **69**

Scheme 4.10

In the course of trying to generate oxete (**69**) *via* cycloreversion of the previously unknown compounds **125** and **126**, new methods for the preparation of oxetanes have been developed. It is envisaged that, in our approach to the construction of the complete carbocyclic framework associated with taxoids (Chapter 3), such methods can be applied in a more "traditional" manner for the assembly of the oxetane D-ring.

4.8 References

1. P. C. Martino and P. B. Shevlin, *J. Am. Chem. Soc.*, 1980, **102**, 5429.
2. L. E. Friedrich and P. Y-S. Lam, *J. Org. Chem.*, 1981, **46**, 306.
3. (a) This phenomenon was first demonstrated by D. A. Evans and A. M. Golob (*J. Am. Chem. Soc.*, 1975, **97**, 4765) in the now extensively utilised anionic oxy-Cope reaction; (b) The first analysis of oxy-anion acceleration in a retro-Diels-Alder context was described by O. Papies and W. Grimme, *Tetrahedron Lett.*, 1980, **21**, 2799. Although apparently unrecognised, the oxy-anion acceleration of a retro-Diels-Alder rection may have been observed over a decade in advance of the Grimmes study, see: A. Oku, T. Kakihana and H. Hart, *J. Am. Chem. Soc.*, 1967, **89**, 4554.
4. S. Knapp, R. M. Ornaf and K. E. Rodriques, *J. Am. Chem. Soc.*, 1983, **105**, 5494.
5. For recent reviews on the oxy-anion assisted retro-Diels-Alder reaction, see: (a) M. E. Bunnage and K. C. Nicolaou, *Chem. Eur. J.*, 1997, **3**, 187; (b) B. Rickborn, The retro-Diels-Alder Reaction Part 1. C-C Dienophiles in *Organic Reactions,* L. A. Paquette, Ed.; John Wiley & Sons, 1998, Vol. 52, Chapter 1, p. 18-24.
6. M. E. Bunnage and K. C. Nicolaou, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1110.
7. S. J. Cristol, R. L. Kaufman, S. M. Opitz, W. Szalecki and T. H. Bindel, *J. Am. Chem. Soc.*, 1983, **105**, 3226.
8. C. M. Cimarusti and J. Wolinsky, *J. Am. Chem. Soc.*, 1968, **90**, 113.
9. J. Ipaktschi, *Chem. Ber.*, 1972, **105**, 1840.
10. J. Paasivirta and H. Krieger, *Suomen Kemistilehti*, B**38**, 1965, 182; (*Chem. Abstr.*, 1966, **64**, 4965g).
11. D. A. Evans, W. L. Scott and L. K. Truesdale, *Tetrahedron Lett.*, 1972, 121.

12. C. S. Shiner, A. M. Fisher and F. Yacoby, *Tetrahedron Lett.*, 1983, **24**, 5867 and references cited there-in.

13. S. J. Selikson and D. S. Watt, *J. Org. Chem.*, 1975, **40**, 267.

14. M. Stanescu, M. Banciu and A. T. Balaban, *Rev. Roum. Chim.*, 1989, **34**, 617; (*Chem. Abstr.*, 1989, **111**, 232506h).

15. L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, 1983, **24**, 5425.

16. A. L. Gemal and J-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.

17. For reviews concerning the synthesis of oxetanes, see: (a) S. Searles, Oxetanes and Oxetenes in *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees, Eds.; Pergamon Press, 1984, Vol. 7, Chapter 5.13, p. 363; (b) R. J. Linderman, Oxetanes and Oxetenes: Fused-ring Derivatives in *Comprehensive Heterocyclic Chemistry II*, A. Padwa, Ed.; Elsevier, Oxford, UK, 1996, Vol. 1B, p. 755.

18. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.

19. R. P Thummel and B. Rickborn, *J. Am. Chem. Soc.*, 1970, **92**, 2064.

20. S. K Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99.

21. (a) G. Zweifel and H. C. Brown, *J. Chem. Soc.*, 1964, **86**, 393; (b) G. Zweifel and H. C. Brown, *J. Chem. Soc.*, 1961, **83**, 2544.

22. A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.

23. M. E. Jung and S. M. Kaas, *Tetrahedron Lett.*, 1989, **30**, 641.

CHAPTER 5

Experimental Section

5.1 General Protocols

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 300 MHz for proton and 75.4 MHz for carbon, respectively. Deuterochloroform ($CDCl_3$) was used as solvent unless otherwise indicated. Chemical shifts are recorded as δ values in parts per million (ppm), the nominal standard being tetramethylsilane (TMS) (0.00 ppm). For proton spectra recorded in deuterochloroform, tetramethylsilane was used as the internal reference, while the central peak (77.0 ppm) of the $CDCl_3$ triplet was used as the internal reference for carbon spectra. In cases where deuteromethanol (CD_3OD) was used as solvent, proton spectra were referenced against residual CH_3OH (3.30 ppm), while carbon spectra were referenced to the central peak (49.0 ppm) of the CD_3OD heptet. Proton spectra recorded in deuterotetrahydrofuran were referenced against residual tetrahydrofuran (3.58 ppm), while carbon spectra were referenced relative to the central peak (67.4 ppm) of the deuterotetrahydrofuran pentet. Data are recorded as follows: chemical shift (δ), multiplicity (s : singlet, d : doublet, t : triplet, q : quartet, m : multiplet, dd : doublet of doublets etc., br : broad), coupling constant(s) (*J* Hz), relative integral (for proton spectra) and assignment (where possible). Distortionless enhancement by polarisation transfer (DEPT) and attached proton test (APT) techniques were employed for the assignment of NMR spectra. APT ^{13}C NMR spectral data are reported in the following format: chemical shift (δ) and protonicity (C = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl, C/CH_2 = quaternary or methylene, CH/CH_3 = methine or methyl). Protonicities were determined by the phase of the resonance relative to the solvent signal, *viz.* C and CH_2 were of the same phase as the $CDCl_3$ triplet, whilst CH and CH_3 resonances were of the opposite phase.

Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier Transform Infrared Spectrophotometer or a Perkin-Elmer 683 Infrared Spectrophotometer. Samples were analysed either as KBr discs (for solids) or as thin liquid films (for oils) on sodium chloride (NaCl) or potassium bromide (KBr) plates.

Low and high resolution mass spectra were recorded on a VG Micromass 7070F double focussing mass spectrometer, using positive ion electron impact techniques (unless otherwise stated) at the voltages indicated. Chemical ionisation (CI) mass spectra were recorded on an AUTOSPEC spectrometer, with NH_3 as the reactant gas. Mass spectral data are listed as mass-to-charge ratio (*m/z*), assignment (where possible) and relative intensity (% of base peak).

Optical rotations {$[\alpha]_D$} were recorded on a Perkin-Elmer 241 polarimeter using spectroscopic grade chloroform as solvent (unless otherwise specified) at the temperature and concentration (*c*) (g/100 mL) indicated.

Melting points were recorded on a Reichert hot-stage microscope and are uncorrected.

Elemental analyses were performed by the Australian National University Microanalytical Services Unit, Canberra, Australia.

Ozonolyses were performed using a Wallace and Tiernan Ozonator with the oxygen flow rate and power adjusted to approximately 25 L/h and 200 V, respectively.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} plates (supplied by Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with a reagent solution [either anisaldehyde/sulfuric acid/ethanol (2 : 5 : 93) dip, phosphomolybdic acid/ethanol (8 g : 200 mL) dip or phosphomolybdic acid/ceric (IV) sulfate/sulfuric acid/water (37.5 g : 7.5 g : 37.5 mL : 720 mL) dip] followed by heating. Flash chromatography was conducted according to the method of Still and coworkers[1] using the analytical reagent (AR) grade solvents indicated.

High performance liquid chromatography (HPLC) was conducted on a Waters μ-Porasil™ semi-preparative silica column (7.8 x 300 mm) using the HPLC grade solvents indicated and connected to an ISCO Model 2350 pump. The peaks were detected using an ERMA ERC-7512 refractive index detector connected to a Spectra-Physics SP4270 reporting integrator.

Gas chromatography (GC) was performed on either a Varian 3400 Gas Chromatograph fitted with a SGE Cydex-B chiral capillary column (25 m x 0.22 mm internal diameter, film thickness = 25 micron) or a Varian Vista Series Gas Chromatograph fitted with a SGE BPX5 silica capillary column (25 m x 0.22 mm internal diameter, film thickness = 25 micron). The peaks were detected using a flame-ionisation detector and helium was the carrier gas in all cases (flow rate *ca.* 35 cm/sec). Specific temperature programs are detailed for each individual case.

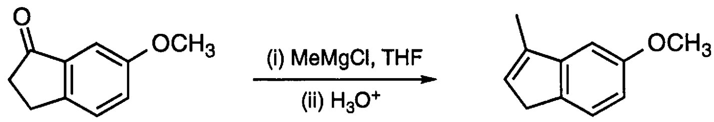
Enantiomeric excesses (ee's) were determined by HPLC techniques, which employed either a Daicel Chiralpak AS column (25 cm x 0.46 cm internal diameter) or a Daicel Chiralcel OD column (25 cm x 0.46 cm internal diameter) connected to a Waters 510 HPLC pump. The peaks were detected using a Waters Lambda-Max Model 481 LC Spectrophotometer (254 nm) and chromatogram print-outs were obtained using Waters Maxima software. Specific conditions employed (i.e. column type, solvent composition and flow rate) are detailed for each individual case.

Many reagents were available from the Aldrich Chemical Company and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reaction solvents and reagents were purified according to established procedures.[2] The concentrations of alkyl lithium solutions obtained from Aldrich were determined by titration with *sec*-butanol (1.0 M solution in toluene) using 1,10-phenanthroline as indicator.[3] Tetrahydrofuran (THF), diethyl ether (ether) and 1,4-dioxane were distilled under nitrogen from sodium benzophenone ketyl, while methanol and ethanol were distilled from their respective magnesium alkoxide salts. Benzene, toluene, dichloromethane, petrol (i.e. petroleum spirits, b.p. 40-60 °C), hexane and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride. Pyridine, diethylamine, triethylamine, diisopropylamine and *N,N*-diisopropylethylamine (Hünig's base) were all distilled from and stored over potassium hydroxide pellets.

Reactions employing air- and/or moisture-sensitive reagents were carried out under an atmosphere of dry, oxygen-free nitrogen in oven- or flame-dried apparatus. Organic solutions obtained from work-up of reaction mixtures were dried with magnesium sulphate ($MgSO_4$) unless otherwise specified. Solutions were concentrated under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 30 °C. When reactions were conducted at, or below 0 °C, the internal temperature was monitored using an alcohol thermometer. ACE™ Pressure Tubes were used for reactions that needed to be heated in a closed system.

5.2 Experimental for Chapter 2

6-Methoxy-1-methyl-3*H*-indene (77)



72 **77**

Methylmagnesium chloride (44 mL of a 3.0 M solution in THF, 132 mmol) was added dropwise to a chilled (ice-water bath) and magnetically stirred solution of 6-methoxyindan-1-one (**72**) (11.5 g, 70.9 mmol) in THF (400 mL) maintained under an atmosphere of nitrogen. Stirring was continued at ambient temperatures for 22 h after which time the reaction mixture was re-chilled (ice-water bath) and treated with HCl (300 mL of a 10% (v/v) aqueous solution). Stirring was continued at room temperature for a further 2.5 h and then the solvent (THF) was removed under reduced pressure. The aqueous residue thus obtained was transferred to a separating funnel containing dichloromethane (500 mL). The separated aqueous layer was extracted with dichloromethane (3 x 100 mL) and the combined organic fractions were washed with brine (1 x 300 mL), then dried, filtered and concentrated under reduced pressure to give a golden-yellow oil which solidified upon standing. Subjection of this material to flash chromatography (silica, 2% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.25), a colourless solid. Recrystallisation (dichloromethane/hexane) of this material afforded the title compound **77** (10.8 g, 97%) as colourless prisms, m.p. 42.5-43.5 °C.

^{1}H NMR (300 MHz) δ 7.33 (d, *J* 8.2 Hz, 1H), 6.89 (d, *J* 2.4 Hz, 1H), 6.76 (dd, *J* 8.1 and 2.4 Hz, 1H), 6.23 (m, 1H), 3.85 (s, 3H, $-OCH_3$), 3.25 (complex m, 2H), 2.15 (dd, *J* 3.8 and 2.0 Hz, 3H, $-CH_3$).

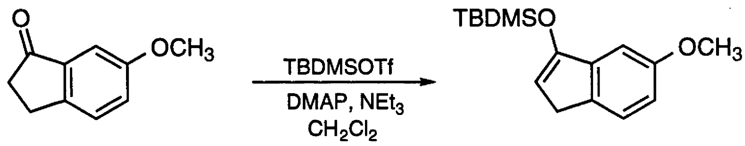
^{13}C NMR (75.4 MHz) δ 158.9 (C), 147.5 (C), 139.7 (C), 136.4 (C), 130.2 (CH), 123.9 (CH), 110.2 (CH), 104.7 (CH), 55.5 (CH_3), 36.9 (CH_2), 13.0 (CH_3).

IR (KBr) ν_{max} 2996, 2938, 1604, 1574, 1471, 1424, 1333, 1256, 1221, 1176 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 160 ($M^{+\cdot}$, 100%), 145 [$(M-H_3C\cdot)^+$, 66], 129 [$(M-H_3CO\cdot)^+$, 39], 117 [$(M-H_7C_3\cdot)^+$, 24].

Elemental Analysis Found: C, 82.69; H, 7.80. $C_{11}H_{12}O$ requires: C, 82.46; H, 7.55%.

1-*tert*-Butyldimethylsilyloxy-6-methoxy-3*H*-indene (76)



72 **76**

Triethylamine (0.5 mL, 3.59 mmol) then *tert*-butyldimethylsilyl triflate (0.7 mL, 3.05 mmol) were added to a chilled (ice-water bath) and magnetically stirred solution of 6-methoxyindan-1-one (**72**) (400 mg, 2.47 mmol) and DMAP (30 mg, 0.25 mmol) in dichloromethane (12 mL) maintained under an atmosphere of nitrogen. The reaction mixture was warmed to room temperature and stirring was continued for 16 h. The resulting dark-brown mixture was concentrated under reduced pressure to afford a viscous oil which was partitioned between ether (200 mL) and $NaHCO_3$ (200 mL of a 5% (w/v) aqueous solution). The phases were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a brown oil (0.70 g). This material was used immediately in the next reaction. Subjection of a small quantity of the crude material to flash chromatography (silica, 10% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.70), the title compound **76** as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.26 (d, *J* 8.2 Hz, 1H), 6.93 (d, *J* 2.5 Hz, 1H), 6.77 (dd, *J* 8.1 and 2.4 Hz, 1H), 5.43 (t, *J* 2.3 Hz, 1H), 3.84 (s, 3H, -OCH_3), 3.20 (d, *J* 2.1 Hz, 2H), 1.02 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.25 (s, 6H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 158.8 (C), 153.4 (C), 143.3 (C), 134.8 (C), 124.2 (CH), 111.1 (CH), 107.2 (CH), 103.7 (CH), 55.5 (CH_3), 33.2 (CH_2), 25.7 (CH_3), 18.2 (C), -4.7 (CH_3).

IR (KBr) ν_{max} 2955, 2858, 1602, 1579, 1480, 1346, 1232 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 276 ($M^{+\cdot}$, 71%), 219 [$(M-H_9C_4\cdot)^+$, 100], 205 (49), 145 [$(M-C_6H_{15}SiO\cdot)^+$, 79].

HRMS Found: $M^{+\cdot}$, 276.1553. $C_{16}H_{24}OSi$ requires $M^{+\cdot}$, 276.1548.

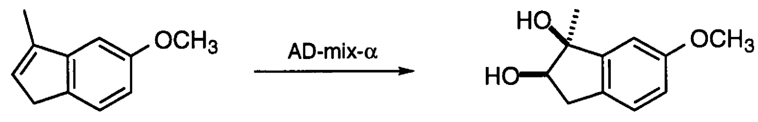
General Procedure for the Sharpless Asymmetric Dihydroxylation (AD) Reaction of Trisubstituted Olefins

A conical flask, fitted with a magnetic stirrer bar, was charged with *tert*-butanol (5 mL), water (5 mL) and catalyst* (1.40 g). The resulting heterogeneous mixture was stirred vigorously until all the solids had dissolved (*ca.* 10 mins). Methanesulfonamide (95 mg) was added in one portion and the solution was chilled (ice-water bath) whereupon some of the dissolved solids had precipitated. The substrate (1 mmol) was then added and vigorous stirring was maintained at 4 °C for 18 h. Sodium sulfite (1.50 g) was then added to the now yellow suspension and stirring was continued at room temperature for a further 1 h. After this time, the reaction mixture was transferred to a separating funnel containing water (50 mL) and ethyl acetate (50 mL). The separated aqueous layer was extracted with ethyl acetate (4 x 20 mL) and the combined organic fractions were washed with KOH (1 x 50 mL of a 2 M aqueous solution) then dried, filtered and concentrated

* Catalyst refers to commercially available AD-mix-α and AD-mix-β, which contain the chiral ligands $PHAL(DHQ)_2$ and $PHAL(DHQD)_2$, respectively. When the chiral ligand $AQN(DHQD)_2$ was used, the catalyst mixture was prepared as follows for 1 mmol substrate: $AQN(DHQD)_2$ (8.6 mg, 0.01 mmol, 1 mol %), $K_3Fe(CN)_6$ (990 mg, 3.00 mmol), K_2CO_3 (420 mg, 3.00 mmol) and $K_2OsO_2(OH)_4$ (1.4 mg, 0.004 mmol, 0.4 mol %).

under reduced pressure to give the crude reaction product, which was generally obtained as a yellow oil. Purification of this material was achieved by flash chromatography as described below for individual cases.

Dihydroxylation of compound 77 using AD-mix-α ¶

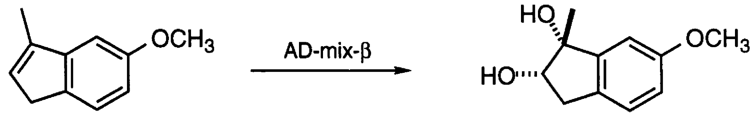


77 **73**

Dihydroxylation of methylindene **77** (3.18 g, 19.85 mmol) using AD-mix-α (27.8 g) was performed as described in the General Procedure (page 99). In this manner, an orange-yellow oil was obtained upon work-up. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), diol **73** (3.50 g, 91%, 69% ee) as a colourless solid. The ^{1}H NMR spectrum of this material was identical with those obtained from both racemic and enantiomerically pure samples, prepared by the methods described on pages 104 and 108, respectively. R_t [(1*R*,2*S*)-enantiomer]: 9.02 mins (15.5%); R_t [(1*S*,2*R*)-enantiomer]: 10.23 mins (84.5%).

¶ HPLC analyses of the products derived from procedures thus marked were conducted on a Daicel Chiralpak AS column using 40% *iso*-propanol/hexane as eluent and with a flow rate of 0.5 mL/min. Peaks were detected using a UV detector operating at 254 nm.

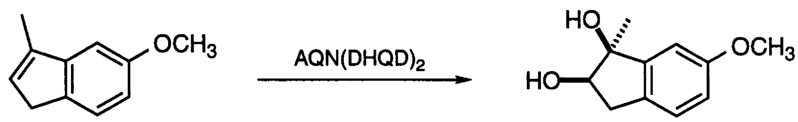
Dihydroxylation of compound 77 using AD-mix-β ¶



77 **73**

Dihydroxylation of methylindene **77** (6.25 g, 39.1 mmol) using AD-mix-β (54.6 g) was performed as described in the General Procedure (page 99). In this manner, a yellow oil was obtained upon work-up. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), diol **73** (6.67 g, 88%, 52% ee) as a colourless solid. The ^{1}H NMR spectrum of this material was identical with those obtained from both racemic and enantiomerically pure samples, prepared by the methods described on pages 104 and 107, respectively. R_t [(1*R*,2*S*)-enantiomer]: 8.76 mins (76%); R_t [(1*S*,2*R*)-enantiomer]: 9.60 mins (24%).

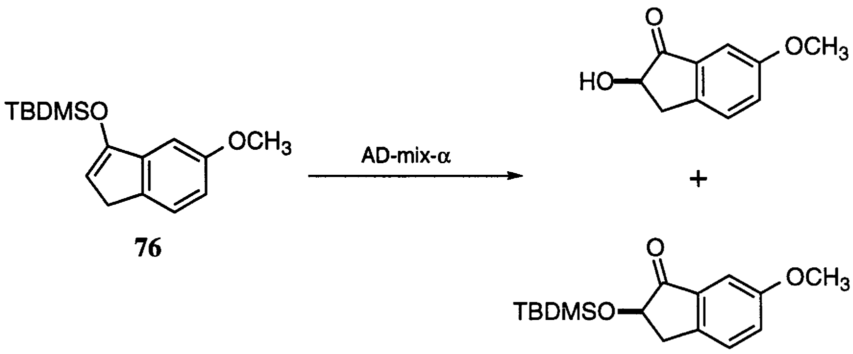
Dihydroxylation of compound 77 using AQN(DHQD)$_2$ as the chiral ligand ¶



77 **73**

Dihydroxylation of methylindene **77** (100 mg, 0.62 mmol) using AQN(DHQD)$_2$ (6 mg, 0.007 mmol) as the chiral ligand, was performed as described in the General Procedure (page 99). In this manner, a yellow oil was obtained upon work-up. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), diol **73** (103 mg, 85%, 25% ee) as a colourless solid. The ^{1}H NMR spectrum of this material was identical with those obtained from both racemic and enantiomerically pure samples, prepared by the methods described on pages 104 and 108, respectively. R_t [(1*R*,2*S*)-enantiomer]: 8.81 mins (37.5%); R_t [(1*S*,2*R*)-enantiomer]: 9.58 mins (62.5%).

Oxidation of compound 76 using AD-mix-α as catalyst §



Oxidation of silyl enol ether **76** (167 mg, 0.60 mmol) using AD-mix-α (840 mg) was performed as described in the General Procedure (page 99). In this manner, an orange-yellow oil was obtained upon work-up. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) furnished two chromophoric fractions, A (R_f 0.40) and B (R_f 0.95).

Concentration of fraction A afforded acyloin **75** (43 mg, 43% at 92% conversion, 55% ee) as a colourless, crystalline solid. The ^{1}H NMR spectrum of this material was identical with those obtained from both racemic and enantiomerically pure samples, prepared by the methods described on pages 104 and 111, respectively. R_t [(*S*)-enantiomer]: 16.16 mins (22.5%); R_t [(*R*)-enantiomer]: 17.19 mins (77.5%).

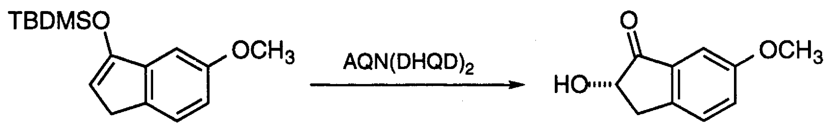
Concentration of fraction B afforded a straw-coloured oil. This material was re-subjected to flash chromatography (silica, 10% ethyl acetate/petrol elution) and furnished two chromophoric fractions, C (R_f 0.80) and D (R_f 0.40).

§ HPLC analyses of the products derived from procedures thus marked were conducted on a Daicel Chiralcel OD column using 10% *iso*-propanol/hexane as eluent and with a flow rate of 1.0 mL/min. Peaks were detected using a UV detector operating at 254 nm.

Concentration of fraction C provided a clear, colourless oil which was identified, by ^1H NMR spectroscopy, as the starting silyl enol ether **76** (13 mg, 8% recovery).

Concentration of fraction D afforded silyl ether **81** (26 mg, 16%) as a colourless oil. The ^1H NMR spectrum of this material was identical, in all respects, with an authentic sample of the (*S*)-enantiomer (see page 113).

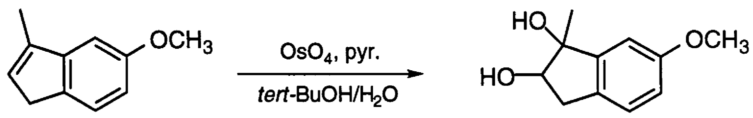
Oxidation of compound 76 using AQN(DHQD)$_2$ as the chiral ligand §



76 **75**

Oxidation of silyl enol ether **76** (150 mg, 0.54 mmol) using AQN(DHQD)$_2$ (5.4 mg, 0.006 mmol) as the chiral ligand, was performed as described in the General Procedure (page 99). In this manner, a yellow oil was obtained upon work-up. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.40), acyloin **75** (50 mg, 52%, 44% ee) as a colourless solid. The ^1H NMR spectrum of this material was identical with those obtained from both racemic and enantiomerically pure samples, prepared by the methods described on pages 104 and 111, respectively. R_t [(*S*)-enantiomer]: 14.73 mins (72%); R_t [(*R*)-enantiomer]: 17.04 mins (28%).

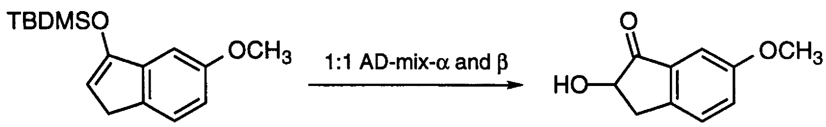
cis-2,3-Dihydro-6-methoxy-1-methyl-1H-indene-1,2-diol [(±)-73]¶



77 **73**

Osmium tetroxide (80 µL of a 2.5 wt % solution in *tert*-butanol) was added to a magnetically stirred mixture of methylindene **77** (152 mg, 0.95 mmol), trimethylamine *N*-oxide (232 mg), *tert*-butanol (3.8 mL), water (1.15 mL) and pyridine (170 µL). The resulting solution was heated at reflux for 18 h then cooled to room temperature and treated with sodium metabisulfite (3.4 mL of a 20% (w/w) aqueous solution). The resulting mixture was concentrated under reduced pressure and the residue thus obtained was partitioned between ether (50 mL) and water (50 mL). The separated aqueous layer was extracted with ether (3 x 20 mL) and the combined ethereal fractions were dried (K_2CO_3), filtered and concentrated under reduced pressure to give a cream-coloured solid. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), diol **73** (146 mg, 79%) as a colourless solid. R_t [(1*R*,2*S*)-enantiomer]: 8.82 mins (49%); R_t [(1*S*,2*R*)-enantiomer]: 9.62 mins (51%).

2-Hydroxy-6-methoxyindan-1-one [(±)-75]§

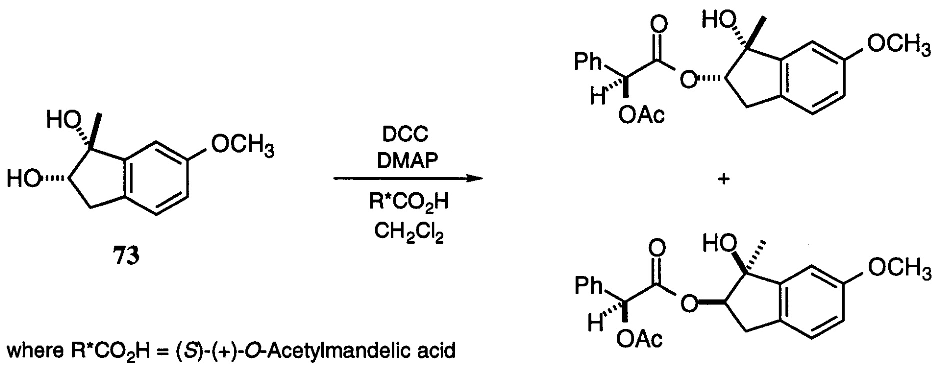


76 **75**

A conical flask, fitted with a magnetic stirrer bar, was charged with *tert*-butanol (15 mL), water (15 mL), AD-mix-α (1.73 g) and AD-mix-β (1.73 g). The resulting heterogeneous mixture was stirred vigorously until all the solids had dissolved (*ca.* 10

mins). Methanesulfonamide (234 mg, 2.46 mmol) was then added in one portion and the solution was chilled (ice-water bath) whereupon some of the dissolved solids had precipitated. Silyl enol ether **76** (683 mg, 2.47 mmol) was added and vigorous stirring was maintained at 4 °C for 18 h. After this time, the now yellow suspension was treated with sodium sulfite (3.76 g) and stirring was continued at room temperature for a further 1 h. The reaction mixture was then transferred to a separating funnel containing water (300 mL) and dichloromethane (300 mL). The separated aqueous layer was extracted with dichloromethane (4 x 100 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a lime-green oil. Subjection of this material to flash chromatography (silica, 40% ethyl acetate/petrol elution) furnished, after concentration of the relevant fractions (R_f 0.25), acyloin **75** (268 mg, 61%) as a colourless solid. R_t [(*S*)-enantiomer]: 15.88 mins (44%); R_t [(*R*)-enantiomer]: 17.78 mins (56%).

(1*R*,2*S*)-1-Hydroxy-6-methoxy-1-methyl-3*H*-indan-2-yl (2*S*)-2-Acetoxy-2-phenylacetate (102) and (1*S*,2*R*)-1-Hydroxy-6-methoxy-1-methyl-3*H*-indan-2-yl (2*S*)-2-Acetoxy-2-phenylacetate (103)



102

103

(*S*)-(+)-*O*-Acetylmandelic acid (1.85 g, 9.52 mmol), DMAP (135 mg, 1.11 mmol) and DCC (1.97 g, 9.56 mmol) were added, in that order, to a chilled (ice-water bath) and magnetically stirred solution of the enantiomerically enriched diol **73** (1.68 g, 8.65 mmol, 42% ee) in dichloromethane (50 mL). Stirring was continued at ambient temperatures for 2 h and the resulting suspension was filtered through a sintered glass funnel. The solids thus retained were washed with dichloromethane (60 mL) and the combined filtrates were concentrated under reduced pressure to give a straw-coloured oil. Subjection of this material to flash chromatography (silica, 25% ethyl acetate/petrol elution) afforded two chromophoric fractions, A (R_f 0.25) and B (R_f 0.20).

Concentration of fraction A provided *(+)-ester **102*** (1.92 g, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.47-7.36 (complex m, 5H), 7.10 (d, *J* 8.2 Hz, 1H), 6.87-6.80 (m, 2H), 5.92 (s, 1H), 5.28 (dd, *J* 5.5 and 2.7 Hz, 1H), 3.80 (s, 3H, $-OCH_3$), 3.17 (dd, *J* 16.5 and 5.5 Hz, 1H), 2.94 (dd, *J* 16.5 and 2.6 Hz, 1H), 2.12 (s, 3H, $-COCH_3$), 1.98 (br s, 1H, -OH), 1.34 (s, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 170.8 (C), 168.0 (C), 159.5 (C), 147.0 (C), 133.7 (C), 129.6 (C), 129.4 (CH), 128.9 (CH), 127.5 (CH), 125.8 (CH), 115.1 (CH), 107.5 (CH), 82.1 (CH), 80.4 (C), 74.6 (CH), 55.4 (CH_3), 34.1 (CH_2), 25.2 (CH_3), 20.5 (CH_3).

IR (KBr) ν_{max} 3511, 2972, 1745, 1490, 1373, 1232, 1175, 1053 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 370 ($M^{+\cdot}$, <1%), 352 [$(M-H_2O)^{+\cdot}$, <2], 295 [$(M-CH_3CO_2H-H_3C\cdot)^+$, <1], 193 [$(M-C_{10}H_9O_3{}^\cdot)^+$, 2], 176 [$(M-C_{10}H_{10}O_4)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 370.1421. $C_{21}H_{22}O_6$ requires $M^{+\cdot}$, 370.1416.

Optical Rotation $[\alpha]_D^{22}$ +139.1° (*c* 1.7).

Concentration of fraction B provided *(-)-ester **103*** (1.00 g, 31%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.46-7.40 (m, 2H), 7.40-7.33 (m, 3H), 7.04 (d, *J* 8.2 Hz, 1H), 6.95 (d, *J* 2.4 Hz, 1H), 6.81 (dd, *J* 8.2 and 2.3 Hz, 1H), 5.82 (s, 1H), 5.30 (dd, *J* 5.6 and 2.9 Hz, 1H), 3.81 (s, 3H, $-OCH_3$), 3.08 (dd, *J* 16.4 and 5.5 Hz, 1H), 2.71

(dd, *J* 16.5 and 2.8 Hz, 1H), 2.65 (br s, 1H, -OH), 2.04 (s, 3H, $-COCH_3$), 1.51 (s, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 170.7 (C), 168.6 (C), 159.5 (C), 147.0 (C), 133.0 (C), 129.6 (C), 129.3 (CH), 128.8 (CH), 127.4 (CH), 127.3 (CH), 125.7 (CH), 115.3 (CH), 107.6 (CH), 82.0 (CH), 80.4 (C), 74.9 (CH), 55.4 (CH_3), 34.6 (CH_2), 25.5 (CH_3), 20.5 (CH_3).

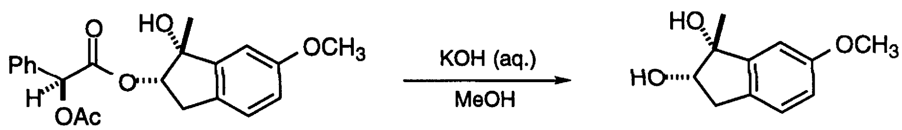
IR (KBr) ν_{max} 3504, 2972, 1744, 1615, 1490, 1373, 1232, 1177 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 370 ($M^{+\cdot}$, <1%), 352 [$(M-H_2O)^{+\cdot}$, 2], 279 [$(M-CH_3CO_2H-H_3CO\cdot)^+$, <1], 193 [$(M-C_{10}H_9O_3^{\cdot})^+$, 1], 176 [$(M-C_{10}H_{10}O_4)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 370.1421. $C_{21}H_{22}O_6$ requires $M^{+\cdot}$, 370.1416.

Optical Rotation $[\alpha]_D^{22}$ -7.5° (*c* 1.3).

(1*R*,2*S*)-2,3-Dihydro-6-methoxy-1-methyl-1*H*-indene-1,2-diol [(+)-73]¶



103 **73**

A mixture of (+)-ester **103** (1.80 g, 4.86 mmol), methanol (90 mL) and KOH (22 mL of a 50% (w/w) aqueous solution) was stirred at room temperature for 16 h. The reaction mixture was then chilled (ice-water bath) and acidified to pH 2 (upon addition of 2 M aqueous HCl solution). The reaction solvent (methanol) was removed under reduced pressure and the residue thus obtained was partitioned between ether (300 mL) and water (300 mL). The separated aqueous layer was extracted with ether (3 x 100 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a colourless, oil which solidified upon standing. Subjection of the crude material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), enantiomerically pure *(+)-diol* ***73*** (427 mg, 45%, >99.5% ee) as a colourless solid, m.p. 100-101 °C.

^{1}H NMR (300 MHz) δ 7.12 (d, *J* 8.3 Hz, 1H), 6.93 (d, *J* 2.5 Hz, 1H), 6.82 (dd, *J* 8.2 and 2.5 Hz, 1H), 4.14 (app q, *J ca.* 4.4 Hz, 1H), 3.81 (s, 3H, $-OCH_3$), 3.11 (dd, *J* 15.9 and 6.0 Hz, 1H), 2.79 (dd, *J* 15.9 and 4.2 Hz, 1H), 2.61 (br s, 1H, -OH), 2.54 (br d, *J ca.* 6.5 Hz, 1H, -OH), 1.50 (s, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 159.4 (C), 146.9 (C), 130.8 (C), 126.1 (CH), 115.1 (CH), 108.2 (CH), 80.1 (C), 79.2 (CH), 55.5 (CH_3), 37.5 (CH_2), 24.7 (CH_3).

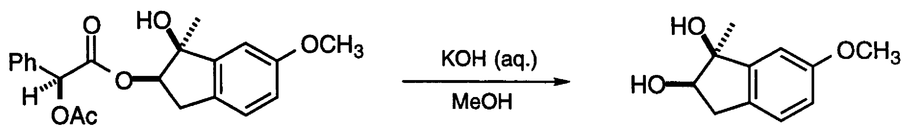
IR (KBr) ν_{max} 3287, 2957, 1585, 1486, 1432, 1327, 1283, 1173, 1056 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 194 ($M^{+\cdot}$, 75%), 176 [$(M-H_2O)^{+\cdot}$, 57], 161 [$(M-CH_3OH-H\cdot)^+$, 86], 151 [$(M-H_7C_3\cdot)^+$, 67], 133 (29), 63 (100).

Elemental Analysis Found: C, 68.05; H, 7.40. $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.26%.

Optical Rotation $[\alpha]_D^{22}$ +69.3° (*c* 1.1).

(1*S*,2*R*)-2,3-Dihydro-6-methoxy-1-methyl-1*H*-indene-1,2-diol [(-)-73]¶



104 **73**

A mixture of (-)-ester **104** (590 mg, 1.59 mmol), methanol (30 mL) and KOH (7 mL of a 50% (w/w) aqueous solution) was stirred at room temperature for 18 h. The reaction mixture was then chilled (ice-water bath) and acidified to pH 2 (upon addition of 2 M aqueous HCl solution). The reaction solvent (methanol) was removed under reduced pressure and the residue thus obtained was partitioned between ether (150 mL) and water (150 mL). The separated aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a straw-coloured oil. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), enantiomerically pure *(-)-diol 73* (155 mg, 50%, >98.5% ee) as a colourless solid, m.p. 101-102 °C.

^{1}H NMR (300 MHz) δ 7.13 (d, *J* 8.2 Hz, 1H), 6.93 (d, *J* 2.4 Hz, 1H), 6.83 (dd, *J* 8.2 and 2.6 Hz, 1H), 4.14 (app q, *J ca.* 4.4 Hz, 1H), 3.81 (s, 3H, -OCH_3), 3.13 (dd, *J* 16.2 and 5.7 Hz, 1H), 2.81 (dd, *J* 15.9 and 4.0 Hz, 1H), 2.52 (br s, 1H, -OH), 2.45 (br s, 1H, -OH), 1.51 (s, 3H, -CH_3).

^{13}C NMR (75.4 MHz) δ 159.2 (C), 146.9 (C), 130.9 (C), 126.0 (CH), 114.9 (CH), 108.2 (CH), 80.0 (C), 79.0 (CH), 55.4 (CH_3), 37.3 (CH_2), 24.6 (CH_3).

IR (KBr) ν_{max} 3287, 2958, 1585, 1486, 1432, 1327, 1283, 1173, 1056 cm^{-1}.

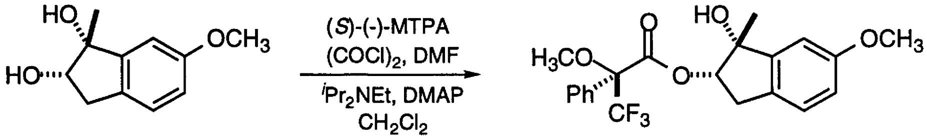
Mass Spectrum (70 eV) *m/z* 194 ($M^{+\cdot}$, 90%), 176 [$(M-H_2O)^{+\cdot}$, 81], 161 [$(M-CH_3OH-H\cdot)^+$, 100], 151 [$(M-H_7C_3\cdot)^+$, 78], 133 (55).

HRMS Found: $M^{+\cdot}$, 194.0942. $C_{11}H_{14}O_3$ requires $M^{+\cdot}$, 194.0943.

Elemental Analysis Found: C, 67.70; H, 7.00. $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.26%.

Optical Rotation $[\alpha]_D^{21}$ -73.2° (*c* 1.2).

(1*R*,2*S*)-1-Hydroxy-6-methoxy-1-methyl-3*H*-indan-2-yl (2*S*)-2-Methoxy-2-phenyl-2-trifluoromethylacetate (104)



73 104

Oxalyl chloride (55 μL, 0.63 mmol) then DMF (1 drop) was added to a chilled (ice-water bath) and magnetically stirred solution of (*S*)-(-)-MTPA (140 mg, 0.60 mmol) in dichloromethane (2 mL) maintained under an atmosphere of nitrogen. The resulting colourless solution was stirred at room temperature for 45 mins then transferred, *via* cannula, to a chilled (ice-water bath) and magnetically stirred solution of (+)-diol **73** (80 mg, 0.41 mmol), *N,N*-diisopropylethylamine (110 μL, 0.63 mmol) and DMAP (<5 mg) in dichloromethane (3 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. The solution was then partitioned between dichloromethane (20 mL) and $NaHCO_3$ (20 mL of a saturated aqueous solution) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of the crude material to flash chromatography (silica, 20% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.30), the *title compound* ***104*** (100 mg, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.56-7.50 (m, 2H), 7.42-7.37 (m, 3H), 7.07 (d, *J* 8.2 Hz, 1H), 6.90 (d, *J* 2.5 Hz, 1H), 6.81 (dd, *J* 8.2 and 2.4 Hz, 1H), 5.38 (dd, *J* 5.8 and 3.3 Hz, 1H), 3.80 (s, 3H, $-OCH_3$), 3.50 (br s, 3H, $-OCH_3$), 3.26 (dd, *J* 16.5 and 5.6 Hz, 1H), 2.90 (dd, *J* 16.5 and 3.3 Hz, 1H), 2.10 (br s, 1H, -OH), 1.55 (s, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 166.3 (C), 159.6 (C), 146.4 (C), 131.8 (C), 129.7 (CH), 129.3 (C), 128.5 (CH), 127.4 (CH), 125.7 (CH), 125.1 (C), 121.3 (C), 115.5 (CH), 107.7 (CH), 83.2 (CH), 80.2 (C), 55.4 (CH_3), 55.3 (CH_3), 34.7 (CH_2), 25.6 (CH_3).

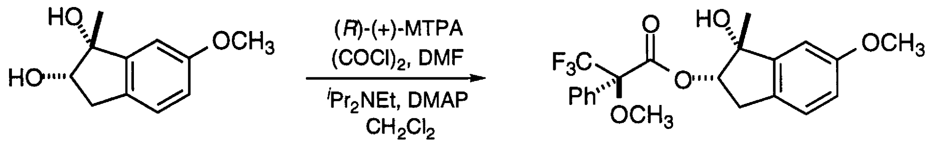
IR (KBr) ν_{max} 3482, 2954, 1748, 1490, 1454, 1271, 1171, 1028 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 410 ($M^{+\cdot}$, <1%), 392 [$(M-H_2O)^{+\cdot}$, <1], 363 [$(M-CH_3OH-H_3C\cdot)^+$, <1], 176 [$(M-C_{10}H_9F_3O_3)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 410.1343. $C_{21}H_{21}F_3O_5$ requires: $M^{+\cdot}$, 410.1341.

Optical Rotation $[\alpha]_D^{22}$ +33.1° (*c* 1.3).

(1*R*,2*S*)-1-Hydroxy-6-methoxy-1-methyl-3*H*-indan-2-yl (2*R*)-2-Methoxy-2-phenyl-2-trifluoromethylacetate (105)



73 **105**

Oxalyl chloride (68 μL, 0.77 mmol) then DMF (2 drops) were added to a chilled (ice-water bath) and magnetically stirred solution of (*R*)-(+)-MTPA (185 mg, 0.79 mmol) in dichloromethane (3 mL) maintained under an atmosphere of nitrogen. The resulting colourless solution was stirred at room temperature for 40 mins then transferred, *via* cannula, to a chilled (ice-water bath) and magnetically stirred solution of (+)-diol **73** (90 mg, 0.46 mmol), *N,N*-diisopropylethylamine (135 μL, 0.77 mmol) and DMAP (<5 mg) in dichloromethane (3 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 18 h. The solution was then partitioned between dichloromethane (20 mL) and $NaHCO_3$ (20 mL of a saturated aqueous solution) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.30), the *title compound* ***105*** (151 mg, 80%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.51-7.48 (m, 2H), 7.40-7.34 (m, 3H), 7.11 (d, *J* 8.3 Hz, 1H), 6.90 (d, *J* 2.4 Hz, 1H), 6.83 (dd, *J* 8.2 and 2.6 Hz, 1H), 5.38 (dd, *J* 5.6 and 3.2 Hz, 1H), 3.80 (s, 3H, $-OCH_3$), 3.52 (br s, 3H, $-OCH_3$), 3.28 (dd, *J* 16.4 and 5.5 Hz, 1H), 3.00 (dd, *J* 16.5 and 3.2 Hz, 1H), 2.00 (br s, 1H, -OH), 1.50 (s, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 165.8 (C), 159.7 (C), 146.6 (C), 132.1 (C), 129.8 (CH), 129.2 (C), 128.5 (CH), 127.2 (CH), 125.7 (CH), 125.2 (C), 121.4 (C), 115.4 (CH), 107.8 (CH), 83.3 (CH), 80.3 (C), 55.5 (CH_3), 55.4 (CH_3), 34.9 (CH_2), 25.2 (CH_3).

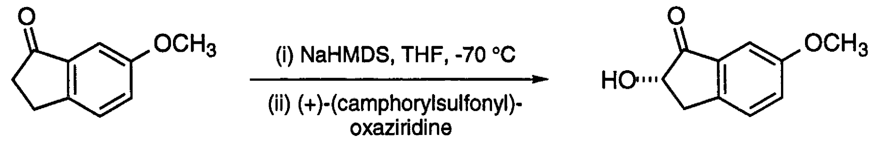
IR (KBr) ν_{max} 3584, 2952, 1751, 1490, 1452, 1271, 1171, 1027 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 410 ($M^{+\cdot}$, <1%), 392 [$(M-H_2O)^{+\cdot}$, <1], 363 [$(M-CH_3OH-H_3C\cdot)^+$, <1], 176 [$(M-C_{10}H_9F_3O_3)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 410.1328. $C_{21}H_{21}F_3O_5$ requires $M^{+\cdot}$, 410.1341.

Optical Rotation $[\alpha]_D^{22}$ +82.9° (*c* 1.5).

(*S*)-2-Hydroxy-6-methoxyindan-1-one [(+)-75][§]



A solution of 6-methoxyindan-1-one (**72**) (100 mg, 0.62 mmol) in THF (3.6 mL) was added dropwise to a chilled (dry ice-acetone bath) and magnetically stirred solution of NaHMDS (0.74 mL of a 1.0 M solution in THF, 0.74 mmol) in THF (3.6 mL) maintained under an atmosphere of nitrogen. Stirring was continued at -70 °C for 35 mins, after which time a solution of (+)-(camphorylsulfonyl)oxaziridine (**78**) (212 mg, 0.93 mmol) in THF (3.6 mL) was transferred, *via* cannula, to the reaction solution. The chilled reaction mixture was stirred for a further 25 mins and then treated with NH_4I (*ca.* 4 mL of a saturated aqueous solution). The residue obtained after concentration of the crude reaction mixture was partitioned between ether (30 mL) and water (30 mL). The separated aqueous layer was extracted with ether (3 x 10 mL) and the combined organic fractions were washed with $Na_2S_2O_3$ (2 x 20 mL of a saturated aqueous solution) then brine (2 x 20 mL), before being dried, filtered and concentrated under reduced pressure to give a brown solid. This material was subjected to flash chromatography (40% ethyl acetate/petrol elution) and, after concentration of the appropriate fractions (R_f 0.25), afforded acyloin **75** (38 mg, 35%, 70% ee) as a straw-coloured, crystalline solid. R_t [(*S*)-enantiomer]: 14.49 mins (85%); R_t [(*R*)-enantiomer]: 16.61 mins (15%). Fractional recrystallisation (ethylene glycol dimethyl ether/hexane) of the enantiomerically enriched material afforded an analytically and optically pure sample of the *title compound (S)-75*, m.p. 113.5-114 °C.

^{1}H NMR (300 MHz) δ 7.36 (d, *J* 8.8 Hz, 1H), 7.26-7.20 (m, 2H), 4.55 (br dd, *J* 7.6 and 5.0 Hz, 1H), 3.84 (s, 3H, $-OCH_3$), 3.52 (dd, *J* 16.3 and 7.7 Hz, 1H), 2.96 (br s, 1H, -OH), 2.94 (dd, *J* 16.3 and 4.2 Hz, 1H).

^{13}C NMR (75.4 MHz) δ 206.6 (C), 159.6 (C), 143.7 (C), 135.0 (C), 127.5 (CH), 125.1 (CH), 105.5 (CH), 74.8 (CH), 55.6 (CH_3), 34.5 (CH_2).

IR (KBr) ν_{max} 3473, 2967, 1703, 1493, 1267, 1170, 1022 cm^{-1}.

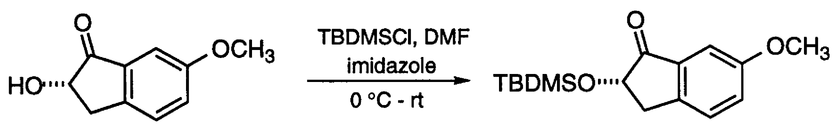
Mass Spectrum (70 eV) *m/z* 178 ($M^{+\cdot}$, 100%), 163 [$(M-H_3C\cdot)^+$, 10], 149 [$(M-CHO^\cdot)^+$, 50], 121 [$(M-C_2HO_2^\cdot)^+$, 57].

HRMS Found: $M^{+\cdot}$, 178.0629. $C_{10}H_{10}O_3$ requires $M^{+\cdot}$, 178.0630.

Elemental Analysis Found: C, 67.24; H, 5.69. $C_{10}H_{10}O_3$ requires: C, 67.41; H, 5.66%.

Optical Rotation $[\alpha]_D^{22}$ +60.7° (*c* 0.8).

(*S*)-2-*tert*-Butyldimethylsilyloxy-6-methoxyindan-1-one (81)



75 81

tert-Butyldimethylsilyl chloride (36 mg, 0.24 mmol) was added in one portion to a chilled (ice-water bath) and magnetically stirred solution of enantiomerically enriched acyloin **75** (21 mg, 0.12 mmol, 60% ee) and imidazole (32 mg, 0.47 mmol) in DMF (0.5 mL) maintained under an atmosphere of nitrogen. Stirring was continued at ambient temperatures for 16 h. The crude reaction mixture was then transferred to a separating funnel containing ether (10 mL) and water (10 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 5 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a straw-coloured oil. Subjection of this material to flash chromatography (silica, 10% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.45), the *title compound 81* (26 mg, 76%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.29 (app d, *J ca.* 8.5 Hz, 1H), 7.20-7.17 (m, 2H), 4.53 (dd, *J* 7.4 and 4.7 Hz, 1H), 3.83 (s, 3H, $-OCH_3$), 3.43 (dd, *J* 16.1 and 7.6 Hz, 1H), 2.90 (dd, *J* 16.2 and 4.6 Hz, 1H), 0.95 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.22 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.19 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

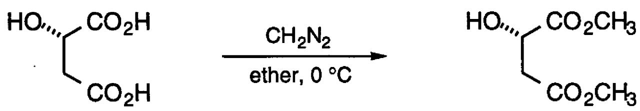
^{13}C NMR (75.4 MHz) δ 204.8 (C), 159.2 (C), 142.9 (C), 135.6 (C), 127.3 (CH), 124.5 (CH), 105.4 (CH), 75.4 (CH), 55.5 (CH_3), 35.9 (CH_2), 25.8 (CH_3), 18.4 (C), -4.4 (CH_3), -5.1 (CH_3).

IR (KBr) ν_{max} 2958, 1716, 1494, 1292, 1118 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 277 [$(M-H_3C\cdot)^+$, 16%], 235 [$(M-H_9C_4\cdot)^+$, 100], 161 [$(M-C_6H_{15}SiO\cdot)^+$, 52].

HRMS Found: $(M-H_3C\cdot)^+$, 277.1258. $C_{15}H_{21}O_3Si$ requires $(M-H_3C\cdot)^+$, 277.1260.

Dimethyl (*S*)-(-)-Malate [(-)-80][Σ]



83 **80**

A chilled (ice-water bath) and magnetically stirred mixture of (*S*)-(-)-malic acid (**83**) (200 mg, 1.49 mmol) and ether (10 mL) was treated with an excess of diazomethane and stirring was continued at room temperature for 18 h. The oily residue obtained after evaporation of the solvent was purified by flash chromatography (silica, 40% ethyl

Σ Gas chromatographic analyses of the products derived from procedures thus marked were conducted on a SGE Cydex-B chiral column; initial temperature: 110 °C (1 min), ramp rate: 2 °C/min, final temperature: 140 °C (2 mins). Helium was the carrier gas used and the peaks were detected using a FID detector.

acetate/petrol elution) and afforded, after concentration of the appropriate fractions (R_f 0.30), (-)-diester **80** (238 mg, 98%) as a clear, colourless liquid. R_t [(*S*)-enantiomer]: 10.4 mins.

^{1}H NMR (300 MHz) δ 4.52 (dd, *J* 6.1 and 4.9 Hz, 1H), 3.82 (s, 3H, $-OCH_3$), 3.72 (s, 3H, $-OCH_3$), 3.31 (br s, 1H, -OH), 2.88 (dd, *J* 16.5 and 5.0 Hz, 1H), 2.80 (dd, *J* 16.5 and 6.1 Hz, 1H).

^{13}C NMR (75.4 MHz) δ 173.5 (C), 170.8 (C), 67.0 (CH), 52.4 (CH_3), 51.7 (CH_3), 38.2 (CH_2).

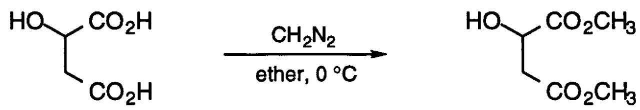
IR (KBr) ν_{max} 3485, 2957, 1741, 1440, 1221, 1173, 1109 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 131 [$(M-H_3CO\cdot)^+$, 7%], 103 [$(M-CH_3CO_2^\cdot)^+$, 100], 71 [$(M-CH_3CO_2^\cdot-CH_3OH)^+$, 67].

HRMS Found: $(M-H_3CO\cdot)^+$, 131.0343. $C_5H_7O_4$ requires $(M-H_3CO\cdot)^+$, 131.0344.

Optical Rotation $[\alpha]_D^{20}$ -6.7° (neat). [Literature:[4] -6.85° (neat)].

Dimethyl (*RS*)-(±)-Malate [(±)-80]$^\Sigma$



83 **80**

A chilled (ice-water bath) and magnetically stirred mixture of (*RS*)-(±)-malic acid (**83**) (200 mg, 1.49 mmol) and ether (10 mL) was treated with an excess of diazomethane and stirring was continued at room temperature for 18 h. The oily residue obtained after evaporation of the solvent was purified by flash chromatography (silica, 40% ethyl acetate/petrol elution) and afforded, after concentration of the appropriate fractions (R_f 0.30), (±)-diester **80** (240 mg, 100%) as a clear, colourless liquid. R_t [(*R*)-enantiomer]: 10.2 mins; R_t [(*S*)-enantiomer]: 10.4 mins.

^{1}H NMR (300 MHz) δ 4.52 (dd, *J* 6.1 and 4.9 Hz, 1H), 3.82 (s, 3H, -OCH_3), 3.72 (s, 3H, -OCH_3), 3.31 (br s, 1H, -OH), 2.88 (dd, *J* 16.5 and 5.0 Hz, 1H), 2.80 (dd, *J* 16.5 and 6.1 Hz, 1H).

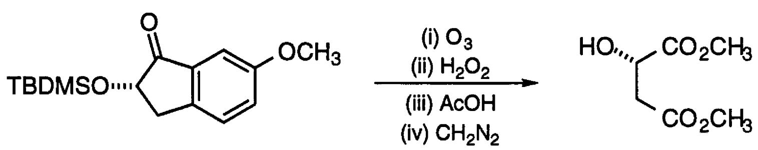
^{13}C NMR (75.4 MHz) δ 173.6 (C), 170.9 (C), 67.0 (CH), 52.5 (CH_3), 51.8 (CH_3), 38.3 (CH_2).

IR (KBr) ν_{max} 3483, 2957, 1742, 1440, 1221, 1109 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 131 [$(M-H_3CO\cdot)^+$, 7%], 103 [$(M-CH_3CO_2^{\cdot})^+$, 100], 71 [$(M-CH_3CO_2^{\cdot}-CH_3OH)^+$, 73].

HRMS Found: $(M-H_3CO\cdot)^+$, 131.0344. $C_5H_7O_4$ requires $(M-H_3CO\cdot)^+$, 131.0344.

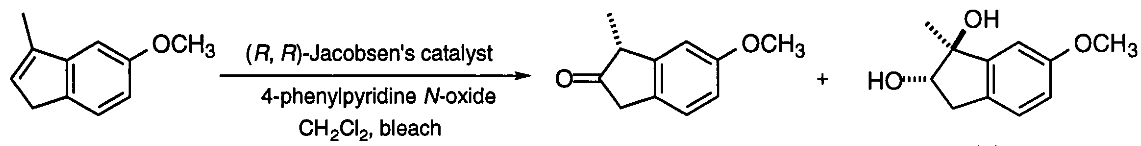
Oxidative Degradation of Compound 81$^{\Sigma}$



81 **80**

Ozone gas was bubbled through a chilled (dry ice-acetone bath) and magnetically stirred solution of the enantiomerically enriched silyl ether **81** (26 mg, 0.09 mmol, 60% ee) in dichloromethane (6 mL) for 2 h. Nitrogen gas was then bubbled through the now blue solution for *ca.* 10 mins, which was then treated with H_2O_2 (0.5 mL of a 30% (v/v) aqueous solution). The cooling bath was removed and stirring was continued at room temperature for 16 h. The colourless solution was concentrated under reduced pressure and the residue so-obtained was treated with acetic acid (8 drops) and heated at 70 °C for 1 h. The reaction mixture was subsequently cooled to room temperature and concentrated to dryness. The residue thus obtained was dissolved in ether (*ca.* 2 mL), chilled (ice-water bath) and treated with an excess of diazomethane. The cooling bath was removed and stirring was maintained at room temperature for 20 h. The crude product was obtained, after evaporation of the solvent, as a colourless oil which was analysed by chiral GC (see page 114 for conditions) directly without further purification. R_t [(*R*)-enantiomer]: 10.2 mins (20%); R_t [(*S*)-enantiomer]: 10.4 mins (80%).

(*R*)-6-Methoxy-1-methylindan-2-one (93) and (1*S*,2*S*)-2,3-Dihydro-6-methoxy-1-methyl-1*H*-indene-1,2-diol (94)



A chilled (ice-water bath) and buffered solution of bleach (1.7 mL of a solution prepared as follows: commercial household bleach was diluted to *ca.* 0.55 M in NaOCl with 0.05 M aqueous Na_2HPO_4 and the pH of the resulting solution was adjusted to pH 11.4 by addition of 1 M aqueous NaOH solution) was added to a cold (ice-water bath) and magnetically stirred solution of methylindene **77** (101 mg, 0.63 mmol), 4-phenylpyridine *N*-oxide (22.2 mg, 0.13 mmol) and (*R*,*R*)-Jacobsen's catalyst[£] (12.8 mg, 0.02 mmol) in dichloromethane (0.8 mL). Stirring was continued at 4 °C for 17 h after which time the reaction mixture was partitioned between dichloromethane (5 mL) and water (5 mL). The separated aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange oil. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded two chromophoric fractions, A (R_f 0.30) and B (R_f 0.90).

Concentration of fraction A afforded *trans-diol* **94** (3 mg, 2%) as a colourless solid, the optical purity of which was not determined. Due to the small quantity of material obtained, diol **94** was not fully characterised.

£ (*R*,*R*)-Jacobsen's catalyst is (*R*,*R*)-(-)-*N*,*N'*-bis(3,5-Di-*tert*-butylsalicyclidene)-1,2-cyclohexane-diamino-manganese chloride.

^{1}H NMR (300 MHz) δ 7.12 (d, *J* 8.2 Hz, 1H), 6.93 (d, *J* 2.5 Hz, 1H), 6.82 (dd, *J* 8.2 and 2.6 Hz, 1H), 4.15 (dd, *J* 5.9 and 4.2 Hz, 1H), 3.81 (s, 3H, $-OCH_3$), 3.11 (dd, *J* 15.8 and 5.7 Hz, 1H), 2.80 (dd, *J* 16.1 and 4.1 Hz, 1H), 2.56 (br s, 2H, 2 x -OH), 1.50 (s, 3H, $-CH_3$).

^{13}C NMR (300 MHz) δ 159.4 (C), 146.9 (C), 130.8 (C), 126.2 (CH), 115.2 (CH), 108.2 (CH), 80.1 (C), 76.6 (CH), 55.3 (CH_3), 37.6 (CH_2), 24.7 (CH_3).

Mass Spectrum (70 eV) *m/z* 194 ($M^{+\cdot}$, 42%), 176 [$(M-H_2O)^{+\cdot}$, 80], 161 [$(M-H\cdot-CH_3OH)^{+}$, 70], 149 (100).

HRMS Found: $M^{+\cdot}$, 194.0938. $C_{11}H_{14}O_3$ requires $M^{+\cdot}$, 194.0943.

Concentration of fraction B afforded a straw-coloured oil. This material was re-subjected to flash chromatography (silica, 10% ethyl acetate/petrol elution) and gave, after concentration of the appropriate fractions (R_f 0.40), *ketone* ***93*** (40 mg, 36%) as a colourless, crystalline solid. The optical purity of this material was not determined.

^{1}H NMR (300 MHz) δ 7.23-7.18 (m, 1H), 6.84-6.79 (br m, 2H), 3.83 (s, 3H, $-OCH_3$), 3.58-3.40 (m, 3H), 1.40 (d, *J* 7.6 Hz, 3H, $-CH_3$).

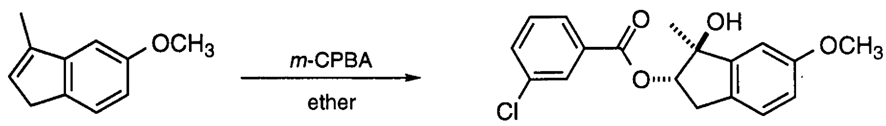
^{13}C NMR (75.4 MHz) δ 218.2 (C), 159.3 (C), 144.6 (C), 128.1 (C), 125.6 (CH), 113.4 (CH), 109.6 (CH), 55.4 (CH_3), 48.2 (CH), 42.3 (CH_2), 15.4 (CH_3).

IR (KBr) ν_{max} 2971, 2936, 1750, 1618, 1494, 1291, 1157 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 176 ($M^{+\cdot}$, 48%), 164 (60), 149 (100), 121 (42).

HRMS Found: $M^{+\cdot}$, 176.0836. $C_{11}H_{12}O_2$ requires $M^{+\cdot}$, 176.0837.

(1*S*,2*S*)-1-Hydroxy-6-methoxy-1-methylindan-2-yl 3'-Chlorobenzoate (96)



77 96

m-CPBA (161 mg, 0.75 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of methylindene **77** (102 mg, 0.64 mmol) in ether (10 mL). Stirring was continued at 0 °C for 1 h and then at room temperature for a further 26 h. The clear, colourless reaction mixture was transferred to a separating funnel containing Na_2SO_3 (30 mL of a saturated aqueous solution) and the phases separated. The ethereal fraction was washed with $NaHCO_3$ (2 x 30 mL of a saturated aqueous solution) then brine (1 x 30 mL), before being dried (Na_2SO_3), filtered and concentrated under reduced pressure to give a straw-coloured oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) afforded, after concentration of the relevant fractions (R_f 0.20), *ester **96*** (44 mg, 21%) as a clear, colourless oil. The optical purity of this material was not determined.

^{1}H NMR (300 MHz) δ 7.95 (m, 1H), 7.89-7.85 (m, 1H), 7.53-7.50 (m, 1H), 7.36 (t, *J* 7.9 Hz, 1H), 7.15 (d, *J* 8.2 Hz, 1H), 6.98 (d, *J* 2.4 Hz, 1H), 6.86 (dd, *J* 8.2 and 2.6 Hz, 1H), 5.47 (dd, *J* 5.9 and 3.1 Hz, 1H), 3.83 (s, 3H, -OCH_3), 3.31 (dd, *J* 16.5 and 5.7 Hz, 1H), 3.04 (dd, *J* 16.5 and 3.1 Hz, 1H), 2.41 (br s, 1H, -OH), 1.59 (s, 3H, -CH_3).

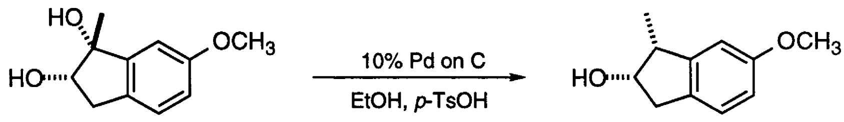
^{13}C NMR (75.4 MHz) δ 165.2 (C), 159.6 (C), 146.9 (C), 134.6 (C), 133.2 (CH), 131.6 (C), 129.8 (C), 129.7 (CH), 129.6 (CH), 127.8 (CH), 125.9 (CH), 115.4 (CH), 107.7 (CH), 81.9 (CH), 80.6 (C), 55.5 (CH_3), 35.3 (CH_2), 25.9 (CH_3).

IR (NaCl) ν_{max} 3490, 2970, 1720, 1490,1258 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 334, 332 ($M^{+\cdot}$, <1 and <1%), 316, 314 [$(M-H_2O)^{+\cdot}$, 2 and <1], 176 [$(M-C_7H_5ClO_2)^{+\cdot}$, 100], 161 [$(M-C_7H_5ClO_2-H_3C\cdot)^+$, 75].

HRMS Found: $M^{+\cdot}$, 332.0827. $C_{18}H_{17}{}^{35}ClO_4$ requires $M^{+\cdot}$, 332.0815.

(1*R*,2*S*)-2,3-Dihydro-6-methoxy-1-methyl-1*H*-indene-2-ol [(+)-71]



73 **71**

A magnetically stirred mixture of (+)-diol **73** (1.16 g, 5.97 mmol), 10% Pd on C (116 mg) and *p*-TsOH (34 mg, 0.18 mmol) in ethanol (30 mL) was maintained under a hydrogen atmosphere (760 mmHg) at room temperature for 16 h. The resulting black suspension was filtered through a small plug of TLC grade silica gel which was washed with several portions of ethanol (*ca.* 30 mL total volume). Concentration of the combined filtrates gave a straw-coloured oil which was subjected to flash chromatography (silica, 30% ethyl acetate/petrol elution). Concentration of the appropriate fractions (R_f 0.40) afforded the *title compound (+)-71* (740 mg, 70%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.15 (d, *J* 7.8 Hz, 1H), 6.77-6.70 (m, 2H), 4.55-4.47 (br m, 1H), 3.80 (s, 3H, $-OCH_3$), 3.20-3.12 (m, 1H), 3.08 (dd, *J* 15.9 and 5.5 Hz, 1H), 2.83 (dd, *J* 15.9 and 2.5 Hz, 1H), 1.51 (br s, 1H, -OH), 1.32 (d, *J* 7.1 Hz, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 158.6 (C), 147.1 (C), 132.4 (C), 125.5 (CH), 112.2 (CH), 109.7 (CH), 76.3 (CH), 55.4 (CH_3), 44.4 (CH), 40.3 (CH_2), 12.1 (CH_3).

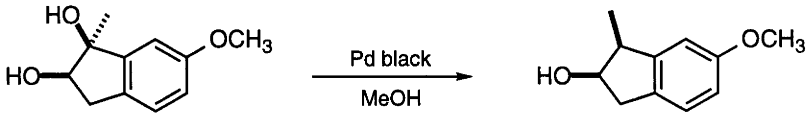
IR (KBr) ν_{max} 3385, 2936, 1610, 1491, 1331, 1288, 1196, 1077 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 178 ($M^{+\cdot}$, 52%), 160 [$(M-H_2O)^{+\cdot}$, 16], 149 [$(M-H_5C_2\cdot)^{+}$, 100], 135 (24), 121 (22), 91 (28).

HRMS Found: $M^{+\cdot}$, 178.1000. $C_{11}H_{14}O_2$ requires $M^{+\cdot}$, 178.0994.

Optical Rotation $[\alpha]_D^{22}$ +19.9° (*c* 1.7).

(1S,2R)-2,3-Dihydro-6-methoxy-1-methyl-1H-indene-2-ol [(-)-71]



73 **71**

A magnetically stirred mixture of (-)-diol **73** (215 mg, 1.11 mmol) and palladium black (130 mg, 1.22 mmol) in methanol (22 mL) was maintained under an atmosphere of hydrogen (760 mmHg) at room temperature for 4 h. The resulting black suspension was filtered through a small plug of TLC grade silica gel, which was washed with several portions of methanol (*ca.* 30 mL total volume). Concentration of the combined filtrates gave the *title alcohol* **71** (191 mg, 97%) as a straw-coloured oil. This material was used, without further purification, in the next reaction. A small quantity of the crude material was subjected to purification by flash chromatography (silica, 30% ethyl acetate/petrol elution) and provided, after concentration of the appropriate fractions (R_f 0.35), an analytically pure sample of the *title compound* (-)-*71* as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.14 (d, *J* 8.2 Hz, 1H), 6.77-6.70 (m, 2H), 4.52 (br m, 1H), 3.80 (s, 3H, -OCH_3), 3.20-3.10 (m, 1H), 3.08 (dd, *J* 16.2 and 4.8 Hz, 1H), 2.83 (dd, *J* 15.9 and 2.6 Hz, 1H), 1.46 (br d, *J* 6.8 Hz, 1H, -OH), 1.32 (d, *J* 7.2 Hz, 3H, -CH_3).

^{13}C NMR (75.4 MHz) δ 158.6 (C), 147.1 (C), 132.2 (C), 125.0 (CH), 111.7 (CH), 109.3 (CH), 75.5 (CH), 54.9 (CH_3), 44.0 (CH), 39.6 (CH_2), 12.0 (CH_3).

IR (KBr) ν_{max} 3356, 2935, 1610, 1490, 1241, 1195 cm^{-1}.

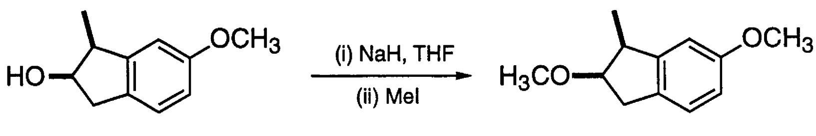
Mass Spectrum (70 eV) *m/z* 178 ($M^{+\cdot}$, 58%), 160 [$(M-H_2O)^{+\cdot}$, 17], 149 [$(M-H_5C_2\cdot)^+$, 100], 135 (22), 121 (21), 91 (23).

Elemental Analysis Found: C, 74.35; H, 8.18. $C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92%.

Optical Rotation $[\alpha]_D^{20}$ -21.8° (*c* 1.2).

5.3 Experimental for Chapter 3

(1*S*,2*R*)-2,3-Dihydro-2,6-dimethoxy-1-methyl-1*H*-indene (106)



71 **106**

A solution of alcohol (-)-**71** (246 mg, 1.38 mmol) in THF (2.5 mL) was added, *via* cannula, to a chilled (ice-water bath) and magnetically stirred suspension of sodium hydride (90 mg, 3.60 mmol) in THF (10 mL) maintained under an atmosphere of nitrogen. Vigorous stirring was continued at 0 °C for 30 mins and then at room temperature for a further 30 mins. The reaction mixture was subsequently cooled (ice-water bath) and treated with methyl iodide (225 μL, 3.60 mmol). The resulting mixture was stirred at room temperature for 17 h then chilled (ice-water bath), before being quenched with water (*ca.* 5 mL). The residue obtained after concentration of the resulting mixture was partitioned between ether (100 mL) and brine (100 mL). The separated aqueous layer was extracted with ether (3 x 50 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 10% ether/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.35), the *title compound* ***106*** (234 mg, 88%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.10 (d, *J* 8.1 Hz, 1H), 6.74 (br s, 1H), 6.70 (dd, *J* 8.1 and 2.5 Hz, 1H), 4.10 (q, *J* 6.0 Hz, 1H), 3.78 (s, 3H, -OCH_3), 3.39 (s, 3H, -OCH_3), 3.29-3.19 (m, 1H), 3.00-2.85 (m, 2H), 1.21 (d, *J* 7.2 Hz, 3H, -CH_3).

^{13}C NMR (75.4 MHz) δ 158.8 (C), 147.8 (C), 131.4 (C), 125.1 (CH), 112.0 (CH), 109.2 (CH), 84.2 (CH), 56.9 (CH_3), 55.1 (CH_3), 42.4 (CH), 35.2 (CH_2), 13.1 (CH_3).

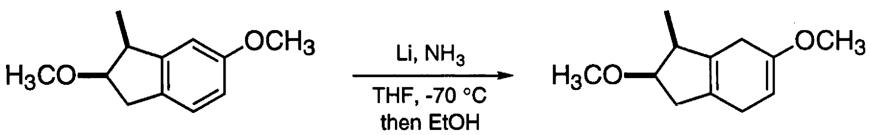
IR (KBr) ν_{max} 2931, 2830, 1611, 1492, 1329, 1243, 1110 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 192 ($M^{+\cdot}$, 89%), 177 [$(M-H_3C\cdot)^+$, 34], 160 [$(M-CH_3OH)^{+\cdot}$, 100], 145 [$(M-CH_3OH-H_3C\cdot)^+$, 32].

HRMS Found: $M^{+\cdot}$, 192.1150. $C_{12}H_{16}O_2$ requires $M^{+\cdot}$, 192.1150.

Optical Rotation $[\alpha]_D^{22}$ -29.0° (*c* 1.6).

(1*S*,2*R*)-4,7-Dihydro-2,6-dimethoxyindane (107)



106 **107**

Lithium pieces (42 mg, 6.19 mmol) were added rapidly to a magnetically stirred solution of methyl ether **106** (170 mg, 0.88 mmol), THF (4 mL) and liquid ammonia (*ca.* 15 mL) maintained at -70 °C (dry ice-acetone bath). The cooling bath was removed and the blue reaction mixture was allowed to reflux for 40 mins. Dry ethanol (*ca.* 8 mL) was then added to the re-chilled (dry ice-acetone bath) reaction mixture, in a dropwise fashion, until the blue colour had discharged. The ammonia was allowed to evaporate and the resulting colourless residue was partitioned between ether (40 mL) and brine (40 mL). The phases were separated and the aqueous layer was extracted with ether (4 x 10 mL). The combined ethereal fractions were dried (K_2CO_3), filtered and concentrated under reduced pressure to furnish *diene 107* (166 mg, 97%) as a straw-coloured oil. This unstable material was used immediately in the next reaction.

^{1}H NMR (300 MHz) δ 4.65 (br m, 1H), 4.00 (q, *J* 7.2 Hz, 1H), 3.56 (s, 3H, $-OCH_3$), 3.34 (s, 3H, $-OCH_3$), 2.80-2.50 (complex m, 5H), 2.45-2.34 (m, 1H), 2.33-2.23 (m, 1H), 0.97 (d, *J* 6.8 Hz, 3H, $-CH_3$).

^{13}C NMR (75.4 MHz) δ 153.7 (C), 134.5 (C), 128.7 (C), 91.0 (CH), 82.6 (CH), 57.4 (CH_3), 54.2 (CH_3), 43.5 (CH), 38.6 (CH_2), 28.1 (CH_2), 26.9 (CH_2), 11.1 (CH_3).

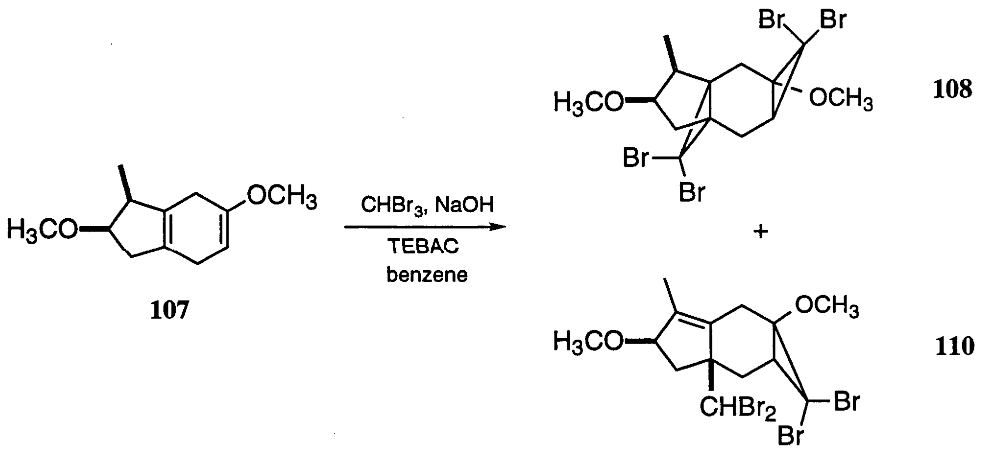
IR (KBr) ν_{max} 2928, 2823, 1700, 1661, 1453, 1373, 1219 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 194 ($M^{+\cdot}$, 100%), 162 [$(M-CH_3OH)^{+\cdot}$, 74], 147 [$(M-CH_3OH-H_3C\cdot)^+$, 98], 131 [$(M-CH_3OH-H_3CO\cdot)^+$, 75].

HRMS Found: $M^{+\cdot}$, 194.1309. $C_{12}H_{18}O_2$ requires $M^{+\cdot}$, 194.1307.

(1a*S*,2a*S*,3*S*,4*R*,5a*R*,6a*R*)-1a,4-Dimethoxy-3-methyl-1,1,7,7-tetrabromo hexahydro-1a-methoxy-1*H*,3*H*-2a,5a-methanocycloprop[f]indene (108) and

(1a*S*,2a*R*,4*R*,6a*R*)-1,1-Dibromo-2a-(dibromomethyl)-4,6a-dimethoxy-5-methyl-1,1a,2,2a,3,4,6,6a-octahydrocycloprop[f]indene (110)



NaOH (3.4 mL of a 50% (w/w) aqueous solution), TEBAC (10 mg, 0.04 mmol) and bromoform (0.41 mL, 4.69 mmol) were added, in that order, to a magnetically stirred solution of diene **107** (122 mg, 0.63 mmol) in benzene (3.4 mL). The reaction vessel was protected from light and vigorous stirring was maintained at room temperature for 17 h. The resulting dark-brown paste was filtered through a plug of Celite™ which was flushed with several portions of ethyl acetate (*ca.* 100 mL total volume). The filtrate thus obtained was partitioned between ethyl acetate (40 mL) and water (40 mL). The separated aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic fractions were treated with decolourising charcoal. The resulting black suspension was filtered through a Celite™ plug and the filtrate so-obtained was dried, filtered and concentrated under reduced pressure to give a viscous, dark-yellow oil. Subjection of this material to flash chromatography (silica, 5% ether/petrol elution) provided two fractions, A (R_f 0.50) and B (R_f 0.20).

Concentration of fraction A afforded *tetracycle **108*** (137 mg, 41%) as a pale-yellow oil.

^{1}H NMR (300 MHz) δ 3.61 (dd, *J* 7.6 and 3.4 Hz, 1H), 3.58 (s, 3H, -OCH_3), 3.15 (s, 3H, -OCH_3), 2.64 (d, *J* 15.3 Hz, 1H), 2.68-2.58 (m, 1H), 2.49 (dd, *J* 15.0 and 2.5 Hz, 1H), 2.47 (d, *J* 15.2 Hz, 1H), 2.20 (d, *J* 15.3 Hz, 1H), 1.99 (dd, *J* 14.7 and 3.3 Hz, 1H), 1.97 (d, *J* 15.5 Hz, 1H), 1.83 (d, *J* 8.6 Hz, 1H), 1.16 (d, *J* 7.7 Hz, 3H, -CH_3).

^{13}C NMR (75.4 MHz) δ 86.2 (CH), 63.0 (C), 57.5 (CH_3), 56.1 (C), 54.2 (CH_3), 46.0 (CH), 45.8 (CH_2), 40.0 (C), 38.2 (C), 36.4 (C), 35.2 (CH), 26.1 (CH_2), 22.5 (CH_2), 12.9 (CH_3).

IR (KBr) ν_{max} 2931, 1440, 1382, 1204, 1158, 1108, 1074 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 542, 540, 538, 536, 534 ($M^{+\cdot}$, 1, 3, 5, 4 and 1%), 461, 459, 457, 455 [$(M-Br\cdot)^+$, 33, 95, 100 and 35], 429, 427, 425, 423 [$(M-Br\cdot-CH_3OH)^+$, 18, 51, 51 and 18], 380, 378, 376 [$(M-Br_2)^{+\cdot}$, 9, 16 and 10].

HRMS Found: $M^{+\cdot}$, 533.8052. $C_{14}H_{18}{}^{79}Br_4O_2$ requires $M^{+\cdot}$, 533.8040.

Concentration of fraction B afforded the unstable *olefin **110*** (30 mg, 9%) as a light-yellow oil.

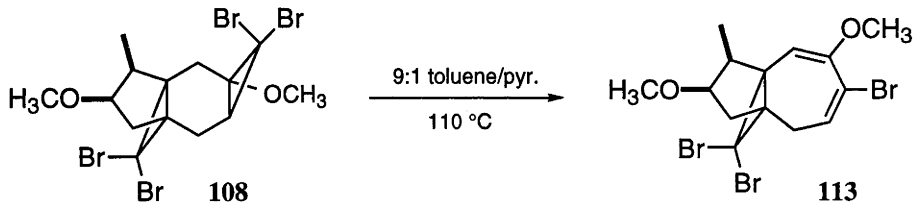
^{1}H NMR (300 MHz) δ 5.70 (s, 1H), 4.07 (dd, *J* 7.2 and 5.5 Hz, 1H), 3.52 (s, 3H, -OCH_3), 3.38 (s, 3H, -OCH_3), 2.70-2.40 (complex m, 4H), 2.17-2.00 (complex m, 2H), 1.98 (d, *J* 8.1 Hz, 1H), 1.25 (s, 3H, -CH_3).

^{13}C NMR (75.4 MHz) δ 132.3 (C), 130.9 (C), 83.3 (CH), 64.6 (C), 60.6 (C), 57.9 (CH_3), 54.7 (CH), 54.4 (CH_3), 41.6 (C), 39.4 (CH_2), 33.6 (CH), 24.5 (CH_2), 23.8 (CH_2), 18.0 (CH_3).

Mass Spectrum (70 eV) *m/z* 542, 540, 538, 536, 534 ($M^{+\cdot}$, <1, 3, 4, 3 and <1%), 461, 459, 457, 455 [$(M-Br\cdot)^+$, 57, 95, 100 and 59], 429, 427, 425, 423 [$(M-Br\cdot-CH_3OH)^+$, 7, 19, 21 and 7], 379, 377, 375 [$(M-Br_2-H\cdot)^+$, 20, 34 and 17].

HRMS Found: $M^{+\cdot}$, 533.8043. $C_{14}H_{18}{}^{79}Br_4O_2$ requires $M^{+\cdot}$, 533.8040.

(1*S*,2*R*,3a*R*,8a*R*)-2,3-Dihydro-2,7-dimethoxy-1-methyl-6,9,9-tribromo 1*H*,4*H*-3a,8a-methanoazulene (113)



108 **113**

A solution of tetracycle **108** (129 mg, 0.24 mmol) in toluene and pyridine (4.8 mL of a 9:1 mixture) was heated at reflux for 23 h. Decolourising charcoal was then added to the cooled (room temperature) reaction mixture which was subsequently filtered through a short pad of TLC grade silica gel and Celite™ (1:1 mixture). This pad was flushed with several portions of ethyl acetate (*ca.* 30 mL total volume) and the combined filtrates were transferred to a separating funnel containing brine (30 mL). The separated aqueous layer was extracted with ethyl acetate (4 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a green solid. Purification of this material by HPLC (μ-Porasil™ silica column, 5% ethyl acetate/petrol elution, 1 mL/min) afforded two components, R_t 17.6 mins and R_t 18.8 mins.

Concentration of the chromatographically more mobile component afforded a colourless, crystalline solid (31 mg, 24% recovery) which was identified, by ^1H NMR spectroscopy, as the starting material **108**.

Concentration of the chromatographically less mobile component afforded the desired *diene* ***113*** (72 mg, 87% at 76% conversion) as a colourless, crystalline solid, m.p. 77-78.5 °C.

^{1}H NMR (300 MHz) δ 6.77 (dd, *J* 8.4 and 5.8 Hz, 1H), 5.19 (s, 1H), 3.88-3.80 (m 1H), 3.67 (s, 3H, -OCH_3), 3.25 (s, 3H, -OCH_3), 2.56-2.30 (m, 4H), 2.04 (dd, *J* 14.6 and 5.4 Hz, 1H), 0.89 (d, *J* 7.6 Hz, 3H, -CH_3).

^{13}C NMR (75.4 MHz) δ 152.9 (C), 135.4 (CH), 118.8 (C), 103.6 (CH), 84.5 (CH), 57.8 (CH_3), 55.4 (CH_3), 54.9 (C), 51.7 (C), 43.9 (CH), 43.3 (C), 41.2 (CH_2), 32.3 (CH_2), 13.2 (CH_3).

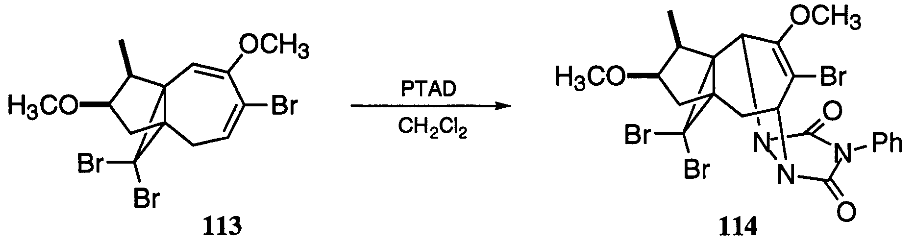
IR (KBr) ν_{max} 2983, 2931, 1637, 1622, 1460, 1372, 1237, 197, 1095 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 460, 458, 456, 454 ($M^{+\cdot}$, <1, 2, 3 and <1%), 379, 377, 375 [$(M-Br\cdot)^{+}$, 47, 100 and 51], 347, 345, 343 [$(M-Br\cdot-CH_3OH)^{+}$, 42, 87 and 44], 298, 296 [$(M-Br_2)^{+\cdot}$, 12 and 13].

Elemental Analysis Found: C, 36.99; H, 3.47; Br, 52.54. $C_{14}H_{17}{}^{79}Br_3O_2$ requires: C, 36.80; H, 3.75; Br, 52.45%.

Optical Rotation $[\alpha]_D^{22}$ -28.8° (*c* 1.0).

(5*R*,5a*S*,6*S*,7*R*,8a*R*,10*R*)-7,13-Dimethoxy-2,3,7,8,9,10-hexahydro-6-methyl-2-phenyl-12,14,14-tribromo-5*H*,6*H*-5,10-etheno-5a,8a-methano-1*H*-cyclopenta[d][1,2,4]triazolo[1,2-a][1,2]diazepine-1,3-dione (114)



113 114

A solution of PTAD (46 mg, 0.26 mmol) in dichloromethane (2 mL) was added dropwise to a magnetically stirred solution of diene **113** (100 mg, 0.22 mmol) in dichloromethane (2 mL). Stirring was continued at room temperature for 19 h after which time the solution was concentrated under reduced pressure to afford a pink foam. Subjection of this crude material to flash chromatography (silica, 60% ether/petrol elution) furnished, after concentration of the relevant fractions (R_f 0.35), a colourless powder. Recrystallisation (ether/hexane) of this powder yielded *adduct **114*** (11 mg, 8%) as colourless prisms, m.p. 99.5-101 °C.

^{1}H NMR (300 MHz) δ 7.50-7.32 (complex m, 5H), 5.47 (s, 1H), 5.14 (t, *J* 3.4 Hz, 1H), 3.85 (s, 3H, -OCH_3), 3.55 (t, *J* 3.8 Hz, 1H), 3.28 (s, 3H, -OCH_3), 2.83 (dd, *J* 7.5 and 4.2 Hz, 1H), 2.58-2.54 (m, 2H), 2.30-2.16 (m, 2H), 1.38 (d, *J* 7.6 Hz, 3H, -CH_3).

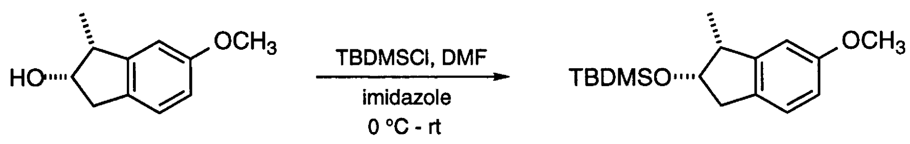
^{13}C NMR (75.4 MHz) δ 154.6 (C), 148.4 (C), 148.2 (C), 131.5 (C), 129.1 (CH), 128.2 (CH), 125.5 (CH), 94.3 (C), 89.7 (CH), 58.7 (CH/CH_3), 56.9 (CH/CH_3), 56.7 (CH/CH_3), 52.2 (CH/CH_3), 50.9 (CH), 46.0 (C), 43.1 (C), 38.5 (CH_2), 33.4 (CH_2), 10.8 (CH_3).

IR (KBr) ν_{max} 3417, 2928, 1764, 1710, 1413, 1115, 1091 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 635, 633, 631, 629 ($M^{+\cdot}$, 2, 7, 7 and 2%), 554, 552, 550 [(M-Br·)$^+$, 10, 16 and 8], 474, 472 [(MH-Br_2)$^+$, 18 and 27], 352, 350, 348 (69, 100 and 70).

HRMS Found: $M^{+\cdot}$, 628.9157. $C_{22}H_{22}{}^{79}Br_3N_3O_4$ requires $M^{+\cdot}$, 628.9160.

(1*R*,2*S*)-2-*tert*-Butyldimethylsilyloxy-2,3-dihydro-6-methoxy-1-methyl-1*H*-indene (115)



71 **115**

tert-Butyldimethylsilyl chloride (756 mg, 5.00 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of alcohol (-)-**71** (809 mg, 4.54 mmol) and imidazole (341 mg, 5.00 mmol) in DMF (14 mL). Stirring was continued at room temperature for 11 h and the reaction mixture was then partitioned between ether (300 mL) and water (300 mL). The separated aqueous layer was extracted with ether (3 x 100 mL) and the combined organic layers were washed with HCl (1 x 100 mL of a 10% (v/v) aqueous solution) then Na_2CO_3 (1 x 100 mL of a 10% (w/v) aqueous solution), before being dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. This material was purified by flash chromatography (5% ethyl acetate/petrol elution) to afford, after concentration of the appropriate fractions (R_f 0.50), *silyl ether 115* (1.30 g, 98%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.07 (d, *J* 8.1 Hz, 1H), 6.73-6.67 (m, 2H), 4.56 (q, *J* 6.0 Hz, 1H), 3.78 (s, 3H, $-OCH_3$), 3.12-3.02 (m, 1H), 2.95 (dd, *J* 15.1 and 6.3 Hz, 1H), 2.79 (dd, *J* 15.6 and 5.3 Hz, 1H), 1.18 (d, *J* 7.2 Hz, 3H, $-CH_3$), 0.89 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.08 (s, 6H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 158.8 (C), 148.3 (C), 132.2 (C), 125.1 (CH), 112.0 (CH), 109.5 (CH), 75.8 (CH), 55.3 (CH_3), 44.5 (CH), 39.6 (CH_2), 25.9 (CH_3), 18.3 (C), 13.6 (CH_3), -4.7 (CH_3), -4.9 (CH_3).

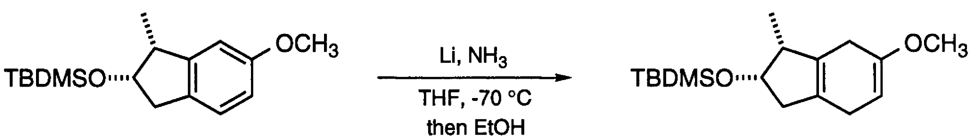
IR (KBr) ν_{max} 2956, 2856, 1612, 1587, 1492, 1253, 1113, 1040 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 292 ($M^{+\cdot}$, <2%), 277 [$(M-H_3C\cdot)^+$, 2], 235 [$(M-H_9C_4\cdot)^+$, 100], 220 [$(M-H_9C_4\cdot-H_3C\cdot)^+$, 17], 161 [$(M-C_6H_{15}SiO\cdot)^+$, 32].

HRMS Found: $M^{+\cdot}$, 292.1853. $C_{17}H_{28}O_2Si$ requires $M^{+\cdot}$, 292.1856.

Optical Rotation $[\alpha]_D^{22}$ +13.2° (*c* 1.4).

(1*R*,2*S*)-2-*tert*-Butyldimethylsilyloxy-4,7-dihydro-6-methoxy-1-methyl indane (116)



115 116

Lithium pieces (368 mg, 53.0 mmol) were added rapidly to a magnetically stirred solution of silyl ether **115** (1.34 g, 4.59 mmol), THF (15 mL) and liquid ammonia (*ca.* 50 mL) maintained at -70 °C (dry ice-acetone bath). The cooling bath was removed and the blue reaction mixture was allowed to reflux for 45 mins. Dry ethanol (*ca.* 30 mL) was then added dropwise to the re-chilled (dry ice-acetone bath) reaction mixture until the blue colour had discharged. The ammonia was allowed to evaporate (*ca.* 2 h) and the residue thus obtained was partitioned between ether (150 mL) and brine (150 mL). The separated aqueous layer was extracted with ether (4 x 50 mL) and the combined ethereal fractions were dried (K_2CO_3), filtered and concentrated under reduced pressure to afford *diene **116*** (1.26 mg, 93%) as a viscous, straw-coloured oil. This unstable material was used immediately in the next reaction without further purification.

^{1}H NMR (300 MHz) δ 4.65 (m, 1H), 4.50-4.43 (m, 1H), 3.56 (s, 3H, -OCH_3), 2.80-2.34 (complex m, 6H), 2.27-2.16 (m, 1H), 0.95 (d, *J* 7.1 Hz, 3H, -CH_3), 0.90 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.06 (s, 6H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

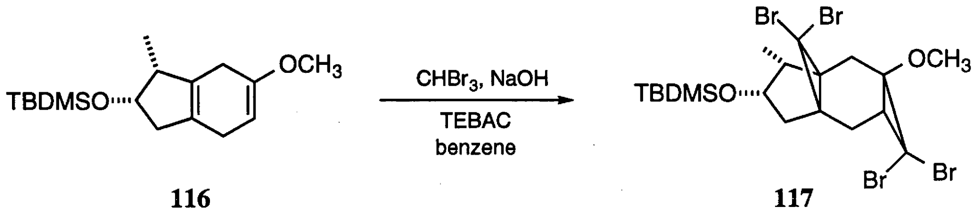
^{13}C NMR (75.4 MHz) δ 153.8 (C), 134.3 (C), 128.8 (C), 91.0 (CH), 73.8 (CH), 54.1 (CH_3), 45.7 (CH), 42.7 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 25.9 (CH_3), 18.3 (C), 11.5 (CH_3), -4.8 (CH_3), -4.9 (CH_3).

IR (KBr) ν_{max} 2929, 2856, 1661, 1463, 1374, 1221, 1105, 1082 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 294 ($M^{+\cdot}$, <1%), 279 [$(M-H_3C\cdot)^+$, <1], 237 [$(M-H_9C_4\cdot)^+$, 19], 161 [$(M-C_6H_{16}SiO-H\cdot)^+$, 57], 75 (100).

HRMS Found: $M^{+\cdot}$, 294.2005. $C_{17}H_{30}O_2Si$ requires $M^{+\cdot}$, 294.2015.

(1a*R*,2a*R*,3*R*,4*S*,5a*R*,6a*R*)-4-*tert*-Butyldimethylsilyloxy-1a-methoxy-3-methyl-1,1,7,7-tetrabromohexahydro-1*H*,3*H*-2a,5a-methanocycloprop[f] indene (117)



116 117

NaOH (22 mL of a 50% (w/w) aqueous solution), TEBAC (120 mg, 0.43 mmol) and bromoform (2.85 mL, 32.6 mmol) were added, in that order, to a magnetically stirred solution of diene **116** (1.20 g, 4.07 mmol) in benzene (22 mL). The reaction vessel was protected from light and vigorous stirring was continued at room temperature for 16 h. The resulting black paste was filtered through a plug of Celite™, which was flushed with several portions of ethyl acetate (*ca.* 300 mL total volume). The combined filtrates were partitioned between ethyl acetate (200 mL) and brine (200 mL) and the phases separated. The aqueous layer was extracted with ethyl acetate (4 x 50 mL) and the combined organic fractions were treated with decolourising charcoal. The black suspension was filtered through a pad of Celite™ and the filtrate so-obtained was dried, filtered and concentrated under reduced pressure to give a dark-yellow oil. Subjection of this material to flash chromatography (silica, 2.5% ethyl acetate/petrol elution) provided, after concentration of the relevant fractions (R_f 0.25), *tetracycle 117* (1.85 g, 71%) as a pale-yellow, crystalline solid. Recrystallisation (dichloromethane/hexane) of a small quantity of this material furnished an analytically pure sample of the *title compound 117* as colourless prisms, m.p. 159-160.5 °C.

^{1}**H NMR** (300 MHz) δ 4.06 (td, *J* 7.2 and 2.3 Hz, 1H), 3.58 (s, 3H, -OCH_3), 2.63 (d, *J* 15.1 Hz, 1H), 2.58-2.48 (m, 2H), 2.45 (d, *J* 8.9 Hz, 1H), 2.18 (d, *J* 15.3 Hz, 1H), 2.01 (d, *J* 15.4 Hz, 1H), 1.92 (dd, *J* 14.8 and 2.3 Hz, 1H), 1.83 (d, *J* 8.6 Hz, 1H), 1.10 (d, *J* 7.6 Hz, 3H, -CH_3), 0.82 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), -0.02 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$), -0.03 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}**C NMR** (75.4 MHz) δ 77.9 (CH), 63.1 (C), 57.6 (C), 54.2 (CH_3), 50.6 (CH_2), 47.4 (CH), 39.7 (C), 38.5 (C), 36.7 (C), 35.2 (CH), 26.3 (CH_2), 25.8 (CH_3), 22.5 (CH_2), 18.0 (C), 13.8 (CH_3), -4.7 (CH_3), -5.2 (CH_3).

IR (KBr) ν_{max} 2928, 2854, 1428, 1382, 1256, 1109, 1044 cm^{-1}.

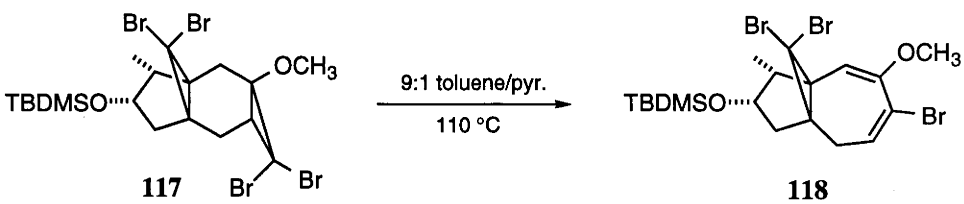
Mass Spectrum (70 eV) *m/z* 642, 640, 638, 636, 634 ($M^{+\cdot}$, <1, <2, 2, <2 and <1%), 561, 599, 557, 555 [$(M-Br\cdot)^+$, 12, 32, 34 and 12], 527, 525, 523, 521 [$(M-Br\cdot-CH_3OH)^+$, 8, 12, 10 and 6], 429, 427, 425, 423 [$(M-Br\cdot-C_6H_{16}OSi)^+$, 5, 15, 16 and 7].

HRMS Found: $M^{+\cdot}$, 633.8736. $C_{19}H_{30}{}^{79}Br_4O_2Si$ requires $M^{+\cdot}$, 633.8749.

Elemental Analysis Found: C, 35.66; H, 4.57; Br, 49.93. $C_{19}H_{30}{}^{79}Br_4O_2Si$ requires: C, 35.76; H, 4.74; Br, 50.09%.

Optical Rotation $[\alpha]_D^{22}$ +42.4° (*c* 0.6).

(1*R*,2*S*,3a*S*,8a*R*)-2-*tert*-Butyldimethylsilyloxy-2,3-dihydro-7-methoxy-1-methyl-6,9,9-tribromo-1*H*,4*H*-3a,8a-methanoazulene (118)



117 118

A solution of tetracycle **117** (1.73 g, 2.71 mmol) in toluene and pyridine (50 mL of a 9:1 mixture) was heated at reflux for 18 h. Decolourising charcoal was added to the cooled (room temperature) reaction mixture which was subsequently filtered through a short pad of TLC grade silica gel and Celite™ (1:1 mixture). This pad was flushed with several portions of ethyl acetate (*ca.* 100 mL total volume) and the combined filtrates were transferred to a separating funnel containing brine (200 mL). The separated aqueous layer was extracted with ethyl acetate (4 x 50 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a green solid. Subjection of the crude material to flash chromatography (silica, 80% carbon tetrachloride/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.40), the *title diene* ***118*** (525 mg, 38% at 81% conversion) as a straw-coloured solid. Recrystallisation (*tert*-butylmethylether/hexane) provided an analytically pure sample of *compound* ***118*** as colourless prisms, m.p. 142-144 °C.

^{1}H NMR (300 MHz) δ 6.76 (dd, *J* 8.5 and 5.8 Hz, 1H), 5.17 (s, 1H), 4.25 (td, *J* 6.0 and 4.1 Hz, 1H), 3.67 (s, 3H, $-OCH_3$), 2.51-2.30 (m, 4H), 1.97 (dd, *J* 14.6 and 4.0 Hz, 1H), 0.89 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.84 (d, *J* 7.4 Hz, 3H, $-CH_3$), 0.03 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.02 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 152.8 (C), 135.5 (CH), 118.5 (C), 103.6 (CH), 76.6 (CH), 56.8 (C), 55.4 (CH_3), 52.2 (C/CH_2), 46.0 (CH), 45.8 (C/CH_2), 43.3 (C), 32.6 (CH_2), 25.9 (CH_3), 18.3 (C), 14.2 (CH_3), -4.8 (CH_3), -4.9 (CH_3).

IR (KBr) ν_{max} 2951, 2855, 1634, 1620, 1451, 1370, 1245, 1179, 1109 cm^{-1}.

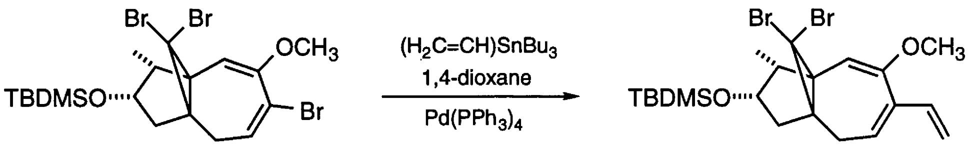
Mass Spectrum (70 eV) *m/z* 560, 558, 556, 554 ($M^{+\cdot}$, <1, 1, 1 and<1%), 503, 501, 499, 497 $[(M-H_9C_4\cdot)^+$, <1, 2, 2 and <1], 479, 477, 475 $[(M-Br\cdot)^+$, 55, 100 and 55], 347, 345, 343 $[(M-Br\cdot-C_6H_{16}OSi)^+$, 33, 68 and 34].

HRMS Found: $M^{+\cdot}$, 553.9498. $C_{19}H_{29}{}^{79}Br_3O_2Si$ requires $M^{+\cdot}$, 553.9487.

Elemental Analysis Found: C, 40.60; H, 5.20; Br, 43.23. $C_{19}H_{29}{}^{79}Br_3O_2Si$ requires: C, 40.95; H, 5.25; Br, 43.02%.

Optical Rotation $[\alpha]_D^{22}$ +36.1° (*c* 1.0).

(1*R*,2*S*,3a*S*,8a*R*)-2-*tert*-Butyldimethylsilyloxy-9,9-dibromo-2,3-dihydro-6-ethenyl-7-methoxy-1-methyl-1*H*,4*H*-3a,8a-methanoazulene (119)



118 **119**

A magnetically stirred suspension of diene **118** (525 mg, 0.94 mmol), $Pd(PPh_3)_4$ (435 mg, 0.38 mmol) and vinyltributylstannane (550 μL, 1.88 mmol) in 1,4-dioxane (90 mL) was heated at 45 °C for 36 h under an atmosphere of nitrogen. The resulting brown solution was cooled to room temperature and concentrated under reduced pressure to give a tan semi-solid. Subjection of this material to flash chromatography (silica, 80% carbon tetrachloride/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), *triene 119* (303 mg, 64%) as a colourless, crystalline solid, m.p. 69.5-70.5 °C.

^{1}H NMR (300 MHz) δ 6.34 (dd, *J* 7.9 and 6.1 Hz, 1H), 6.23 (dd, *J* 17.5 and 10.9 Hz, 1H), 5.28 (dd, *J* 17.4 and 1.5 Hz, 1H), 5.10 (s, 1H), 5.04 (dd, *J* 11.0 and 1.5 Hz, 1H), 4.22 (td, *J* 7.2 and 4.3 Hz, 1H), 3.65 (s, 3H, $-OCH_3$), 2.52-2.28 (complex m, 4H), 1.93 (dd, *J* 14.5 and 4.3 Hz, 1H), 0.85 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.77 (d, *J* 7.6 Hz, 3H, $-CH_3$), 0.00 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$), -0.20 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 155.3 (C), 138.7 (C), 136.4 (CH), 131.8 (CH), 114.8 (CH_2), 102.7 (CH), 76.4 (CH), 57.9 (C), 54.6 (CH_3), 52.0 (C), 45.7 (CH_2), 45.5 (CH), 42.9 (C), 30.7 (CH_2), 25.8 (CH_3), 18.2 (C), 14.2 (CH_3), -4.8 (CH_3), -5.0 (CH_3).

IR (KBr) ν_{max} 2930, 2856, 1638, 1462, 1393, 1247, 1103 cm^{-1}.

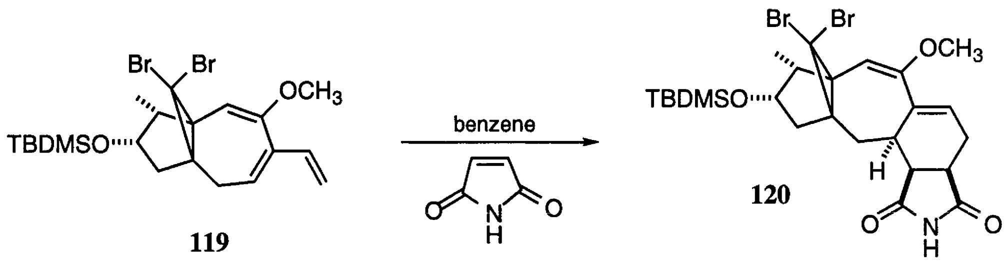
Mass Spectrum (70 eV) *m/z* 506, 504, 502 ($M^{+\cdot}$, 16, 30 and 14%), 425, 423 [$(M-Br\cdot)^+$, 62 and 58], 344 [$(M-Br_2)^{+\cdot}$, 26], 293, 291 [$(M-Br\cdot-C_6H_{16}OSi)^+$, 56 and 57].

HRMS Found: $M^{+\cdot}$, 502.0538. $C_{21}H_{32}{}^{79}Br_2O_2Si$ requires $M^{+\cdot}$, 502.0544.

Elemental Analysis Found: C, 49.54; H, 6.36; Br, 31.52. $C_{21}H_{32}Br_2O_2Si$ requires: C, 50.01; H, 6.39; Br, 31.68%.

Optical Rotation $[\alpha]_D^{23}$ +3.5° (*c* 1.2).

(3a*S*,7a*R*,8*R*,9*S*,10a*S*,11a*S*,11b*R*)-9-*tert*-Butyldimethylsilyloxy-12,12-dibromo-3a,9,10,11,11a,11b-hexahydro-6-methoxy-3-methyl-7a,10a-methano-8*H*-azuleno[5,6-e]isoindole-1,3-(2*H*,4*H*)-dione (120)



A solution of triene **119** (291 mg, 0.58 mmol) and maleimide (**60**) (70 mg, 0.69 mmol) in benzene (5 mL) was stirred at room temperature for 18 h. The resulting milky reaction mixture was concentrated under reduced pressure to give the *title Diels-Alder adduct **120*** (333 mg, 96%) as a very unstable, colourless solid. This material was used in the next reaction without further purification.

^{1}H NMR (300 MHz) δ 8.22 (br s, 1H, -NH), 6.27 (p, *J* 3.5 Hz, 1H), 4.57 (s, 1H), 4.16 (td, *J* 6.5 and 1.7 Hz, 1H), 3.55 (s, 3H, $-OCH_3$), 3.20 (app t, *J ca.* 8.0 Hz, 1H), 3.06 (dd, *J* 8.8 and 5.2 Hz, 1H), 2.95-2.84 (complex m, 1H), 2.78 (dd, *J* 15.4 and 7.7 Hz, 1H), 2.66 (app t, *J ca.* 14.0 Hz, 1H), 2.52 (dd, *J* 15.1 and 6.1 Hz, 1H), 2.41 (app t, *J ca.* 7.0 Hz, 1H), 2.30-2.18 (complex m, 1H), 2.10 (dd, *J* 14.4 and 2.2 Hz, 1H), 2.00 (dd, *J* 14.5 and 1.7 Hz, 1H), 0.86 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.77 (d, *J* 7.4 Hz, 3H, $-CH_3$), 0.03 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$), -0.02 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 180.0 (C), 178.0 (C), 154.9 (C), 139.6 (C), 127.8 (CH), 98.5 (CH), 78.5 (CH), 60.9 (C), 60.4 (C), 55.3 (CH_3), 47.7 (CH), 46.3 (CH), 46.0

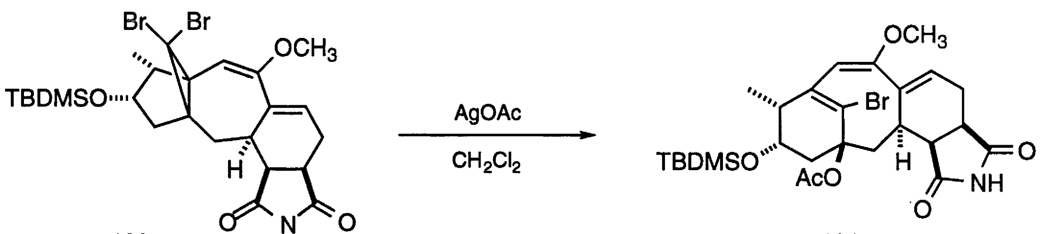
(C), 42.6 (CH_2), 41.8 (CH), 34.3 (CH), 32.4 (CH_2), 25.9 (CH_3), 24.4 (CH_2), 18.3 (C), 14.2 (CH_3), -4.9 (CH_3).

IR (KBr) ν_{max} 3281, 2931, 1778, 1720, 1447, 1355, 1193, 1096 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 603, 601, 599 ($M^{+\cdot}$, <1, 1 and <1%), 471, 469, 467 [$(M-C_6H_{16}SiO\cdot)^+$, 1, 2 and 1], 440 [$(M-Br_2-H\cdot)^+$, 52], 425 [$(M-Br_2-H_3C\cdot-H\cdot)^+$, <5].

HRMS Found: $M^{+\cdot}$, 599.0698. $C_{25}H_{35}{}^{79}Br_2NO_4Si$ requires $M^{+\cdot}$, 599.0702.

(3a*S*,9*R*,10*S*,12*S*,13a*S*,13b*R*)-12-(Acetyloxy)-10-*tert*-butyldimethylsilyl oxy-14-bromo-3a,9,10,11,12,13,13a,13b-octahydro-6-methoxy-9-methyl -12,8-metheno-8*H*-cyclodec[e]isoindole-1,3-(2*H*,4*H*)-dione (121)



120 **121**

A magnetically stirred suspension of adduct **120** (303 mg, 0.50 mmol) and silver acetate (840 mg, 5.00 mmol) in dichloromethane (30 mL) was heated at reflux for 20 h. The reaction mixture was then cooled to room temperature and filtered through a short pad of TLC grade silica gel and Celite™ (1:1 mixture). This pad was flushed with several portions of ethyl acetate (*ca.* 200 mL total volume) and concentration of the filtrates so-obtained under reduced pressure gave an orange oil. Purification of this material by HPLC (μ-Porasil™ silica column, 35% ethyl acetate/petrol elution, 1 mL/min) afforded, after concentration of the appropriate fractions (R_t 27.7 mins), *tetracycle 121* (51 mg, 18%) as a colourless foam.

^{1}H NMR (300 MHz) δ 8.07 (br s, 1H, -NH), 6.56 (dd, *J* 8.0 and 3.1 Hz, 1H), 5.17 (s, 1H), 4.97-4.90 (m, 1H), 3.68 (s, 3H, -OCH_3), 3.08-2.70 (complex m, 4H), 2.35 (dd, *J* 11.0 and 6.0 Hz, 1H), 2.25-1.90 (complex m, 4H), 2.05 (s, 3H, -$COCH_3$), 1.74

(d, J 12.2 Hz, 1H), 1.22 (d, J 7.3 Hz, 3H, -CH_3), 0.88 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.05 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.03 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 179.6 (C), 177.8 (C), 169.0 (C), 161.7 (C), 141.9 (C), 140.7 (C), 131.0 (CH), 128.3 (C), 101.6 (CH), 83.6 (C), 67.2 (CH), 56.4 (CH_3), 46.9 (CH), 42.9 (CH), 40.3 (CH), 39.6 (CH_2), 36.5 (CH), 29.7 (CH_2), 25.8 (CH_3), 22.1 (CH_2), 21.6 (CH_3), 18.0 (C), 13.5 (CH_3), -4.8 (CH_3), -5.0 (CH_3).

IR (KBr) ν_{max} 3241, 2956, 1780, 1723, 1359, 1245, 1159, 1088 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 581, 579 ($M^{+\cdot}$, <1 and <1%), 500 [$(M-Br\cdot)^+$, 71], 440 [$(M-Br\cdot-CH_3CO_2H)^+$, 65], 308 [$(M-Br\cdot-CH_3CO_2H-C_6H_{16}OSi)^+$, 100].

HRMS Found: $M^{+\cdot}$, 579.1660. $C_{27}H_{38}{}^{79}BrNO_6Si$ requires $M^{+\cdot}$, 579.1652.

Optical Rotation $[\alpha]_D^{20}$ -68.5° (*c* 1.0).

(3a*S*,9*R*,10*S*,12*S*,13a*S*,13b*R*)-12-(Acetyloxy)-14-bromo-10-hydroxy-3a,9,10,11,12,13,13a,13b-octahydro-6-methoxy-9-methyl-12,8-metheno-8*H*-cyclodec[e]isoindole-1,3-(2*H*,4*H*)-dione (122)

121 **122**

A magnetically stirred solution of silyl ether **121** (11 mg, 0.02 mmol) and tetra-*n*-butylammonium fluoride (0.4 mL of a 1 M solution in THF, 0.40 mmol) in THF (0.5 mL) was stirred at room temperature for 18 h. The resulting yellow mixture was diluted with ethyl acetate (15 mL) and brine (15 mL) and the phases separated. The aqueous layer was extracted with ethyl acetate (4 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to provide a dark-yellow oil. Subjection of this material to flash chromatography (silica, 70% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.30), *alcohol* ***122*** (6 mg, 68%) as a light-yellow oil. This material was found to be very unstable and could not be fully characterised.

^{1}H NMR (300 MHz) δ 8.05 (br s, 1H, -NH), 6.56 (br dd, *J* 8.0 and 3.0 Hz, 1H), 5.19 (s, 1H), 5.00-4.90 (br m, 1H), 3.69 (s, 3H, $-OCH_3$), 3.10-2.76 (complex m, 6H), 2.30 (dd, *J* 10.8 and 6.3 Hz, 1H), 2.25-2.10 (obscured m, 1H), 2.16 (d, *J* 8.4 Hz, 1H), 2.06 (s, 3H, $-COCH_3$), 1.95 (br t, *J ca.* 11.0 Hz, 1H), 1.75 (br m, 1H, -OH), 1.26 (d, *J* 7.3 Hz, 3H, $-CH_3$).

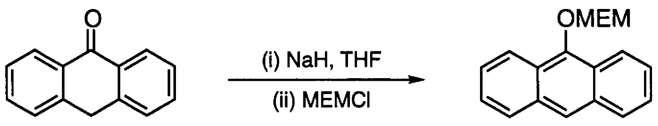
IR (KBr) ν_{max} 3329, 2962, 1772, 1717, 1245, 1198 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 386 [(M-Br·)$^+$, 30%], 326 [(M-Br·-CH_3CO_2H)$^+$, 63], 296 [(M-Br·-CH_3CO_2H-H_3CO·)$^+$, 26], 149 (94).

HRMS Found: (M-Br·)$^+$, 386.1602. $C_{21}H_{24}NO_6$ requires (M-Br·)$^+$, 386.1604.

5.4 Experimental for Chapter 4

9-[(2'-Methoxyethoxy)methoxy]anthracene (130)



129 130

Anthrone (**129**) (10.0 g, 51.5 mmol) was added in one portion to a chilled (ice-water bath) and magnetically stirred suspension of sodium hydride (2.28 g, 95.0 mmol) in THF (250 mL) maintained under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h then treated with 2-methoxyethoxymethyl chloride (MEMCl) (8.8 mL, 77.1 mmol). The cooling bath was removed and stirring was continued at room temperature for a further 5 h. The resulting yellow suspension was re-chilled (ice-water bath) and treated with water (50 mL) (CAUTION ! Vigorous bubbling observed !). The residue obtained after concentration of the crude reaction mixture was partitioned between dichloromethane (500 mL) and water (500 mL). The separated aqueous layer was extracted with dichloromethane (3 x 200 mL) and the combined organic phases were dried, filtered and concentrated under reduced pressure to give a light-orange oil. This material was subjected to flash chromatography (silica, 20% ethyl acetate/petrol elution) to afford, after concentration of the appropriate fractions (R_f 0.45), a dark-yellow oil which crystallised upon standing. Recrystallisation (hexane) of this material afforded the *title compound **130*** (13.6 g, 93%) as light-yellow needles, m.p. 44-45 °C.

^{1}H NMR (300 MHz) δ 8.43-8.30 (m, 2H), 8.25 (s, 1H), 8.02-7.96 (m, 2H), 7.51-7.42 (m, 4H), 5.47 (s, 2H), 4.10-4.04 (m, 2H), 3.65-3.60 (m, 2H), 3.39 (s, 3H, $-OCH_3$).

^{13}C NMR (75.4 MHz) δ 132.3 (C), 128.3 (CH), 125.5 (CH), 125.3 (CH), 124.9 (C), 122.7 (CH), 122.6 (CH), 100.1 (CH_2), 71.8 (CH_2), 69.8 (CH_2), 59.1 (CH_3).

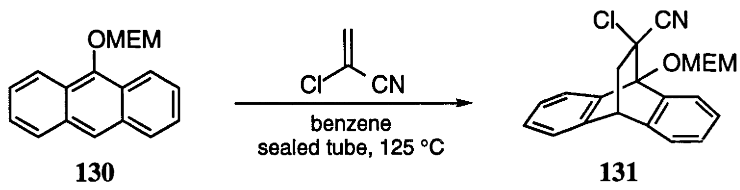
IR (KBr) ν_{max} 2920, 2873, 1344, 1277, 1176, 1110, 1052, 1028, 935 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 282 ($M^{+\cdot}$, 44%), 207 [$(M-C_3H_7O_2^{\cdot})^+$, 19], 194 [$(M-C_4H_8O_2)^{+\cdot}$, 61], 176 [$(M-C_4H_{10}O_3)^{+\cdot}$, 14], 165 (48), 89 (90).

HRMS Found: $M^{+\cdot}$, 282.1251. $C_{18}H_{18}O_3$ requires $M^{+\cdot}$, 282.1256.

Elemental Analysis Found: C, 76.86; H, 6.38. $C_{18}H_{18}O_3$ requires: C, 76.57; H, 6.43%.

12-Chloro-12-cyano-9,10-dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracene (131)



A magnetically stirred solution of compound **130** (8.00 g, 28.3 mmol) and 2-chloroacrylonitrile (10.4 mL, 130 mmol) in benzene (64 mL), contained in an ACE™ pressure tube, was heated at 120-125 °C (oil bath temperature) for 16 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to afford a cream-coloured solid. Recrystallisation (dichloromethane/hexane) of this material afforded the *title compound 131* (10.3 g, 98%) as colourless prisms, m.p. 193-194 °C.

^{1}H NMR (300 MHz) δ 7.90 (m, 2H), 7.37-7.23 (complex m, 6H), 5.56 (br s, 2H), 4.32 (t, *J* 2.5 Hz, 1H), 4.20 (m, 2H), 3.80 (t, *J* 4.7 Hz, 2H), 3.49 (s, 3H), 2.85 (dd, *J* 13.9 and 2.7 Hz, 1H), 2.40 (dd, *J* 13.8 and 2.7 Hz, 1H).

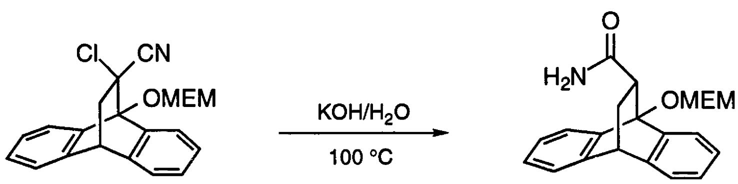
^{13}C NMR (75.4 MHz) δ 141.2 (C), 139.5 (C), 136.7 (C), 136.1 (C), 128.4 (CH), 128.0 (CH), 127.2 (CH), 126.7 (CH), 125.1 (CH), 124.3 (CH), 123.4 (CH), 123.3 (CH), 118.4 (C), 93.5 (CH_2), 88.2 (C), 71.8 (CH_2), 68.4 (CH_2), 60.8 (C), 59.0 (CH_3), 49.0 (CH_2), 42.6 (CH).

IR (KBr) ν_{max} 2948, 2885, 2240, 1459, 1238, 1167, 1112, 1050, 1017, 957 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 303 [(M-Cl·-H_3CO·)$^+$, 1%], 282 [(M-C_3H_2ClN)$^{+\cdot}$, 18], 245 (60), 194 [(M-C_3H_2ClN-$C_4H_8O_3$)$^{+\cdot}$, 41], 89 (100).

Elemental Analysis Found: C, 67.96; H, 5.46; Cl, 9.62; N, 3.52. $C_{21}H_{20}ClNO_3$ requires: C, 68.20; H, 5.45; Cl, 9.59; N, 3.79%.

9,10-Dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracene-12-yl carboxamide (133)



131 133

A magnetically stirred mixture of compound **131** (100 mg, 0.27 mmol) and KOH (2 mL of a *ca.* 14 M aqueous solution) was heated at reflux for 18 h. The resulting dark-brown suspension was cooled to room temperature and partitioned between ether (40 mL) and water (40 mL). The separated aqueous layer was extracted with ether (4 x 10 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to give a dark-yellow oil. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded two fractions, A (R_f 0.60) and B (R_f 0.20).

Concentration of fraction A provided the starting material **131** (60 mg, 60% recovery) which was identical, by ^{1}H NMR spectroscopy, with an authentic sample.

Concentration of fraction B furnished the *amide 133* (22 mg, 58% at 40% conversion) as a clear, colourless oil.

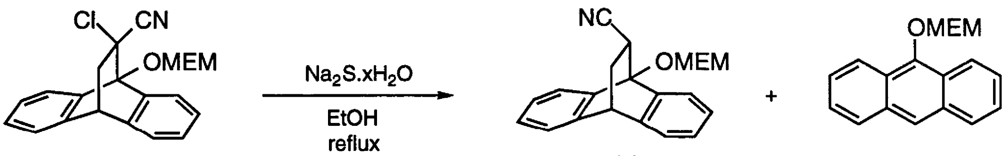
^{1}H NMR (300 MHz) δ 7.72-7.68 (m, 1H), 7.55-7.51 (m, 1H), 7.33-7.25 (complex m, 2H), 7.23-7.11 (complex m, 4H), 6.18 (br s, 1H, -NH_2), 5.50 (s, 2H), 5.20 (br s, 1H, $-NH_2$), 4.28 (app t, *J ca.* 3.0 Hz, 1H), 4.10-4.00 (m, 2H), 3.73-3.68 (m, 2H), 3.43 (s, 3H, $-OCH_3$), 3.00 (dd, *J* 9.0 and 3.0 Hz, 1H), 2.27-2.09 (m, 2H).

^{13}C NMR (75.4 MHz) δ 174.2 (C), 143.2 (C), 141.7 (C), 139.3 (C), 126.7 (CH), 126.6 (CH), 126.0 (CH), 125.7 (CH), 123.5 (CH), 123.3 (CH), 121.9 (CH), 121.2 (CH), 93.1 (CH_2), 84.7 (C), 71.8 (CH_2), 68.6 (CH_2), 59.1 (CH_3), 48.0 (CH), 43.2 (CH), 33.4 (CH_2).

Mass Spectrum (70 eV) *m/z* 353 ($M^{+\cdot}$, <1%), 282 [$(M-C_3H_5NO)^{+\cdot}$, 44], 194 (43), 89 (100).

HRMS Found: $M^{+\cdot}$, 353.1620. $C_{21}H_{23}NO_4$ requires $M^{+\cdot}$, 353.1627.

12-Cyano-9,10-dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracene (134)



131 **134** **130**

A magnetically stirred solution of adduct **131** (100 mg, 0.27 mmol) and $Na_2S.xH_2O$ (228 mg) in ethanol (2 mL) was heated at reflux for 24 h. The resulting black-brown reaction mixture was cooled to room temperature and partitioned between ether (20 mL) and HCl (20 mL of a 10% (v/v) aqueous solution). The phases were separated and the aqueous layer was extracted with ether (4 x 10 mL). The combined organic fractions were dried, filtered and concentrated under reduced pressure to give a brown solid. This material was subjected to flash chromatography (silica, 20% ethyl acetate/petrol elution) and furnished two fractions, A (R_f 0.45) and B (R_f 0.20).

Concentration of fraction A afforded compound **130** (18 mg, 24%) as a straw-coloured, crystalline solid which was identical, by ^1H NMR spectroscopy, with an authentic sample.

Concentration of fraction B afforded a colourless solid which was recrystallised (ethylene glycol dimethyl ether/hexane) to provide *nitrile* ***134*** (29 mg, 32%) as colourless prisms, m.p. 110-112 °C.

^{1}H NMR (300 MHz) δ 7.71 (d, *J* 7.1 Hz, 1H), 7.35-7.14 (complex m, 7H), 5.62 (d, *J* 7.7 Hz, 1H), 5.42 (d, *J* 7.4 Hz, 1H), 4.38 (dt, *J* 10.4 and 6.2 Hz, 1H), 4.32 (br s, 1H), 3.92 (td, *J* 10.4 and 2.0 Hz, 1H), 3.80 (td, *J* 10.7 and 2.0 Hz, 1H), 3.64 (dt, *J* 10.8 and 3.0 Hz, 1H), 3.43 (s, 3H, $-OCH_3$), 3.35 (dd, *J* 10.3 and 3.7 Hz, 1H), 2.35 (td, *J* 12.6 and 1.0 Hz, 1H), 2.15 (dt, *J* 12.5 and 3.4 Hz, 1H).

^{13}C NMR (75.4 MHz) δ 142.8 (C), 140.2 (C), 140.0 (C), 139.3 (C), 127.1 (CH), 126.5 (CH), 126.1 (CH), 123.6 (CH), 123.4 (CH), 123.3 (CH), 121.8 (CH), 121.5 (CH), 120.9 (C), 92.4 (CH_2), 82.5 (C), 71.7 (CH_2), 68.3 (CH_2), 59.1 (CH_3), 42.2 (CH), 34.5 (CH_2), 33.8 (CH).

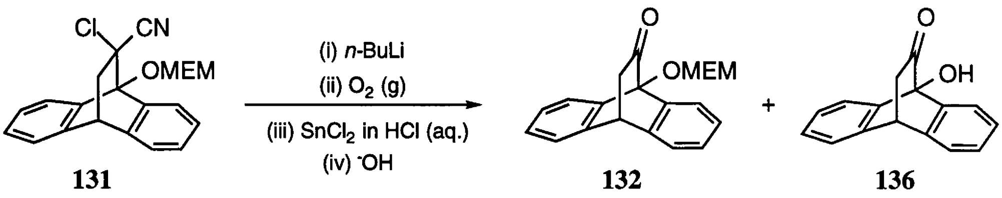
IR (KBr) ν_{max} 2926, 2873, 2240, 1458, 1304, 1242, 1142, 1096 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 282 [$(M-C_3H_3N)^{+\cdot}$, 35%], 194 (55), 89 (100).

Elemental Analysis Found: C, 74.88; H, 6.24; N, 4.13. $C_{21}H_{21}NO_3$ requires: C, 75.20; H, 6.31; N, 4.18%.

9,10-Dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-12-one (132) and

9,10-Dihydro-9-hydroxy-9,10-ethanoanthracen-12-one (136)



n-BuLi (6 mL of a 2.7 M solution in hexanes, 16.2 mmol) was added dropwise to a chilled (dry ice-acetone bath) and magnetically stirred solution of compound **131** (3.00 g, 8.11 mmol) in THF (150 mL) maintained under an atmosphere of nitrogen. The resulting mixture was stirred at -70 °C for 40 mins, then oxygen gas was bubbled vigorously through the now crimson-red solution for 1.5 h (the internal reaction temperature was maintained at or below -70 °C during this time). The cold bath was removed and $SnCl_2$ (18 mL of a 1 M solution in 2 M aqueous HCl) was added slowly to the now gold-coloured reaction mixture. Stirring was continued for 10 mins[Ω] after which time the reaction mixture was concentrated under reduced pressure. The oily residue thus obtained was partitioned between ether (300 mL) and water (300 mL). The separated aqueous layer was extracted with ether (3 x 150 mL) and the combined organic fractions were washed with NaOH (1 x 150 mL of a 1 M aqueous solution) then brine (1 x 150 mL), before being dried, filtered and concentrated under reduced pressure to give a viscous, orange oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) provided two fractions, A (R_f 0.80) and B (R_f 0.30).

Concentration of fraction A afforded a colourless solid which was recrystallised (hot hexane) to give *alcohol* ***136*** (100 mg, 5%) as colourless needles, m.p. 154-155 °C.

Ω If stirring was continued for any longer than the specified time, significant quantities of the unwanted alcohol **136** were obtained.

^{1}H NMR (300 MHz) δ 7.63 (m, 2H), 7.36 (m, 2H), 7.24 (m, 4H), 4.60 (app t, *J* 2.7 Hz, 1H), 4.28 (s, 1H), 2.50 (d, *J* 2.7 Hz, 2H).

^{13}C NMR (75.4 MHz) δ 205.9 (C), 140.6 (C), 138.3 (C), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 123.5 (CH), 121.9 (CH), 84.0 (C), 42.6 (CH), 37.7 (CH_2).

IR (KBr) ν_{max} 3467, 2970, 1724, 1457, 1282, 1244, 1090, 1066, 759 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 236 ($M^{+\cdot}$, 11%), 218 [$(M-H_2O)^{+\cdot}$, 26], 208 [$(M-CO)^{+\cdot}$, 27], 194 [$(M-C_2H_2O)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 236.0834. $C_{16}H_{12}O_2$ requires $M^{+\cdot}$, 236.0837.

Elemental Analysis Found: C, 81.22; H, 5.12. $C_{16}H_{12}O_2$ requires: C, 81.34; H, 5.12%.

Concentration of fraction B afforded a clear, colourless oil which crystallised upon standing. Recrystallisation (hot hexane) of this material afforded *compound **132*** (1.52 g, 58%) as colourless prisms, m.p. 84-85 °C.

^{1}H NMR (300 MHz) δ 7.83 (m, 2H), 7.36 (m, 2H), 7.22 (m, 4H), 5.55 (s, 2H), 4.50 (t, *J* 2.7 Hz, 1H), 4.15 (m, 2H), 3.76 (m, 2H), 3.47 (s, 3H), 2.45 (d, *J* 2.7 Hz, 2H).

^{13}C NMR (75.4 MHz) δ 204.8 (C), 141.3 (C), 137.32 (C), 137.29 (C), 127.7 (CH), 126.7 (CH), 123.6 (CH), 122.9 (CH), 93.9 (CH_2), 91.2 (C), 71.9 (CH_2), 68.2 (CH_2), 59.0 (CH_3), 43.2 (CH), 38.5 (CH_2).

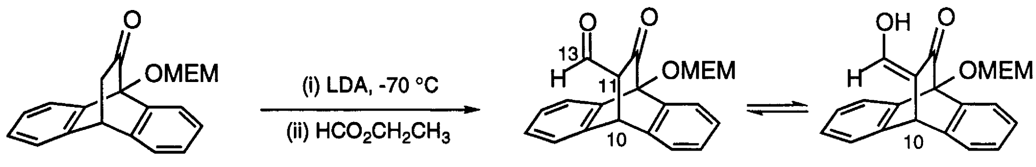
IR (KBr) ν_{max} 2912, 2894, 1731, 1460, 1249, 1110, 1048, 987 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 324 ($M^{+\cdot}$, <2%), 296 [$(M-CO)^{+\cdot}$, <1], 282 [$(M-C_2H_2O)^{+\cdot}$, 54], 249 [$(M-C_3H_7O_2{}^{\cdot})^+$, 22], 219 [$(M-C_4H_9O_3{}^{\cdot})^+$, 17].

HRMS Found: $M^{+\cdot}$, 324.1365. $C_{20}H_{20}O_4$ requires $M^{+\cdot}$, 324.1362.

Elemental Analysis Found: C, 74.21; H, 6.51. $C_{20}H_{20}O_4$ requires: C, 74.06; H, 6.21%.

9,10-Dihydro-11-formyl-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-12-one (139) and 9,10-Dihydro-11-hydroxymethylene-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-12-one (140)



132 **139** **140**

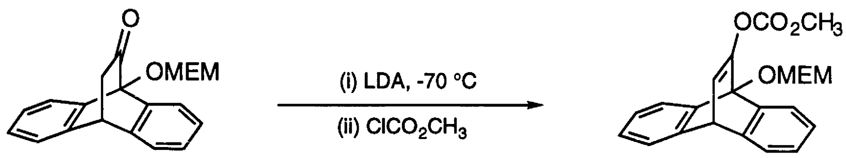
n-BuLi (145 µL of a 2.6 M solution in hexanes, 0.38 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of diisopropylamine (50 µL, 0.38 mmol) in THF (2 mL) maintained under an atmosphere of nitrogen. After stirring at 0 °C for 30 mins, the reaction mixture was cooled to -70 °C (dry ice-acetone bath) then treated dropwise with a solution of ketone **132** (100 mg, 0.31 mmol) in THF (1 mL). Stirring was continued at -70 °C for 1 h after which time freshly distilled ethyl formate (100 µL, 1.24 mmol) was added to the reaction mixture. Stirring was continued for a further 18 h (during which time the mixture was allowed to warm to room temperature) and the resulting yellow solution was partitioned between ether (50 mL) and water (50 mL). The separated aqueous layer was extracted with ether (3 x 20 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 40% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), a mixture of interconverting tautomers ***139*** and ***140*** (32% combined yield) as a pale-yellow oil. Given that these compounds were inseparable, only the 70 eV EI mass spectrometric and ^{1}H NMR spectroscopic data were acquired.

^{1}H NMR (300 MHz) (a 1:2 mixture of tautomers **139** and **140** was observed) δ 9.34 (s, 1H, **139**H_{13}), 7.92-7.88 (m, 1H), 7.85-7.80 (m, 2H), 7.78-7.74 (m, 1H), 7.52-7.47 (m, 1H), 7.42-7.38 (m, 1H), 7.35-7.14 (complex m, 10H), 5.62 (s, 2H, **140**[OCH_2O]), 5.60 (d, *J* 6.5 Hz, 1H, **139**[OCH_2]), 5.54 (d, *J* 6.5 Hz, 1H,

139[OCH_2O]), 4.87 (d, *J* 2.3 Hz, 1H, **139**H_{10}), 4.78 (s, 1H, **140**H_{10}), 4.22-4.10 (complex m, 4H, 2 x [OCH_2]), 3.80-3.72 (complex m, 4H, 2 x [OCH_2]), 3.45 (s, 6H, 2 x -OCH_3), 3.32 (d, *J* 2.3 Hz, 1H, **139**H_{11}).

Mass Spectrum (70 eV) *m/z* 352 ($M^{+\cdot}$, 6%), 324 [$(M-CO)^{+\cdot}$, 19], 282 [$(M-C_3H_2O_3)^{+\cdot}$, 38], 89 (100).

9,10-Dihydro-12-methoxyformate-9-[(2'-methoxyethoxy)methoxy-9,10-ethenoanthracene (141)



132 **141**

n-BuLi (240 μL of a 2.6 M solution in hexanes, 0.62 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of diisopropylamine (82 μL, 0.63 mmol) in THF (2 mL) maintained under an atmosphere of nitrogen. After 40 mins, the reaction mixture was cooled to -70 °C (dry ice-acetone bath) then treated with a solution of ketone **132** (100 mg, 0.31 mmol) in THF (1.5 mL) in a dropwise manner. Stirring was continued at -70 °C for 1 h after which time freshly distilled methyl chloroformate (100 μL, 1.29 mmol) was added to the reaction mixture. Stirring was continued at -70 °C for 1 h then for a further 18 h at room temperature. The reaction mixture was then diluted with ether (20 mL) and water (20 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (silica, 30% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.35), the *title compound* ***141*** (80 mg, 68%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.69 (app d, *J ca.* 7.0 Hz, 2H), 7.28-7.23 (m, 2H), 7.06-6.94 (m, 4H), 6.73 (d, *J* 6.9 Hz, 1H), 5.47 (s, 2H), 4.93 (d, *J* 7.1 Hz, 1H), 4.15-4.10 (m, 2H), 3.78 (s, 3H, $-OCH_3$), 3.78-3.72 (m, 2H), 3.47 (s, 3H, $-OCH_3$).

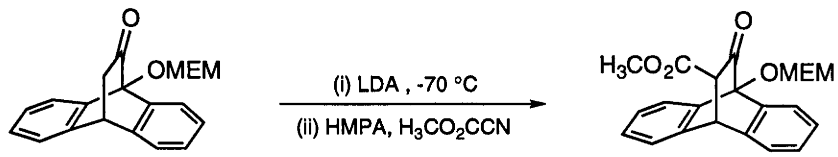
^{13}C NMR (75.4 MHz) δ 160.9 (C), 152.4 (C), 145.0 (C), 144.7 (C), 125.1 (CH), 124.7 (CH), 122.7 (CH), 120.7 (CH), 118.8 (CH), 94.5 (CH_2), 86.4 (C), 71.9 (CH_2), 68.3 (CH_2), 58.1 (CH_3), 55.4 (CH_3), 47.7 (CH).

IR (KBr) ν_{max} 2926, 1773, 1455, 1256, 1160, 1050 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 382 ($M^{+\cdot}$, 3%), 293 [$(M-C_4H_9O_2^{\cdot})^+$, 8], 282 [$(M-C_4H_4O_3)^{+\cdot}$, 6], 249 [$(M-C_4H_4O_3-CH_3OH-H\cdot)^+$, 100].

HRMS Found: $M^{+\cdot}$, 382.1434. $C_{22}H_{22}O_6$ requires $M^{+\cdot}$, 382.1416.

11-Carbomethoxy-9,10-dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-12-one (142)



132 **142**

n-BuLi (480 μL of a 2.5 M solution in hexanes, 1.26 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of diisopropylamine (164 μL, 1.26 mmol) in THF (4 mL) maintained under an atmosphere of nitrogen. After 15 mins, the reaction mixture was cooled to -70 °C (dry ice-acetone bath) then treated with a solution of ketone **132** (200 mg, 0.62 mmol) in THF (4 mL) in a dropwise fashion. Stirring was continued at -70 °C for 1 h after which time HMPA (220 μL, 1.26 mmol) then methyl cyanoformate (100 μL, 1.26 mmol) were added to the reaction mixture. Stirring was continued at -70 °C for a further 30 mins and then the reaction solution was partitioned between ether (40 mL) and water (40 mL). The separated aqueous layer was extracted with ether (4 x 10 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 30% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.30), the *title compound* ***142*** (172 mg, 73%) as a straw-coloured oil.

^{1}H NMR (300 MHz) δ 7.82 (m, 2H), 7.39 (m, 2H), 7.25 (m, 4H), 5.55 (d, *J* 11.1 Hz, 1H), 5.54 (d, *J* 11.1 Hz, 1H), 4.76 (d, *J* 2.5 Hz, 1H), 4.14 (m, 2H), 3.75 (m, 2H), 3.55 (s, 3H, -OCH_3), 3.47 (s, 3H, -OCH_3), 3.42 (d, *J* 2.6 Hz, 1H).

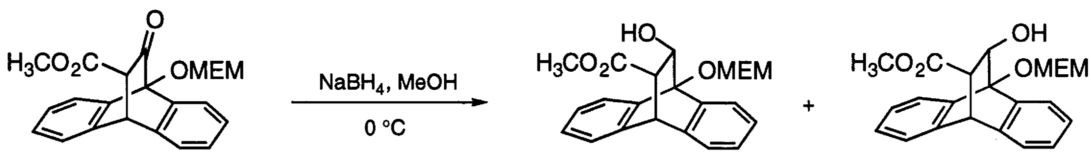
^{13}C NMR (75.4 MHz) δ 198.1 (C), 167.4 (C), 139.3 (C), 138.5 (C), 137.7 (C), 136.1 (C), 127.7 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 125.1 (CH), 123.9 (CH), 122.9 (CH), 122.7 (CH), 94.0 (CH_2), 90.6 (C), 71.8 (CH_2), 68.4 (CH_2), 59.0 (CH_3), 52.4 (CH_3), 51.7 (CH), 46.1 (CH).

IR (NaCl) ν_{max} 2920, 1758, 1730, 1460, 1250, 1158, 1052 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 382 ($M^{+\cdot}$, 1%), 354 [$(M-CO)^{+\cdot}$, 26], 307 [$(M-C_3H_7O_2^{\cdot})^+$, 21], 282 [$(M-CO-CHCO_2CH_3^{\cdot})^+$, 49].

HRMS Found: $M^{+\cdot}$, 382.1422. $C_{22}H_{22}O_6$ requires $M^{+\cdot}$, 382.1416.

Sodium Borohydride-Mediated Reduction of Compound 142. Formation of (11α,12α)-11-Carbomethoxy-9,10-dihydro-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-12-ol (147) and (11α,12β)-11-Carbomethoxy-9,10-dihydro-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-12-ol (148)



142 **147** **148**

$NaBH_4$ (24 mg, 0.60 mmol) was added in one portion to a chilled (ice-water bath) and magnetically stirred solution of ester **142** (115 mg, 0.30 mmol) in dry methanol (4 mL) maintained under a nitrogen atmosphere. Stirring was continued at 0 °C for 1.5 h after which time water (1 mL) was added (CAUTION ! Vigorous bubbling observed !) to the colourless reaction mixture. The mixture was then partitioned between ether (20 mL) and brine (20 mL) and the phases separated. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a straw-coloured oil. ^{1}H NMR spectroscopic analysis of this material indicated that it comprised of a 7:1 mixture of alcohols **147** and **148**. The crude material was subjected to flash chromatography (silica, 40% ethyl acetate/petrol elution) and furnished two chromophoric fractions, A (R_f 0.50) and B (R_f 0.25).

Concentration of fraction A provided the *title ester 147* (69 mg, 59%) as a colourless solid, m.p. 128-129 °C.

^{1}H NMR (300 MHz) δ 7.57 (m, 1H), 7.49 (m, 1H), 7.33-7.10 (complex m, 6H), 5.61 (d, *J* 7.6 Hz, 1H), 5.36 (d, *J* 7.6 Hz, 1H), 4.80 (dd, *J* 9.0 and 4.5 Hz, 1H), 4.42 (d, *J* 1.7 Hz, 1H), 4.33-4.26 (m, 1H), 4.10 (d, *J* 4.5 Hz, 1H), 3.84-3.77 (m, 1H), 3.65-3.63 (obscured m, 2H), 3.63 (s, 3H, $-OCH_3$), 3.33 (s, 3H, $-OCH_3$), 3.23 (dd, *J* 9.0 and 1.7 Hz, 1H).

^{13}C NMR (75.4 MHz) δ 171.1 (C), 143.3 (C), 140.4 (C), 140.1 (C), 138.2 (C), 126.5 (CH), 126.0 (CH), 125.7 (CH), 123.1 (CH), 122.0 (CH), 121.8 (CH), 91.6 (CH_2), 86.4 (C), 71.2 (CH_2), 69.5 (CH), 67.4 (CH_2), 58.8 (CH_3), 51.4 (CH/CH_3), 50.6 (CH/CH_3), 44.5 (CH).

IR (KBr) ν_{max} 3498, 2916, 1743, 1457, 1352, 1204, 1168, 1107, 1045 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 309 [$(M-C_3H_7O_2^{\cdot})^+$, <1%], 282 [$(M-C_4H_6O_3^{\cdot})^+$, 26], 194 [$(M-C_4H_6O_3-C_4H_8O_2^{\cdot})^+$, 32], 165 (21), 89 (100).

HRMS Found: $(M-C_3H_7O_2^{\cdot})^+$, 309.1118. $C_{19}H_{17}O_4$ requires $(M-C_3H_7O_2^{\cdot})^+$, 309.1127.

Elemental Analysis Found: C, 68.44; H, 6.34. $C_{22}H_{24}O_6$ requires: C, 68.74; H, 6.29%.

Concentration of fraction B provided the *title ester* ***148*** (11 mg, 9%) as a colourless foam.

^{1}H NMR (300 MHz) δ 7.61 (d, *J* 6.6 Hz, 1H), 7.33-7.07 (m, 7H), 5.64 (d, *J* 7.8 Hz, 1H), 5.31 (d, *J* 7.8 Hz, 1H), 4.74 (app t, *J ca.* 3.0 Hz, 1H, -OH), 4.54 (d, *J* 2.6 Hz, 1H), 4.36 (d, *J* 3.1 Hz, 1H), 4.35-4.26 (m, 1H), 3.88-3.80 (m, 1H), 3.65 (obscured m, 2H), 3.64 (s, 3H, -OCH_3), 3.35 (s, 3H, -OCH_3), 2.77 (app t, *J ca.* 2.8 Hz, 1H).

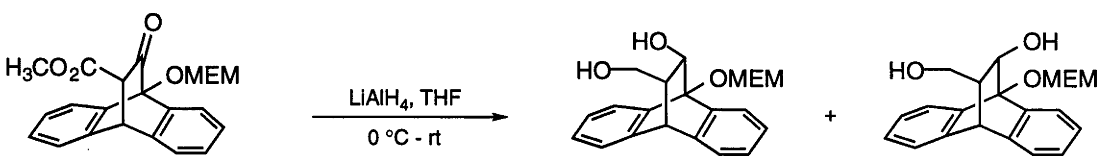
^{13}C NMR (75.4 MHz) δ 172.5 (C), 140.5 (C), 140.4 (C), 139.8 (C), 139.3 (C), 126.6 (CH), 126.34 (CH), 126.28 (CH), 126.0 (CH), 124.8 (CH), 123.1 (CH), 122.7 (CH), 121.2 (CH), 91.6 (CH_2), 86.6 (C), 71.6 (CH), 71.3 (CH_2), 68.0 (CH_2), 58.9 (CH_3), 54.2 (CH), 52.1 (CH_3), 45.4 (CH).

IR (KBr) ν_{max} 3480, 2929, 1736, 1458, 1201, 1136, 1068 cm^{-1}.

Mass Spectrum (CI) *m/z* 402 (MNH_4^+, 100%), 385 (MH^+, 77).

HRMS Found: MNH_4^+, 402.1902. $C_{22}H_{28}NO_6$ requires MNH_4^+, 402.1917.

Lithium Aluminium Hydride-Mediated Reduction of Compound 142. Formation of (11α,12α)-9,10-Dihydro-11-hydroxymethyl-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-12-ol (145) and (11α,12β)-9,10-Dihydro-11-hydroxymethyl-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-12-ol (146)



142 **145** **146**

$LiAlH_4$ powder (36 mg, 0.95 mmol) was added in one portion to a cold (ice-water bath) and magnetically stirred solution of ester **142** (91 mg, 0.24 mmol) in THF (2 mL) maintained under an atmosphere of nitrogen. Stirring was continued for 8.5 h during which time the reaction mixture was allowed to warm to room temperature. The suspension was then re-chilled (ice-water bath) and treated with water (1 mL), sodium sulphate (*ca.* 50 mg) and more water (*ca.* 2 mL). The ensuing precipitate was removed *via* filtration of the mixture through a Celite™ pad, which was washed with copious amounts of ether (*ca.* 50 mL total volume). The combined filtrates were transferred to a separating funnel containing brine (20 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 10 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 70% ethyl acetate/petrol elution) furnished two fractions, A (R_f 0.35) and B (R_f 0.20).

Concentration of fraction A afforded a colourless solid which was recrystallised (ethylene glycol dimethyl ether/hexane) to furnish the *title diol* ***145*** (30 mg, 35%) as colourless prisms, m.p. 112-113 °C.

^{1}H NMR (300 MHz) δ 7.64-7.58 (m, 1H), 7.30-7.10 (complex m, 7H), 5.62 (d, *J* 7.8 Hz, 1H), 5.32 (d, *J* 7.8 Hz, 1H), 4.56 (dd, *J* 9.0 and 2.9 Hz, 1H), 4.44 (d, *J* 3.1 Hz, 1H), 4.34-4.25 (m, 1H), 4.02 (d, *J* 1.8 Hz, 1H, -OH), 3.87-3.80 (m, 1H), 3.70-3.53 (complex m, 3H), 3.35 (obscured m, 1H), 3.34 (s, 3H, $-OCH_3$), 2.80 (br d, *J ca.* 7.0 Hz, 1H, -OH), 2.65-2.55 (complex m, 1H).

^{13}C NMR (75.4 MHz) δ 143.6 (C), 140.2 (C), 139.5 (C), 138.8 (C), 126.6 (CH), 126.0 (CH), 125.6 (CH), 124.3 (CH), 123.3 (CH), 122.5 (CH), 121.4 (CH), 91.6 (CH_2), 86.8 (C), 71.2 (CH_2), 69.9 (CH), 68.1 (CH_2), 64.0 (CH_2), 58.9 (CH_3), 45.7 (CH), 45.1 (CH).

IR (KBr) ν_{max} 3498, 3465, 2927, 1457, 1396, 1220, 1112, 1047 cm^{-1}.

Mass Spectrum (CI) *m/z* 357 (MH^+, 5%), 282 [$(M-C_3H_6O_2)^{+\cdot}$, 68], 251 (48), 194 (64), 89 (100).

HRMS Found: MH^+, 357.1688. $C_{21}H_{25}O_5$ requires MH^+, 357.1702.

Elemental Analysis Found: C, 70.44; H, 7.13. $C_{21}H_{24}O_5$ requires: C, 70.77; H, 6.79%.

Concentration of fraction B afforded the *title diol* **146** (9 mg, 11%) as a viscous, colourless oil.

^{1}H NMR (300 MHz) δ 7.60 (d, *J* 7.2 Hz, 1H), 7.32-7.10 (complex m, 7H), 5.58 (d, *J* 7.8 Hz, 1H), 5.31 (d, *J* 7.8 Hz, 1H), 4.34-4.24 (m, 3H), 3.86-3.80 (m, 2H), 3.70-3.60 (m, 3H), 3.35 (s, 3H, -OCH_3), 3.22 (br t, *J ca.* 9.0 Hz, 1H, -OH), 2.05-1.96 (m, 1H), 1.65 (br s, 1H, -OH).

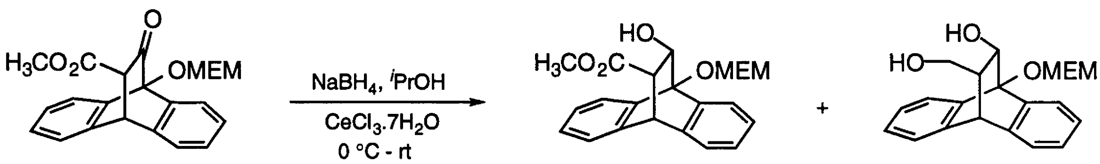
^{13}C NMR (75.4 MHz) δ 141.0 (C), 140.9 (C), 140.4 (C), 139.7 (C), 126.4 (CH), 126.2 (CH), 125.9 (CH), 125.7 (CH), 125.4 (CH), 123.0 (CH), 122.5 (CH), 121.1 (CH), 91.4 (CH_2), 86.9 (C), 72.2 (CH), 71.2 (CH_2), 68.0 (CH_2), 64.6 (CH_2), 58.9 (CH_3), 51.2 (CH), 44.4 (CH).

IR (KBr) ν_{max} 3474, 2927, 1457, 1334, 1213, 1131, 1042 cm^{-1}.

Mass Spectrum (CI) *m/z* 374 (MNH_4^+, <3%), 357 (MH^+, <3), 282 [$(M-C_3H_6O_2)^{+\cdot}$, 49], 251 (70), 194 (40), 89 (100).

HRMS Found: MH^+, 357.1711. $C_{21}H_{25}O_5$ requires MH^+, 357.1702.

Reduction of Compound 142 with the Luche Reagent. Formation of (11α,12α)-11-Carbomethoxy-9,10-dihydro-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-12-ol (147) and (11α,12α)-9,10-Dihydro-11-hydroxymethyl-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-12-ol (145)



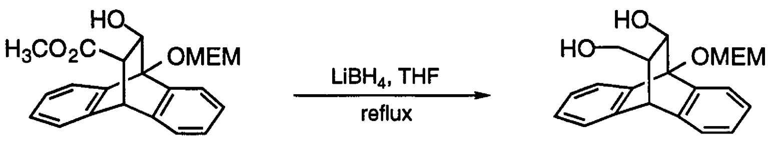
142 **147** **145**

$CeCl_3.7H_2O$ (1.00 g, 2.69 mmol) was added in one portion to a magnetically stirred solution of ketone **142** (856 mg, 2.24 mmol) in *iso*-propanol (18 mL). Stirring was continued at room temperature for 30 mins after which time, the reaction mixture was chilled (ice-water bath) and treated with $NaBH_4$ (170 mg, 4.48 mmol). Stirring was continued for 16 h during which time the reaction mixture was allowed to warm to room temperature. The resulting colourless suspension was transferred to a separating funnel containing ether (200 mL) and water (200 mL). The separated aqueous layer was extracted with ether (4 x 80 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to provide a pale-yellow oil. Subjection of this material to flash chromatography (silica, 40% ethyl acetate/petrol elution) afforded two fractions, A (R_f 0.50) and B (R_f 0.20).

Concentration of fraction A afforded the title compound **147** (636 mg, 74%) which was identical, by ^1H NMR spectroscopic analysis, with a sample obtained previously.

Concentration of fraction B afforded diol **145** (20 mg, <3%) which was identical, by ^1H NMR spectroscopic analysis, with a sample obtained previously.

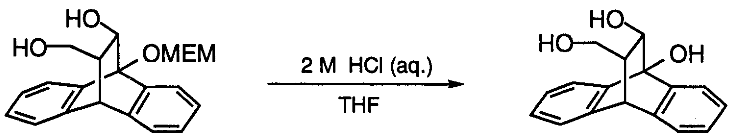
Lithium Borohydride-Mediated Reduction of Compound 147. Formation of (11α,12α)-9,10-Dihydro-11-hydroxymethyl-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-12-ol (145)



147 **145**

$LiBH_4$ (2.40 mL of a 2 M solution in THF, 4.77 mmol) was added to a magnetically stirred solution of ester **147** (610 mg, 1.59 mmol) in THF (18 mL) maintained under an atmosphere of nitrogen. The solution was heated at reflux for 13 h then cooled to room temperature and treated with NH_4Cl (*ca.* 5 mL of a saturated aqueous solution). The mixture thus obtained was partitioned between ether (200 mL) and brine (200 mL) and the separated aqueous layer was extracted with ether (4 x 50 mL). The combined ethereal fractions were dried, filtered and concentrated under reduced pressure to give a cloudy oil. Subjection of this material to flash chromatography (silica, 70% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.40), the title compound **145** (452 mg, 80%) which was identical, by ^{1}H NMR spectroscopic analysis, with a sample obtained previously.

(11α,12α)-9,10-Dihydro-11-hydroxymethyl-9,10-ethanoanthracene-9,12-diol (149)



145 **149**

A mixture of diol **145** (460 mg, 1.29 mmol), THF (5 mL) and HCl (5 mL of a 2 M aqueous solution) was stirred at room temperature for 22 h then concentrated under reduced pressure. The residue thus obtained was partitioned between ether (150 mL) and brine (150 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 50 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a colourless solid. Recrystallisation (THF/hexane) of this material afforded the *title compound* ***149*** (330 mg, 95%) as colourless needles, m.p. 175-177 °C.

^{1}H NMR (300 MHz, d_4-CD_3OD) δ 7.52 (m, 2H), 7.29 (d, *J* 7.1 Hz, 1H), 7.22 (d, *J* 7.8 Hz, 1H), 7.19-7.06 (m, 4H), 4.29 (d, *J* 1.8 Hz, 1H), 3.97 (d, *J* 8.8 Hz, 1H), 3.48 (dd, *J* 11.0 and 6.0 Hz, 1H), 3.02 (t, *J* 10.2 Hz, 1H), 2.30-2.20 (complex m, 1H).

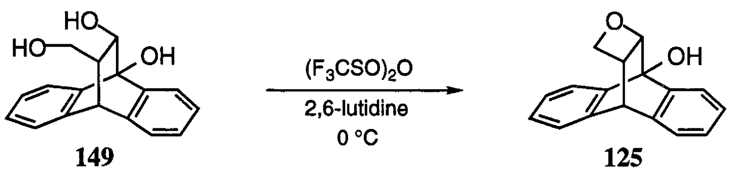
^{13}C NMR (75.4 MHz, d_4-CD_3OD) δ 144.0 (C), 143.9 (C), 142.8 (C), 140.5 (C), 127.3 (CH), 126.8 (CH), 126.7 (CH), 126.6 (CH), 125.7 (CH), 123.7 (CH), 123.4 (CH), 121.8 (CH), 80.7 (C), 75.1 (CH), 62.6 (CH_2), 46.9 (CH), 46.0 (CH).

IR (KBr) ν_{max} 3417, 3200 (broad sh), 2946, 1457, 1214, 1101, 1070, 1026 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 236 [(M-$CH_4O^{\cdot}$)$^+$, 3%], 194 [(M-$C_3H_6O_2^{\cdot}$)$^+$, 100], 178 (7), 165 (37).

HRMS Found: (M-$CH_4O^{\cdot}$)$^+$, 236.0830. $C_{16}H_{12}O_2$ requires (M-$CH_4O^{\cdot}$)$^+$, 236.0837.

9,10,13,14-Tetrahydro-11*H*-9,10[3',2']-*endo*-oxetoanthracen-10-ol (125)



Triflic anhydride (30 μL, 0.18 mmol) was added dropwise to a chilled (ice-water bath) and magnetically stirred solution of compound **149** (44 mg, 0.16 mmol) in 2,6-lutidine (500 μL) maintained under an atmosphere of nitrogen. The resulting purple-coloured reaction mixture was stirred at room temperature for 1.5 h then concentrated under reduced pressure. The red-brown residue thus obtained was subjected to flash chromatography (silica, 40% ethyl acetate/chloroform elution) and furnished, after concentration of the appropriate fractions (R_f 0.30), a colourless solid. Recrystallisation (ethylene glycol dimethyl ether/petrol) of this material gave the *title compound 125* (28 mg, 67%) as colourless needles, m.p. 189-191 °C.

^{1}H NMR (300 MHz) δ 7.63 (d, *J* 8.6 Hz, 1H), 7.59 (d, *J* 7.0 Hz, 1H), 7.40-7.12 (complex m, 6H), 4.78 (d, *J* 7.7 Hz, 1H), 4.50 (app t, *J ca.* 6.4 Hz, 1H), 4.31 (d, *J* 4.3 Hz, 1H), 3.72 (br s, 1H, -OH), 3.53 (app t, *J ca.* 6.4 Hz, 1H), 3.33-3.25 (m, 1H).

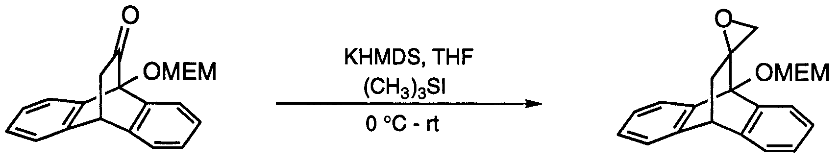
^{13}C NMR (75.4 MHz, d_8-THF) δ 144.4 (C), 142.6 (C), 142.1 (C), 139.6 (C), 126.8 (CH), 126.49 (CH), 126.46 (CH), 126.3 (CH), 125.4 (CH), 123.7 (CH), 123.5 (CH), 122.6 (CH), 87.7 (CH), 80.7 (C), 70.3 (CH_2), 46.3 (CH), 40.2 (CH).

IR (KBr) ν_{max} 3384, 2918, 1456, 1316, 1244, 1184, 1028, 989 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 250 ($M^{+\cdot}$, 6%), 231 [$(M-H_2O-H\cdot)^{+\cdot}$, 7], 194 [$(M-C_3H_4O)^{+\cdot}$, 100], 165 (44).

HRMS Found: $M^{+\cdot}$, 250.0991. $C_{17}H_{14}O_2$ requires $M^{+\cdot}$, 250.0994.

Spiro[9,10-Dihydro-10-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-11,2'-oxirane] (150)



132 **150**

KHMDS (3.2 mL of a 0.5 M solution in toluene, 1.60 mmol) was added, dropwise over 15 mins, to a chilled (ice-water bath) and magnetically stirred suspension of $(CH_3)_3SI$[5] (377 mg, 1.85 mmol) in THF (2 mL) maintained under an atmosphere of nitrogen. Stirring was continued at 0 °C for 1 h and then a solution of ketone **132** (200 mg, 0.62 mmol) in THF (2 mL) was added dropwise, over 15 mins, to the reaction mixture. The resulting red suspension was stirred at room temperature for 1 h after which time the reaction was quenched by the addition of water (*ca.* 5 mL). Concentration of the crude mixture under reduced pressure gave a yellow residue which was partitioned between ether (40 mL) and brine (40 mL). The separated aqueous layer was extracted with ether (4 x 10 mL) and the combined ethereal fractions were dried, filtered and concentrated to give a gold-coloured oil. This unstable material was used in the next reaction without further purification. Compound **150** could, however, be purified for the purposes of characterisation by subjection of the crude material to flash chromatography (silica, 30% ethyl acetate/petrol elution). Concentration of the appropriate fractions (R_f 0.40) afforded the *title compound* ***150*** (163 mg, 78%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.78-7.70 (m, 2H), 7.38-7.32 (m, 1H), 7.30-7.26 (m, 1H), 7.25-7.12 (complex m, 4H), 5.52 (d, *J* 6.5 Hz, 1H), 5.32 (d, *J* 6.5 Hz, 1H), 4.27 (t, *J*

2.7 Hz, 1H), 4.20-4.10 (m, 1H), 4.00-3.92 (m, 1H), 3.80-3.66 (complex m, 2H), 3.46 (s, 3H, $-OCH_3$), 3.25 (d, *J* 5.2 Hz, 1H), 2.58 (d, *J* 5.3 Hz, 1H), 2.25 (dd, *J* 13.1 and 2.9 Hz, 1H), 1.90 (dd, *J* 13.1 and 2.6 Hz, 1H).

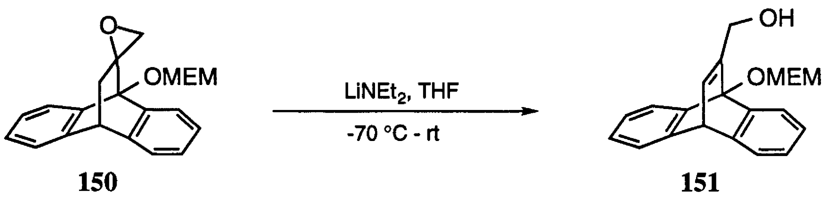
^{13}C NMR (75.4 MHz) δ 142.4 (C), 140.8 (C), 139.6 (C), 126.5 (CH), 126.1 (CH), 125.9 (CH), 123.5 (CH), 123.1 (CH), 122.8 (CH), 121.9 (CH), 93.0 (CH_2), 82.0 (C), 71.8 (CH_2), 67.9 (CH_2), 64.5 (C), 59.0 (CH_3), 50.5 (CH_2), 42.9 (CH), 36.2 (CH_2).

IR (KBr) ν_{max} 2929, 2880, 1457, 1248, 1108, 1053 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 338 ($M^{+\cdot}$, <1%), 282 [$(M-C_3H_4O)^{+\cdot}$, 78], 231 [$(M-C_4H_{11}O_3^{\cdot})^+$, 31], 194 [$(M-C_3H_4O-C_4H_8O_2^{\cdot})^+$, 51].

HRMS Found: $M^{+\cdot}$, 338.1507. $C_{21}H_{22}O_4$ requires $M^{+\cdot}$, 338.1518.

9,10-Dihydro-12-hydroxymethyl-9-[(2'-methoxyethoxy)methoxy]-9,10-ethenoanthracene (151)



n-BuLi (4.6 mL of a 2.6 M solution in hexanes, 12.0 mmol) was added dropwise to a magnetically stirred solution of diethylamine (1.25 mL, 12.0 mmol) in THF (75 mL) maintained under an atmosphere of nitrogen. The resulting yellow solution was cooled to -70 °C (dry ice-acetone bath) to which a solution of epoxide **150** (507 mg, 1.5 mmol) in THF (8 mL) was added. The reaction mixture was stirred at -70 °C for 2.5 h then warmed to room temperature over a period of 1.5 h. The reaction was quenched by the addition of water (*ca.* 10 mL) and the crude reaction mixture was then concentrated under reduced pressure. The orange residue thus obtained was partitioned between ether (200 mL) and brine (200 mL) and the phases separated. The aqueous layer was extracted with ether (3 x 40 mL) and the combined ethereal layers were dried, filtered and concentrated under reduced pressure to afford an orange oil. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/chloroform elution) furnished, after concentration of the appropriate fractions (R_f 0.40), the *allylic alcohol* ***151*** (292 mg, 58%) as a clear, straw-coloured oil.

^{1}**H NMR** (300 MHz) δ 7.64 (app d, *J ca.* 7.0 Hz, 2H), 7.28 (app d, *J ca.* 7.0 Hz, 2H), 7.05-6.96 (m, 4H), 6.78 (d, *J* 6.0 Hz, 1H), 5.62 (s, 2H), 4.98 (d, *J* 6.1 Hz, 1H), 4.37 (br s, 2H), 4.17-4.12 (m, 2H), 3.80-3.74 (m, 2H), 3.45 (s, 3H, $-OCH_3$), 2.83 (br s, 1H, -OH).

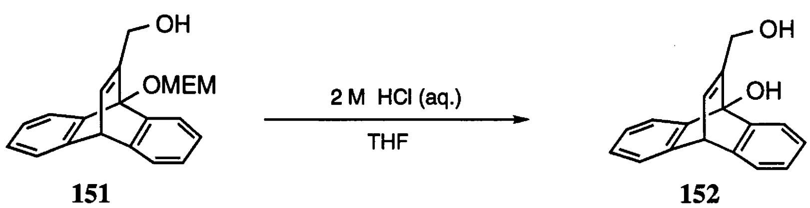
^{13}**C NMR** (75.4 MHz) δ 152.4 (C), 145.4 (C), 144.4 (C), 134.8 (CH), 124.9 (CH), 124.4 (CH), 122.8 (CH), 120.5 (CH), 94.0 (CH_2), 90.9 (C), 71.8 (CH_2), 68.5 (CH_2), 61.0 (CH_2), 59.0 (CH_3), 49.7 (CH).

IR (KBr) ν_{max} 3420, 2880, 1456, 1222, 1186, 1104, 1052, 998 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 262 [$(M-C_3H_8O_2)^{+\cdot}$, 7%], 249 [$(M-C_4H_9O_2^{\cdot})^+$, 3], 232 [$(M-C_4H_{10}O_3)^{+\cdot}$, 100], 203 (56), 194 [$(M-C_3H_4O-C_4H_8O_2^{\cdot})^+$, 20].

HRMS Found: $(M-C_3H_8O_2)^{+\cdot}$, 262.0995. $C_{18}H_{14}O_2$ requires $(M-C_3H_8O_2)^{+\cdot}$, 262.0994.

9,10-Dihydro-9-hydroxy-12-hydroxymethyl-9,10-ethenoanthracene (152)



A mixture of compound **151** (517 mg, 1.53 mmol), THF (10 mL) and HCl (10 mL of a 2 M aqueous solution) was stirred at room temperature for 16 h then concentrated under reduced pressure. The residue thus obtained was partitioned between ether (100 mL) and brine (100 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 50 mL) and the combined ethereal layers were dried, filtered and concentrated under reduced pressure to give a cream-coloured foam. Subjection of this material to flash chromatography (silica, 50% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.50), the *title diol* ***152*** (376 mg, 98%) as a colourless foam.

^{1}H NMR (300 MHz) δ 7.53 (d, *J* 7.1 Hz, 2H), 7.26 (d, *J* 8.5 Hz, 2H), 7.07-6.94 (m, 4H), 6.73 (d, *J* 6.1 Hz, 1H), 5.03 (d, *J* 6.0 Hz, 1H), 4.67 (br s, 1H), 4.41 (br s, 2H), 1.80 (br s, 1H).

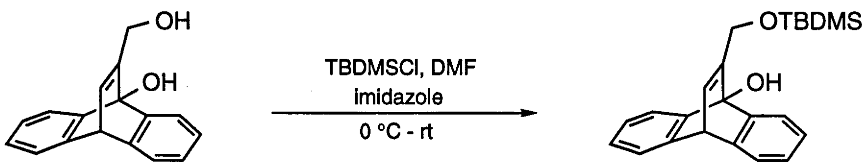
^{13}C NMR (75.4 MHz) δ 151.3 (C), 147.1 (C), 143.8 (C), 134.4 (CH), 124.7 (CH), 124.6 (CH), 122.5 (CH), 119.1 (CH), 83.2 (C), 61.8 (CH_2), 49.3 (CH).

IR (KBr) ν_{max} 3385, 3066, 2970, 1643, 1454, 1249, 1224, 1173, 1068, 985 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 250 ($M^{+\cdot}$, 16%), 232 [$(M-H_2O)^{+\cdot}$, 100], 203 [$(M-CH_3O_2^{\cdot})^+$, 66], 194 [$(M-C_3H_4O)^{+\cdot}$, 80].

HRMS Found: $M^{+\cdot}$, 250.0992. $C_{17}H_{14}O_2$ requires $M^{+\cdot}$, 250.0994.

12-(*tert*-Butyldimethylsilyloxymethyl)-9,10-dihydro-9-hydroxy-9,10-ethenoanthracene (153)



152 **153**

tert-Butyldimethylsilyl chloride (219 mg, 1.45 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of diol **152** (327 mg, 1.31 mmol) and imidazole (223 mg, 3.28 mmol) in DMF (15 mL). The resulting mixture was stirred at ambient temperatures for 13 h after which time the clear solution was transferred to a separating funnel containing ether (100 mL) and brine (100 mL). The separated aqueous layer was extracted with ether (4 x 50 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 5% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.30), the *title compound* ***153*** (339 mg, 71%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.55 (dd, *J* 7.3 and 1.1 Hz, 2H), 7.24 (dd, *J* 6.9 and 1.6 Hz, 2H), 7.05-6.92 (m, 4H), 6.62 (dt, *J* 6.0 and 1.3 Hz, 1H), 5.28 (br s, 1H, -OH), 4.99 (d, *J* 6.0 Hz, 1H), 4.45 (d, *J* 1.1 Hz, 1H), 0.85 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), -0.10 (s, 6H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

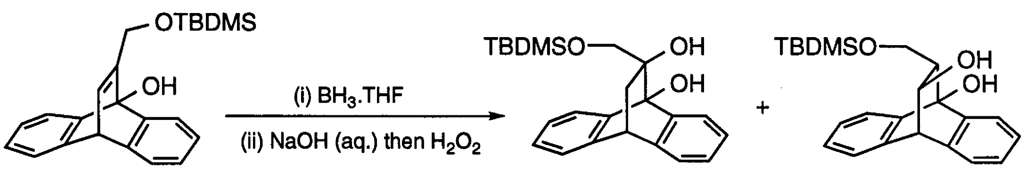
^{13}C NMR (75.4 MHz) δ 151.2 (C), 147.4 (C), 143.8 (C), 132.9 (CH), 124.5 (CH), 124.4 (CH), 122.3 (CH), 119.4 (CH), 83.2 (C), 62.8 (CH_2), 49.3 (CH), 25.7 (CH_3), 18.0 (C), -5.6 (CH_3).

IR (NaCl) ν_{max} 3470, 2930, 2860, 1645, 1450, 1362, 1254, 1172 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 364 ($M^{+\cdot}$, 1%), 349 [$(M-H_3C\cdot)^+$, 3], 307 [$(M-H_9C_4\cdot)^+$, 100], 231 [$(M-C_6H_{17}SiO\cdot)^+$, 51], 194 [$(M-C_9H_{18}OSi)^{+\cdot}$, 50].

HRMS Found: $M^{+\cdot}$, 364.1855. $C_{23}H_{28}O_2Si$ requires $M^{+\cdot}$, 364.1859.

12-(*tert*-Butyldimethylsilyloxymethyl)-9,10-dihydro-9,10-ethanoanthracene-9,12-diol (154) and 12-(*tert*-Butyldimethylsilyloxymethyl)-(11β,12α)-9,10-dihydro-9,10-ethanoanthracene-9,11-diol (155)



153 154 155

BH_3.THF complex (1.75 mL of a 1 M solution in THF, 1.75 mmol) was added dropwise to a magnetically stirred solution of alkene **153** (157 mg, 0.43 mmol) in THF (2 mL) maintained under an atmosphere of nitrogen. Stirring was continued at room temperature for 1.5 h then water (160 μL), NaOH (190 μL of a 3 M aqueous solution) and H_2O_2 (200 μL of a 30% (v/v) aqueous solution) were added, in that order, to the colourless reaction solution. After stirring at room temperature for a further 1 h, the reaction mixture was partitioned between ether (50 mL) and brine (50 mL). The separated aqueous layer was extracted with ether (3 x 20 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) afforded two fractions, A (R_f 0.50) and B (R_f 0.20).

Concentration of fraction A furnished *diol **154*** (13 mg, 8%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.62 (d, *J* 6.9 Hz, 1H), 7.59 (d, *J* 7.0 Hz, 1H), 7.27-7.10 (complex m, 6H), 5.32 (br s, 1H), 4.20 (t, *J* 2.6 Hz, 1H), 3.49 (d, *J* 10.0 Hz, 1H), 3.14 (d, *J* 10.3 Hz, 1H), 1.82 (dd, *J* 13.1 and 2.6 Hz, 1H), 1.56 (dd, *J* 13.1 and 2.9 Hz, 1H), 0.95 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.07 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.04 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 143.0 (C), 141.4 (C), 141.1 (C), 140.8 (C), 126.4 (CH), 126.3 (CH), 125.9 (CH), 123.0 (CH), 122.6 (CH), 122.3 (CH), 120.6 (CH), 82.9 (C), 75.7 (C/CH_2), 70.7 (C/CH_2), 42.6 (CH), 40.9 (CH_2), 25.8 (CH_3), 18.1 (C), -5.7 (CH_3), -5.8 (CH_3).

IR (KBr) ν_{max} 3437, 2929, 2858, 1459, 1255, 1112, 1076, 1055 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 349 [$(M-H_2O-H_3C\cdot)^+$, <2%], 307 [$(M-H_2O-H_9C_4\cdot)^+$, 26], 194 [$(M-C_9H_{20}O_2Si)^{+\cdot}$, 100], 165 (23).

HRMS Found: $(M-H_2O-H_3C\cdot)^+$, 349.1616. $C_{22}H_{25}O_2Si$ requires $(M-H_2O-H_3C\cdot)^+$, 349.1624.

Concentration of fraction B afforded the *title diol **155*** (100 mg, 61%) as a straw-coloured oil.

^{1}H NMR (300 MHz) δ 7.70 (d, *J* 7.1 Hz, 1H), 7.62 (d, *J* 7.7 Hz, 1H), 7.36-7.10 (complex m, 6H), 5.68 (br s, 1H, -OH), 4.24 (d, *J* 3.2 Hz, 1H), 3.88 (dd, *J* 10.1 and 4.4 Hz, 1H), 3.34 (app t, *J ca.* 3.0 Hz, 1H), 2.98 (dd, *J* 11.5 and 1.4 Hz, 1H), 1.44 (br s, 1H, -OH), 1.90 (dt, *J* 11.5 and 3.6 Hz, 1H), 0.94 (s, 9H, -$(CH_3)_2SiC(CH_3)_3$), 0.06 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.05 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

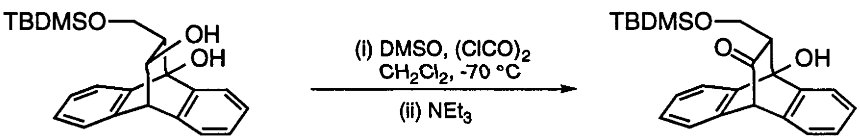
^{13}**C NMR** (75.4 MHz) δ 144.9 (C), 142.9 (C), 137.3 (C), 136.4 (C), 126.8 (CH), 126.4 (CH), 126.3 (CH), 126.0 (CH), 125.8 (CH), 124.2 (CH), 122.0 (CH), 120.8 (CH), 79.2 (C), 73.3 (CH), 66.1 (CH_2), 54.1 (CH), 51.3 (CH), 25.7 (CH_3), 18.0 (C), -5.7 (CH_3), -5.8 (CH_3).

IR (KBr) ν_{max} 3443, 3330, 2950, 2857, 1459, 1265, 1240, 1077, 1032, 835 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 349 [$(M-H_2O-H_3C\cdot)^+$, <1%], 325 [$(M-H_9C_4\cdot)^+$, 5], 307 [$(M-H_2O-H_9C_4\cdot)^+$, 11], 194 [$(M-C_9H_{20}O_2Si)^{+\cdot}$, 100].

HRMS Found: $(M-H_9C_4\cdot)^+$, 325.1255. $C_{19}H_{21}O_3Si$ requires $(M-H_9C_4\cdot)^+$, 325.1260.

12-(*tert*-Butyldimethylsilyloxymethyl)-9,10-dihydro-9-hydroxy-9,10-ethanoanthracen-11-one (157)



155 157

DMSO (76 μL, 1.07 mmol) was added dropwise to a chilled (dry ice-acetone bath) and magnetically stirred solution of oxalyl chloride (45 μL, 0.52 mmol) in dichloromethane (3 mL) maintained under a nitrogen atmosphere. Stirring was continued at -70 °C for 40 mins after which time a solution of alcohol **155** (142 mg, 0.37 mmol) in dichloromethane (1 mL) was added to the colourless solution. After stirring at -70 °C for 1 h, the reaction mixture was treated with triethylamine (134 μL, 0.96 mmol). Stirring was continued at -70 °C for 10 mins, then the mixture was warmed to room temperature (over a period of 15 mins). The resulting pale-yellow solution was partitioned between $NaHCO_3$ (80 mL of a saturated aqueous solution) and dichloromethane (80 mL). The separated aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions were washed with water (2 x 50 mL) then brine (2 x 50 mL), before being dried, filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 10% ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.50), the *title ketone* ***157*** (140 mg, 99%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.73 (d, *J* 7.8 Hz, 2H), 7.38-7.30 (complex m, 4H), 7.25-7.18 (m, 2H), 5.68 (s, 1H), 4.76 (s, 1H), 3.95 (dd, *J* 10.3 and 4.5 Hz, 1H), 3.11 (t, *J* 10.7 Hz, 1H), 2.72 (dd, *J* 11.1 and 4.6 Hz, 1H), 0.94 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.06 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.04 (s, 3H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

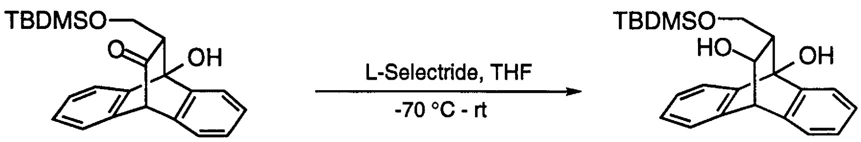
^{13}C NMR (75.4 MHz) δ 201.4 (C), 144.1 (C), 142.5 (C), 133.7 (C), 133.6 (C), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 124.7 (CH), 124.6 (CH), 122.3 (CH), 121.1 (CH), 79.3 (C), 65.3 (CH_2), 61.9 (CH), 51.7 (CH), 25.7 (CH_3), 18.0 (C), -5.7 (CH_3), -5.8 (CH_3).

IR (NaCl) ν_{max} 3440, 2950, 2858, 1730, 1460, 1255, 1060, 835 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 323 [$(M-H_9C_4\cdot)^+$, 30%], 231 [$(M-H_2O-C_6H_{15}SiO\cdot)^+$, 9], 194 [$(M-C_9H_{18}O_2Si)^{+\cdot}$, 100].

HRMS Found: $(M-H_9C_4\cdot)^+$, 323.1101. $C_{19}H_{19}O_3Si$ requires $(M-H_9C_4\cdot)^+$, 323.1103.

12-(*tert*-Butyldimethylsilyloxymethyl)-(11α,12α)-9,10-dihydro-9,10-ethanoanthracene-9,11-diol (156)



157 156

L-Selectride (1.5 mL of a 1 M solution in THF, 1.50 mmol) was added dropwise to a magnetically stirred solution of ketone **157** (112 mg, 0.29 mmol) in THF (3.5 mL) maintained at -70 °C (dry ice-acetone bath) under a nitrogen atmosphere. The cold bath was removed and stirring was continued at room temperature for a further 5 h. The reaction mixture was then treated with HCl (*ca.* 2 mL of a 10% (v/v) aqueous solution) and partitioned between dichloromethane (80 mL) and brine (80 mL). The separated aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were dried, filtered and concentrated under reduced pressure to afford a cloudy oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.40), the *title compound* ***156*** (48 mg, 43%) as a colourless, crystalline solid, m.p. 149-151 °C.

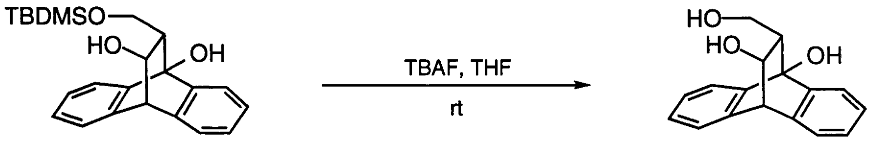
^{1}H NMR (300 MHz) δ 7.69 (d, *J* 7.2 Hz, 1H), 7.59 (d, *J* 7.2 Hz, 1H), 7.34-7.10 (m, 6H), 5.58 (s, 1H), 4.32 (td, *J* 8.5 and 3.2 Hz, 1H), 4.27 (d, *J* 3.3 Hz, 1H), 3.79 (dd, *J* 10.7 and 4.9 Hz, 1H), 3.22 (t, *J* 10.6 Hz, 1H), 2.32 (app dd, *J* 10.3 and 4.8 Hz, 1H), 1.45 (d, *J* 8.2 Hz, 1H), 0.92 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), 0.06 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$), 0.05 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 145.3 (C), 143.1 (C), 137.2 (C), 137.0 (C), 126.6 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 125.7 (CH), 124.0 (CH), 122.0 (CH), 120.2 (CH), 79.0 (C), 71.1 (CH), 63.6 (CH_2), 51.5 (CH), 46.8 (CH), 25.8 (CH_3), 18.0 (C), -5.6 (CH_3), -5.7 (CH_3).

Mass Spectrum (70 eV) *m/z* 325 [$(M-H_9C_4\cdot)^+$, 4%], 307 [$(M-H_2O-H_9C_4\cdot)^+$, 8], 251 [$(M-C_6H_{15}SiO\cdot)^+$, 1], 194 [$(M-C_9H_{20}O_2Si)^{+\cdot}$, 100].

HRMS Found: $(M-H_9C_4\cdot)^+$, 325.1261. $C_{19}H_{21}O_3Si$ requires $(M-H_9C_4\cdot)^+$, 325.1260.

(11α,12α)-9,10-Dihydro-12-(hydroxymethyl)-9,10-ethanoanthracene-9,11-diol (158)



156 **158**

A magnetically stirred solution of compound **156** (48 mg, 0.13 mmol) and tetra-*n*-butylammonium fluoride (190 μL of a 1 M solution in THF, 0.19 mmol) in THF (1 mL) was stirred at room temperature for 5 mins. The resulting pink solution was then diluted with ether (20 mL) and brine (20 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 10 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to provide a colourless solid. Recrystallisation (THF/hexane) of this material furnished the *title compound **158*** (30 mg, 90%) as colourless prisms, m.p. 272-274 °C.

^{1}H NMR (300 MHz, d_4-CD_3OD) δ 7.52 (dd, *J* 8.7 and 1.5 Hz, 1H), 7.45 (dd, *J* 7.3 and 1.4 Hz, 1H), 7.32-7.25 (m, 2H), 7.22-7.07 (complex m, 4H), 4.27-4.21 (m, 2H), 3.49 (dd, *J* 11.0 and 7.6 Hz, 1H), 3.38 (dd, *J* 11.0 and 7.1 Hz, 1H), 2.25 (dd, *J* 15.7 and 7.4 Hz, 1H).

^{13}C NMR (75.4 MHz, d_8-THF) δ 147.5 (C), 144.3 (C), 139.8 (C), 139.8 (C), 126.5 (CH), 126.3 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 124.4 (CH), 121.9 (CH), 120.7 (CH), 79.2 (C), 72.0 (CH_2), 62.5 (CH), 53.0 (CH), 48.9 (CH).

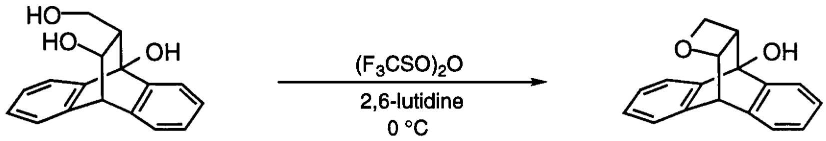
IR (KBr) ν_{max} 3602, 3456, 3218, 2920, 1460, 1386, 1235, 1192, 1062, 1032 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 250 [$(M-H_2O)^{+\cdot}$, 3%], 231 [$(M-2H_2O-H\cdot)^{+}$, 4], 219 [$(M-H_2O-CH_2OH^{\cdot})^{+}$, <3], 194 [$(M-C_3H_6O_2)^{+\cdot}$, 100].

HRMS Found: $(M-H_2O)^{+\cdot}$, 250.0993. $C_{17}H_{14}O_2$ requires $(M-H_2O)^{+\cdot}$, 250.0994.

Elemental Analysis Found: C, 76.38; H, 6.36. $C_{17}H_{16}O_3$ requires: C, 76.10; H, 6.01%.

9,10,13,14-Tetrahydro-11*H*-9,10[3',2']-*endo*-oxetoanthracen-9-ol (126)



Triflic anhydride (25 µL, 0.15 mmol) was added dropwise to a chilled (ice-water bath) and magnetically stirred solution of compound **158** (30 mg, 0.11 mmol) in 2,6-lutidine (500 µL) maintained under a nitrogen atmosphere. The resulting red-coloured reaction mixture was stirred at room temperature for 2 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10% THF/chloroform elution) which provided two fractions, A (R_f 0.40) and B (R_f 0.10).

Concentration of fraction A afforded a colourless solid which was recrystallised (THF/hexane) to give the *title oxetane* ***126*** (12 mg, 75% at 57% conversion) as colourless needles, m.p. 202-204 °C.

^{1}H NMR (300 MHz) δ 7.60 (d, *J* 7.3 Hz, 1H), 7.48 (d, *J* 7.3 Hz, 1H), 7.43 (d, *J* 7.3 Hz, 1H), 7.35-7.13 (complex m, 5H), 5.02 (dd, *J* 7.7 and 4.5 Hz, 1H), 4.54 (d, *J* 4.6 Hz, 1H), 4.45 (t, *J* 6.8 Hz, 1H), 3.58 (dd, *J* 6.5 and 5.0 Hz, 1H), 3.12-3.05 (m, 1H), 2.73 (br s, 1H, -OH).

^{13}C NMR (75.4 MHz, d_8-THF) δ 146.5 (C), 143.6 (C), 140.3 (C), 138.2 (C), 126.8 (CH), 126.6 (CH), 126.57 (CH), 126.4 (CH), 126.2 (CH), 125.5 (CH), 122.3 (CH), 120.8 (CH), 83.4 (CH), 78.0 (C), 70.0 (CH_2), 50.8 (CH), 44.7 (CH).

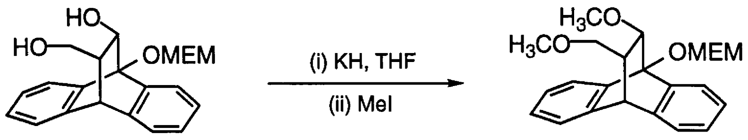
IR (KBr) ν_{max} 3296, 3330 (broad sh), 2950, 1457, 1309, 1236, 1134, 1062 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 250 ($M^{+\cdot}$, 2%), 231 [$(M-H_2O-H\cdot)^+$, 2], 221 [$(M-CHO^\cdot)^+$, 6], 194 [$(M-C_3H_4O)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 250.0995. $C_{17}H_{14}O_2$ requires $M^{+\cdot}$, 250.0994.

Concentration of fraction B afforded the starting triol **158** (13 mg, 43% recovery) which was identical, by ^{1}H NMR spectroscopic analysis, with an authentic sample.

(11α,12α)-9,10-Dihydro-12-methoxy-9-[(2'-methoxyethoxy) methoxy]-11-methoxymethyl-9,10-ethanoanthracene (159)



145 159

Potassium hydride (115 mg, 2.88 mmol) was added in one portion to a magnetically stirred solution of diol **145** (200 mg, 0.56 mmol) in THF (9 mL) maintained under a nitrogen atmosphere. Stirring was continued at room temperature for 1 h then methyl iodide (175 μL, 2.81 mmol) was added dropwise to the now bright orange reaction mixture. Stirring was continued for a further 3 h after which time the suspension was cooled (ice-water bath) and treated with ethanol/water (*ca.* 10 mL of a 1:1 (v/v) mixture). The reaction mixture was concentrated under reduced pressure and the residue thus obtained was partitioned between dichloromethane (40 mL) and brine (40 mL). The separated aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 10% ethyl acetate/chloroform elution) afforded, after concentration of the appropriate fractions (R_f 0.20), the *title compound **159*** (140 mg, 65%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.60 (dd, *J* 7.3 and 1.4 Hz, 1H), 7.54 (dd, *J* 7.2 and 1.6 Hz, 1H), 7.30-7.09 (complex m, 6H), 5.51 (d, *J* 6.4 Hz, 1H), 5.41 (d, *J* 6.4 Hz, 1H), 4.25 (d, *J* 2.8 Hz, 1H), 4.10-4.05 (m, 2H), 3.72-3.68 (m, 2H), 3.44 (s, 3H, -OCH_3), 3.30 (obscured m, 1H), 3.29 (s, 3H, -OCH_3), 3.26 (s, 3H, -OCH_3), 3.13 (dd, *J* 9.3 and 6.4 Hz, 1H), 2.81 (t, *J* 9.4 Hz, 1H), 2.18-2.10 (m, 1H).

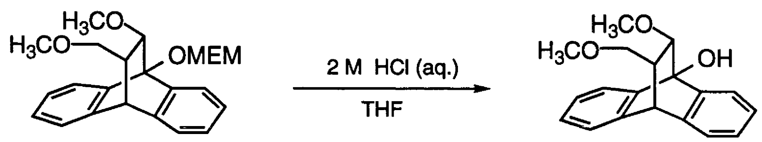
^{13}C NMR (75.4 MHz) δ 140.93 (C), 140.90 (C), 140.3 (C), 139.9 (C), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 124.7 (CH), 123.3 (CH), 122.2 (CH), 122.1 (CH), 92.0 (CH_2), 84.5 (C), 82.8 (CH), 75.3 (CH_2), 71.8 (CH_2), 67.6 (CH_2), 59.0 (CH_3), 58.8 (CH_3), 56.9 (CH_3), 47.2 (CH), 44.6 (CH).

IR (NaCl) ν_{max} 2920, 2870, 1458, 1105, 1050, 1022, 768, 752 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 309 [$(M-C_3H_7O_2^{\cdot})^+$, 1%], 282 [$(M-C_5H_{10}O_2)^{+\cdot}$, 42], 194 [$(M-C_5H_{10}O_2-C_4H_8O_2^{\cdot})^+$, 32], 165 (19), 89 (100).

HRMS Found: $(M-C_3H_7O_2^{\cdot})^+$, 309.1493. $C_{20}H_{21}O_3$ requires $(M-C_3H_7O_2^{\cdot})^+$, 309.1491.

(11α,12α)-9,10-Dihydro-12-methoxy-11-methoxymethyl-9,10-ethano anthracen-9-ol (127)



159 127

A mixture of compound **159** (130 mg, 0.34 mmol), THF (5 mL) and HCl (5 mL of a 2 M aqueous solution) was stirred at room temperature for 16 h then concentrated under reduced pressure. The residue thus obtained was partitioned between ether (30 mL) and brine (30 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a colourless solid. Recrystallisation (chloroform/hexane) of this material furnished the *title alcohol **127*** (91 mg, 91%) as colourless prisms, m.p. 154-155 °C.

^{1}H NMR (300 MHz) δ 7.60 (dd, *J* 8.5 and 1.6 Hz, 1H), 7.53 (dd, *J* 8.7 and 1.5 Hz, 1H), 7.30-7.10 (complex m, 6H), 4.28 (d, *J* 2.5 Hz, 1H), 3.59 (br s, 1H, -OH), 3.31 (s, 6H, 2 x $-OCH_3$), 3.13 (dd, *J* 9.3 and 6.5 Hz, 1H), 2.97 (d, *J* 2.8 Hz, 1H), 2.90 (t, *J* 9.3 Hz, 1H), 2.11-2.03 (m, 1H).

^{13}C NMR (75.4 MHz) δ 141.8 (C), 140.7 (C), 140.4 (C), 139.5 (C), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.9 (CH), 124.6 (CH), 123.0 (CH), 121.5 (CH), 120.6

(CH), 86.3 (CH), 78.6 (C), 75.4 (CH_2), 58.8 (CH_3), 57.8 (CH_3), 46.1 (CH), 44.5 (CH).

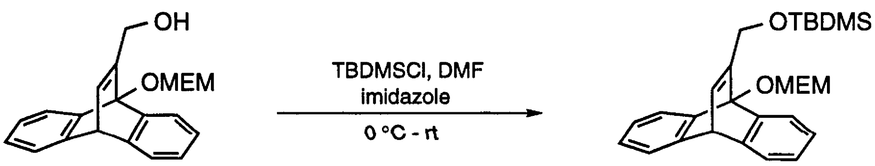
IR (KBr) ν_{max} 3558, 2987, 2882, 1457, 1179, 1127, 1095, 768 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 296 ($M^{+\cdot}$, <1%), 279 [$(M-HO\cdot)^+$, <1], 264 [$(M-CH_3OH)^{+\cdot}$, <1], 219 [$(M-CH_3OH-C_2H_5O\cdot)^+$, 1], 194 [$(M-C_5H_{10}O_2)^{+\cdot}$, 100].

HRMS Found: $(M-CH_3OH)^{+\cdot}$, 264.1155. $C_{18}H_{16}O_2$ requires $(M-CH_3OH)^{+\cdot}$, 264.1150.

Elemental Analysis Found: C, 76.62; H, 6.92. $C_{19}H_{20}O_3$ requires: C, 77.00; H, 6.80%.

12-(*tert*-Butyldimethysilyloxymethyl)-9,10-dihydro-9-[(2'-methoxy ethoxy)methoxy]-9,10-ethenoanthracene (160)



151 **160**

tert-Butyldimethylsilyl chloride (538 mg, 3.57 mmol) was added to a chilled (ice-water bath) and magnetically stirred solution of alcohol **151** (809 mg, 2.39 mmol) and imidazole (408 mg, 6.00 mmol) in DMF (20 mL) maintained under an atmosphere of nitrogen. The cooling bath was removed and stirring was continued at room temperature for 10 h. The reaction mixture was then diluted with ether (200 mL) and water (200 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 50 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 10% ethyl acetate/petrol elution) furnished, after concentration of the appropriate fractions (R_f 0.40), the *title compound **160*** (339 mg, 71%) as a straw-coloured oil.

^{1}H **NMR** (300 MHz) δ 7.68-7.64 (m, 2H), 7.28-7.24 (m, 2H), 7.02-6.92 (complex m, 4H), 6.74 (dt, *J* 6.1 and 2.2 Hz, 1H), 5.51 (s, 2H), 4.98 (d, *J* 6.2 Hz, 1H), 4.45 (d, *J* 2.2 Hz, 2H), 4.13-4.08 (m, 2H), 3.80-3.74 (m, 2H), 3.48 (s, 3H, $-OCH_3$), 0.83 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH_3})_3$), -0.07 (s, 6H, $-(\mathbf{CH_3})_2SiC(CH_3)_3$).

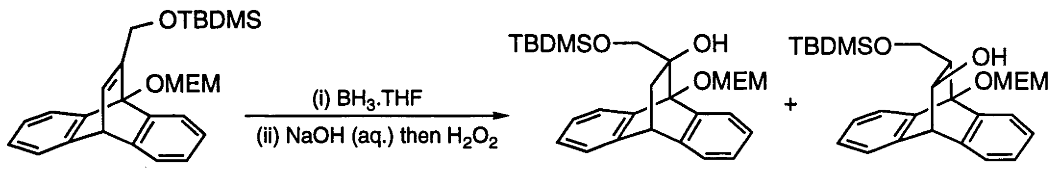
^{13}C **NMR** (75.4 MHz) δ 153.4 (C), 145.6 (C), 145.0 (C), 131.6 (CH), 124.7 (CH), 124.2 (CH), 122.6 (CH), 120.6 (CH), 93.7 (CH_2), 90.2 (C), 71.9 (CH_2), 68.0 (CH_2), 60.7 (CH_2), 59.1 (CH_3), 49.8 (CH), 25.8 (CH_3), 18.2 (C), -5.5 (CH_3).

IR (KBr) ν_{max} 2928, 2856, 1638, 1455, 1251, 1185, 1142, 1105, 1052, 992 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 452 ($M^{+\cdot}$, <1%), 395 [$(M-H_9C_4\cdot)^+$, 23], 363 [$(M-C_4H_9O_2\cdot)^+$, 29], 347 [$(M-C_4H_9O_3\cdot)^+$, 26], 319 [$(M-C_6H_{16}OSi-H\cdot)^+$, 100].

HRMS Found: $(M-H_9C_4\cdot)^+$, 395.1682. $C_{23}H_{27}O_4Si$ requires $(M-H_9C_4\cdot)^+$, 395.1679.

12-(*tert*-Butyldimethylsilyloxymethyl)-9,10-dihydro-9-[(2'-methoxy ethoxy)methoxy]-9,10-ethanoanthracen-12-ol (161) and 12-(*tert*-Butyldimethylsilyloxymethyl)-(11β,12α)-9,10-dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-11-ol (162)



160 **161** **162**

BH_3.THF complex (7.30 mL of a 1 M solution in THF, 7.30 mmol) was added dropwise to a magnetically stirred solution of alkene **160** (830 mg, 1.83 mmol) in THF (9 mL) maintained under an atmosphere of nitrogen. Stirring was continued at room temperature for 2 h then water (680 μL), NaOH (800 μL of a 3 M aqueous solution) and H_2O_2 (850 μL of a 30% (v/v) aqueous solution) were added, in that order, to the colourless reaction solution. After stirring for a further 1 h, the reaction mixture was partitioned between ether (300 mL) and brine (300 mL). The separated aqueous layer was extracted with ether (3 x 50 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. This material was subjected to flash chromatography (silica, 10% THF/chloroform elution) to provide two fractions, A (R_f 0.30) and B (R_f 0.20).

Concentration of fraction A afforded *alcohol* **161** (160 mg, 19%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.73-7.67 (m, 2H), 7.34-7.29 (m, 1H), 7.26-7.00 (complex m, 5H), 5.54 (s, 2H), 4.18 (br s, 1H), 4.18-4.10 (m, 1H), 4.10-4.00 (m, 1H), 3.83 (d, *J* 10.4 Hz, 1H), 3.74 (app t, *J ca.* 4.0 Hz, 2H), 3.47 (s, 3H, -OCH_3), 3.05 (d, *J* 10.0 Hz, 1H), 2.70 (br s, 1H, -OH), 2.10 (dd, *J* 12.6 and 2.6 Hz, 1H), 1.69 (dd, *J* 12.3 and 2.6 Hz, 1H), 0.81 (s, 9H, -$(CH_3)_2SiC(\mathbf{CH_3})_3$), -0.03 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$), -0.07 (s, 3H, -$(\mathbf{CH_3})_2SiC(CH_3)_3$).

^{13}C NMR (75.4 MHz) δ 142.4 (C), 141.7 (C), 140.1 (C), 139.9 (C), 126.5 (CH), 126.4 (CH), 125.8 (CH), 125.7 (CH), 123.4 (CH), 123.3 (CH), 122.8 (CH), 122.7 (CH), 93.6 (CH_2), 88.5 (C), 79.0 (C), 71.9 (CH_2), 68.0 (CH_2), 59.1 (CH_3), 43.3 (CH), 43.0 (CH_2), 25.8 (CH_3), 18.2 (C), -5.4 (CH_3), -5.5 (CH_3).

IR (KBr) ν_{max} 3424, 2929, 2856, 1459, 1254, 1105, 1024 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 307 [$(M-C_4H_{10}O_3-H_9C_4\cdot)^+$, 35%], 282 [$(M-C_9H_{20}O_2Si)^{+\cdot}$, 66], 194 (36), 89 (100).

HRMS Found: $(M-C_4H_{10}O_3-H_9C_4\cdot)^+$, 307.1147. $C_{23}H_{29}O_5Si$ requires $(M-C_4H_{10}O_3-H_9C_4\cdot)^+$, 307.1154.

Concentration of fraction B afforded *compound* ***162*** (474 mg, 55%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.55-7.50 (m, 2H), 7.38 (dd, *J* 5.6 and 2.2 Hz, 1H), 7.29 (dd, *J* 6.4 and 2.1 Hz, 1H), 7.22-7.08 (complex m, 4H), 5.42 (d, *J* 11.8 Hz, 1H), 5.40 (d, *J* 12.0 Hz, 1H), 4.28 (d, *J* 3.2 Hz, 1H), 4.11 (dd, *J* 9.9 and 4.7 Hz, 1H), 4.10-4.02 (m, 4H), 3.78-3.70 (m, 2H), 3.46 (s, 3H, -OCH_3), 2.78 (t, *J* 10.1 Hz, 1H), 2.02

(ddd, *J* 10.3, 5.6 and 2.6 Hz, 1H), 0.80 (s, 9H, $-(CH_3)_2SiC(CH_3)_3$), -0.03 (s, 3H, $-(CH_3)_2SiC(CH_3)_3$), -0.07 (s, 3H, $-(CH_3)_2SiC(CH_3)_3$).

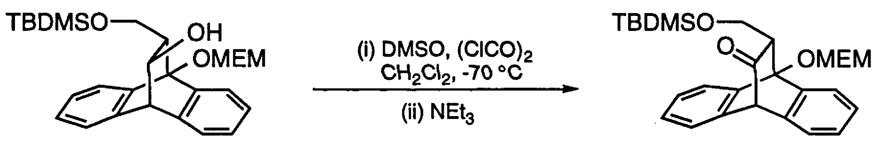
^{13}C NMR (75.4 MHz) δ 142.9 (C), 141.1 (C), 139.1 (C), 138.2 (C), 126.4 (CH), 126.24 (CH), 126.20 (CH), 126.1 (CH), 124.3 (CH), 121.6 (CH), 120.8 (CH), 92.1 (CH_2), 84.0 (C), 74.9 (CH), 71.8 (CH_2), 68.1 (CH_2), 63.5 (CH_2), 59.1 (CH_3), 54.5 (CH), 50.7 (CH), 25.8 (CH_3), 18.1 (C), -5.4 (CH_3), -5.5 (CH_3).

IR (KBr) ν_{max} 3458, 2928, 2856, 1459, 1390, 1254, 1188, 1108, 1035, 983 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 413 [$(M-H_9C_4\cdot)^+$, 8%], 337 [$(M-C_6H_{16}OSi-H\cdot)^+$, 10], 307 [$(M-C_4H_{10}O_3-H_9C_4\cdot)^+$, 57], 282 [$(M-C_9H_{20}O_2Si)^{+\cdot}$, 100], 194 (81).

HRMS Found: $(M-H_9C_4\cdot)^+$, 413.1781. $C_{23}H_{29}O_5Si$ requires $(M-H_9C_4\cdot)^+$, 413.1784.

12-(*tert*-Butyldimethylsilyloxymethyl)-9,10-dihydro-9-[(2'-methoxy ethoxy)methoxy]-9,10-ethanoanthracen-11-one (163)



162 **163**

DMSO (185 μL, 2.61 mmol) was added dropwise to a chilled (dry ice-acetone bath) and magnetically stirred solution of oxalyl chloride (110 μL, 1.26 mmol) in dichloromethane (3.2 mL) maintained under a nitrogen atmosphere. Stirring was continued at -70 °C for 50 mins then a solution of alcohol **162** (470 mg, 1.00 mmol) in dichloromethane (3 mL) was added to the colourless solution. After stirring at -70 °C for 1.5 h, the reaction mixture was treated with triethylamine (360 μL, 2.58 mmol). Stirring was continued for a further 10 mins at -70 °C and then the mixture was warmed to room temperature (over a period of 15 mins). The crude reaction mixture was partitioned between $NaHCO_3$ (150 mL of a saturated aqueous solution) and dichloromethane (150 mL). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic fractions were washed with water (2 x 100 mL) then brine (2 x 100 mL), before being dried, filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.40), the *title ketone* ***163*** (393 mg, 84%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.69 (dd, *J* 7.0 and 2.1 Hz, 2H), 7.35 (d, *J* 7.2 Hz, 1H), 7.30-7.22 (complex m, 3H), 7.20-7.11 (m, 2H), 5.41 (d, *J* 9.1 Hz, 1H), 5.40 (d, *J* 9.1 Hz, 1H), 4.77 (s, 1H), 4.15-4.04 (m, 2H), 3.79-3.67 (complex m, 4H), 3.46 (s, 3H), 2.68 (dd, *J* 4.7 and 3.1 Hz, 1H), 0.73 (s, 9H, -$(\mathbf{CH}_3)_2SiC(CH_3)_3$), -0.15 (s, 6H, -$(C\mathbf{H}_3)_2SiC(CH_3)_3$).

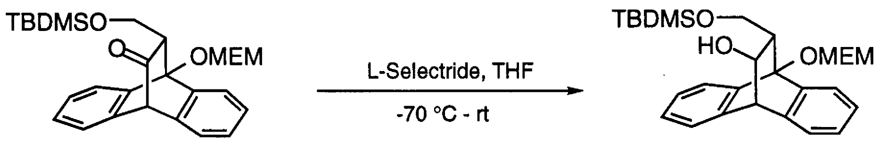
^{13}C NMR (75.4 MHz) δ 201.3 (C), 142.6 (C), 141.3 (C), 135.6 (C), 134.2 (C), 127.1 (CH), 127.0 (CH), 126.9 (CH), 126.7 (CH), 125.0 (CH), 124.3 (CH), 122.2 (CH), 121.5 (CH), 92.3 (CH_2), 83.5 (C), 71.7 (CH_2), 68.1 (CH_2), 62.4 (CH), 61.4 (CH_2), 59.1 (CH_3), 51.8 (CH), 25.8 (CH_3), 18.2 (C), -5.76 (CH_3), -5.83 (CH_3).

IR (KBr) ν_{max} 2953, 2856, 1734, 1458, 1253, 1174, 1106, 1047 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 468 ($M^{+\cdot}$, <1%), 411 [$(M-H_9C_4\cdot)^+$, 7], 335 [$(M-C_6H_{16}OSi-H\cdot)^+$, 82], 282 [$(M-C_9H_{18}O_2Si)^{+\cdot}$, 90], 194 (94).

HRMS Found: $(M-H_9C_4\cdot)^+$, 411.1626. $C_{23}H_{27}O_5Si$ requires $(M-H_9C_4\cdot)^+$, 411.1628.

12-(*tert*-Butyldimethylsilyloxymethyl)-(11α,12α)-9,10-dihydro-9-[(2'-methoxyethoxy)methoxy]-9,10-ethanoanthracen-11-ol (164)



163 **164**

L-Selectride (2.4 mL of a 1 M solution in THF, 2.40 mmol) was added dropwise to a chilled (dry ice-acetone bath) and magnetically stirred solution of ketone **163** (369 mg, 0.79 mmol) in THF (11 mL) maintained under a nitrogen atmosphere. The cold bath was removed and stirring was continued at ambient temperatures for a further 6 h. The reaction mixture was then treated with HCl (*ca.* 5 mL of a 10% (v/v) aqueous solution) and diluted with dichloromethane (150 mL) and brine (150 mL). The separated aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were dried, filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.40), *alcohol **164*** (276 mg, 74%) as a viscous, colourless oil.

^{1}H NMR (300 MHz) δ 7.58-7.54 (m, 1H), 7.48-7.44 (m, 1H), 7.40-7.36 (m, 1H), 7.35-7.31 (m, 1H), 7.20-7.10 (complex m, 4H), 5.42 (d, *J* 16.2 Hz, 1H), 5.40 (d, *J* 16.4 Hz, 1H), 4.41-4.34 (m, 2H), 4.19 (dd, *J* 10.3 and 4.3 Hz, 1H), 4.12-4.00 (m, 3H), 3.75-3.70 (m, 2H), 3.46 (s, 3H, $-OCH_3$), 3.18 (t, *J* 10.5 Hz, 1H), 2.52 (ddd, *J* 10.6, 8.1 and 4.3 Hz, 1H), 0.79 (s, 9H, $-(CH_3)_2SiC(\mathbf{CH}_3)_3$), 0.04 (s, 3H, $-(\mathbf{CH}_3)_2SiC(CH_3)_3$), -0.03 (s, 3H, $-(\mathbf{CH}_3)_2SiC(CH_3)_3$).

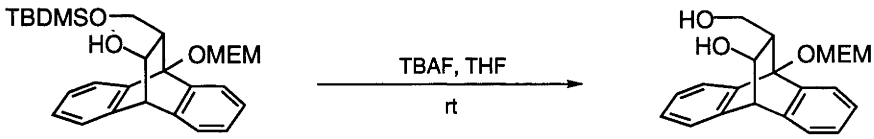
^{13}C NMR (75.4 MHz) δ 143.3 (C), 140.2 (C), 139.0 (C), 138.9 (C), 126.3 (CH), 126.2 (CH), 126.1 (CH), 125.81 (CH), 125.77 (CH), 124.8 (CH), 121.2 (CH), 120.8 (CH), 92.2 (CH_2), 84.1 (C), 71.8 (CH_2), 71.2 (CH), 68.2 (CH_2), 61.8 (CH_2), 59.0 (CH_3), 50.5 (CH), 46.7 (CH), 25.6 (CH_3), 17.7 (C), -5.5 (CH_3).

IR (KBr) ν_{max} 3485, 2953, 2857, 1460, 1258, 1193, 1112, 1059 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 413 [(M-$H_9C_4\cdot$)$^+$, 8%], 364 [(M-$C_4H_{10}O_3$)$^{+\cdot}$, 13], 307 [(M-$C_6H_{16}OSi$-$H_3CO\cdot$)$^+$, 12], 282 [(M-$C_9H_{20}O_2Si$)$^{+\cdot}$, 18], 194 [(M-$C_9H_{20}O_2Si$-$C_4H_8O_2^{\cdot}$)$^+$, 19].

HRMS Found: (M-$H_9C_4\cdot$)$^+$, 413.1779. $C_{23}H_{29}O_5Si$ requires (M-$H_9C_4\cdot$)$^+$, 413.1784.

(11α,12α)-9,10-Dihydro-12-hydroxymethyl-9-[(2'-methoxyethoxy) methoxy]-9,10-ethanoanthracen-11-ol (165)



164 **165**

A magnetically stirred solution of compound **164** (264 mg, 0.56 mmol) and tetra-*n*-butylammonium fluoride (1.10 mL of a 1 M solution in THF, 1.10 mmol) in THF (6 mL) was stirred at room temperature for 15 mins. The resulting mixture was partitioned between ether (80 mL) and brine (80 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 20 mL) and the combined ethereal fractions were dried, filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 80% ethyl acetate/chloroform elution) provided, after concentration of the appropriate fractions (R_f 0.30), the *title diol* ***165*** (158 mg, 79%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.58 (dd, *J* 6.7 and 1.7 Hz, 1H), 7.40-7.31 (m, 3H), 7.25-7.11 (complex m, 4H), 5.43 (d, *J* 15.8 Hz, 1H), 5.41 (d, *J* 15.8 Hz, 1H), 4.39 (br d, *J* 8.7 Hz, 1H), 4.32 (d, *J* 2.9 Hz, 1H), 4.15-4.09 (m, 1H), 3.96-3.90 (m, 2H), 3.69 (app t, *J ca.* 4.6 Hz, 2H), 3.43 (s, 3H, -OCH_3), 3.14 (br dd, *J* 10.0 and 9.1 Hz, 1H), 2.90 (br s, 1H, -OH), 2.55 (td, *J* 8.7 and 3.7 Hz, 1H).

^{13}C NMR (75.4 MHz) δ 142.4 (C), 140.9 (C), 139.1 (C), 137.8 (C), 126.4 (CH), 126.33 (CH), 126.29 (CH), 126.2 (CH), 126.0 (CH), 124.7 (CH), 121.0 (CH), 92.5

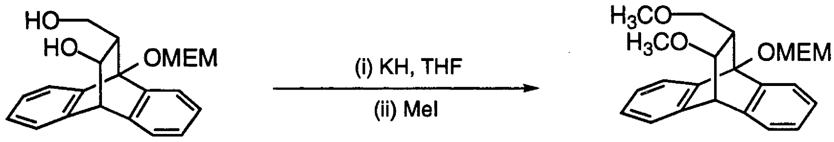
(CH_2), 84.5 (C), 71.7 (CH_2), 71.4 (CH), 67.9 (CH_2), 60.5 (CH_2), 59.0 (CH_3), 51.3 (CH), 46.9 (CH).

IR (KBr) ν_{max} 3406, 2925, 2893, 1458, 1223, 1192, 1104, 1044, 1004, 981 cm^{-1}.

Mass Spectrum (CI) *m/z* 374 (MNH_4^+, 42%), 357 (MH^+, 7).

HRMS Found: MNH_4^+, 374.1962. $C_{21}H_{28}NO_5$ requires MNH_4^+, 374.1967.

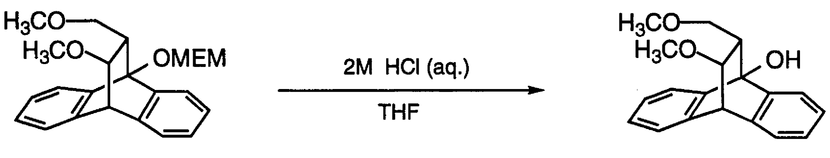
(11α,12α)-9,10-Dihydro-11-methoxy-9-[(2'-methoxyethoxy) methoxy]-12-methoxymethyl-9,10-ethanoanthracene (166)



Potassium hydride (94 mg, 2.35 mmol) was added in one portion to a magnetically stirred solution of diol **165** (158 mg, 0.44 mmol) in THF (7.4 mL) maintained under a nitrogen atmosphere. Stirring was continued at room temperature for 1 h then methyl iodide (142 µL, 2.28 mmol) was added to the now bright orange reaction mixture in a dropwise fashion. Stirring was continued for a further 3 h after which time the suspension was cooled (ice-water bath) and treated with ethanol/water (*ca.* 10 mL of a 1:1 (v/v) mixture). The reaction mixture was concentrated under reduced pressure and the residue thus obtained was partitioned between dichloromethane (40 mL) and brine (40 mL). The separated aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried, filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash chromatography (silica, 20% ethyl acetate/chloroform elution) provided, after concentration of the appropriate fractions (R_f 0.40), the *title compound **166*** (133 mg, 78%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 7.60-7.56 (m, 1H), 7.51 (dd, *J* 8.6 and 1.8 Hz, 1H), 7.32-7.28 (m, 2H), 7.21-7.10 (complex m, 4H), 5.42 (d, *J* 11.3 Hz, 1H), 5.40 (d, *J* 11.2 Hz, 1H), 4.42 (d, *J* 2.8 Hz, 1H), 4.15-4.04 (m, 2H), 3.80 (dd, *J* 8.7 and 2.8 Hz, 1H), 3.76 (m, 2H), 3.52 (dd, *J* 9.1 and 2.1 Hz, 1H), 3.46 (s, 3H, $-OCH_3$), 3.45 (s, 3H, $-OCH_3$), 3.19 (s, 3H, $-OCH_3$), 2.77 (t, *J* 8.6 Hz, 1H), 2.60 (td, *J* 8.5 and 2.1 Hz, 1H).
^{13}C NMR (75.4 MHz) δ 142.9 (C), 140.6 (C), 139.0 (C), 138.3 (C), 126.3 (CH), 126.2 (CH), 126.1 (CH), 125.8 (CH), 125.1 (CH), 124.4 (CH), 121.4 (CH), 121.2 (CH), 92.2 (CH_2), 83.4 (C), 80.4 (CH), 71.9 (CH_2), 68.7 (CH_2), 68.2 (CH_2), 59.1 (CH_3), 58.4 (CH), 58.1 (CH_3), 48.4 (CH_3), 45.1 (CH).
IR (KBr) ν_{max} 2926, 2885, 1458, 1223, 1199, 1112, 1046, 984 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 309 [$(M-C_3H_7O_2^{\cdot})^+$, <2%], 282 [$(M-C_5H_{10}O_2)^{+\cdot}$, 35], 194 [$(M-C_5H_{10}O_2-C_4H_8O_2^{\cdot})^+$, 27], 165 (16), 89 (100).
HRMS Found: $(M-C_3H_7O_2^{\cdot})^+$, 309.1484. $C_{20}H_{21}O_3$ requires $(M-C_3H_7O_2^{\cdot})^+$, 309.1491.

(11α,12α)-9,10-Dihydro-11-methoxy-12-methoxymethyl-9,10-ethano anthracen-9-ol (128)



166 128

A mixture of compound **166** (111 mg, 0.29 mmol), THF (4 mL) and HCl (4 mL of a 2 M aqueous solution) was stirred at room temperature for 18 h then concentrated under reduced pressure. The residue thus obtained was partitioned between ether (30 mL) and brine (30 mL) and the phases separated. The aqueous layer was extracted with ether (4 x 10 mL) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a cloudy oil. Subjection of this material to flash chromatography (silica, 10% ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.30), a colourless solid. Recrystallisation (chloroform/hexane) of this material afforded the *title alcohol **128*** (68 mg, 80%) as colourless prisms, m.p. 131-131.5 °C.

^{1}H NMR (300 MHz) δ 7.66 (d, *J* 7.6 Hz, 1H), 7.62 (d, *J* 7.6 Hz, 1H), 7.32-7.10 (complex m, 6H), 5.70 (br s, 1H), 4.49 (d, *J* 2.9 Hz, 1H), 3.82 (dd, *J* 9.3 and 3.0 Hz, 1H), 3.53 (dd, *J* 10.3 and 3.7 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 2.88 (dd, *J* 10.4 and 0.9 Hz, 1H), 2.56-2.47 (m, 1H).

^{13}C NMR (75.4 MHz) δ 145.5 (C), 142.9 (C), 137.8 (C), 137.3 (C), 126.5 (CH), 126.1 (CH), 126.0 (CH), 125.0 (CH), 123.8 (CH), 121.6 (CH), 120.6 (CH), 80.8 (CH), 79.0 (C), 73.1 (CH_2), 59.0 (CH_3), 57.3 (CH_3), 46.6 (CH), 44.9 (CH).

IR (KBr) ν_{max} 3420, 2928, 2825, 1459, 1288, 1225, 1190, 1122, 1104, 1090 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 296 ($M^{+\cdot}$, <1%), 264 [$(M-CH_3OH)^{+\cdot}$, <1], 231 [$(M-2CH_3OH-H\cdot)^+$, <2], 194 [$(M-C_5H_{10}O_2)^{+\cdot}$, 100].

HRMS Found: $M^{+\cdot}$, 296.1416. $C_{19}H_{20}O_3$ requires $M^{+\cdot}$, 296.1412.

Elemental Analysis Found: C, 76.79; H, 6.70. $C_{19}H_{20}O_3$ requires: C, 77.00; H, 6.80%.

Cycloreversion Studies - General Procedure

Potassium hydride (7 mole equiv.) was added in one portion to a magnetically stirred solution of substrate **125**, **126**, **127** or **128** (typically 5 mg) and 18-crown-6 (3 mole equiv.) in dry 1,4-dioxane (0.5 mL) maintained under an atmosphere of nitrogen. Stirring was continued at room temperature (*ca.* 18 °C) for 1 h after which time a 50 μL aliquot of the crude reaction mixture was quenched in methanol (200 μL) and analysed by gas chromatography. If anthrone (**129**) was not detected (which was taken as evidence that the cycloreversion reaction was not occuring), the temperature of the reaction mixture was then raised (to 50, 80 and/or 100 °C) and heated at that temperature for 1 h. After this time, a 50 μL aliquot of the crude reaction mixture was quenched in methanol (200 μL) and, once again, analysed by gas chromatography. If, however, anthrone (**129**) was detected, the reaction mixture was worked-up in the following manner: methanol (*ca.* 0.5 mL) was added to the crude reaction mixture which was then partitioned between ether (5 mL) and water (5 mL). The phases were separated and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic fractions were dried, filtered and concentrated under reduced pressure to give, in all cases, a pale-yellow oil. The ^{1}H NMR spectrum of this material was acquired in order to check for the presence of the substrate and/or anthrone (**129**).

Gas chromatographic analyses were conducted on a SGE BPX5 silica capillary column; initial temperature: 40 °C (2 mins), ramp rate: 20 °C/min, final temperature: 290 °C (15 mins). Helium was the carrier gas used and the peaks were detected using a FID detector. R_t **125**: 14.2 mins; R_t **126**: 14.3 mins; R_t **127**: 16.2 mins; R_t **128**: 16.4 mins; R_t anthrone (**129**): 15.1 mins.

5.5 References

1. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

2. D. D. Perrin and W. L. F. Amarego, *Purification of Laboratory Chemicals*, 3rd Edition, Pergamon Press, 1988.

3. S. C. Watson and J. F. Eastham, *J. Organometallic Chem.*, 1967, **9**, 165.

4. *Dictionary of Organic Compounds*, 5th Edition, Chapman and Hall, 1982, Vol. 3, p. 3010.

5. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.

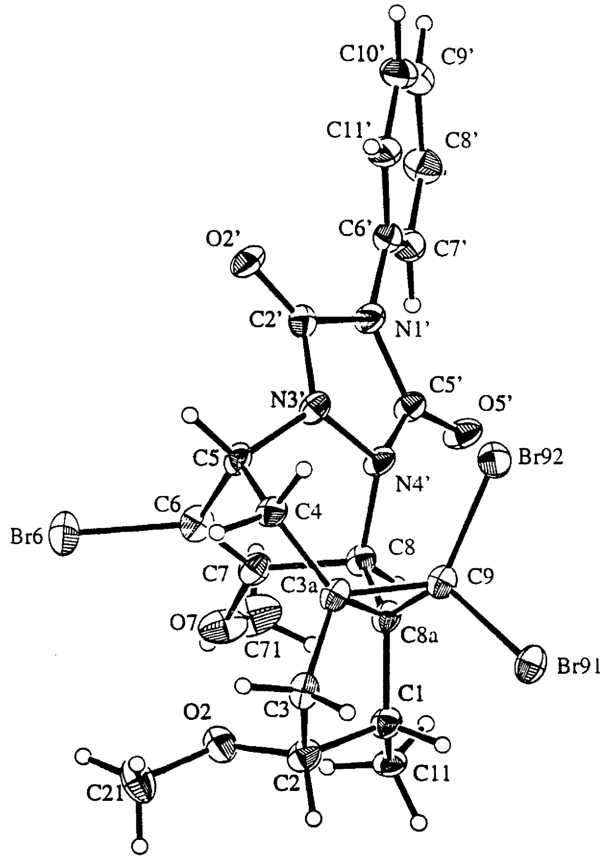
APPENDICES

APPENDIX 1

APPENDIX 2

A2.1 X-ray Structure Report for Compound 114.

X-ray crystal data are presented as provided by Dr. D. C. R. Hockless, The Australian National University.



Experimental

Data Collection

A colorless plate crystal of $C_{26}H_{32}Br_3N_3O_5$ having approximate dimensions of 0.20 x 0.12 x 0.02 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections in the range $59.28 < 2\theta < 76.27°$ corresponded to a primitive monoclinic cell with dimensions:

a = 12.070(4) Å
b = 7.676(3) Å β = 94.69(3)°
c = 14.639(5) Å
V = 1351.7(8) Å^3

For Z = 2 and F.W. = 706.27, the calculated density is 1.74 g/cm^3. Based on the systematic absences of:

0k0: k ± 2n

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P2_1$ (#4)

The data were collected at a temperature of -60 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 120.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.43° with a take-off angle of 6.0°. Scans of $(1.30 + 0.30 \tan \theta)^\circ$ were made at a speed of 32.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 2300 reflections which were collected, 2185 were unique ($R_{int} = 0.028$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 5.4%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 58.9 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.75 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques.[2] Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1669 observed reflections ($I > 3.00\sigma(I)$) and 307 variable parameters and converged (largest parameter shift was 0.06 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.037$$

$$R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.038$$

The standard deviation of an observation of unit weight[4] was 1.59. The weighting scheme was based on counting statistics and included a factor (p = 0.010) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.45 and -0.31 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[5] Anomalous dispersion effects were included in Fcalc;[6] the values for Δf' and Δf" were those of Creagh and McAuley.[7] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[8] All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{26}H_{32}Br_3N_3O_5$
Formula Weight	706.27
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.20 X 0.12 X 0.02 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	20 (59.3 - 76.3°)
Omega Scan Peak Width at Half-height	0.43°
Lattice Parameters	a = 12.070(4)Å b = 7.676(3) Å c = 14.639(5) Å β = 94.69(3)° V = 1351.7(8) $Å^3$
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.735 g/cm^3
F_{000}	708.00
$\mu(CuK\alpha)$	58.93 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R
Radiation	$CuK\alpha$ (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-60.0 °C
Scan Type	ω-2θ

Scan Rate	32.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.30 + 0.30 \tan \theta)°$
$2\theta_{max}$	120.2°
No. of Reflections Measured	Total: 2300 Unique: 2185 (R_{int} = 0.028)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.7531 - 1.0000) Decay (5.40% decline)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (\lvert Fo \rvert - \lvert Fc \rvert)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1669
No. Variables	307
Reflection/Parameter Ratio	5.44
Residuals: R; Rw	0.037 ; 0.038
Goodness of Fit Indicator	1.59
Max Shift/Error in Final Cycle	0.06
Maximum peak in Final Diff. Map	0.45 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.31 $e^-/Å^3$

Table 1: Atomic coordinates and B_{iso}/B_{eq}.

atom	x	y	z	B_{eq}
Br(6)	0.88529(8)	0.7765	0.03293(5)	6.00(2)
Br(91)	0.94756(6)	0.6580	0.53717(4)	4.52(2)
Br(92)	1.15862(6)	0.6535(2)	0.43370(5)	4.70(2)
O(01)	1.414(2)	1.184(3)	1.413(1)	37.9(8)
O(2)	0.7165(4)	0.6682(8)	0.2322(3)	4.8(1)
O(2')	1.2692(4)	0.6963(7)	0.1212(3)	4.8(1)
O(5')	1.1523(4)	0.1870(7)	0.2499(3)	4.8(1)
O(7)	0.8383(4)	0.4142(8)	0.1212(3)	6.0(1)
N(1')	1.2489(5)	0.4146(8)	0.1843(4)	3.8(1)
N(3')	1.1339(4)	0.6293(8)	0.2184(3)	3.7(1)
N(4')	1.0972(4)	0.4708(8)	0.2557(4)	3.7(1)
C(1)	0.8099(6)	0.515(1)	0.3572(4)	3.8(1)
C(01)	1.441(3)	1.375(4)	1.424(2)	48.6(8)
C(2)	0.7432(6)	0.679(1)	0.3293(5)	4.3(1)
C(02)	1.480(3)	1.515(4)	1.496(2)	32.3(9)
C(2')	1.2229(6)	0.595(1)	0.1680(4)	3.8(1)
C(03)	1.412(2)	0.998(3)	1.380(1)	25.3(8)
C(3a)	0.9406(6)	0.757(1)	0.3366(4)	3.6(1)
C(3)	0.8225(6)	0.8294(9)	0.3546(4)	3.9(2)
C(4)	1.0090(6)	0.8573(9)	0.2723(5)	3.7(2)
C(04)	1.424(3)	0.800(3)	1.394(2)	45.2(8)
C(5)	1.0479(5)	0.759(1)	0.1902(4)	3.8(1)
C(5')	1.1651(6)	0.339(1)	0.2313(5)	3.8(1)
C(6)	0.9529(5)	0.662(1)	0.1366(4)	4.3(1)
C(6')	1.3427(6)	0.330(1)	0.1530(4)	3.8(1)
C(7)	0.9217(6)	0.508(1)	0.1659(4)	4.0(1)
C(7')	1.3354(5)	0.157(1)	0.1249(5)	4.5(1)
C(8)	0.9774(6)	0.4517(9)	0.2609(4)	3.5(1)
C(8a)	0.9307(6)	0.5574(9)	0.3375(4)	3.5(1)
C(8')	1.4270(6)	0.082(1)	0.0929(5)	5.1(2)
C(9)	0.9986(5)	0.650(1)	0.4138(4)	3.70(8)
C(9')	1.5254(6)	0.170(1)	0.0863(5)	5.3(2)
C(10')	1.5314(6)	0.340(1)	0.1173(5)	5.4(2)
C(11)	0.7590(5)	0.343(1)	0.3213(4)	3.8(2)
C(11')	1.4409(6)	0.419(1)	0.1500(5)	4.8(2)
C(21)	0.6440(7)	0.802(1)	0.1965(5)	6.2(2)
C(71)	0.8562(8)	0.245(1)	0.0976(7)	8.7(3)
H(1)	0.8104	0.5086	0.4220	4.5430
H(2)	0.6779	0.6866	0.3612	5.1928
H(3a)	0.8045	0.9280	0.3171	4.6471
H(3b)	0.8199	0.8605	0.4172	4.6471
H(4a)	0.9654	0.9531	0.2493	4.4754
H(4b)	1.0733	0.8992	0.3073	4.4754
H(5)	1.0784	0.8401	0.1504	4.5778
H(7')	1.2684	0.0932	0.1279	5.4047
H(8)	0.9615	0.3321	0.2702	4.2024
H(8')	1.4227	-0.0369	0.0744	6.1214
H(9')	1.5869	0.1162	0.0613	6.3352
H(10')	1.5992	0.4024	0.1160	6.4224
H(11c)	0.7035	0.3071	0.3596	4.5666
H(11a)	0.8154	0.2571	0.3214	4.5666
H(11b)	0.7265	0.3596	0.2606	4.5666
H(11')	1.4462	0.5362	0.1706	5.7046
H(21a)	0.6461	0.8072	0.1318	7.4346
H(21b)	0.5703	0.7768	0.2110	7.4346
H(21c)	0.6670	0.9102	0.2228	7.4346
H(71a)	0.8036	0.2119	0.0488	10.4604
H(71b)	0.8482	0.1716	0.1490	10.4604
H(71c)	0.9292	0.2332	0.0785	10.4604

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 2: Anisotropic Displacement Parameters.

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(6)	0.0963(6)	0.0732(6)	0.0561(4)	-0.0026(6)	-0.0093(4)	0.0162(5)
Br(91)	0.0801(5)	0.0484(4)	0.0432(3)	-0.0049(6)	0.0055(3)	-0.0020(5)
Br(92)	0.0613(4)	0.0541(5)	0.0615(4)	-0.0069(6)	-0.0041(3)	0.0040(6)
O(2)	0.060(3)	0.049(3)	0.070(2)	-0.004(3)	-0.008(2)	0.005(3)
O(2')	0.065(3)	0.059(4)	0.059(3)	-0.017(3)	0.019(2)	0.013(2)
O(5')	0.063(3)	0.040(3)	0.083(3)	-0.004(3)	0.031(2)	0.009(3)
O(7)	0.073(3)	0.071(4)	0.084(3)	-0.035(3)	0.019(3)	-0.031(3)
N(1')	0.051(3)	0.041(3)	0.054(3)	-0.005(3)	0.010(2)	0.008(3)
N(3')	0.062(3)	0.028(3)	0.051(3)	-0.005(3)	0.014(2)	0.004(3)
N(4')	0.053(3)	0.032(3)	0.056(3)	-0.011(2)	0.014(3)	0.011(3)
C(1)	0.054(3)	0.041(3)	0.049(4)	-0.009(3)	0.003(3)	0.005(3)
C(2)	0.064(4)	0.038(4)	0.065(3)	-0.003(3)	0.014(3)	0.006(4)
C(2')	0.054(4)	0.042(3)	0.046(4)	0.000(3)	-0.001(2)	0.006(3)
C(3a)	0.064(4)	0.029(3)	0.044(3)	-0.012(3)	0.006(3)	0.000(3)
C(3)	0.071(4)	0.033(4)	0.042(4)	0.003(3)	0.004(3)	-0.005(3)
C(4)	0.052(4)	0.030(4)	0.061(4)	-0.008(3)	0.010(3)	0.008(3)
C(5)	0.058(4)	0.038(4)	0.049(3)	-0.007(3)	0.005(3)	0.016(3)
C(5')	0.053(4)	0.042(3)	0.051(4)	-0.004(3)	0.014(3)	0.006(3)
C(6)	0.073(4)	0.047(4)	0.042(3)	-0.010(4)	0.003(2)	-0.013(3)
C(6')	0.046(3)	0.049(4)	0.048(4)	-0.003(3)	0.002(3)	0.011(3)
C(7)	0.062(4)	0.049(4)	0.041(3)	0.001(3)	0.015(3)	-0.004(3)
C(7')	0.052(3)	0.049(3)	0.070(4)	-0.007(5)	0.001(3)	0.008(5)
C(8)	0.052(3)	0.029(4)	0.052(3)	-0.007(3)	0.003(3)	0.004(3)
C(8a)	0.055(3)	0.029(3)	0.047(3)	-0.010(3)	0.003(3)	0.008(3)
C(8')	0.061(4)	0.055(5)	0.078(5)	0.005(3)	0.006(4)	-0.005(4)
C(9)	0.061(1)	0.036(3)	0.044(2)	-0.006(4)	0.005(2)	-0.001(3)
C(9')	0.054(4)	0.073(5)	0.075(4)	0.013(5)	0.009(4)	0.013(5)
C(10')	0.045(4)	0.070(5)	0.088(6)	-0.005(4)	0.005(4)	0.016(5)
C(11)	0.043(4)	0.044(4)	0.059(4)	-0.013(3)	0.008(3)	0.003(3)
C(11')	0.049(3)	0.055(5)	0.077(5)	-0.009(3)	0.006(3)	0.016(4)
C(21)	0.084(6)	0.056(5)	0.092(6)	0.022(4)	-0.015(5)	0.008(5)
C(71)	0.122(8)	0.070(5)	0.147(8)	-0.024(7)	0.058(6)	-0.031(7)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 3: Bond Lengths (Å).

atom	atom	distance	atom	atom	distance
Br(6)	C(6)	1.881(9)	Br(91)	C(9)	1.956(7)
Br(92)	C(9)	1.930(8)	O(01)	C(01)	1.51(1)*
O(01)	C(03)	1.51(1)*	O(2)	C(2)	1.43(1)
O(2)	C(21)	1.42(1)	O(2')	C(2')	1.20(1)
O(5')	C(5')	1.21(1)	O(7)	C(7)	1.36(1)
O(7)	C(71)	1.37(2)	N(1')	C(2')	1.43(1)
N(1')	C(5')	1.39(1)	N(1')	C(6')	1.41(1)
N(3')	N(4')	1.42(1)	N(3')	C(2')	1.38(1)
N(3')	C(5)	1.47(1)	N(4')	C(5')	1.37(1)
N(4')	C(8)	1.46(1)	C(1)	C(2)	1.53(1)
C(1)	C(8a)	1.54(1)	C(1)	C(11)	1.53(1)

Table 3: Bond Lengths (Å) continued.

atom	atom	distance	atom	atom	distance
C(01)	C(02)	1.55(1)*	C(2)	C(3)	1.53(1)
C(03)	C(04)	1.54(1)*	C(3a)	C(3)	1.57(1)
C(3a)	C(4)	1.51(1)	C(3a)	C(8a)	1.53(1)
C(3a)	C(9)	1.52(1)	C(4)	C(5)	1.53(1)
C(5)	C(6)	1.53(1)	C(6)	C(7)	1.33(1)
C(6')	C(7')	1.39(1)	C(6')	C(11')	1.37(1)
C(7)	C(8)	1.56(1)	C(7')	C(8')	1.36(1)
C(8)	C(8a)	1.53(1)	C(8a)	C(9)	1.51(1)
C(8')	C(9')	1.38(1)	C(9')	C(10')	1.38(2)
C(10')	C(11')	1.37(1)			

* restrained during refinement

Table 4: Bond Lengths (Å).

atom	atom	distance	atom	atom	distance
C(1)	H(1)	0.95	C(2)	H(2)	0.95
C(3)	H(3a)	0.95	C(3)	H(3b)	0.95
C(4)	H(4a)	0.95	C(4)	H(4b)	0.95
C(5)	H(5)	0.95	C(7')	H(7')	0.95
C(8)	H(8)	0.95	C(8')	H(8')	0.95
C(9')	H(9')	0.95	C(10')	H(10')	0.95
C(11)	H(11c)	0.95	C(11)	H(11a)	0.95
C(11)	H(11b)	0.95	C(11')	H(11')	0.95
C(21)	H(21a)	0.95	C(21)	H(21b)	0.95
C(21)	H(21c)	0.95	C(71)	H(71a)	0.95
C(71)	H(71b)	0.95	C(71)	H(71c)	0.95

* restrained during refinement

Table 5: Bond Angles (°).

atom	atom	atom	angle
C(01)	O(01)	C(03)	162(3)
C(7)	O(7)	C(71)	119.9(9)
C(2')	N(1')	C(6')	123.9(8)
N(4')	N(3')	C(2')	108.8(7)
C(2')	N(3')	C(5)	122.9(7)
N(3')	N(4')	C(8)	116.6(7)
C(2)	C(1)	C(8a)	105.2(7)
C(8a)	C(1)	C(11)	118.5(8)
O(2)	C(2)	C(1)	106.8(7)
C(1)	C(2)	C(3)	104.6(7)
O(2')	C(2')	N(3')	126.8(9)
O(01)	C(03)	C(04)	153(3)
C(3)	C(3a)	C(8a)	106.3(8)
C(4)	C(3a)	C(8a)	124.2(8)
C(8a)	C(3a)	C(9)	59.1(6)
C(3a)	C(4)	C(5)	117.0(7)
N(3')	C(5)	C(6)	107.5(8)
O(5')	C(5')	N(1')	128.5(9)
N(1')	C(5')	N(4')	107.2(7)
Br(6)	C(6)	C(7)	124.2(7)

Table 5: Bond Angles (°) continued.

atom	atom	atom	angle
N(1')	C(6')	C(7')	120.0(8)
C(7')	C(6')	C(11')	120.0(9)
O(7)	C(7)	C(8)	122.2(8)
C(6')	C(7')	C(8')	118.2(9)
N(4')	C(8)	C(8a)	114.3(7)
C(1)	C(8a)	C(3a)	106.7(8)
C(1)	C(8a)	C(9)	115.2(7)
C(3a)	C(8a)	C(9)	60.0(6)
C(7')	C(8')	C(9')	123(1)
Br(91)	C(9)	C(3a)	120.6(6)
Br(92)	C(9)	C(3a)	119.9(6)
C(3a)	C(9)	C(8a)	60.9(5)
C(9')	C(10')	C(11')	121(1)
C(2)	O(2)	C(21)	114.0(7)
C(2')	N(1')	C(5')	109.0(7)
C(5')	N(1')	C(6')	127.0(8)
N(4')	N(3')	C(5)	116.8(6)
N(3')	N(4')	C(5')	108.8(6)
C(5')	N(4')	C(8)	123.8(7)
C(2)	C(1)	C(11)	115.4(7)
O(01)	C(01)	C(02)	143(4)
O(2)	C(2)	C(3)	111.6(7)
O(2')	C(2')	N(1')	127.8(8)
N(1')	C(2')	N(3')	105.4(7)
C(3)	C(3a)	C(4)	118.1(8)
C(3)	C(3a)	C(9)	115.8(7)
C(4)	C(3a)	C(9)	119.8(7)
C(2)	C(3)	C(3a)	104.4(7)
N(3')	C(5)	C(4)	111.6(6)
C(4)	C(5)	C(6)	112.3(7)
O(5')	C(5')	N(4')	124.3(8)
Br(6)	C(6)	C(5)	116.5(7)
C(5)	C(6)	C(7)	119.2(8)
N(1')	C(6')	C(11')	120.0(9)
O(7)	C(7)	C(6)	122.4(8)
C(6)	C(7)	C(8)	115.0(8)
N(4')	C(8)	C(7)	106.4(7)
C(7)	C(8)	C(8a)	110.5(7)
C(1)	C(8a)	C(8)	115.8(7)
C(3a)	C(8a)	C(8)	119.3(8)
C(8)	C(8a)	C(9)	125.6(8)
Br(91)	C(9)	Br(92)	104.3(3)
Br(91)	C(9)	C(8a)	120.5(6)
Br(92)	C(9)	C(8a)	126.6(6)
C(8')	C(9')	C(10')	118(1)
C(6')	C(11')	C(10')	120(1)

* restrained during refinement

Table 6: Bond Angles (°).

atom	atom	atom	angle
C(2)	C(1)	H(1)	105.6
C(11)	C(1)	H(1)	105.6
C(1)	C(2)	H(2)	111.2
C(2)	C(3)	H(3a)	110.7

Table 6: Bond Angles (°) continued.

atom	atom	atom	angle
C(3a)	C(3)	H(3a)	110.7
H(3a)	C(3)	H(3b)	109.5
C(3a)	C(4)	H(4b)	107.6
C(5)	C(4)	H(4b)	107.6
N(3')	C(5)	H(5)	108.4
C(6)	C(5)	H(5)	108.4
C(8')	C(7')	H(7')	120.9
C(7)	C(8)	H(8)	108.5
C(7')	C(8')	H(8')	118.6
C(8')	C(9')	H(9')	121.1
C(9')	C(10')	H(10')	119.6
C(1)	C(11)	H(11c)	109.5
C(1)	C(11)	H(11b)	109.5
H(11c)	C(11)	H(11b)	109.5
C(6')	C(11')	H(11')	119.8
O(2)	C(21)	H(21a)	109.5
O(2)	C(21)	H(21c)	109.5
H(21a)	C(21)	H(21c)	109.5
O(7)	C(71)	H(71a)	109.5
O(7)	C(71)	H(71c)	109.5
H(71a)	C(71)	H(71c)	109.5
C(8a)	C(1)	H(1)	105.6
O(2)	C(2)	H(2)	111.2
C(3)	C(2)	H(2)	111.2
C(2)	C(3)	H(3b)	110.7
C(3a)	C(3)	H(3b)	110.7
C(3a)	C(4)	H(4a)	107.6
C(5)	C(4)	H(4a)	107.6
H(4a)	C(4)	H(4b)	109.5
C(4)	C(5)	H(5)	108.4
C(6')	C(7')	H(7')	120.9
N(4')	C(8)	H(8)	108.5
C(8a)	C(8)	H(8)	108.5
C(9')	C(8')	H(8')	118.6
C(10')	C(9')	H(9')	121.1
C(11')	C(10')	H(10')	119.6
C(1)	C(11)	H(11a)	109.5
H(11c)	C(11)	H(11a)	109.5
H(11a)	C(11)	H(11b)	109.5
C(10')	C(11')	H(11')	119.8
O(2)	C(21)	H(21b)	109.5
H(21a)	C(21)	H(21b)	109.5
H(21b)	C(21)	H(21c)	109.5
O(7)	C(71)	H(71b)	109.5
H(71a)	C(71)	H(71b)	109.5
H(71b)	C(71)	H(71c)	109.5

* restrained during refinement

Table 7: Torsion Angles (°).

atom	atom	atom	atom	angle
Br(6)	C(6)	C(5)	N(3')	-140.4(6)
Br(6)	C(6)	C(7)	O(7)	2(1)
Br(91)	C(9)	C(3a)	C(3)	-16(1)
Br(91)	C(9)	C(3a)	C(8a)	110.2(8)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle
Br(91)	C(9)	C(8a)	C(3a)	110.3(8)
Br(92)	C(9)	C(3a)	C(3)	-148.0(7)
Br(92)	C(9)	C(3a)	C(8a)	117.8(8)
Br(92)	C(9)	C(8a)	C(3a)	-107.2(9)
O(2)	C(2)	C(1)	C(8a)	83.2(8)
O(2)	C(2)	C(3)	C(3a)	-80.7(8)
O(2')	C(2')	N(1')	C(6')	6(1)
O(2')	C(2')	N(3')	C(5)	32(1)
O(5')	C(5')	N(1')	C(6')	-5(2)
O(5')	C(5')	N(4')	C(8)	-34(1)
O(7)	C(7)	C(8)	N(4')	134.9(8)
N(1')	C(2')	N(3')	N(4')	-6.9(8)
N(1')	C(5')	N(4')	N(3')	4.0(9)
N(1')	C(6')	C(7')	C(8')	178.3(8)
N(3')	N(4')	C(8)	C(7)	47.3(9)
N(3')	C(2')	N(1')	C(5')	9.5(9)
N(3')	C(5)	C(4)	C(3a)	-70(1)
N(4')	N(3')	C(5)	C(4)	78.2(9)
N(4')	C(5')	N(1')	C(2')	-8.3(9)
N(4')	C(8)	C(7)	C(6)	-52(1)
N(4')	C(8)	C(8a)	C(3a)	61(1)
C(1)	C(2)	O(2)	C(21)	173.5(8)
C(1)	C(8a)	C(3a)	C(3)	0.9(9)
C(1)	C(8a)	C(3a)	C(9)	109.8(7)
C(1)	C(8a)	C(9)	C(3a)	-95.5(9)
C(2)	C(1)	C(8a)	C(3a)	22.1(9)
C(2)	C(1)	C(8a)	C(9)	86.3(9)
C(2)	C(3)	C(3a)	C(8a)	-20.6(9)
C(02)	C(01)	O(01)	C(03)	-129(10)
C(2')	N(1')	C(6')	C(11')	35(1)
C(2')	N(3')	N(4')	C(8)	-143.7(7)
C(2')	N(3')	C(5)	C(6)	93.8(9)
C(3a)	C(8a)	C(1)	C(11)	152.7(8)
C(3a)	C(9)	C(8a)	C(8)	106(1)
C(3)	C(2)	C(1)	C(8a)	-35.2(8)
C(3)	C(3a)	C(4)	C(5)	-123.6(8)
C(3)	C(3a)	C(8a)	C(9)	-110.7(7)
C(4)	C(3a)	C(8a)	C(8)	-9(1)
C(4)	C(3a)	C(9)	C(8a)	-114(1)
C(5)	N(3')	N(4')	C(5')	146.6(7)
C(5)	C(4)	C(3a)	C(8a)	15(1)
C(5)	C(6)	C(7)	C(8)	7(1)
C(5')	N(1')	C(6')	C(11')	-147.8(9)
C(5')	N(4')	C(8)	C(8a)	144.9(8)
C(6)	C(7)	C(8)	C(8a)	73(1)
C(6')	C(11')	C(10')	C(9')	1(2)
C(7')	C(6')	C(11')	C(10')	2(1)
C(8)	C(7)	O(7)	C(71)	-60(1)
C(8)	C(8a)	C(3a)	C(9)	-116.6(9)
C(8')	C(9')	C(10')	C(11')	-3(2)
Br(6)	C(6)	C(5)	C(4)	96.5(7)
Br(6)	C(6)	C(7)	C(8)	-171.1(6)
Br(91)	C(9)	C(3a)	C(4)	135.5(7)
Br(91)	C(9)	C(8a)	C(1)	15(1)
Br(91)	C(9)	C(8a)	C(8)	-143.3(7)
Br(92)	C(9)	C(3a)	C(4)	3(1)
Br(92)	C(9)	C(8a)	C(1)	157.3(7)
Br(92)	C(9)	C(8a)	C(8)	-1(1)
O(2)	C(2)	C(1)	C(11)	-49.3(9)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle
O(2')	C(2')	N(1')	C(5')	-171.4(8)
O(2')	C(2')	N(3')	N(4')	173.9(8)
O(5')	C(5')	N(1')	C(2')	172.6(9)
O(5')	C(5')	N(4')	N(3')	-177.0(9)
O(7)	C(7)	C(6)	C(5)	-179.6(8)
O(7)	C(7)	C(8)	C(8a)	-100.4(9)
N(1')	C(2')	N(3')	C(5)	-148.9(7)
N(1')	C(5')	N(4')	C(8)	146.7(7)
N(1')	C(6')	C(11')	C(10')	178.2(8)
N(3')	N(4')	C(8)	C(8a)	-74.9(9)
N(3')	C(2')	N(1')	C(6')	173.1(7)
N(3')	C(5)	C(6)	C(7)	41(1)
N(4')	N(3')	C(5)	C(6)	-45.4(8)
N(4')	C(5')	N(1')	C(6')	174.3(8)
N(4')	C(8)	C(8a)	C(1)	-168.9(7)
N(4')	C(8)	C(8a)	C(9)	-11(1)
C(1)	C(2)	C(3)	C(3a)	34.3(8)
C(1)	C(8a)	C(3a)	C(4)	143.1(8)
C(1)	C(8a)	C(8)	C(7)	71.1(9)
C(01)	O(01)	C(03)	C(04)	126.2(1)
C(2)	C(1)	C(8a)	C(8)	-113.4(8)
C(2)	C(3)	C(3a)	C(4)	124.4(8)
C(2)	C(3)	C(3a)	C(9)	83.7(9)
C(2')	N(1')	C(6')	C(7')	-144.4(8)
C(2')	N(3')	N(4')	C(5')	2.0(9)
C(2')	N(3')	C(5)	C(4)	-142.6(8)
C(3a)	C(4)	C(5)	C(6)	50(1)
C(3a)	C(8a)	C(8)	C(7)	-59(1)
C(3)	C(2)	O(2)	C(21)	-72.8(9)
C(3)	C(2)	C(1)	C(11)	-167.7(8)
C(3)	C(3a)	C(8a)	C(8)	132.8(8)
C(3)	C(3a)	C(9)	C(8a)	94.2(9)
C(4)	C(3a)	C(8a)	C(9)	107.1(9)
C(4)	C(5)	C(6)	C(7)	-82(1)
C(5)	N(3')	N(4')	C(8)	1(1)
C(5)	C(4)	C(3a)	C(9)	86(1)
C(5')	N(1')	C(6')	C(7')	33(1)
C(5')	N(4')	C(8)	C(7)	-92.8(9)
C(6)	C(7)	O(7)	C(71)	128(1)
C(6')	C(7')	C(8')	C(9')	-1(2)
C(7)	C(8)	C(8a)	C(9)	-130.9(9)
C(7')	C(8')	C(9')	C(10')	3(2)
C(8)	C(8a)	C(1)	C(11)	17(1)
C(8')	C(7')	C(6')	C(11')	-1(1)
C(9)	C(8a)	C(1)	C(11)	-143.1(8)

Table 8: Non-bonded Contacts out to 3.60 Å.

atom	atom	distance	ADC	atom	atom	distance	ADC
Br(6)	C(7')	3.502(9)	75502	Br(91)	O(5')	3.440(6)	75602
Br(92)	C(04)	3.49(4)	55401	O(01)	C(02)	2.19(3)	84802
O(01)	C(04)	3.42(4)	85802	O(2')	C(71)	3.45(1)	75502
O(2')	C(8')	3.56(1)	56501	O(5')	C(4)	3.10(1)	54501
C(01)	C(04)	3.06(5)	85802	C(01)	C(02)	3.12(5)	84802
C(01)	C(04)	3.30(3)	56501	C(01)	C(03)	3.38(4)	85802
C(02)	C(03)	2.15(5)	85802	C(02)	C(04)	2.52(6)	85802

Table 8: Non-bonded Contacts out to 3.60 Å continued.

atom	atom	distance	ADC	atom	atom	distance	ADC
C(02)	C(04)	2.71(5)	56501	C(9')	C(21)	3.50(2)	64501

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:
(1) X, Y, Z (2) -X, 1/2+Y, -Z

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|F_o|-|F_c|)^2$ where

where: $w = 1/[\sigma^2(Fo)] = [\sigma^2{}_c(Fo) + p^2Fo^2/4]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$

where: N_o = number of observations

N_v = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

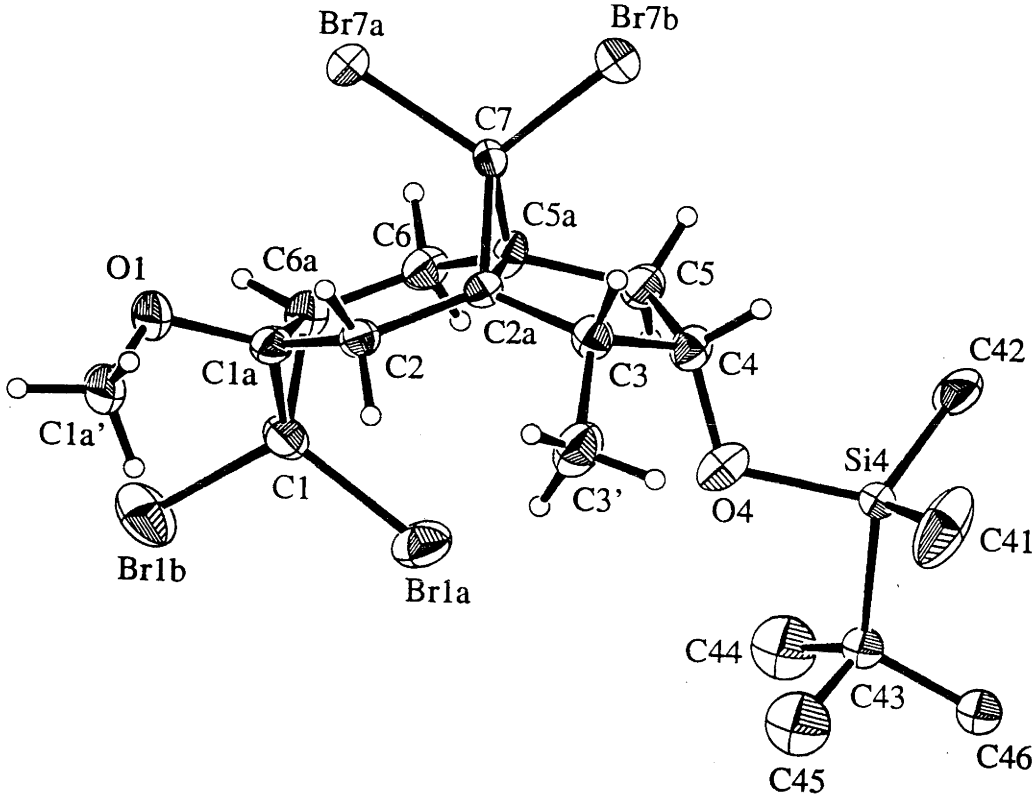
(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

A2.2 X-ray Structure Report for Compound 117.

X-ray crystal data are presented as provided by Dr. D. C. R. Hockless, The Australian National University.



Experimental

Data Collection

A colourless block crystal of $C_{19}H_{30}Br_4O_2Si$ having approximate dimensions of 0.20 x 0.16 x 0.08 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $60.57 < 2\theta < 75.92^{\circ}$ corresponded to a primitive orthorhombic cell with dimensions:

a = 7.512(2) Å
b = 13.354(2) Å
c = 24.066(2) Å
V = 2414.7(6) $Å^3$

For Z = 4 and F.W. = 638.15, the calculated density is 1.75 g/cm^3. The systematic absences of:

h00: $h \neq 2n$
0k0: $k \neq 2n$
00l: $l \neq 2n$

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of 23 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 119.9°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.33° with a take-off angle of 6.0°. Scans of (1.40 + 0.30 tan θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 2101 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 16.9%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 88.1 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.66 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques.[2] Most non-hydrogen atoms were refined anisotropically, but the structure contained a disordered group which was most successfully refined over two separate locations each with half occupancy and isotropic temperature factor values. Hydrogen atoms were omitted from this group. Those which were included over the rest of the molecule were inserted at calculated positions and held fixed. The final cycle of full-matrix least-squares refinement[3] was based on 1451 observed reflections ($I > 3.00\sigma(I)$) and 249 variable parameters and converged (largest parameter shift was 0.04 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.039$$

$$R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.047$$

The standard deviation of an observation of unit weight[4] was 2.15. The weighting scheme was based on counting statistics and included a factor ($p = 0.017$) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.37 and -0.37 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[5] Anomalous dispersion effects were included in Fcalc;[6] the values for Δf' and Δf" were those of Creagh and McAuley.[7] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[8] All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

EXPERIMENTAL D)ETAILS

A. Crystal Datta

Empirical Formula	$C_{19}H_{30}Br_4O_2Si$
Formula Weight	638.15
Crystal Color, Habit	colourless, block
Crystal Dimensions	0.20 X 0.16 X 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (60.6 - 75.9°)
Omega Scan Peak Width at Half-height	0.33°
Lattice Parameters	a = 7.514(2)Å b = 13.354(2) Å c = 24.066(2) Å V = 2414.7(6) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.755 g/cm^3
F_{000}	1256.00
$\mu(CuK\alpha)$	88.07 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R
Radiation	$CuK\alpha$ (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	23.0 °C
Scan Type	ω-2θ
Scan Rate	16.0°/min (in ω) (up to 4 scans)

Scan Width	$(1.40 + 0.30 \tan \theta)^{o}$
$2\theta_{max}$	119.9^{o}
No. of Reflections Measured	Total: 2101
Corrections	Lorentz-polarization Absorption (trans. factors: 0.6553 - 1.0000) Decay (16.93% decline)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (\lvert Fo \rvert - \lvert Fc \rvert)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0170
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	1451
No. Variables	249
Reflection/Parameter Ratio	5.83
Residuals: R; Rw	0.039 ; 0.047
Goodness of Fit Indicator	2.15
Max Shift/Error in Final Cycle	0.04
Maximum peak in Final Diff. Map	$0.37\ e^-/Å^3$
Minimum peak in Final Diff. Map	$-0.37\ e^-/Å^3$

Table 1: Atomic coordinates and B_{iso}/B_{eq} and occupancy.

atom	x	y	z	Beq	occ
Br(1a)	-0.6749(3)	0.1777(1)	0.04406(7)	7.39(5)	
Br(1b)	-0.6881(3)	0.2135(1)	-0.08563(8)	8.89(6)	
Br(7a)	-0.6645(2)	-0.2208(1)	-0.03170(5)	5.07(3)	
Br(7b)	-0.6656(2)	-0.2831(1)	0.09344(5)	5.63(4)	
Si(4)	-0.734(2)	0.0507(7)	0.2475(5)	4.7(2)	1/2
Si(4')	-0.664(2)	0.098(1)	0.2354(5)	8.3(4)	1/2
O(1)	-0.499(1)	0.0079(7)	-0.0899(3)	5.5(3)	
O(4)	-0.663(2)	0.0435(7)	0.1777(3)	6.3(3)	
C(1)	-0.678(2)	0.116(1)	-0.0282(5)	5.3(3)	
C(1a)	-0.571(2)	0.021(1)	-0.0370(6)	4.3(4)	
C(1a')	-0.328(3)	0.053(1)	-0.0955(6)	6.8(4)	
C(2a)	-0.561(2)	-0.075(1)	0.0567(5)	3.6(3)	
C(2)	-0.457(2)	-0.023(1)	0.0093(5)	4.1(3)	
C(3)	-0.495(2)	-0.069(1)	0.1157(5)	4.5(4)	
C(3')	-0.352(2)	0.007(1)	0.1268(6)	7.2(5)	
C(4)	-0.657(2)	-0.054(1)	0.1530(5)	4.7(3)	
C(5)	-0.831(2)	-0.067(1)	0.1157(5)	5.2(4)	
C(5a)	-0.764(2)	-0.077(1)	0.0547(5)	4.4(4)	
C(6)	-0.870(2)	-0.028(1)	0.0106(5)	5.2(4)	
C(6a)	-0.770(2)	0.020(1)	-0.0347(6)	4.7(4)	
C(7)	-0.665(2)	-0.1709(8)	0.0427(4)	3.7(3)	
C(41)	-0.540(3)	0.026(2)	0.2912(7)	12.1(8)	
C(42)	-0.897(6)	-0.033(3)	0.266(2)	8(1)	1/2
C(42')	-0.549(6)	0.241(3)	0.226(2)	10(1)	1/2
C(43)	-0.784(4)	0.188(2)	0.251(1)	4.3(6)	1/2
C(43')	-0.888(6)	0.135(4)	0.257(2)	9(1)	1/2
C(44')	-0.894(4)	0.186(2)	0.314(1)	5.9(8)	1/2
C(44)	-0.905(6)	0.226(3)	0.208(2)	10(1)	1/2
C(45')	-1.006(5)	0.184(3)	0.214(2)	7.6(9)	1/2
C(45)	-0.671(7)	0.249(4)	0.234(2)	10(1)	1/2
C(46)	-0.813(4)	0.224(2)	0.309(1)	5.1(6)	1/2
C(46')	-0.975(7)	0.013(4)	0.267(2)	9(1)	1/2
H(1a'b)	-0.3257	0.1139	-0.0750	8.1258	
H(1a'c)	-0.3061	0.0669	-0.1336	8.1258	
H(1a'a)	-0.2398	0.0090	-0.0817	8.1258	
H(2b)	-0.3887	0.0294	0.0251	4.9345	
H(2a)	-0.3789	-0.0714	-0.0068	4.9345	
H(3'b)	-0.3859	0.0701	0.1119	8.6276	
H(3'c)	-0.2440	-0.0142	0.1097	8.6276	
H(3'a)	-0.3338	0.0132	0.1658	8.6276	
H(3)	-0.4470	-0.1324	0.1247	5.3513	
H(4)	-0.6563	-0.1030	0.1815	5.6755	
H(5b)	-0.9065	-0.0107	0.1195	6.2194	
H(5a)	-0.8932	-0.1260	0.1264	6.2194	
H(6b)	-0.9416	0.0217	0.0276	6.2530	
H(6)	-0.8242	0.0121	-0.0700	5.6438	
H(6a)	-0.9438	-0.0780	-0.0055	6.2530	

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 2: Anisotropic Displacement Parameters.

atom	U11	U22	U33	U12	U13	U23
Br(1a)	0.100(1)	0.074(1)	0.018(1)	0.007(1)	0.013(1)	-0.031(1)
Br(1b)	0.120(2)	0.088(1)	0.130(1)	0.028(2)	0.013(2)	0.046(1)
Br(7a)	0.079(1)	0.0634(8)	0.0503(7)	-0.003(1)	0.002(1)	-0.0115(7)
Br(7b)	0.087(1)	0.0631(9)	0.0642(8)	-0.00791)	0.005(1)	0.0086(8)
Si(4)	0.086(8)	0.047(5)	0.044(5)	-0.018(5)	0.005(5)	-0.001(4)
Si(4')	0.11(1)	0.14(1)	0.061(7)	0.05(1)	-0.013(9)	-0.039(8)
O(1)	0.072(7)	0.078(7)	0.057(6)	-0.003(6)	0.018(6)	0.003(5)
O(4)	0.085(7)	0.086(7)	0.067(5)	0.006(8)	-0.009(7)	-0.028(5)
C(1)	0.08(1)	0.061(8)	0.064(8)	-0.01(1)	-0.01(1)	0.014(7)
C(1a)	0.07(1)	0.043(9)	0.050(8)	0.005(8)	-0.007(9)	-0.001(7)
C(1a')	0.12(1)	0.08(1)	0.066(9)	0.00(1)	0.04(1)	-0.001(8)
C(2a)	0.047(9)	0.043(8)	0.046(8)	0.003(7)	-0.001(7)	-0.006(7)
C(2)	0.053(9)	0.051(9)	0.052(8)	-0.003(8)	0.001(7)	-0.005(7)
C(3)	0.045(9)	0.07(1)	0.056(8)	-0.006(9)	0.007(8)	-0.002(8)
C(3')	0.08(1)	0.12(1)	0.068(9)	-0.02(1)	0.00(1)	-0.02(1)
C(4)	0.068(9)	0.063(9)	0.049(7)	0.01(1)	-0.012(9)	0.000(7)
C(5)	0.067(9)	0.07(1)	0.057(8)	-0.01(1)	0.00(1)	-0.010(8)
C(5a)	0.05(1)	0.08(1)	0.035(8)	-0.003(9)	-0.005(7)	-0.009(8)
C(6)	0.07(1)	0.06(1)	0.061(9)	0.000(9)	-0.008(8)	-0.010(8)
C(6a)	0.049(9)	0.08(1)	0.055(9)	0.001(8)	-0.008(8)	0.001(9)
C(7)	0.053(7)	0.050(7)	0.039(6)	-0.007(8)	0.003(8)	0.005(5)
C(41)	0.21(2)	0.18(2)	0.07(1)	0.11(2)	-0.05(1)	-0.02(1)
C(42)	0.013(4)	0.10(3)	0.09(2)	-0.04(3)	0.05(3)	-0.05(2)
C(42')	0.14(4)	0.10(3)	0.15(4)	-0.08(3)	0.08(3)	-0.06(3)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 3: Bond Lengths (Å).

atom	atom	distance	atom	atom	distance
Br(1a)	C(1)	1.92(1)	Br(1b)	C(1)	1.90(1)
Br(7a)	C(7)	1.91(1)	Br(7b)	C(7)	1.93(1)
Si(4)	Si(4')	0.87(2)	Si(4)	O(4)	1.77(1)
Si(4)	C(41)	1.83(2)	Si(4)	C(42)	1.72(4)
Si(4)	C(43)	1.87(3)	Si(4)	C(43')	1.63(5)
Si(4)	C(46')	1.94(6)	Si(4')	O(4)	1.57(1)
Si(4')	C(41)	1.89(2)	Si(4')	C(42')	2.10(4)
Si(4')	C(43)	1.55(3)	SI(4')	C(43')	1.83(5)
Si(4')	C(45)	2.02(5)	O(1)	C(1a)	1.40(2)
O(1)	C(1a')	1.42(2)	O(4)	C94)	1.43(1)
C(1)	C(1a)	1.52(2)	C(1)	C(6a)	1.46(2)
C(1a)	C(2)	1.52(2)	C(1a)	C(6a)	1.49(2)
C(2a)	C(2)	1.55(2)	C(2a)	C(3)	1.51(2)
C(2a)	C(5a)	1.53(2)	C(2a)	C(7)	1.53(2)
C(3)	C(3')	1.50(2)	C(3)	C(4)	1.52(2)
C(4)	C(5)	1.60(2)	C(5)	C(5a)	1.55(2)
C(5a)	C(6)	1.47(2)	C(5a)	C(7)	1.49(2)
C(6)	C(6a)	1.47(2)	C(42)	C(46')	0.85(6)
C(42')	C(45)	0.94(6)	C(43)	C(43')	1.06(5)
C(43)	C(44')	1.72(4)	C(43)	C(44)	1.47(5)
C(43)	C(45)	1.24(5)	C(43)	C(46)	1.49(4)
C(43')	C(44')	1.52(5)	C(43')	C(44)	1.71(6)
C(43')	C(45')	1.52(5)	C(43')	C(46)	1.81(5)
C(43')	C(46')	1.78(6)	C(44')	C(46)	0.79(4)

Table 3: Bond Lengths (Å) continued.

atom	atom	distance	atom	atom	distance
C(44)	C(45')	0.95(5)			

Table 4: Bond Lengths (Å).

atom	atom	distance	atom	atom	distance
C(1a')	H(1a'b)	0.95	C(1a')	H(1a'c)	0.95
C(1a')	H(1a'a)	0.95	C(2)	H(2b)	0.95
C(2)	H(2a)	0.95	C(3)	H(3)	0.95
C(3')	H(3a'b)	0.95	C(3')	H(3'c)	0.95
C(3')	H(3'a)	0.95	C(4)	H(4)	0.95
C(5)	H(5b)	0.95	C(5)	H(5a)	0.95
C(6)	H(6a)	0.95	C(6)	H(6a)	0.95
C(6a)	H(6)	0.95			

Table 5: Bond Angles (°).

atom	atom	atom	angle	atom	atom	atom	angle
Si(4')	Si(4)	O(4)	63(1)	Si(4')	Si(4)	C(41)	81(2)
Si(4')	Si(4)	C(42)	172(3)	Si(4')	Si(4)	C(43)	55(2)
Si(4')	Si(4)	C(43')	89(2)	Si(4')	Si(4)	C(46')	147(2)
O(4)	Si(4)	C(41)	107(1)	O(4)	Si(4)	C(42)	116(1)
O(4)	Si(4)	C(43)	99(1)	O(4)	Si(4)	C(43')	113(2)
O(4)	Si(4)	C(46')	120(2)	C(41)	Si(4)	C(42)	107(2)
C(41)	Si(4)	C(43)	108(1)	C(41)	Si(4)	C(43')	127(2)
C(41)	Si(4)	C(46')	124(2)	C(42)	Si(4)	C(43)	119(2)
C(42)	Si(4)	C(43')	85(2)	C(42)	Si(4)	C(46')	26(2)
C(43)	Si(4)	C(43')	34(2)	C(43)	Si(4)	C(46')	93(2)
C(43')	Si(4)	C(46')	59(2)	Si(4)	Si(4')	O(4)	88(2)
Si(4)	Si(4')	C(41)	72(2)	Si(4)	Si(4')	C(42')	160(2)
Si(4)	Si(4')	C(43)	97(2)	Si(4)	Si(4')	C(43')	63(2)
Si(4)	Si(4')	C(45)	135(3)	O(4)	Si(4')	C(41)	113(1)
Si(4)	Si(4')	C(45)	135(3)	O(4)	Si(4')	C(41)	113(1)
O(4)	Si(4')	C(42')	109(1)	O(4)	Si(4')	C(43)	125(1)
O(4)	Si(4')	C(43')	113(2)	O(4)	Si(4')	C(45)	117(2)
C(41)	Si(4')	C(42')	109(2)	C(41)	Si(4')	C(43)	121(1)
C(41)	Si(4')	C(43')	113(2)	C(41)	Si(4')	C(45)	122(2)
C(42')	Si(4')	C(43)	64(2)	C(42')	Si(4')	C(43')	99(2)
C(42')	Si(4')	C(45)	26(2)	C(43)	Si(4')	C(43')	36(2)
C(43)	Si(4')	C(45)	38(2)	C(43')	Si(4')	C(45)	73(2)
C(1a)	O(1)	C(1a')	113(1)	Si(4)	O(4)	Si(4')	29.6(7)
Si(4)	O(4)	C(4)	117.1(9)	Si(4')	O(4)	C(4)	142(1)
Br(1a)	C(1)	Br(1b)	111.3(7)	Br(1a)	C(1)	C(1a)	119(1)
Br(1a)	C(1)	C(6a)	118(1)	Br(1b)	C(1)	C(1a)	120(1)
Br(1b)	C(1)	C(6a)	120(1)	C(1a)	C(1)	C(6a)	60.2(8)
O(1)	C(1a)	C(1)	116(1)	O(1)	C(1a)	C(2)	113(1)
O(1)	C(1a)	C(6a)	115(1)	C(1)	C(1a)	C(2)	121(1)
C(1)	C(1a)	C(6a)	58(1)	C(2)	C(1a)	C(6a)	122(1)
C(2)	C(2a)	C(3)	120(1)	C(2)	C(2a)	C(5a)	119(1)
C(2)	C(2a)	C(7)	118(1)	C(3)	C(2a)	C(5a)	111(1)
C(3)	C(2a)	C(7)	115(1)	C(5a)	C(2a)	C(7)	58.4(9)
C(1a)	C(2)	C(2a)	115(1)	C(2a)	C(3)	C(3')	116(1)
C(2a)	C(3)	C(4)	108(1)	C(3')	C(3)	C(4)	112(1)
O(4)	C(4)	C(3)	113(1)	O(4)	C(4)	C(5)	108(1)

Table 5: Bond Angles (°) continued.

atom	atom	atom	angle	atom	atom	atom	angle
C(3)	C(4)	C(5)	107.8(9)	C(4)	C(5)	C(5a)	106(1)
C(2a)	C(5a)	C(5)	107(1)	C(2a)	C(5a)	C(6)	124(1)
C(2a)	C(5a)	C(7)	61.0(9)	C(5)	C(5a)	C(6)	118(1)
C(5)	C(5a)	C(7)	114(1)	C(6)	C(5a)	C(7)	120(1)
C(5a)	C(6)	C(6a)	117(1)	C91)	C(6a)	C(1a)	62(1)
C(1)	C(6a)	C(6)	123(1)	C(1a)	C(6a)	C(6)	123(1)
Br(7a)	C(7)	Br(7b)	108.8(5)	Br(7a)	C(7)	C(2a)	119.7(8)
Br(7a)	C(7)	C(5a)	118.5(9)	Br(7b)	C(7)	C(2a)	120.6(8)
Br(7b)	C(7)	C(5a)	122.9(9)	C(2a)	C(7)	C(5a)	60.6(7)
Si(4)	C(41)	Si(4')	27.0(6)	Si(4)	C(42)	C(46')	92(6)
Si(4')	C(42')	C(45)	72(4)	Si(4)	C(43)	Si(4')	27.5(9)
Si(4)	C(43)	C(43')	60(3)	Si(4)	C(43)	C(44')	97(2)
Si(4)	C(43)	C(44)	116(3)	Si(4)	C(43)	C(45)	119(3)
Si(4)	C(43)	C(46)	112(2)	Si(4')	C(43)	C(43')	87(3)
Si(4)	C(43)	C(44')	119(2)	Si(4')	C(43)	C(44)	118(3)
Si(4')	C(43)	C(45)	92(3)	Si(4')	C(43)	C(46)	124(2)
C(43')	C(43)	C(44')	61(3)	C(43')	C(43)	C(44)	83(3)
C(43')	C(43)	C(45)	169(5)	C(43')	C(43)	C(46)	88(3)
C(44')	C(43)	C(44)	109(3)	C(44')	C(43)	C(45)	128(3)
C(44')	C(43)	C(46)	27(2)	C(44)	C(43)	C(45)	88(3)
C(44)	C(43)	C(46)	117(3)	C(45)	C(43)	C(46)	101(3)
Si(4)	C(43')	Si(4')	28.5(9)	Si(4)	C(43')	C(43)	85(3)
Si(4)	C(43')	C(44')	118(3)	Si(4)	C(43')	C(44)	117(3)
Si(4)	C(43')	C(45')	128(3)	Si(4)	C(43')	C(46)	110(3)
Si(4)	C(43')	C(46')	69(2)	Si(4')	C(43')	C(43)	58(3)
Si(4')	C(43')	C(44')	114(3)	Si(4')	C(43')	C(44)	94(3)
Si(4')	C(43')	C(45')	117(3)	Si(4')	C(43')	C(46)	95(2)
Si(4')	C(43')	C(46')	97(3)	C(43)	C(43')	C(44')	82(4)
C(43)	C(43')	C(44)	59(3)	C(43)	C(43')	C(45')	92(4)
C(43)	C(43')	C(46)	56(3)	C(43)	C(43')	C(46')	154(5)
C(44')	C(43')	C(44)	107(3)	C(44')	C(43')	C(45')	114(4)
C(44')	C(43')	C(46)	26(2)	C(44')	C(43')	C(46')	107(4)
C(44)	C(43')	C(45')	34(2)	C(44)	C(43')	C(46)	92(3)
C(44)	C(43')	C(46')	136(4)	C(45')	C(43')	C(46)	112(3)
C(45')	C(43')	C(46')	106(4)	C(46)	C(43')	C(46')	129(3)
C(43)	C(44')	C(43')	38(2)	C(43)	C(44')	C(46)	60(3)
C(43')	C(44')	C(46)	97(4)	C(43)	C(44)	C(43')	38(2)
C(43)	C(44)	C(45')	101(5)	C(43')	C(44)	C(45')	62(4)
C(43')	C(45')	C(44)	84(4)	Si(4')	C(45)	C(42')	82(5)
Si(4')	C(45)	C(43)	50(2)	C(42')	C(45)	C(43)	131(7)
C(43)	C(46)	C(43')	36(2)	C(43)	C(46)	C(44')	93(4)
C(43')	C(46)	C(44')	57(4)	Si(4)	C(46')	C(42)	63(5)
Si(4)	C(46')	C(43')	52(2)	C(42)	C(46')	C(43')	114(6)

Table 6: Bond Angles (°).

atom	atom	atom	angle	atom	atom	atom	angle
O(1)	C(1a')	H(1a'b)	109.3	O(1)	C(1a')	H(1a'c)	109.3
O(1)	C(1a')	H(1a'a)	109.5	H(1a'b)	C(1a')	H(1a'c)	109.4
H(1a'b)	C(1a')	H(1a'a)	109.6	H(1a'c)	C(1a')	H(1a'a)	109.6
C(1a)	C(2)	H(2b)	108.1	C(1a)	C(2)	H(2a)	108.8
C(2a)	C(2)	H(2b)	108.1	C(2a)	C(2)	H(2a)	108.0
H(2b)	C(2)	H(2a)	109.5	C(2a)	C(3)	H(3)	106.7
C(3')	C(3)	H(3)	106.9	C(4)	C(3)	H(3)	106.7
C(3)	C(3')	H(3a'b)	109.8	C(3)	C(3')	H(3'c)	109.5
C(3)	C(3')	H(3'a)	109.7	H(3'b)	C(3')	H(3'c)	109.2

Table 6: Bond Angles (°) continued.

atom	atom	atom	angle	atom	atom	atom	angle
H(3'b)	C(3')	H(3'a)	109.6	H(3'c)	C(3')	H(3'a)	109.0
O(4)	C(4)	H(4)	109.2	C(3)	C(4)	H(4)	109.3
C(5)	C(4)	H(4)	109.3	C(4)	C(5)	H(5b)	110.5
C(4)	C(5)	H(5a)	110.4	C(5a)	C(5)	H(5b)	110.3
C(5a)	C(5)	H(5a)	110.3	H(5b)	C(5a)	H(5a)	109.3
C(5a)	C(6)	H(6b)	107.5	C(5a)	C(6)	H(6a)	107.7
C(6a)	C(6)	H(6b)	107.5	C(6a)	C(6)	H(6a)	107.6
H(6b)	C(6)	H(6a)	109.5	C(1)	C(6a)	H(6)	113.4
C(1a)	C(6a)	H(6)	113.4	C(6)	C(6a)	H(6)	113.3

Table 7: Torsion Angles (°).

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Br(1a)	C(1)	C(1a)	O(1)	-147(1)	Br(1a)	C(1)	C(1a)	C(2)	-3(2)
Br(1a)	C(1)	C(1a)	C(6a)	108(1)	Br(1a)	C(1)	C(6a)	C(1a)	-109(1)
Br(1a)	C(1)	C(6a)	C(6)	4(2)	Br(1b)	C(1)	C(1a)	O(1)	-5(2)
Br(1b)	C(1)	C(1a)	C(2)	139(1)	Br(1b)	C(1)	C(1a)	C(6a)	-110(1)
Br(1b)	C(1)	C(6a)	C(1a)	109(1)	Br(1b)	C(1)	C(6a)	C(6)	-139(1)
Br(7a)	C(7)	C(2a)	C(2)	-1(2)	Br(7a)	C(7)	C(2a)	C(3)	-152(1)
Br(7a)	C(7)	C(2a)	C(5a)	108(1)	Br(7a)	C(7)	C(5a)	C(2a)	-110(1)
Br(7a)	C(7)	C(5a)	C(5)	154(1)	Br(7a)	C(7)	C(5a)	C(6)	4(2)
Br(7b)	C97)	C(2a)	C(2)	139(1)	Br(7b)	C(7)	C(2a)	C(3)	-12(2)
Br(7b)	C(7)	C(2a)	C(5a)	-112(1)	Br(7b)	C(7)	C(5a)	C(2a)	110(1)
Br(7b)	C(7)	C(5a)	C(5)	13(2)	Br(7b)	C(7)	C(5a)	C(6)	-136(1)
Si(4)	Si(4')	O(4)	C(4)	-40(3)	Si(4)	Si(4')	C(42')	C(45)	-33(10)
Si(4)	Si(4')	C(43)	C(43')	-13(3)	Si(4)	Si(4')	C(43)	C(44')	41(3)
Si(4)	Si(4')	C(43)	C(44)	-93(3)	Si(4)	Si(4')	C(43)	C(45)	178(3)
Si(4)	Si(4')	C(43)	C(46)	73(3)	Si(4)	Si(4')	C(43')	C(43)	166(4)
Si(4)	Si(4')	C(43')	C(44')	104(4)	Si(4)	Si(4')	C(43')	C(44)	-145(3)
Si(4)	Si(4')	C(43')	C(45')	-120(4)	Si(4)	Si(4')	C(43')	C(46)	122(3)
Si(4)	Si(4')	C(43')	C(46')	-8(3)	Si(4)	Si(4')	C(45)	C(42')	165(4)
Si(4)	Si(4')	C(45)	C(43)	-3(5)	Si(4)	O(4)	Si(4')	C(41)	70(2)
Si(4)	O(4)	Si(4')	C(42')	-169(3)	Si(4)	O(4)	Si(4')	C(43)	-98(3)
Si(4)	O(4)	Si(4')	C(43')	-59(2)	Si(4)	O(4)	Si(4')	C(45)	-141(3)
Si(4)	O(4)	C(4)	C(3)	-140(1)	Si(4)	O(4)	C(4)	C(5)	100(1)
Si(4)	C(41)	Si(4')	O(4)	-80(2)	Si(4)	C(41)	Si(4')	C(42')	159(2)
Si(4)	C(41)	Si(4')	C(43)	88(2)	Si(4)	C(41)	Si(4')	C(43')	49(2)
Si(4)	C(41)	Si(4')	C945)	13393)	Si(4)	C942)	C(46')	C(43')	-7(6)
Si(4)	C(43)	Si(4')	O(4)	93(2)	Si(4)	C943)	Si(4')	C(41)	-74(2)
Si(4)	C(43)	Si(4')	C(42')	-172(2)	Si(4)	C(43)	Si(4')	C(43')	13(3)
Si(4)	C(43)	Si(4')	C(45)	-178(3)	Si(4)	C(43)	C(43')	Si(4')	-7(2)
Si(4)	C(43)	C(43')	C(44')	119(3)	Si(4)	C(43)	C(43')	C(44)	-125(2)
Si(4)	C(43)	C(43')	C(45')	-127(3)	Si(4)	C(43)	C(43')	C(46)	117(2)
Si(4)	C(43)	C(43')	C(46')	7(10)	Si(4)	C(43)	C(44')	C(43')	-50(3)
Si(4)	C(43)	C(44')	C(46)	127(4)	Si(4)	C(43)	C(44)	C(43')	52(3)
Si(4)	C(43)	C(44)	C(45')	56(5)	Si(4)	C(43)	C(45)	Si(4')	1(2)
Si(4)	C(43)	C(45)	C(42')	-14.9(1)	Si(4)	C(43)	C(46)	C(43')	-56(3)
Si(4)	C(43)	C(46)	C(44')	-59(4)	Si(4)	C(43')	Si(4')	O(4)	75(2)
Si(4)	C(43')	Si(4')	C(41)	-54(2)	Si(4)	C(43')	Si(4')	C(42')	-170(2)
Si(4)	C(43')	Si(4')	C(43)	-166(4)	Si(4)	C(43')	Si(4')	C(45)	-173(3)
Si(4)	C(43')	C(43)	Si(4')	7(2)	Si(4)	C(43')	C(43)	C(44')	-119(3)
Si(4)	C(43')	C(43)	C(44)	125(2)	Si(4)	C(43')	C(43)	C(45)	89.8(2)
Si(4)	C(43')	C(43)	C(46)	-117(2)	Si(4)	C(43')	C(44')	C(43)	80(4)
Si(4)	C(43')	C(44')	C(46)	78(5)	Si(4)	C(43')	C944)	C(43)	-66(4)
Si(4)	C(43')	C(44)	C(45')	118(5)	Si(4)	C(43')	C(45')	C(44)	-82(6)
Si(4)	C(43')	C(46)	C(43)	70(3)	Si(4)	C(43')	C(46)	C(44')	-113(5)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Si(4)	C(43')	C(46')	C(42)	8(6)	Si(4)	C(46')	C(43)	Si(4')	4(1)
Si(4)	C(46')	C(43')	C(43)	-7.9(1)	Si(4)	C(46')	C(43')	C(44')	-114(3)
Si(4)	C(46')	C(43')	C(44)	107(5)	Si(4)	C(46')	C(43')	C(45')	125(3)
Si(4)	C(46')	C(43')	C(46)	-99(4)	Si(4')	Si(4)	O(4)	C(4)	154(2)
Si(4')	Si(4)	C(42)	C(46')	-31.3(2)	Si(4')	Si(4)	C(43)	C(43')	165(4)
Si(4')	Si(4)	C(43)	C(44')	-144(2)	Si(4')	Si(4)	C(43)	C(44)	101(3)
Si(4')	Si(4)	C(43)	C(45)	-3(4)	Si(4')	Si(4)	C(43)	C(46)	-121(3)
Si(4')	Si(4)	C(43')	C(43)	-12(3)	Si(4')	Si(4)	C(43')	C944')	-90(4)
Si(4')	Si(4)	C(43')	C(44)	39(4)	Si(4')	Si(4)	C(43')	C(45')	77(5)
Si(4')	Si(4)	C(43')	C(46)	-63(3)	Si(4')	Si(4)	C(43')	C(46')	171(3)
Si(4')	Si(4)	C(46')	C(42)	172(5)	Si(4')	Si(4)	C(46')	C(43')	-16(5)
Si(4')	O(4)	Si(4)	C(41)	-69(2)	Si(4')	O(4)	Si(4)	C(42)	171(3)
Si(4')	O(4)	Si(4)	C943)	43(2)	Si(4')	O(4)	Si(4)	C(43')	76(2)
Si(4')	O(4)	Si(4)	C(46')	142(3)	Si(4')	O(4)	C(4)	C(3)	-119(2)
Si(4')	O(4)	C(4)	C(5)	121(2)	Si(4')	C(41)	Si(4)	O(4)	57(1)
Si(4')	C(41)	Si(4)	C(42)	-178()	Si(4')	C(41)	Si(4)	C(43)	-48(1)
Si(4')	C(41)	Si(4)	C(43')	-81(3)	Si(4')	C(41)	Si(4)	C(46')	-156(3)
Si(4')	C(42')	C(45)	C(43)	12(7)	Si(4')	C(43)	Si(4)	O(4)	-47(2)
Si(4')	C(43)	Si(4)	C(41)	64(2)	Si(4')	C(43)	Si(4)	C(42)	-173(3)
Si(4')	C(43)	Si(4)	C(43')	-165(4)	Si(4')	C(43)	Si(4)	C(46')	-168(2)
Si(4')	C(43)	C(43')	C(44')	126(2)	Si(4')	C(43)	C(43')	C(44)	-118(2)
Si(4')	C(43)	C(43')	C(45')	-121(2)	Si(4')	C(43)	C(43')	C(46)	124(2)
Si(4')	C(43)	C(43')	C(46')	14.1(1)	Si(4')	C(43)	C(44')	C(43')	-68(4)
Si(4')	C(43)	C(44')	C(46)	109(4)	Si(4')	C(43)	C(44)	C(43')	83(4)
Si(4')	C(43)	C(44)	C(45')	87(5)	Si(4')	C(43)	C(45)	C(42')	-16(9)
Si(4')	C(43)	C(46)	C(43')	-85(4)	Si(4')	C(43)	C(46)	C(44')	-88(4)
Si(4')	C(43')	Si(4)	O(4)	-59(1)	Si(4')	C(43')	Si(4)	C(41)	77(2)
Si(4')	C(43')	Si(4)	C(42)	-175(2)	Si(4')	C(43')	Si(4)	C(43)	12(3)
Si(4')	C(43')	Si(4)	C(46')	-171(3)	Si(4')	C(43')	C(43)	C(44')	-126(2)
Si(4')	C(43')	C(43)	C(44)	118(2)	Si(4')	C(43')	C(43)	C(45)	83.1(2)
Si(4')	C(43')	C(43)	C(46)	-124(2)	Si(4')	C(43')	C(44')	C(43)	49(3)
Si(4')	C(43')	C(44')	C(46)	46(5)	Si(4')	C(43')	C(44)	C(43)	-48(3)
Si(4')	C(43')	C(44)	C(45')	136(5)	Si(4')	C(43')	C(45')	C(44)	-51(5)
Si(4')	C(43')	C(46)	C(43)	45(2)	Si(4')	C(43')	C(46)	C(44')	-139(4)
Si(4')	C(43')	C(46')	C(42)	12(7)	Si(4')	C(45)	C(43)	C(43')	-82.6(2)
Si(4')	C(45)	C(43)	C(44')	130(4)	Si(4')	C(45)	C(43)	C(44)	-118(3)
Si(4')	C(45)	C(43)	C(46)	125(3)	O(1)	C(1a)	C(1)	C(6a)	105(2)
O(1)	C(1a)	C(2)	C(2a)	-141(1)	O(1)	C(1a)	C(6a)	C(1)	-106(1)
O(1)	C(1a)	C(6a)	C(6)	141(1)	O(4)	Si(4)	Si(4')	C(41)	-115(1)
O(4)	Si(4)	Si(4')	C(42')	147(7)	O(4)	Si(4)	Si(4')	C(43)	125(2)
O(4)	Si(4)	Si(4')	C(43')	117(2)	O(4)	Si(4)	Si(4')	C(45)	127(3)
O(4)	Si(4)	C(42)	C(46')	-106(5)	O(4)	Si(4)	C(43)	C(43')	118(3)
O(4)	Si(4)	C(43)	C(44')	168(2)	O(4)	Si(4)	C(43)	C(44)	54(3)
O(4)	Si(4)	C(43)	C(45)	-50(4)	O(4)	Si(4)	C(43)	C(46)	-168(2)
O(4)	Si(4)	C(43')	C(43)	-71(3)	O(4)	Si(4)	C(43')	C(44')	-149(3)
O(4)	Si(4)	C(43')	C(44)	-20(4)	O(4)	Si(4)	C(43')	C(45')	18(5)
O(4)	Si(4)	C(43')	C(46)	-122(2)	O(4)	Si(4)	C(43')	C(46')	112(2)
O(4)	Si(4)	C(46')	C(42)	88(6)	O(4)	Si(4)	C(46')	C(43')	-100(2)
O(4)	Si(4')	Si(4)	C(41)	115(1)	O(4)	Si(4')	Si(4)	C(42)	-78.9(1)
O(4)	Si(4')	Si(4)	C(43)	-125(2)	O(4)	Si(4')	Si(4)	C(43')	-117(2)
O(4)	Si(4')	Si(4)	C(46')	-103(4)	O(4)	Si(4')	C(42')	C(45)	112(5)
O(4)	Si(4')	C(43)	C(43')	80(4)	O(4)	Si(4')	C(43)	C(44')	134(2)
O(4)	Si(4')	C(43)	C(44)	-1(4)	O(4)	Si(4')	C(43)	C(45)	-90(3)
O(4)	Si(4')	C(43)	C(46)	166(2)	O(4)	Si(4')	C(43')	C(43)	-119(3)
O(4)	Si(4')	C(43')	C(44')	179(3)	O(4)	Si(4')	C(43')	C(44)	-70(3)
O(4)	Si(4')	C(43')	C(45')	-45(4)	O(4)	Si(4')	C(43')	C(46)	-163(2)
O(4)	Si(4')	C(43')	C(46')	67(3)	O(4)	Si(4')	C(45)	C(42')	-79(5)
O(4)	Si(4')	C(45)	C(43)	114(3)	O(4)	C(4)	C(3)	C(2a)	-111(1)
O(4)	C(4)	C(3)	C(3')	18(2)	O(4)	C(4)	C(5)	C(5a)	115(1)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle
C(1)	C(1a)	O(1)	C(1a')	87(2)
C(1)	C(1a)	C(6a)	C(6)	-113(2)
C(1)	C(6a)	C(6)	C(5a)	-75(2)
C(1a)	C(2)	C(2a)	C(3)	-145(1)
C(1a)	C(2)	C(2a)	C(7)	66(2)
C(1a')	O(1)	C(1a)	C(2)	-60(2)
C(2a)	C(2)	C(1a)	C(6a)	4(2)
C(2a)	C(5a)	C(5)	C(4)	3(2)
C(2a)	C9&0	C(5a)	C(5)	-97(1)
C(2)	C(1a)	C(1)	C(6a)	-111(2)
C(2)	C(2a)	C(3)	C(3')	13(2)
C(2)	C(2a)	C(5a)	C(5)	-145(1)
C(2)	C(2a)	C(5a)	C(7)	107(1)
C(3)	C(2a)	C(5a)	C(5)	2(2)
C(3)	C(2a)	C(5a)	C(7)	-107(1)
C(3)	C(4)	C(5)	C(5a)	-7(1)
C(3')	C(3)	C(2a)	C(7)	163(1)
C(4)	O(4)	Si(4)	C(41)	84(2)
C(4)	O(4)	Si(4)	C(43)	-164(1)
C(4)	O(4)	Si(4)	C(46')	-64(2)
C(4)	O(4)	Si(4')	C(42')	151(2)
C(4)	O(4)	Si(4')	C(43')	-99(3)
C(4)	C(3)	C(2a)	C(5a)	-6(2)
C(4)	C(5)	C(5a)	C(6)	-142(1)
C(5)	C(5a)	C(2a)	C(7)	109(1)
C(6)	C(5a)	C(2a)	C(7)	-108(2)
C(41)	Si(4)	Si(4')	C(42')	-98(7)
C(41)	Si(4)	Si(4')	C(43')	-128(2)
C(41)	Si(4)	C(42)	C(46')	134(5)
C(41)	Si(4)	C(43)	C(44')	-80(2)
C(41)	Si(4)	C(43)	C(45)	62(4)
C(41)	Si(4)	C(43')	C(43)	65(4)
C(41)	Si(4)	C(43')	C(44)	117(3)
C(41)	Si(4)	C(43')	C(46)	14(4)
C(41)	C(43)	C(46')	C(42)	-56(6)
C(41)	Si(4')	Si(4)	C(42)	166(1)
C(41)	Si(4')	Si(4)	C(43')	128(2)
C(41)	Si(4')	C(42')	C(45)	-124(5)
C(41)	Si(4')	C(43)	C(44')	-33(3)
C(41)	Si(4')	C(43)	C(45)	104(3)
C(41)	Si(4')	C(43')	C(43)	112(3)
C(41)	Si(4')	C(43')	C(44)	160(2)
C(41)	Si(4')	C(43')	C(46)	68(3)
C(41)	Si(4')	C(45)	C(42')	68(5)
C(42)	Si(4)	Si(4')	C(42')	68.1(2)
C(42)	Si(4)	Si(4')	C(43')	38.0(1)
C(42)	Si(4)	C(43)	C(43')	-8(4)
C(42)	Si(4)	C(43)	C(44)	-72(3)
C(42)	Si(4)	C(43)	C(46)	66(3)
C(42)	Si(4)	C(43')	C(44')	95(4)
C(42)	Si(4)	C(43')	C(45')	-98(5)
C(42)	Si(4)	C(43')	C(46')	-3(3)
C(42)	C(46')	Si(4)	C(43)	-170(5)
C(42)	C(46')	C(43')	C(43)	-0.1(2)
C(42)	C(46')	C(43')	C(44)	115(7)
C(42)	C(46')	C(43')	C(46)	-91(8)
C(42')	Si(4')	Si(4)	C(43')	30(7)
C(42')	Si(4')	C(43)	C(43')	176(4)
C(42')	Si(4')	C(43)	C(44)	95(3)

atom	atom	atom	atom	angle
C(1)	C(1a)	C(2)	C(2a)	74(2)
C(1)	C(6a)	C(1a)	C(2)	109(2)
C(1a)	C(1)	C(6a)	C(6)	112(2)
C(1a)	C(2)	C(2a)	C(5a)	-1(2)
C(1a)	C(6a)	C(6)	C(5a)	0(2)
C(1a')	O(1)	C(1a)	C(6a)	153(1)
C(2a)	C(3)	C(4)	C(5)	8(1)
C(2a)	C(5a)	C(6)	C(6a)	2(2)
C(2a)	C(7)	C(5a)	C(6)	114(2)
C(2)	C(1a)	C(6a)	C(6)	-4(3)
C(2)	C(2a)	C(3)	C(4)	140(1)
C(2)	C(2a)	C(5a)	C(6)	-2(2)
C(2)	C(2a)	C(7)	C(5a)	-109(1)
C(3)	C(2a)	C(5a)	C(6)	144(1)
C(3)	C(2a)	C(7)	C(5a)	100(1)
C(3')	C(3)	C(2a)	C(5a)	-133(1)
C(3')	C(3)	C(4)	C(5)	137(1)
C(4)	O(4)	Si(4)	C(42)	-35(2)
C(4)	O(4)	Si(4)	C(43')	-131(2)
C(4)	O(4)	Si(4')	C(41)	30(3)
C(4)	O(4)	Si(4')	C(43)	-138(3)
C(4)	O(4)	Si(4')	C(45)	179(3)
C(4)	C(3)	C(2a)	C(7)	-70(2)
C(4)	C(5)	C(5a)	C(7)	69(2)
C(5)	C(5a)	C(6)	C(6a)	141(1)
C(6a)	C(6)	C(5a)	C(7)	-71(2)
C(41)	Si(4)	Si(4')	C(43)	-120(1)
C(41)	Si(4)	Si(4')	C(45)	-118(3)
C(41)	Si(4)	C(43)	C(43')	-131(3)
C(41)	Si(4)	C(43)	C(44)	165(3)
C(41)	Si(4)	C(43)	C(46)	-57(3)
C(41)	Si(4)	C(43')	C(44')	-13(5)
C(41)	Si(4)	C(43')	C(45')	155(4)
C(41)	Si(4)	C(43')	C(46')	-111(3)
C(41)	Si(4)	C(46')	C(43')	116(2)
C(41)	Si(4')	Si(4)	C(43)	120(1)
C(41)	Si(4')	Si(4)	C(46')	142(4)
C(41)	Si(4')	C(43)	C(43')	-87(4)
C(41)	Si(4')	C(43)	C(44)	-167(3)
C(41)	Si(4')	C(43)	C(46)	-1(4)
C(41)	Si(4')	C(43')	C(44')	50(4)
C(41)	Si(4')	C(43')	C(45')	-174(3)
C(41)	Si(4')	C(43')	C(46')	-62(3)
C(41)	Si(4')	C(45)	C(43)	-100(3)
C(42)	Si(4)	Si(4')	C(43)	46.2(1)
C(42)	Si(4)	Si(4')	C(45)	48.2(2)
C(42)	Si(4)	C(43)	C(44')	43(3)
C(42)	Si(4)	C(43)	C(45)	-176(4)
C(42)	Si(4)	C(43')	C(43)	173(4)
C(42)	Si(4)	C(43')	C(44)	-135(4)
C(42)	Si(4)	C(43')	C(46)	122(3)
C(42)	Si(4)	C(46')	C(43')	172(7)
C(42)	C(46')	Si(4)	C(43')	-172(7)
C(42)	C(46')	C(43')	C(44')	-106(7)
C(42)	C(46')	C(43')	C(45')	132(7)
C(42')	Si(4')	Si(4)	C(43)	22(6)
C(42')	Si(4')	Si(4)	C(46')	44(9)
C(42')	Si(4')	C(43)	C(44')	-130(3)
C(42')	Si(4')	C(43)	C(45)	6(3)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(42')	Si(4')	C(43)	C(46)	-99(3)	C(42')	Si(4')	C(43')	C(43)	-4(3)
C(42')	Si(4')	C(43')	C(44')	-66(4)	C(42')	Si(4')	C(43')	C(44)	45(3)
C(42')	Si(4')	C(43')	C(45')	70(4)	C(42')	Si(4')	C(43')	C(46)	-47(2)
C(42')	Si(4')	C(43')	C(46')	-178(3)	C(42')	Si(4')	C(45)	C(43)	-168(7)
C(42')	C(45)	Si(4')	C(43)	168(7)	C(42')	C(45)	Si(4')	C(43')	174(5)
C(42')	C(45)	C(43)	C(43')	-98.7(3)	C(42')	C(45)	C(43)	C(44')	114(8)
C(42')	C(45)	C(43	C(44)	-134(8)	C(42')	C(45)	C(43)	C(46)	109(8)
C(43)	Si(4)	Si(4')	C(43')	-8(2)	C(43)	Si(4)	Si(4')	C(45)	2(3)
C(43)	Si(4)	C(42)	C(46')	11(6)	C(43)	Si(4)	C(43')	C(44')	-78(4)
C(43)	Si(4)	C(43')	C(44)	51(3)	C(43)	Si(4)	(43')	C(45')	89(5)
C(43)	Si(4)	C(43')	C(46)	-51(3)	C(43)	Si(4)	C(43')	C(46')	-177(5)
C(43)	Si(4)	C(46')	C(43')	2(3)	C(43)	Si(4')	Si(4)	C(43')	8(2)
C(43)	Si(4')	Si(4)	C(46')	22(4)	C(43)	Si(4')	C(42')	C(45)	-8(5)
C(43)	Si(4')	C(43')	C(44')	-62(4)	C(43)	Si(4')	C(43')	C(44)	49(3)
C(43)	Si(4')	C(43')	C(45')	74(4)	C(43)	Si(4')	C(43')	C(46)	-43(3)
C(43)	Si(4')	C(43')	C(46')	-174(5)	C(43)	C(43')	Si(4)	C(46')	177(5)
C(43)	C(43')	Si(4')	C(45)	-7(3)	C(43)	C(43')	C(44')	C(46)	-3(5)
C(43)	C(43')	C(44)	C945')	-176(6)	C(43)	C(43')	C(45')	C(44)	4(5)
C(43)	C(43')	C(46)	C(44')	177(5)	C(43)	C(44')	C(43')	C(44)	-53(3)
C(43)	C(44')	C(43')	C(45')	-89(4)	C(43)	C(44')	C(43')	C(46)	3(5)
C(43)	C(44')	C(43')	C(46')	155(5)	C(43)	C(44')	C(46)	C(43')	-2(3)
C(43)	C(44)	C(43')	C(44')	68(4)	C(43)	C(44)	C(43')	C(45')	176(6)
C(43)	C(44)	C(43')	C(46)	47(3)	C(43)	C(44)	C(43')	C(46')	-153(6)
C(43)	C(44)	C(45')	C(43')	-3(4)	C(43)	C(45)	Si(4')	C(43')	6(3)
C(43)	C(46)	C(43')	C(44')	-177(5)	C(43)	C(46)	C(43')	C(44)	-49(3)
C(43)	C(46)	C(43')	C(45')	-77(4)	C(43)	C(46)	C(43')	C(46')	149(6)
C(43)	C(46)	C(44')	C(43')	2(3)	C(43')	Si(4)	Si(4')	C(45)	10(3)
C(43')	Si(4)	C(42)	C(46')	7(6)	C(43')	Si(4)	C(43)	C(44')	50(3)
C(43')	Si(4)	C(43)	C(44)	-64(4)	C(43')	Si(4)	C(43)	C(45)	-168(6)
C(43')	Si(4)	C(43)	C(46)	74(4)	C(43')	Si(4')	Si(4)	C(46')	14(4)
C(43')	Si(4')	C(42')	C(45)	-6(5)	C(43')	Si(4')	C(43)	C(44')	54(3)
C(43')	Si(4')	C(43)	C(44)	-80(4)	C(43')	Si(4')	C(43)	C(45)	-170(5)
C(43')	Si(4')	C(43)	C(46)	86(4)	C(43')	C(43)	Si(4)	C(46')	-3(4)
C(43')	C(43)	Si(4')	C(45)	170(5)	C(43')	C(43)	C(44')	C(46)	177(5)
C(43')	C(43)	C(44)	C(45')	4(6)	C(43')	C(43)	C(46)	C(44')	-3(5)
C(43')	C(44')	C(43)	C(44)	70(4)	C(43')	C(44')	C(43)	C(45)	174(6)
C(43')	C(44')	C(43)	C(46)	-177(5)	C(43')	C(44)	C(43)	C(44')	-56(3)
C(43')	C(44)	C(43)	C(45)	174(5)	C(43')	C(44)	C(43)	C(46)	-84(4)
C(43')	C(46)	C(43)	C(44')	3(5)	C(43')	C(46)	C(43)	C(44)	81(4)
C(43')	C(46)	C(43)	C(45)	175(5)	C(44')	C(43)	Si(4)	C(46')	47(2)
C(44')	C(43)	Si(4')	C(45)	-136(4)	C(44')	C(43)	C(43')	C(44)	116(3)
C(44')	C(43)	C(43)	C(45')	114(3)	C(44')	C(43)	C(43')	C(46)	-1(2)
C(44')	C(43)	C(43')	C(46')	-111(1)	C(44')	C(43)	C(44)	C(45')	-52(5)
C(44')	C(43')	Si(4)	C(46')	99(4)	C(44')	C(43')	Si(4')	C(45)	-68(3)
C(44')	C(43')	C(43)	C(44)	-116(3)	C(44')	C(43')	C(43)	C(45)	-151(2)
C(44')	C(43')	C(43)	C(46)	1(2)	C(44')	C(43')	C(44)	C(45')	-107(5)
C(44')	C(43')	C(45')	C(44)	86(5)	C(44')	C(46)	C(43)	C(44)	78(4)
C(44')	C(46)	C(43)	C(45)	172(4)	C(44')	C(46)	C(43')	C(44)	127(5)
C(44')	C(46)	C(43')	C(45')	100(5)	C(44')	C(46)	C(43')	C(46')	-35(5)
C(44)	C(43)	Si(4)	C(46')	-67(3)	C(44)	C(43)	Si(4')	C(45)	89(4)
C(44)	C(43)	C(43')	C(45')	-2(4)	C(44)	C(43)	C(43')	C(46)	-118(3)
C(44)	C(43)	C(43')	C(46')	132(1)	C(44)	C(43)	C(44')	C(46)	-113(4)
C(44)	C(43')	Si(4)	C(46')	-132(4)	C(44)	C(43')	Si(4')	C(45)	42(2)
C(44)	C(43')	C(43)	C(45)	-35.3(2)	C(44)	C(43')	C(43)	C(46)	118(3)
C(44)	C(43')	C(44')	C(46)	-56(5)	C(44)	C(43')	C(43')	C(46)	57(5)
C(44)	C(45')	C(43')	C(46')	-158(4)	C(45')	C(43')	Si(4)	C(46')	-94(5)
C(45')	C(43')	Si(4')	C(45)	68(4)	C(45')	C(43')	C(43)	C(45)	-37.6(3)
C(45')	C(43')	C(43)	C(46)	115(3)	C(45')	C(43')	C(44')	C(46)	-91(5)
C(45')	C(44)	C(43)	C(45)	178(5)	C(45')	C(44)	C(43)	C(46)	-80(5)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(45')	C(44)	C(43')	C(46)	-128(5)	C(45')	C(44)	C(43')	C(46')	32(6)
C(45)	Si(4')	Si(4)	C(46')	2496)	C(45)	Si(4')	C(43)	C(46)	-105(4)
C(45)	Si(4')	C(43')	C(46)	-50(2)	C(45)	Si(4')	C(43')	C(46')	179(3)
C(45)	C(43)	Si(4)	C(46')	-171(4)	C(45)	C(43)	C(43')	C(46)	-152(3)
C(45)	C(43)	C(43')	C(46')	97.2(3)	C(45)	C(43)	C(44')	C(46)	-10(5)
C(46)	C(43)	Si(4)	C(46')	71(3)	C(46)	C(43)	C(43')	C(46')	-110(1)
C(46)	C(43')	Si(4)	C(46')	126(4)	C(46)	C(44')	C(43')	C(46')	152(4)

Table 8: Non-bonded Contacts out to 3.60 Å.

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(46')	3.46(5)	35402	O(1)	C(42)	3.56(4)	35402
O(1)	C(44')	3.57(3)	35402	C(42)	C(44)	3.59(6)	34504

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	1/2X,	-Y,	1/2+Z
(3)	1/2+X,	1/2-Y,	-Z	(4)	-X,	1/2+Y,	1/2-Z

References

(1) SIR92: Altomoare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|F_o|-|F_c|)^2$ where
where: $w = 1/[\sigma^2(Fo)] = [\sigma^2{}_c(Fo) + p^2Fo^2/4]^{-1}$
$\sigma_c(Fo)$ = e.s.d. based on counting statistics
p = p-factor

(4) Standard deviation of an observation of unit weight:
$[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$
where: N_o = number of observations
N_v = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

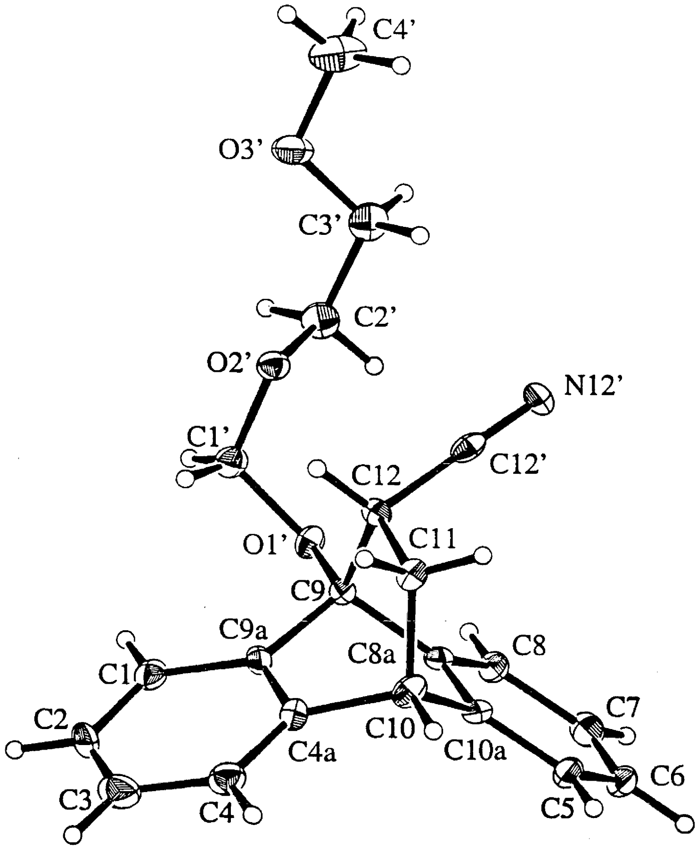
(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

A2.3 X-ray Structure Report for Compound 134.

X-ray crystal data are presented as provided by Dr. D. C. R. Hockless, The Australian National University.



Experimental

Data Collection

A yellow plate crystal of $C_{21}H_{21}NO_3$ having approximate dimensions of 0.24 x 0.12 x 0.04 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections in the range $57.42 < 2\theta < 65.33^{o}$ corresponded to a primitive orthorhombic cell with dimensions:

a = 7.866(9) Å
b = 21.156(3) Å
c = 10.506(3) Å
V = 1748(3) Å^3

For Z = 4 and F.W. = 335.40, the calculated density is 1.27 g/cm^3. Based on the systematic absences of:

0kl: $k+l \neq 2n$
h0l: $h \neq 2n$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$Pna2_1$ (#33)

The data were collected at a temperature of -60 $\pm$ 1 °C using the ω-2θ scan technique to a maximum 2θ value of 120.6°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.28° with a take-off angle of 6.0°. Scans of (0.89 + 0.30 tan θ)° were made at a speed of 2.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 2916 reflections which were collected, 1500 were unique (R_{int} = 0.000). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 11.8%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 6.8 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques.[2] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 891 observed reflections ($I > 3.00\sigma(I)$) and 226 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.046$$

$$R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2)]^{1/2} = 0.049$$

The standard deviation of an observation of unit weight[4] was 2.05. The weighting scheme was based on counting statistics and included a factor (p = 0.015) to downweight the intense reflections. Plots of $\Sigma w (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and -0.18 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[5] Anomalous dispersion effects were included in Fcalc;[6] the values for Δf' and Δf" were those of Creagh and McAuley.[7] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[8] All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{21}H_{21}NO_3$
Formula Weight	335.40
Crystal Color, Habit	yellow, plate
Crystal Dimensions	0.24 X 0.12 X 0.04 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	20 (57.4 - 65.3°)
Omega Scan Peak Width at Half-height	0.28°
Lattice Parameters	a = 7.866(9)Å b = 21.156(3) Å c = 10.506(3) Å V = 1351.7(8) Å^3
Space Group	$Pna2_1$ (#33)
Z value	4
D_{calc}	1.274 g/cm^3
F_{000}	712.00
$\mu(CuK\alpha)$	6.84 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R
Radiation	$CuK\alpha$ (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-60.0 °C
Scan Type	ω-2θ
Scan Rate	2.0°/min (in ω) (up to 4 scans)

Scan Width	$(0.89 + 0.30 \tan \theta)^{o}$
$2\theta_{max}$	120.6^{o}
No. of Reflections Measured	Total: 2916 Unique: 1550 (R_{int} = 0.000)
Corrections	Lorentz-polarization Decay (11.83% decline)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (\lvert Fo \rvert - \lvert Fc \rvert)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0150
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	891
No. Variables	226
Reflection/Parameter Ratio	3.94
Residuals: R; Rw	0.046 ; 0.049
Goodness of Fit Indicator	2.05
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	$0.18\ e^-/Å^3$
Minimum peak in Final Diff. Map	$-0.18\ e^-/Å^3$

Table 1: Atomic coordinates and B_{iso}/B_{eq}.

atom	x	y	z	Beq
O(1')	0.7739(7)	0.3139(3)	0.040(2)	2.8(1)
O(2')	0.5037(7)	0.3211(2)	-0.051(2)	3.0(1)
O(3')	0.2577(9)	0.3521(3)	-0.233(2)	4.4(2)
N(12')	0.617(1)	0.4796(3)	0.005(2)	3.9(2)
C(1)	0.772(1)	0.2343(4)	0.272(2)	3.3(2)
C(1')	0.620(1)	0.2832(4)	0.009(2)	3.4(2)
C(2)	0.776(1)	0.2015(4)	0.386(3)	4.6(3)
C(2')	0.547(1)	0.3330(4)	-0.182(2)	4.1(3)
C(3)	0.788(1)	0.2323(5)	0.500(2)	5.4(3)
C(3')	0.422(1)	0.3770(4)	-0.232(2)	4.4(2)
C(4a)	0.796(1)	0.3323(4)	0.391(2)	2.9(2)
C(4)	0.799(1)	0.2996(4)	0.503(2)	3.9(3)
C(4')	0.137(1)	0.3933(6)	-0.285(2)	6.6(3)
C(5)	1.080(1)	0.4600(4)	0.306(2)	3.6(2)
C(6)	1.198(1)	0.4692(4)	0.211(2)	4.0(2)
C(7)	1.185(1)	0.4383(5)	0.095(2)	4.0(2)
C(8)	1.050(1)	0.3952(4)	0.074(2)	3.2(2)
C(8a)	0.931(1)	0.3854(3)	0.169(2)	2.4(2)
C(9)	0.777(1)	0.3450(4)	0.160(2)	2.5(2)
C(9a)	0.779(1)	0.3019(3)	0.274(2)	2.6(2)
C(10)	0.806(1)	0.4030(4)	0.376(2)	3.3(2)
C(10a)	0.947(1)	0.4183(3)	0.286(2)	2.9(2)
C(11)	0.639(1)	0.4230(4)	0.314(2)	2.9(2)
C(12)	0.622(1)	0.3906(3)	0.180(2)	2.5(2)
C(12')	0.619(1)	0.4404(4)	0.079(2)	3.0(2)
H(1)	0.7635	0.2123	0.1939	4.0009
H(1'a)	0.6456	0.2485	-0.0447	4.1183
H(1'b)	0.5711	0.2681	0.0862	4.1183
H(2)	0.7702	0.1566	0.3842	5.5321
H(2'a)	0.6576	0.3509	0.1873	4.9513
H(2'b)	0.5443	0.2946	-0.2290	4.9513
H(3)	0.7880	0.2089	0.5777	6.5177
H(3'a)	0.4225	0.4141	-0.1814	5.3219
H(3'b)	0.4523	0.3876	-0.3172	5.3219
H(4)	0.8094	0.3214	0.5815	4.7254
H(4'a)	0.1528	0.4344	-0.2502	7.9572
H(4'b)	0.1502	0.3947	-0.3744	7.9572
H(4'c)	0.0261	0.3786	-0.2644	7.9572
H(5)	1.0894	0.4821	0.3843	4.3502
H(6)	1.2896	0.4974	0.2245	4.7540
H(7)	1.2664	0.4458	0.0306	4.8258
H(8)	1.0412	0.3734	-0.0049	3.8652
H(10)	0.8219	0.4233	0.4556	3.9407
H(11b)	0.6370	0.4676	0.3040	3.4991
H(11a)	0.5465	0.4103	0.3666	3.4991
H(12)	0.5193	0.3670	0.1772	3.0004

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 2: Anisotropic Displacement Parameters.

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1')	0.034(4)	0.034(3)	0.039(3)	-0.005(3)	0.005(3)	-0.009(3)
O(2')	0.039(4)	0.040(3)	0.035(3)	0.001(3)	-0.005(3)	-0.002(3)

Table 2: Anisotropic Displacement Parameters continued.

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(3'	)0.057(5)	0.053(4)	0.057(4)	0.013(4)	-0.022(4)	-0.008(4)
N(12')	0.050(5)	0.040(4)	0.058(5)	-0.001(4)	-0.008(5)	0.020(4)
C(1)	0.027(5)	0.041(5)	0.058(6)	0.000(4)	-0.001(5)	-0.002(5)
C(1')	0.049(6)	0.036(5)	0.045(5)	0.000(5)	-0.010(5)	-0.010(5)
C(2)	0.054(7)	0.048(5)	0.074(7)	-0.014(5)	-0.007(7)	0.034(6)
C(2')	0.058(7)	0.055(6)	0.044(6)	-0.001(5)	-0.001(6)	-0.002(5)
C(3)	0.056(8)	0.09(1)	0.058(7)	-0.009(7)	-0.007(7)	0.034(7)
C(3')	0.078(8)	0.061(6)	0.029(5)	-0.009(6)	-0.007(6)	-0.009(5)
C(4a)	0.038(5)	0.032(4)	0.042(6)	-0.005(4)	0.001(5)	0.000(5)
C(4)	0.047(7)	0.062(7)	0.040(6)	-0.009(5)	-0.004(5)	0.004(6)
C(4')	0.067(8)	0.108(9)	0.077(9)	0.023(8)	-0.020(8)	-0.027(8)
C(5)	0.036(5)	0.033(5)	0.068(7)	-0.003(4)	-0.012(5)	-0.004(5)
C(6)	0.032(6)	0.037(5)	0.082(8)	-0.005(5)	-0.011(6)	0.003(6)
C(7)	0.033(6)	0.055(6)	0.065(7)	0.001(5)	0.009(6)	0.019(6)
C(8)	0.028(5)	0.043(5)	0.051(6)	-0.003(4)	0.003(5)	0.007(5)
C(8a)	0.024(5)	0.034(4)	0.035(5)	0.004(4)	-0.005(4)	0.004(4)
C(9)	0.027(5)	0.028(4)	0.040(5)	-0.001(4)	-0.004(5)	0.003(4)
C(9a)	0.027(4)	0.027(4)	0.043(5)	0.000(4)	0.002(5)	0.006(4)
C(10)	0.040(6)	0.047(5)	0.038(5)	-0.006(4)	0.001(5)	-0.015(5)
C(10a)	0.027(5)	0.041(5)	0.041(6)	-0.003(4)	-0.011(5)	0.005(4)
C(11)	0.035(5)	0.039(5)	0.036(5)	-0.004(4)	0.004(4)	-0.005(4)
C(12)	0.028(5)	0.036(4)	0.031(5)	0.004(4)	0.005(4)	0.006(4)
C(12')	0.021(5)	0.045(5)	0.048(6)	0.001(4)	0.001(5)	-0.017(5)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 3: Bond Lengths (Å).

atom	atom	distance	atom	atom	distance
O(1')	C(1')	1.41(1)	O(1')	C(9)	1.42(1)
O(2')	C(1')	1.372(9)	O(2')	C(2')	1.44(1)
O(3')	C(3')	1.39(1)	O(3')	C(4')	1.40(1)
N(12')	C(12')	1.14(1)	C(1)	C(2)	1.38(1)
C(1)	C(9a)	1.43(1)	C(2)	C(3)	1.38(2)
C(2')	C(3')	1.46(1)	C(3)	C(4)	1.43(1)
C(4a)	C(4)	1.37(1)	C(4a)	C(9a)	1.39(1)
C(4a)	C(10)	1.51(1)	C(5)	C(6)	1.38(1)
C(5)	C(10a)	1.38(1)	C(6)	C(7)	1.38(1)
C(7)	C(8)	1.42(1)	C(8)	C(8a)	1.39(1)
C(8a)	C(9)	1.48(1)	C(8a)	C(10a)	1.41(1)
C(9)	C(9a)	1.51(1)	C(9)	C(12)	1.57(1)
C(10)	C(10a)	1.49(1)	C(10)	C(11)	1.53(1)
C(11)	C(12)	1.57(1)	C(12)	C(12')	1.50(1)

Table 4: Bond Lengths (Å).

atom	atom	distance	atom	atom	distance
C(1)	H(1)	0.92	C(1')	H(1'a)	0.93
C(1')	H(1'b)	0.98	C(2)	H(2)	0.95
C(2')	H(2'a)	0.95	C(2')	H(2'b)	0.93
C(3)	H(3)	0.98	C(3')	H(3'a)	0.97

Table 4: Bond Lengths (Å) continued.

atom	atom	distance	atom	atom	distance
C(3')	H(3'b)	0.91	C(4)	H(4)	0.99
C(4')	H(4'a)	0.97	C(4')	H(4'b)	0.91
C(4')	H(4'c)	0.96	C(5)	H(5)	0.99
C(6)	H(6)	0.96	C(7)	H(7)	0.92
C(8)	H(8)	0.92	C(10)	H(10)	0.99
C(11)	H(11b)	0.95	C(11)	H(11a)	0.97
C(12)	H(12)	0.95			

Table 5: Bond Angles (°).

atom	atom	atom	angle	atom	atom	atom	angle
C(1')	O(1')	C(9)	115.4(6)	C(1')	O(2')	C(2')	112.6(7)
C(3')	O(3')	C(4')	113.2(8)	C(2)	C(1)	C(9a)	119(1)
O(1')	C(1')	O(2')	114.2(6)	C(1)	C(2)	C(3)	121.4(9)
O(2')	C(2')	C(3')	107.4(8)	C(2)	C(3)	C(4)	119.5(9)
O(3')	C(3')	C(2')	112.7(8)	C(4)	C(4a)	C(9a)	121.7(7)
C(4)	C(4a)	C(10)	126.3(9)	C(9a)	C(4a)	C(10)	112.0(8)
C(3)	C(4)	C(4a)	119.3(9)	C(6)	C(5)	C(10a)	119.0(9)
C(5)	C(6)	C(7)	121.4(8)	C(6)	C(7)	C(8)	120.1(9)
C(7)	C(8)	C(8a)	119.1(8)	C(8)	C(8a)	C(9)	126.1(8)
C(8)	C(8a)	C(10a)	119.3(7)	C(9)	C(8a)	C(10a)	114.5(7)
O(1')	C(9)	C(8a)	109.8(7)	O(1')	C(9)	C(9a)	115.3(6)
O(1')	C(9)	C(12)	113.1(7)	C(8a)	C(9)	C(9a)	106.6(7)
C(8a)	C(9)	C(12)	105.7(6)	C(9a)	C(9)	C(12)	105.8(7)
C(1)	C(9a)	C(4a)	118.7(8)	C(1)	C(9a)	C(9)	126.3(9)
C(4a)	C(9a)	C(9)	115.0(7)	C(4a)	C(10)	C(10a)	108.7(7)
C(4a)	C(10)	C(11)	105.8(7)	C(10a)	C(10)	C(11)	108.2(7)
C(5)	C(10a)	C(8a)	121.1(8)	C(5)	C(10a)	C(10)	127.0(8)
C(8a)	C(10a)	C(10)	111.9(7)	C(10)	C(11)	C(12)	109.4(7)
C(9)	C(12)	C(11)	109.0(7)	C(9)	C(12)	C(12')	110.2(7)
C(11)	C(12)	C(12)	109.5(6)	N(12')	C(12')	C(12)	177.7(9)

Table 6: Bond Angles (°).

atom	atom	atom	angle
C(2)	C(1)	H(1)	119.1
O(1')	C(1')	H(1'a)	108.2
O(2')	C(1')	H(1'a)	110.0
H(1'a)	C(1')	H(1'b)	108.5
C(3)	C(2)	H(2)	116.9
O(2')	C(2')	H(2'b)	107.9
C(3')	C(2')	H(2'b)	111.4
C(2)	C(3)	H(3)	121.5
O(3')	C(3')	H(3'a)	108.2
C(2')	C(3')	H(3'a)	107.3
H(3'a)	C(3')	H(3'b)	110.7
C(4a)	C(4)	H(4)	121.5
O(3')	C(4')	H(4'b)	109.3
H(4'a)	C(4')	H(4'b)	111.5
H(4'b)	C(4')	H(4'c)	112.1
C(10a)	C(5)	H(5)	119.7
C(7)	C(6)	H(6)	121.5
C(8)	C(7)	H(7)	121.5

Table 6: Bond Angles (°) continued.

atom	atom	atom	angle
C(8a)	C(8)	H(8)	119.6
C(10a)	C(10)	H(10)	112.1
C(10)	C(11)	H(11b)	108.5
C(12)	C(11)	H(11b)	111.9
H(11b)	C(11)	H(11a)	107.8
C(11)	C(12)	H(12)	107.1
C(9a)	C(1)	H(1)	121.5
O(1')	C(1')	H(1'b)	107.1
O(2')	C(1')	H(1'b)	108.8
C(1)	C(2)	H(2)	121.7
O(2')	C(2')	H(2'a)	107.6
C(3')	C(2')	H(2'a)	111.0
H(2'a)	C(2')	H(2'b)	111.4
C(4)	C(3)	H(3)	119.0
O(3')	C(3')	H(3'b)	109.5
C(2')	C(3')	H(3'b)	108.5
C(3)	C(4)	H(4)	119.2
O(3')	C(4')	H(4'a)	108.2
O(3')	C(4')	H(4'c)	108.3
H(4'a)	C(4')	H(4'c)	107.3
C(6)	C(5)	H(5)	121.3
C(5)	C(6)	H(6)	117.1
C(6)	C(7)	H(7)	118.5
C(7)	C(8)	H(8)	121.3
C(4a)	C(10)	H(10)	110.2
C(11)	C(10)	H(10)	111.6
C(10)	C(11)	H(11a)	107.9
C(12)	C(11)	H(11a)	111.2
C(9)	C(12)	H(12)	109.8
C(12')	C(12)	H(12)	111.3

Table 7: Torsion Angles (°).

atom	atom	atom	atom	angle
O(1')	C(1')	O(2')	C(2')	74.6(9)
O(1')	C(9)	C(8a)	C(10a)	-179.5(7)
O(1')	C(9)	C(9a)	C(4a)	175.3(8)
O(1')	C(9)	C(12)	C(12')	-59.2(8)
O(2')	C(2')	C(3')	O(3')	-63(1)
N(12')	C(12')	C(12)	C(11)	-6.3(2)
C(1)	C(9a)	C(4a)	C(4)	-2(1)
C(1)	C(9a)	C(9)	C(8a)	-125.0(9)
C(1')	O(1')	C(9)	C(8a)	-168.9(7)
C(1')	O(1')	C(9)	C(12)	-51.2(8)
C(2)	C(1)	C(9a)	C(4a)	2(1)
C(2)	C(3)	C(4)	C(4a)	1(2)
C(3)	C(2)	C(1)	C(9a)	0(2)
C(3)	C(4)	C(4a)	C(10)	179.8(9)
C(4a)	C(9a)	C(9)	C(12)	-59.0(9)
C(4a)	C(10)	C(10a)	C(8a)	53(1)
C(4)	C(4a)	C(9a)	C(9)	179.8(9)
C(4)	C(4a)	C(10)	C(11)	-118(1)
C(5)	C(10a)	C(8a)	C(8)	0(1)
C(5)	C(10a)	C(10)	C(11)	117.4(9)
C(6)	C(5)	C(10a)	C(10)	-178.7(8)
C(7)	C(6)	C(5)	C(10a)	1(1)

Table 7: Torsion Angles (°) continued.

atom	atom	atom	atom	angle
C(7)	C(8)	C(8a)	C(10a)	0(1)
C(8)	C(8a)	C(9)	C(12)	-118.6(9)
C(8a)	C(9)	C(12)	C(11)	-59.1(8)
C(8a)	C(10a)	C(10)	C(11)	-61.0(8)
C(9)	C(9a)	C(4a)	C(10)	0(1)
C(9a)	C(4a)	C(10)	C(10a)	-55(1)
C(9a)	C(9)	C(8a)	C(10a)	-54.0(9)
C(9a)	C(9)	C(12)	C(12')	173.8(7)
C(10a)	C(8a)	C(9)	C(12)	58.2(9)
O(1')	C(9)	C(8a)	C(8)	4(1)
O(1')	C(9)	C(9a)	C(1)	3(1)
O(1')	C(9)	C(12)	C(11)	-179.3(6)
O(2')	C(1')	O(1')	C(9)	88.2(9)
N(12')	C(12')	C(12)	C(9)	-126.2(2)
C(1)	C(2)	C(3)	C(4)	-1(2)
C(1)	C(9a)	C(4a)	C(10)	178.7(8)
C(1)	C(9a)	C(9)	C(12)	122.9(9)
C(1')	O(1')	C(9)	C(9a)	70.7(9)
C(1')	O(2')	C(2')	C(3')	-175.8(7)
C(2)	C(1)	C(9a)	C(9)	179.7(9)
C(2')	C(3')	O(3')	C(4')	-178.1(8)
C(3)	C(4)	C(4a)	C(9a)	1(2)
C(4a)	C(9a)	C(9)	C(8a)	53(1)
C(4a)	C(10)	C(10a)	C(5)	-128.1(9)
C(4a)	C(10)	C(11)	C(12)	-61.3(9)
C(4)	C(4a)	C(10)	C(10a)	126(1)
C(5)	C(6)	C(7)	C(8)	-1(2)
C(5)	C(10a)	C(8a)	C(9)	-176.9(7)
C(6)	C(5)	C(10a)	C(8a)	0(1)
C(6)	C(7)	C(8)	C(8a)	1(1)
C(7)	C(8)	C(8a)	C(9)	176.3(8)
C(8)	C(8a)	C(9)	C(9a)	129.2(8)
C(8)	C(8a)	C(10a)	C(10)	178.7(7)
C(8a)	C(9)	C(12)	C(12')	61.0(9)
C(9)	C(8a)	C(10a)	C(10)	2(1)
C(9)	C(12)	C(11)	C(10)	4.0(9)
C(9a)	C(4a)	C(10)	C(11)	61(1)
C(9a)	C(9)	C(12)	C(11)	53.7(8)
C(10)	C(11)	C(12)	C(12')	-116.6(7)
C(10a)	C(10)	C(11)	C(12)	55.0(8)

Table 8: Non-bonded Contacts out to 3.60 Å.

atom	atom	distance	ADC
O(1')	C(1')	3.43(1)	4
O(3')	C(3)	3.33(1)	45404
N(12')	C(11)	3.51(1)	66402
C(7)	C(12')	3.42(1)	65501
O(1')	O(2')	3.511(7)	4
N(12')	C(5)	3.42(1)	76402
N(12')	C(6)	3.58(1)7	6402

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) +

TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) X,	Y,	Z	(2) -X,	-Y,	1/2+Z
(3) 1/2-X,	1/2+Y,	1/2+Z	(4) 1/2+X,	1/2-Y,	Z

References

(1) SHELXS86: Sheldrick, G. M. (1985). In: "Crystallographic Computing 3" (Eds G. M. Sheldrick, C. Kruger and R. Goddard) Oxford University Press, pp. 175-189.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M.(1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|F_o|-|F_c|)^2$ where
where: $w = 1/[\sigma^2(Fo)] = [\sigma^2{}_c(Fo) + p^2Fo^2/4]^{-1}$
$\sigma_c(Fo)$ = e.s.d. based on counting statistics
p = p-factor

(4) Standard deviation of an observation of unit weight:
$[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$
where: N_o = number of observations
N_v = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

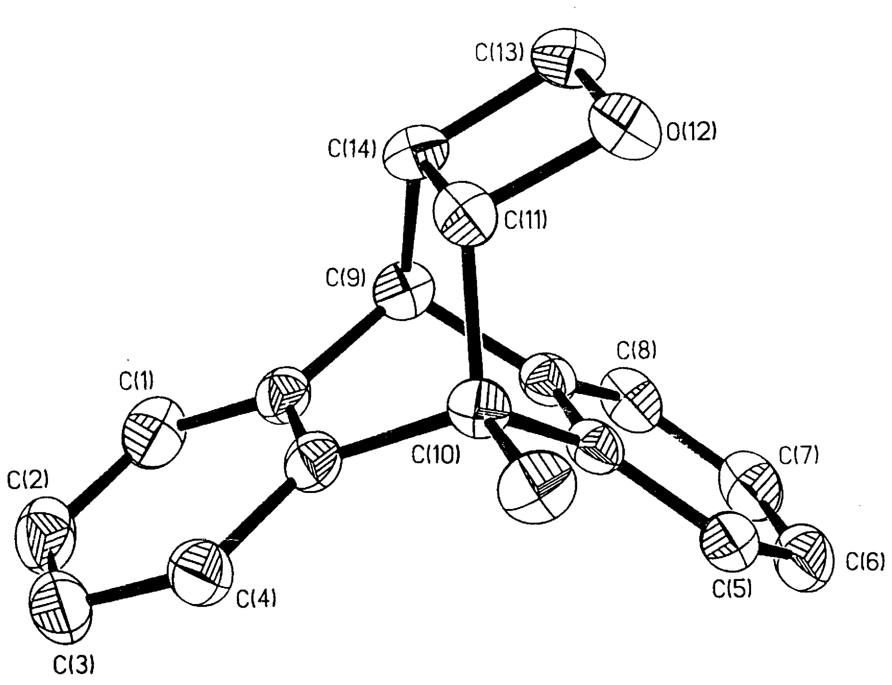
(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

A2.4 X-ray Structure Report for Compound 125.

X-ray crystal data are presented as provided by Dr. G. R. Clark, The University of Auckland.



Abstract

The X-ray crystal structure of compound **125** was determined. The crystal system is the monoclinic space group $P2_1$(No.4), with a = 9.0526(4), b = 6.8994(3), c = 10.8782(5) Å, β = 97.8660(10)°; Z = 2; V = 673.03(5) Å^3; R = 0.0390, wR_2 = 0.0821.

X-ray Crystal Structure Determination

A crystal suitable for intensity data collection was mounted on a glass fibre and positioned on a Siemens SMART CCD diffractometer. Unit cell dimensions were derived from least squares fits to the observed setting angles of all reflections with $I > 10\sigma(I)$, using monochromated Mo K_α radiation at a temperature of -70 °C. The unit cell is monoclinic, $P2_1$ with cell constants given in Table 1. The data were corrected for Lorentz and polarisation effects. Absorption corrections were applied using the method of Blessing [ref. 1], and equivalent reflections averaged. Full details of crystal data, intensity data collection parameters and refinement parameters are given in Table 1.

The structure was solved by direct methods using the programme SHELXS-86 [ref. 2]. Refinement on F^2 employed SHELXL-96 [ref. 3] minimizing the function $\Sigma w||F_o|^2-|F_c|^2|^2$. Atomic scattering factors were for neutral atoms [ref. 4]. After initial isotropic refinement, anisotropic thermal parameters were refined for all non-hydrogen atoms. Hydrogen atoms were located crystallographically and were refined with individual isotropic temperature factors. The X-ray analysis showed the presence of 1 water molecule of solvation in the asymmetric unit and this was included in subsequent calculations. Weights used in the least squares refinements were $w = 1/[(\sigma^2(Fo)^2 + (aP)^2 + bP)]$ where $P = [(Fo)^2 + 2(Fc)^2]/3$, and the final values of a and b are given in Table 1. Final atomic coordinates (Table 2) and selected bond distances (Table 3) and angles (Table 4) are given.

Table 1: Crystal data and Structure Refinement.

Empirical Formula	$C_{17}H_{16}O_3$	
Formula Weight	268.30	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*2$_1$	
Unit cell dimensions	a = 9.0526(4) Å	α = 90°
	b = 6.8994(3) Å	β = 97.8660(10)°
	c = 10.8782(5) Å	γ = 90°
Volume	673.03(5) Å^3	
Z	2	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	284	
Crystal size	0.36 x 0.16 x 0.05 mm	
Theta range for data collection	1.89 to 28.22°	
Index ranges	-11<=h<=11, -9<=k<=7, 0<=l<=13	
Reflections collected	2239	
Independent reflections	2239 [R(int) = 0.0000]	
Max. and min. transmission	0.9964 and 0.9839	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2239 / 1 / 245	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2σ(I)]	R1 = 0.0390, wR2 = 0.0821	
R indices (all data)	R1 = 0.0521, wR2 = 0.0911	
Absolute structure parameter	-0.6(13)	
Largest diff. peak and hole	0.141 and -0.180 eÅ^{-3}	

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O(15)	522(2)	7927(3)	6225(2)	31(1)
C(4)	3268(3)	5989(4)	5698(2)	33(1)
O(12)	1457(2)	11844(3)	7576(1)	32(1)
C(3)	4600(3)	5077(4)	5557(3)	40(1)
C(2)	5884(3)	5469(4)	6358(3)	43(1)
C(1)	5867(3)	6808(4)	7312(2)	36(1)
C(9a)	4542(2)	7715(4)	7472(2)	27(1)
C(9)	4317(2)	9193(4)	8460(2)	28(1)
C(8a)	3069(2)	8416(3)	9116(2)	26(1)
C(8)	3121(3)	8145(4)	10385(2)	33(1)
C(7)	1917(3)	7338(4)	10846(2)	41(1)
C(6)	644(3)	6835(4)	10058(2)	40(1)
C(5)	552(3)	7158(4)	8787(2)	31(1)
C(10a)	1768(2)	7953(3)	8326(2)	24(1)
C(10)	1875(2)	8385(3)	6971(2)	24(1)
C(4a)	3243(2)	7299(3)	6660(2)	26(1)
C(14)	3753(3)	11025(4)	7728(2)	29(1)
C(11)	2302(2)	10531(4)	6884(2)	26(1)
C(13)	2833(3)	12494(4)	8344(2)	33(1)
O(16)	516(2)	9136(3)	3904(2)	35(1)

Table 3: Bond lengths (Å).

bond	distance	bond	distance
O(15)-C(10)	1.409(3)	C(8a)-C(8)	1.388(3)
C(4)-C(4a)	1.385(3)	C(8a)-C(10a)	1.396(3)
C(4)-C(3)	1.388(4)	C(8)-C(7)	1.378(4)
O(12)-C(11)	1.460(3)	C(7)-C(6)	1.383(4)
O(12)-C(13)	1.471(3)	C(6)-C(5)	1.391(3)
C(3)-C(2)	1.380(4)	C(5)-C(10a)	1.384(3)
C(2)-C(1)	1.391(4)	C(10a)-C(10)	1.520(3)
C(1)-C(9a)	1.385(3)	C(10)-C(4a)	1.524(3)
C(9a)-C(4a)	1.401(3)	C(10)-C(11)	1.536(3)
C(9a)-C(9)	1.515(3)	C(14)-C(13)	1.524(4)
C(9)-C(8a)	1.515(3)	C(14)-C(11)	1.535(3)
C(9)-C(14)	1.544(3)		

Table 4: Bond angles (°).

atoms	angle	atoms	angle
C(4a)-C(4)-C(3)	118.9(2)	C(5)-C(10a)-C(10)	126.1(2)
C(11)-O(12)-C(13)	91.12(16)	C(8a)-C(10a)-C(10)	113.06(19)
C(2)-C(3)-C(4)	120.8(3)	O(15)-C(10)-C(10a)	110.41(17)
C(3)-C(2)-C(1)	120.4(2)	O(15)-C(10)-C(4a)	115.48(18)
C(9a)-C(1)-C(2)	119.5(2)	C(10a)-C(10)-C(4a)	106.26(17)
C(1)-C(9a)-C(4)	119.7(2)	O(15)-C(10)-C(11)	112.79(18)
C(1)-C(9a)-C(9)	126.6(2)	C(10a)-C(10)-C(11)	107.37(18)
C(4a)-C(9a)-C(9)	113.74(19)	C(4a)-C(10)-C(11)	103.95(17)
C(8a)-C(9)-C(9a)	106.1(2)	C(4)-C(4a)-C(9a)	120.7(2)
C(8a)-C(9)-C(14)	108.49(18)	C(4)-C(4a)-C(10)	125.9(2)
C(9a)-C(9)-C(14)	104.58(17)	C(9a)-C(4a)-C(10)	113.4(2)
C(8)-C(8a)-C(10)	119.5(2)	C(13)-C(14)-C(11)	86.33(18)

Table 4: Bond angles (°) continued.

atoms	angle	atoms	angle
C(8)-C(8a)-C(9)	126.1(2)	C(13)-C(14)-C(9)	118.7(2)
C(10)-C(8a)-C(9)	114.36(18)	C(11)-C(14)-C(9)	108.8(2)
C(7)-C(8)-C(8a)	119.7(2)	O(12)-C(11)-C(14)	91.09(18)
C(8)-C(7)-C(6)	120.6(2)	O(12)-C(11)-C(10)	114.35(18)
C(7)-C(6)-C(5)	120.4(2)	C(14)-C(11)-C(10)	112.32(19)
C(10a)-C(5)-C(6)	118.8(2)	O(12)-C(13)-C(14)	91.10(18)
C(5)-C(10a)-C(8a)	120.9(2)		

Table 5: Anisotropic displacement parameters ($Å^2 \times 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^{*2}U11 + ... + 2hka^*b^*U12]$.

atom	U11	U22	U33	U23	U13	U12
O(15)	29(1)	34(1)	27(1)	0(1)	-2(1)	-4(1)
C(4)	44(1)	29(1)	28(1)	1(1)	12(1)	0(1)
O(12)	34(1)	26(1)	32(1)	-3(1)	0(1)	5(1)
C(3)	55(2)	31(2)	37(1)	3(1)	22(1)	8(1)
C(2)	44(2)	40(2)	49(2)	12(1)	22(1)	15(1)
C(1)	30(1)	40(2)	39(1)	11(1)	6(1)	7(1)
C(9a)	28(1)	25(1)	29(1)	6(1)	8(1)	2(1)
C(9)	25(1)	29(1)	28(1)	3(1)	-1(1)	0(1)
C(8a)	31(1)	22(1)	25(1)	2(1)	5(1)	3(1)
C(8)	42(1)	34(2)	24(1)	1(1)	2(1)	10(1)
C(7)	59(2)	38(2)	28(1)	8(1)	15(1)	12(1)
C(6)	51(2)	34(2)	40(1)	7(1)	24(1)	6(1)
C(5)	35(1)	26(1)	35(1)	-1(1)	13(1)	0(1)
C(10a)	30(1)	20(1)	22(1)	1(1)	5(1)	4(1)
C(10)	26(1)	24(1)	22(1)	-1(1)	0(1)	-1(1)
C(4a)	31(1)	25(1)	23(1)	5(1)	8(1)	1(1)
C(14)	30(1)	25(1)	30(1)	2(1)	2(1)	-6(1)
C(11)	29(1)	27(1)	22(1)	1(1)	2(1)	4(1)
C(13)	36(1)	26(1)	36(1)	-2(1)	-1(1)	-1(1)
O(16)	37(1)	32(1)	33(1)	2(1)	-6(1)	-1(1)

Supplementary Material Available

Supplementary data comprises hydrogen atom positions, anisotropic thermal parameters, and full listings of bonds and angles. Structure factor tables are available from the Authors (GRC).

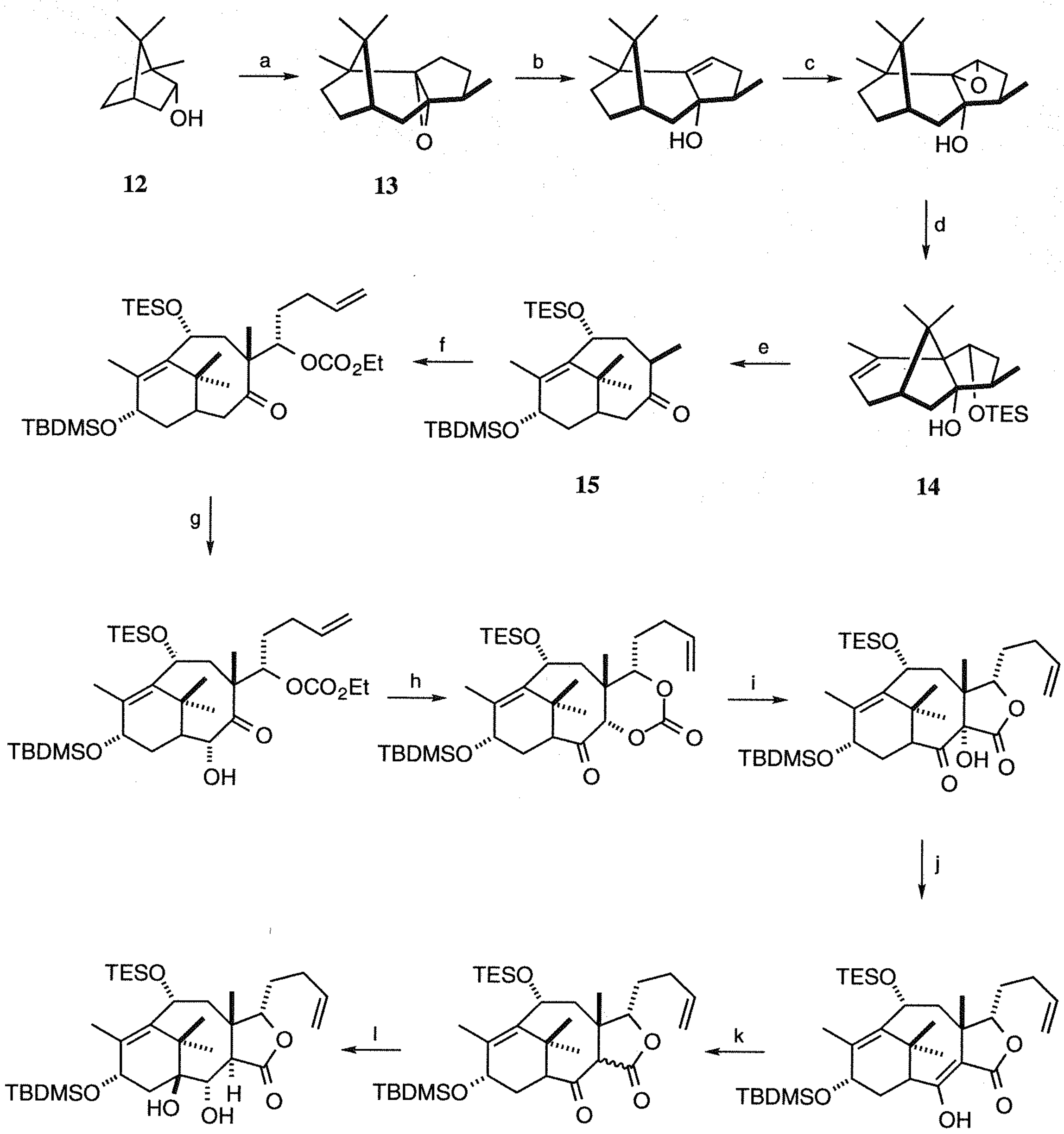
References:

1. Blessing, R. H. Acta Crystallographica, **A51** (1995) 33-38.

2. Sheldrick, G. M. , SHELXS-86, Crystallographic Computing 3; Sheldrick, G. M. Ed.; Oxford University Press, 1995, pp 175.

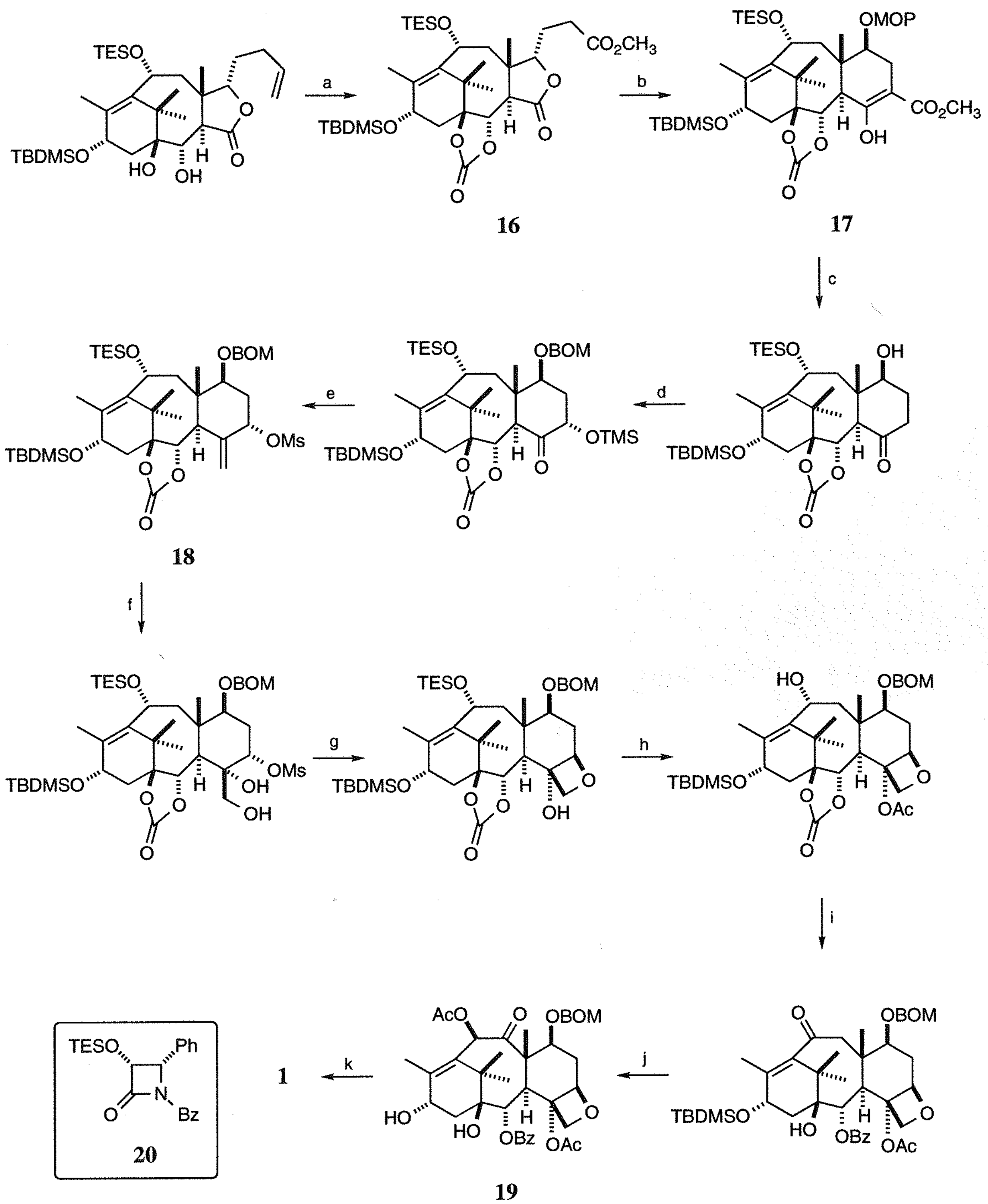
3. Sheldrick, G. M., SHELXL-93, Program for Refinement of Crystal Structures. Institut für Anorganische Chemie, Universität Göttingen, Germany, 1993.

4. *International Tables for X-ray Crystallography*, Kluhwer Academic Publishers, Dortrecht, The Netherlands, Vol. C, tables 4.2.6.8 and 6.1.1.4, (1992).



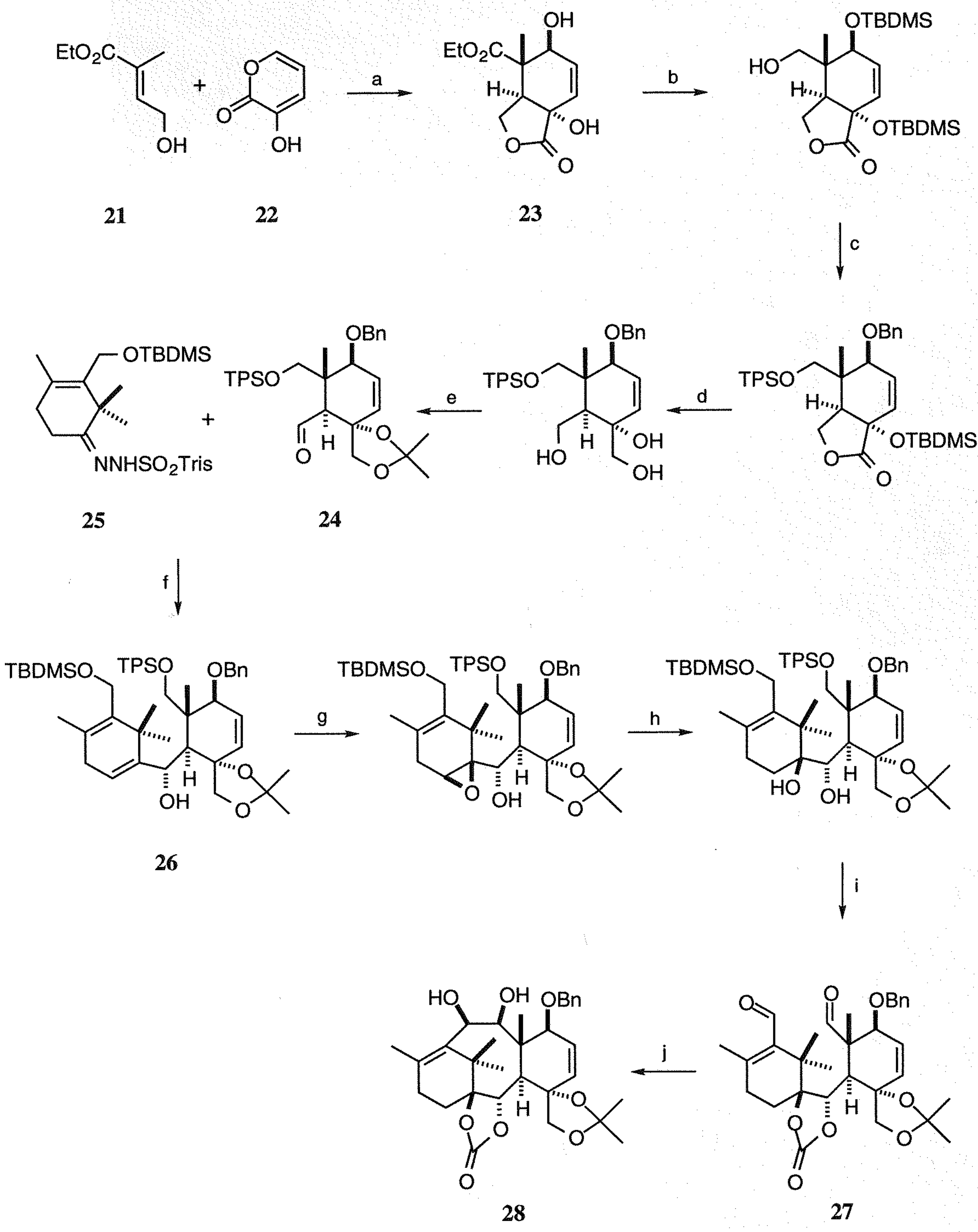
Scheme 1.2

Reagents and Conditions: a. Chapter 1, ref. 17; b. *t*-BuLi, hexane, reflux; c. ^{t}BuOOH, Ti(O^{i}Pr)$_4$, CH_2Cl_2; d. (i) $BF_3.OEt_2$, CF_3SO_3H, CH_2Cl_2, -80 °C; (ii) TESCl, DMAP, NEt_3, CH_2Cl_2; e. (i) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, CH_2Cl_2, 0 °C then $S(CH_3)_2$, 0 °C - reflux; (ii) TBDMSOTf, pyr., -23 °C; f. (i) BrMgN^{i}Pr$_2$, THF then 4-pentenal, -23 °C; (ii) $COCl_2$, CH_2Cl_2, pyr., -23 °C then EtOH; g. LDA, THF, -35 °C then (+)-(camphorsulfonyl)oxaziridine, -78 °C; h. (i) Red-Al®, toluene, -78 °C - rt; (ii) $COCl_2$, CH_2Cl_2, pyr.; (iii) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2; i. LTMP, THF, -25 °C; j. SmI_2, THF; k. silica gel, hexane; l. (i) LTMP, THF, -10 °C then (±)-(camphorylsulfonyl)oxaziridine; (ii) Red-Al®, THF, -78 °C then NaOH (aq.).



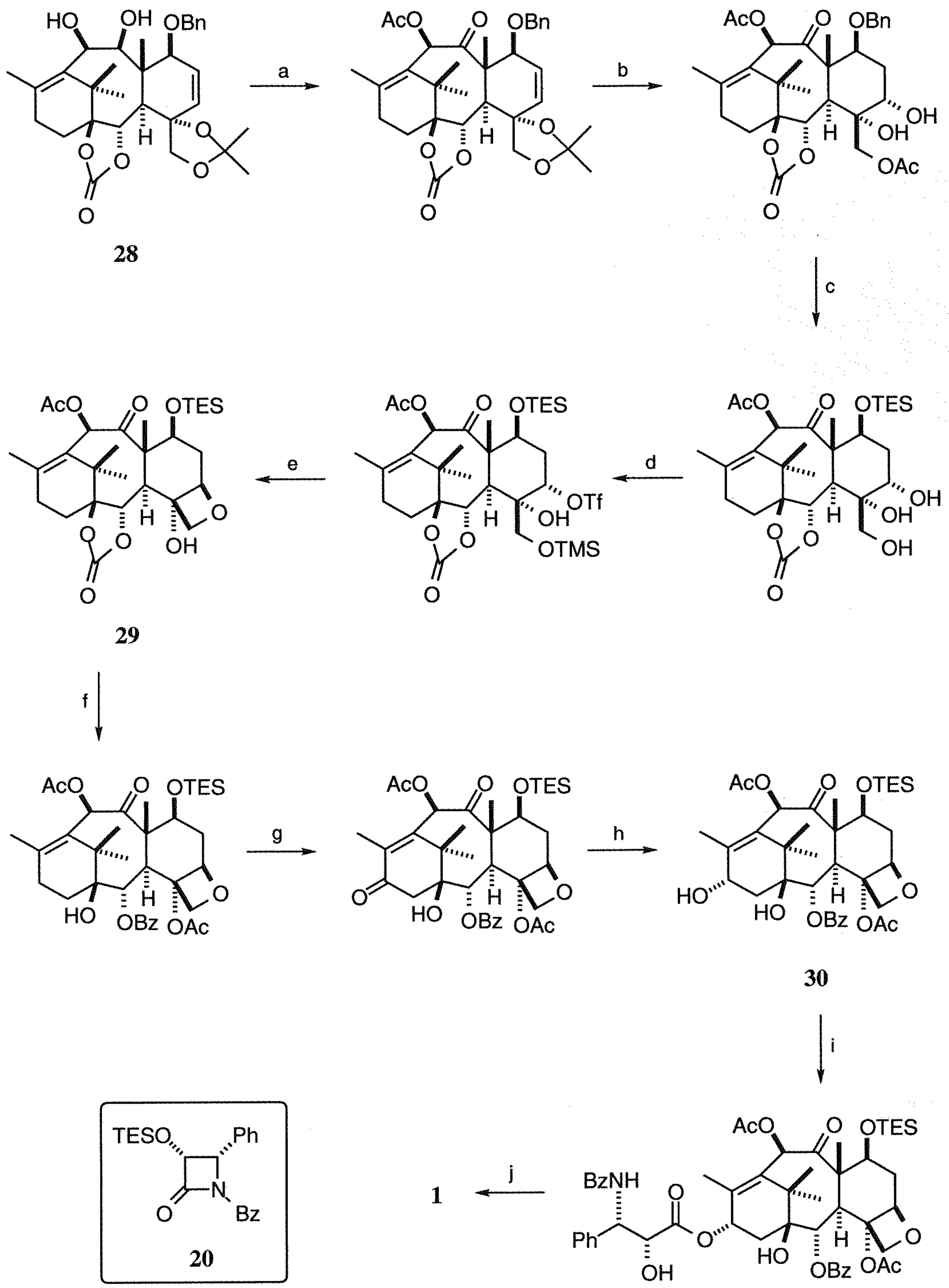
Scheme 1.2

Reagents and Conditions: a. (i) $COCl_2$, CH_2Cl_2, pyr., -78 °C; (ii) O_3, CH_2Cl_2, -78 °C then NEt_3, $P(OMe)_3$; (iii) $KMnO_4$, KH_2PO_4, ^tBuOH, acetone; (iv) CH_2N_2, Et_2O; b. (i) LDA, THF, -78 °C; (ii) 2-methoxypropene, THF, *p*-TsOH, 0 °C; c. (i) KSPh, PhSH, DMF, 86 °C; (ii) PPTS, THF; d. (i) BOMCl, TBAI, $^iPr_2NEt$, CH_2Cl_2, reflux; (ii) TMSCl, NEt_3, LDA, -78 °C; (iii) *m*-CPBA, hexanes; e. (i) MeMgBr, CH_2Cl_2, -65 °C; (ii) Burgess reagent, toluene, 110 °C; (iii) 48% HF, pyr., CH_3CN; (iv) MsCl, pyr.; f. OsO_4, THF, pyr.; g. DBU, toluene, 80-110 °C; h. (i) Ac_2O, DMAP, pyr.; (ii) HF.pyr., CH_3CN; i. (i) PhLi, THF, -78 °C; (ii) TPAP, NMO, CH_2Cl_2; j. (i) ^tBuOK, THF, -78 °C then added to $(PhSeO)_2O$, 0 °C; (ii) ^tBuOK, THF, -78 °C; (iii) Ac_2O, DMAP, pyr.; (iv) TASF, THF; k. (i) LHMDS, THF, -45 °C then **20**; (ii) 48% HF, pyr., CH_3CN; (iii) H_2, 10% Pd on C, EtOH.



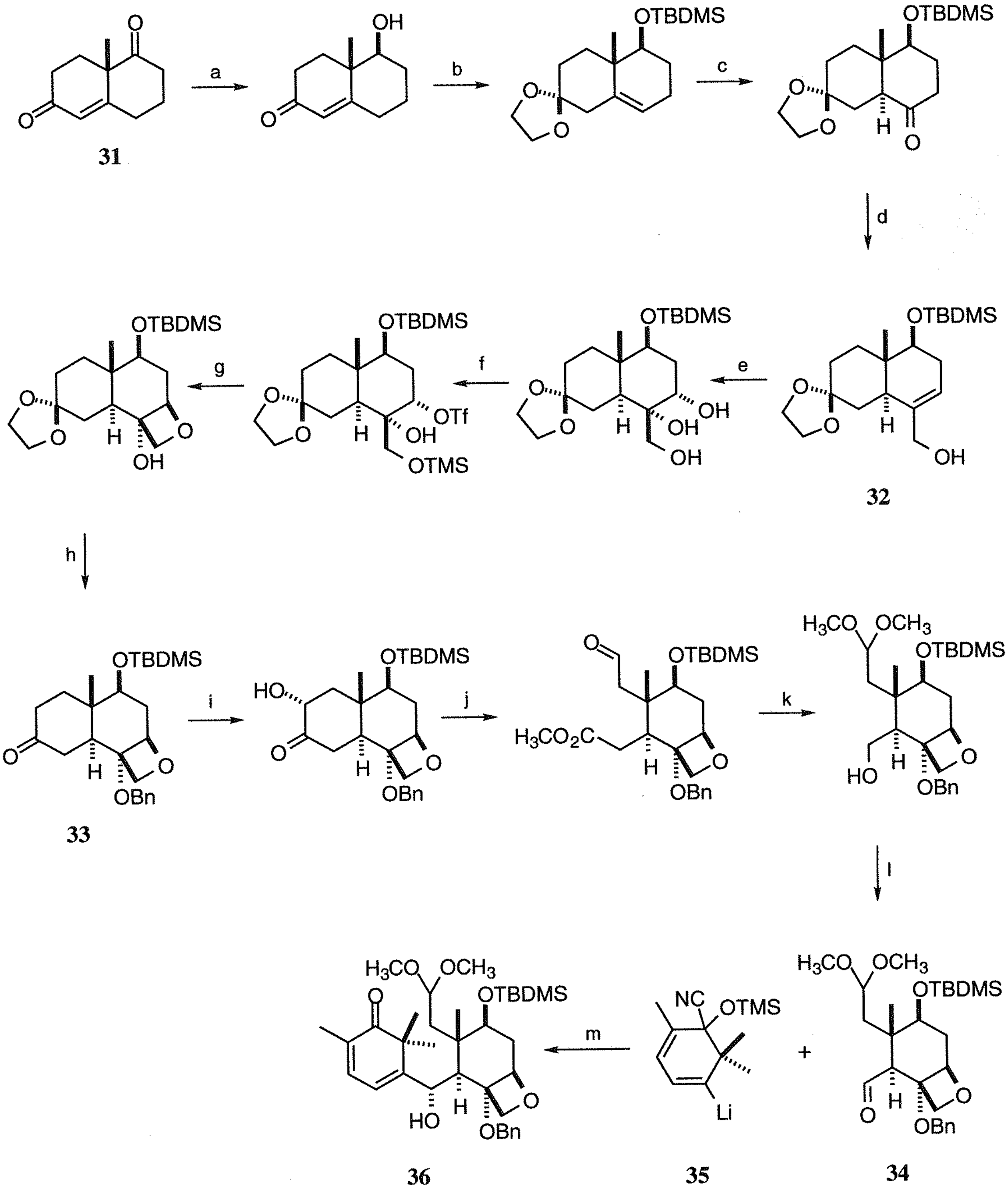
Scheme 1.3

Reagents and Conditions: a. $PhB(OH)_2$, C_6H_6, 90 °C then 2,2-dimethylpropane-1,3-diol; b. (i) TBDMSOTf, 2,6-lutidine, DMAP, CH_2Cl_2, 0 °C; (ii) $LiAlH_4$, Et_2O, 0 °C; c. (i) CSA, MeOH, CH_2Cl_2; (ii) $^tBuPh_2SiCl$, imidazole, DMF; (iii) KH, BnBr, TBAI, Et_2O; d. $LiAlH_4$, Et_2O; e. (i) 2,2-dimethoxypropane, CSA, CH_2Cl_2; (ii) TPAP, NMO, CH_3CN; f. **25** then *n*-BuLi, THF, -78 °C to rt then **24** at 0 °C; g. $VO(acac)_2$, ^tBuOOH, 4 Å molecular sieves, C_6H_6; h. $LiAlH_4$, Et_2O; i. (i) KH, HMPA/Et_2O, $COCl_2$; (ii) TBAF, THF; (iii) TPAP, NMO, CH_3CN/CH_2Cl_2; j. $(TiCl_3)_2.(DME)_3$, Zn-Cu, DME, 70 °C.



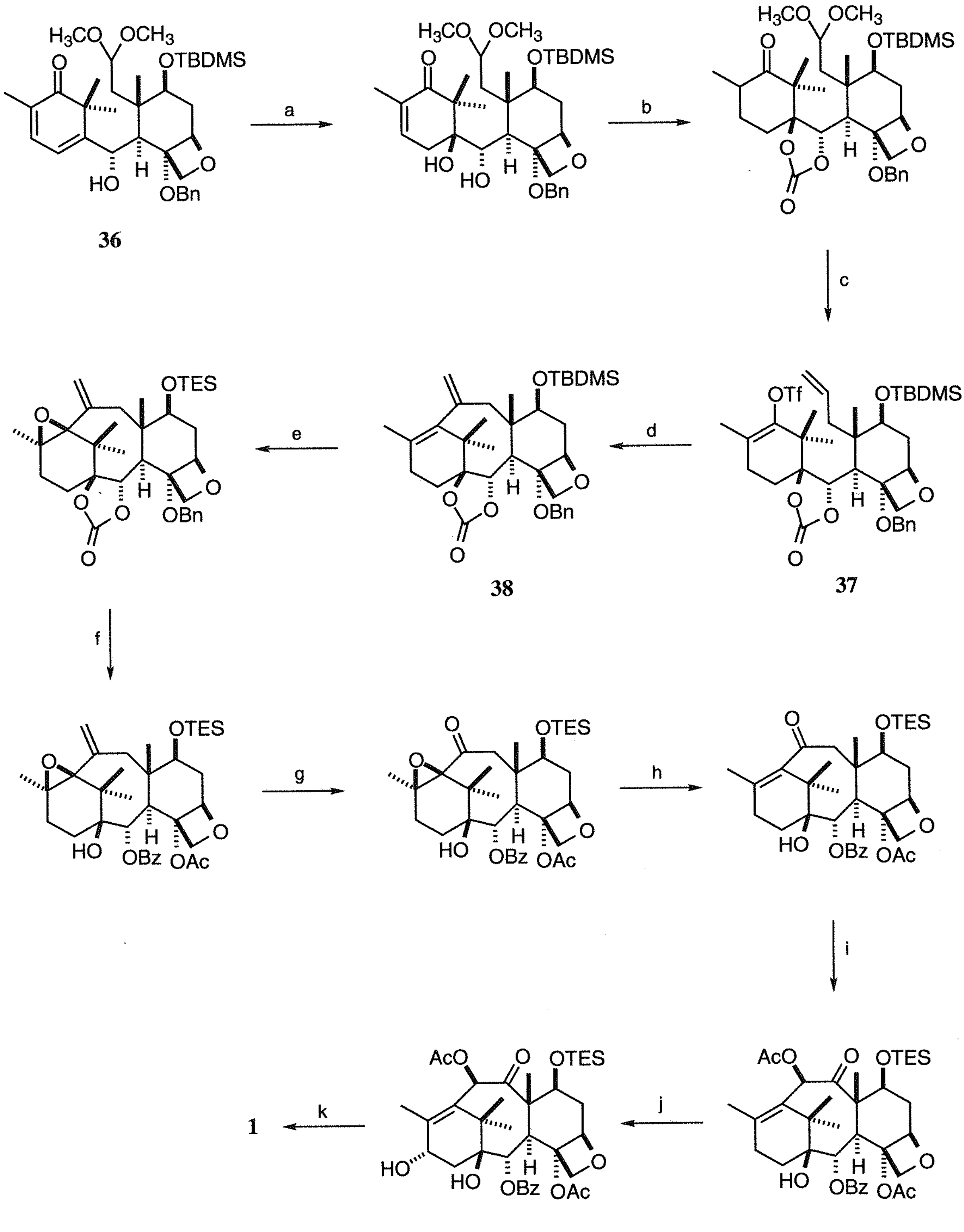
Scheme 1.3

Reagents and Conditions: a. (i) 1-(*S*)-camphanyl chloride then chromatographic separation; (ii) MeOH, K_2CO_3; (iii) Ac_2O, DMAP, CH_2Cl_2; (iv) TPAP, NMO, CH_3CN; b. (i) BH_3.THF, THF, 0 °C then H_2O_2, $NaHCO_3$ (aq.); (ii) conc. HCl, MeOH, H_2O; (iii) Ac_2O, DMAP, CH_2Cl_2; c. (i) H_2, 10% $Pd(OH)_2$ on C, EtOAc; (ii) TESCl, pyr.; (iii) K_2CO_3, MeOH, 0 °C; d. (i) TMSCl, pyr., CH_2Cl_2, 0 °C; (ii) Tf_2O, ${}^iPr_2NEt$, CH_2Cl_2; e. CSA, MeOH then silica gel, CH_2Cl_2; f. (i) Ac_2O, DMAP, CH_2Cl_2; (ii) PhLi, THF, -78 °C; g. PCC, NaOAc, Celite™, C_6H_6, 80 °C; h. $NaBH_4$, MeOH; i. NaHMDS, **20**, THF, 0 °C; j. HF.pyr., THF.



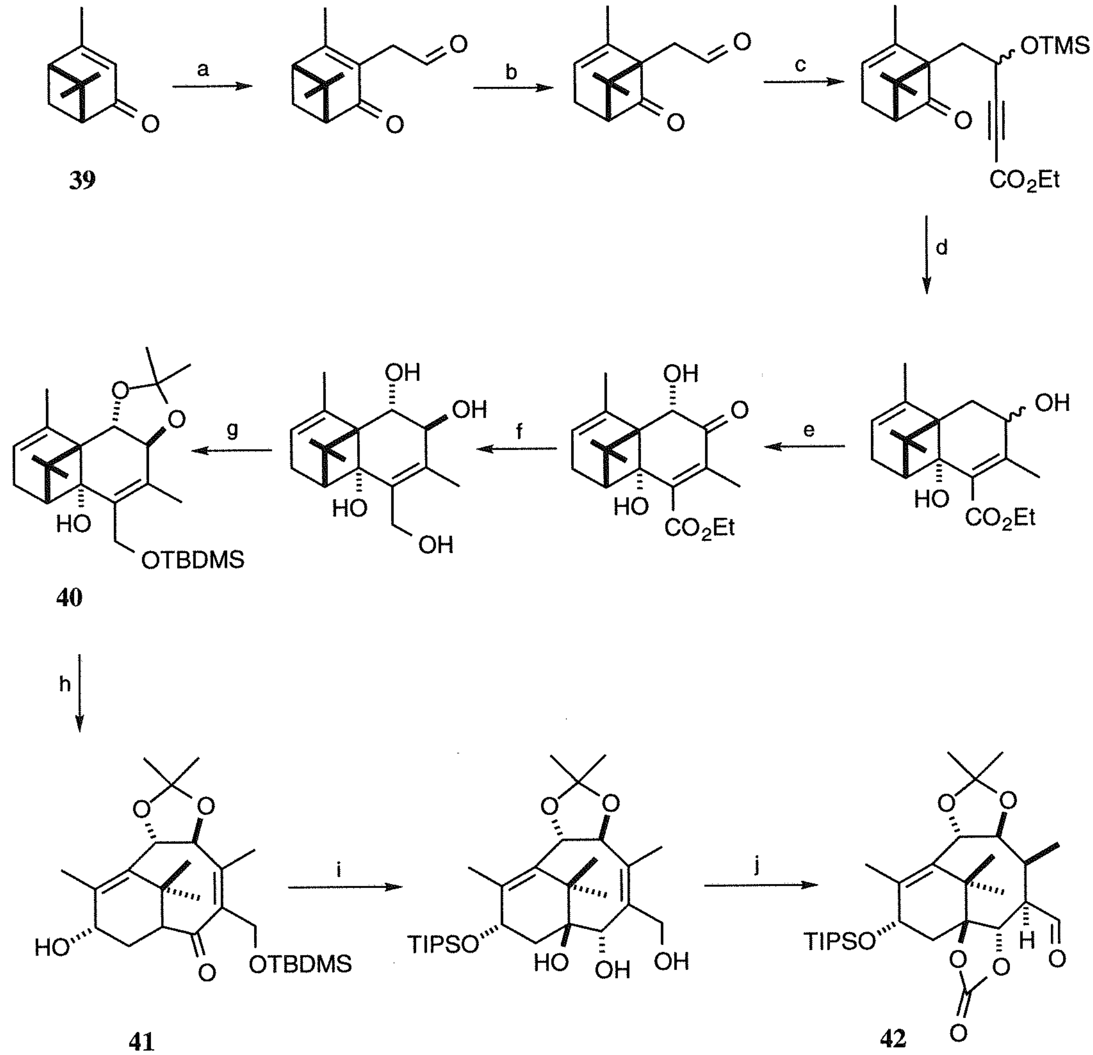
Scheme 1.4

Reagents and Conditions: a. $NaBH_4$, EtOH, 0 °C; b. (i) Ac_2O, DMAP, pyr., CH_2Cl_2; (ii) $(HOCH_2)_2$, naphthalenesulfonic acid, C_6H_6, 80 °C; (iii) NaOMe, MeOH, THF; (iv) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; c. (i) BH_3.THF, THF, 0 °C to rt then H_2O_2, NaOH, H_2O; (ii) PDC, CH_2Cl_2, 0 °C; d. (i) KHMDS, Me_3SI, THF, 0 °C; (ii) $Al(O^iPr)_3$, toluene, 110 °C; e. OsO_4, NMO, acetone, H_2O; f. (i) TMSCl, pyr., CH_2Cl_2, -78 °C; (ii) Tf_2O, -78 °C; g. $(HOCH_2)_2$, 40 °C; h. (i) NaH, BnBr, TBAI, THF, 0 °C; (ii) *p*-TsOH, acetone, H_2O, 70 °C; i. (i) TMSOTf, NEt_3, CH_2Cl_2, -78 °C; (ii) 3,3-dimethyldioxirane, CH_2Cl_2, 0 °C then CSA, acetone; j. $Pb(OAc)_4$, MeOH, C_6H_6, 0 °C; k. (i) CPTS, MeOH, 70 °C; (ii) $LiAlH_4$, THF, 0 °C; l. (i) *o*-$NO_2C_6H_4SeCN$, PBu_3, THF; (ii) 30% H_2O_2, THF; (iii) O_3, CH_2Cl_2, -78 °C then PPh_3; m. (i) THF, -78 °C; (ii) TBAF, THF, -78 °C.



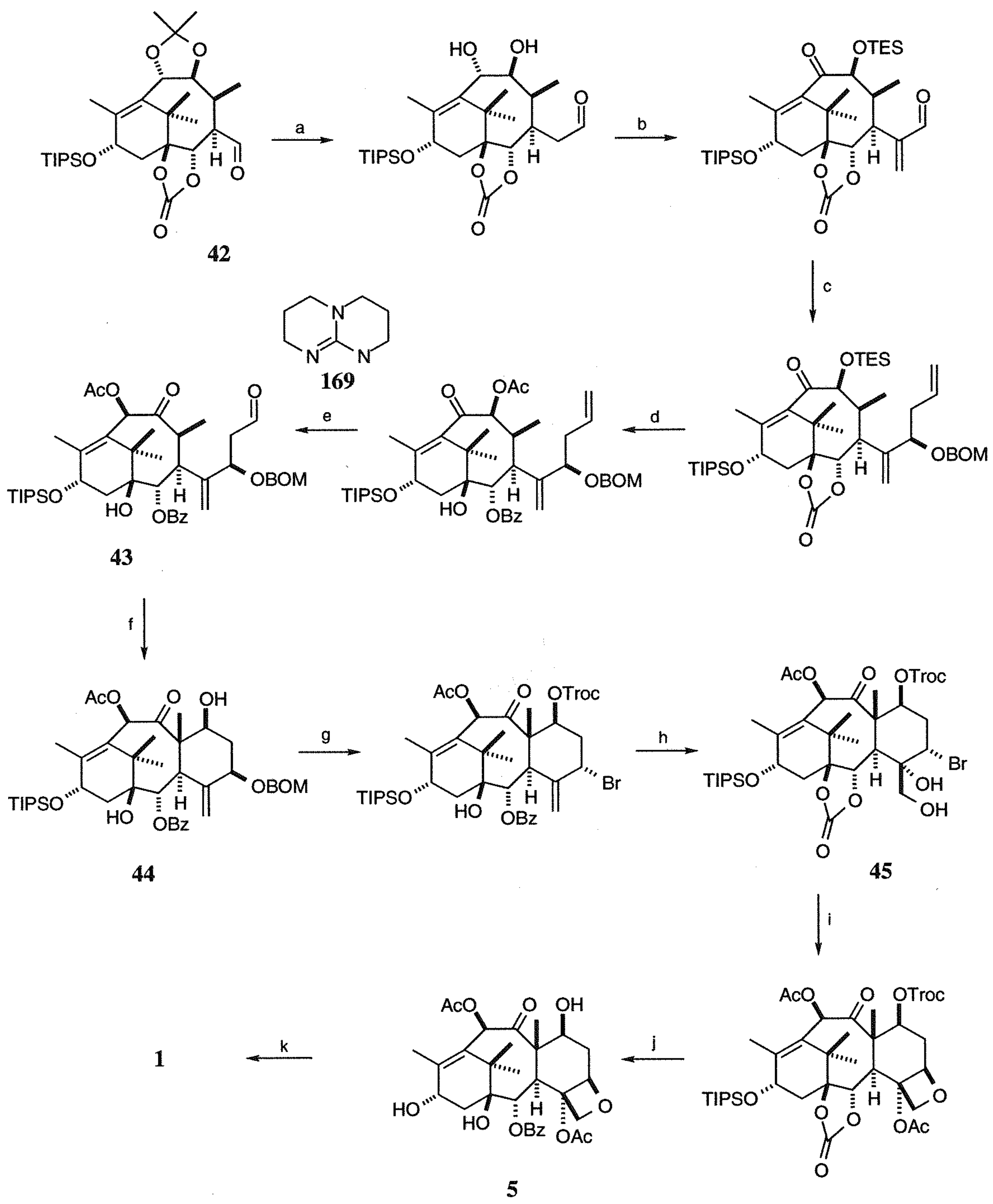
Scheme 1.4

Reagents and Conditions: a. (i) *m*-CPBA, CH_2Cl_2; (ii) H_2, Pd on C, EtOH, -5 °C; b. (i) CDI, NaH, DMF; (ii) L-Selectride, THF, -78 °C; c. (i) $PhNTf_2$, KHMDS, THF, -78 °C; (ii) PPTS, acetone, H_2O; (iii) $Ph_3P{=}CH_2$, THF, -78 °C; d. $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 85 °C; e. (i) TBAF, THF; (ii) TESOTf, NEt_3, CH_2Cl_2, -78 °C; (iii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; f. (i) H_2, Pd on C, EtOH; (ii) Ac_2O, DMAP, pyr.; (iii) PhLi, THF, -78 °C; g. (i) OsO_4, pyr., 105 °C; (ii) $Pb(OAc)_4$, C_6H_6, MeOH, 0 °C; h. SmI_2, Ac_2O, THF, -78 °C; i. (i) ^{t}BuOK, $(PhSeO)_2O$, THF, -78 °C then ^{t}BuOK; (ii) Ac_2O, DMAP, pyr.; j. (i) PCC, NaOAc, C_6H_6, 80 °C; (ii) $NaBH_4$, MeOH; k. Chapter 1, ref. 19.



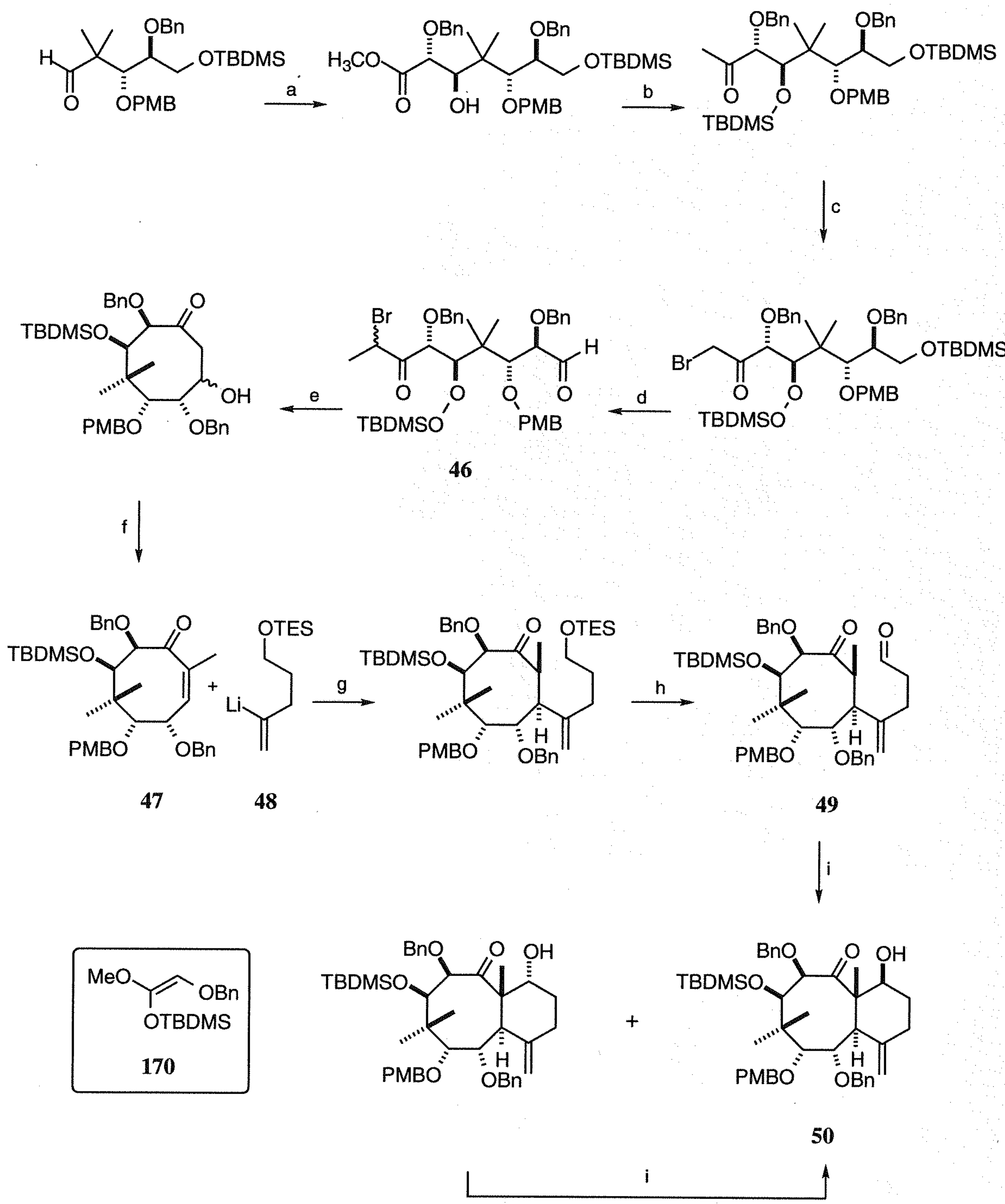
Scheme 1.5

Reagents and Conditions: a. (i) ^{t}BuOK, 1-bromo-3-methyl-2-butene, DME, -78 °C to rt; (ii) O_3, CH_2Cl_2, MeOH, -78 °C; b. *hv*, MeOH; c. LDA, ethyl propiolate, THF, -78 °C then TMSCl; d. Me_2CuLi, Et_2O, -78 °C to rt then AcOH, H_2O; e. (i) $RuCl_2(PPh_3)_3$, NMO, acetone; (ii) KHMDS, Davis oxaziridine, THF, -78 °C; f. $LiAlH_4$, Et_2O; g. TBDMSCl, imidazole then PPTS, 2-methoxypropene; h. (i) *m*-CPBA, Na_2CO_3, CH_2Cl_2; (ii) DABCO (cat.), CH_2Cl_2, reflux; i. (i) TIPSOTf, 2,6-lutidine, -78 °C; (ii) ^{t}BuOK, O_2, $P(OEt)_3$, THF, -40 °C; (iii) NH_4Cl, MeOH; (iv) $NaBH_4$; j. (i) H_2, Crabtree's catalyst, CH_2Cl_2; (ii) TMSCl, pyr., -78 °C; (iii) triphosgene; (iv) PCC, 4 Å molecular sieves, CH_2Cl_2.



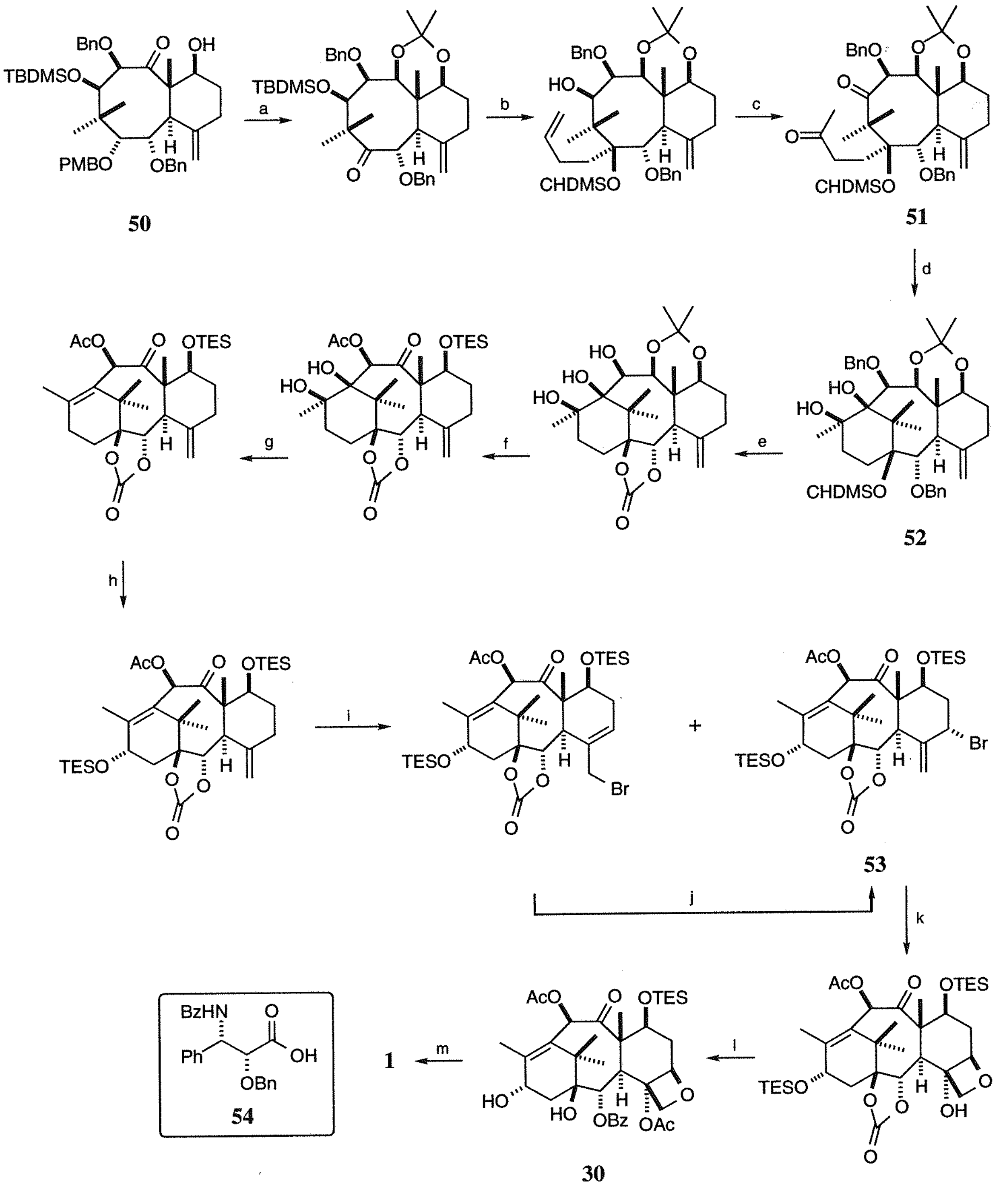
Scheme 1.5

Reagents and Conditions: a. (i) $Ph_3PCHOMe$, THF, -78 °C; (ii) 1 N HCl (aq.), NaI, 1,4-dioxane; b. (i) TESCl, pyr., CH_2Cl_2, -30 °C; (ii) Dess-Martin periodinane, CH_2Cl_2 then NEt_3, Eschenmoser's salt; c. (i) allyl-MgBr, $ZnCl_2$, THF, -78 °C; (ii) BOMCl, $^iPr_2NEt$, 55 °C; d. (i) NH_4F, MeOH; (ii) PhLi, THF, -78 °C; (iii) Ac_2O, DMAP, pyr.; e. (i) **169**, CH_2Cl_2; (ii) O_3, CH_2Cl_2, -78 °C; (iii) $P(OEt)_3$; f. (i) DMAP (excess), CH_2Cl_2; (ii) TrocCl; g. (i) NaI, HCl (aq.), acetone; (ii) MsCl, pyr., DMAP, CH_2Cl_2; (iii) LiBr, acetone; h. (i) OsO_4, pyr., THF then $NaHSO_3$ then imidazole, $CHCl_3$; (ii) triphosgene, pyr., CH_2Cl_2; (iii) KCN, EtOH, 0 °C; i. (i) $^iPr_2NEt$, toluene, 110 °C; (ii) Ac_2O, DMAP; j. (i) TASF, THF, 0 °C; (ii) PhLi, THF, -78 °C; k. Chapter 1, ref. 19.



Scheme 1.6

Reagents and Conditions: a. **170**, $MgBr_2.OEt_2$; b. (i) TBDMSOTf, 2,6-lutidine; (ii) DIBAL; (iii) Swern oxidation; (iv) MeMgBr; (v) Swern oxidation; c. (i) LHMDS, TMSCl; (ii) NBS; d. (i) LHMDS, MeI, HMPA; (ii) 1 N HCl; (iii) Swern oxidation; e. SmI_2; f. (i) Ac_2O, pyr.; (ii) DBU; g. CuCN; h. (i) 0.5 N HCl; (ii) TPAP, NMO; i. NaOMe.



Scheme 1.6

Reagents and Conditions: a. (i) DIBAL; (ii) $Me_2C(OMe)_2$, CSA; (iii) DDQ, H_2O; (iv) PDC; b. (i) $H_2C{=}CH(CH_2)_2Li$; (ii) TBAF; (iii) *c*-$HexMeSiCl_2$, imidazole; (iv) MeLi; c. (i) PDC; (ii) $PdCl_2$, H_2O; d. $TiCl_2$, $LiAlH_4$; e. (i) Na, NH_3; (ii) TBAF; (iii) triphosgene, pyr.; f. (i) 3 N HCl; (ii) TESCl, pyr.; (iii) Ac_2O, DMAP; (iv) PDC; g. (i) TCDI, DMAP; (ii) $P(OMe)_3$; h. (i) PCC, NaOAc; (ii) $NaBH(OMe)_3$; (iii) TESOTf, pyr.; i. $PhCO_3{}^tBu$, CuBr; j. CuBr; k. (i) OsO_4, pyr.; (ii) DBU; l. (i) Ac_2O, pyr.; (ii) PhLi; (iii) TBAF; (iv) TESCl, imidazole; m. (i) **54**, DMAP, di-2-pyridinylthionocarbonate; (ii) H_2, $Pd(OH)_2$ on C; (iii) HF.pyr.