CHARGE TRANSFER INDUCED OSMYLATION OF AROMATIC COMPOUNDS

A Thesis Presented By

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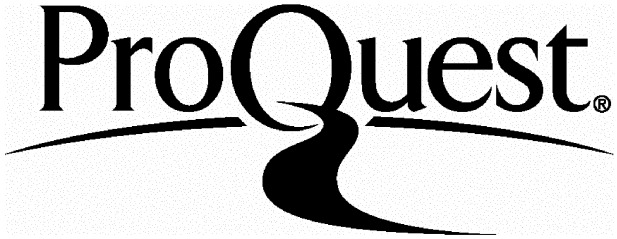


Abstract

This thesis is divided into three chapters.

The first chapter is a review of the published methods of inositol and conduritol syntheses with emphasis on the starting materials used. The routes from aromatics, carbohydrates and those involving Diels-Alder reactions are covered.

The second chapter gives an in depth account of a new, one pot route to these cyclitols. This route employs stoichiometric chlorate salts and catalytic osmium tetroxide in a photochemically initiated cycle to oxidise simple aromatic substrates to inositols and conduritols. This new methodology is shown to be applicable to a number of substrates including alkyl benzenes and halobenzenes. It is shown that under dilute, room temperature conditions purely oxygenated cyclitols are obtained. With a greater concentration of reagents and reactants deoxy-chloro-inositols are obtained. The conduritol : inositol ratio of a given reaction is temperature dependant. On changing the stoichiometric oxidant to bromate deoxy-bromo-conduritols and inositols are accessible, the latter being used as a precursor for the synthesis of natural products pinitol and sequoyitol and other inositol methyl-ethers.

The third chapter provides a formal description of experimental results and procedures.

Contents

Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
aq	Aqueous
Ar	Unspecified aromatic group
atm.	atmosphere(s)
B:	Unspecified base
Bn	Benzyl
Bz	Benzoyl
br	Broad
Bu	Butyl
c.	Concentrated
cat	Catalytic quantity
CI	Chemical ionisation
CMC	Critical micellar concentration
CSA	Camphorsulphonic acid
CT	Charge transfer
CTAB	Cetyltrimethylammonium bromide
Δ	Heat
d	Doublet
D-A	Diels-Alder reaction
dd	Double doublet
ddd	Double double doublet
DEAD	Diethyl azodicarboxylate
DIBAH	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulphoxide
DMP	2,2-Dimethoxypropane

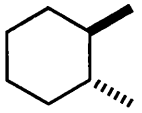
ε	Extinction coefficient
EA	Electron affinity
EDA	Electron donor-electron acceptor
ee	Enantiomeric excess
EI	Electron impact
eq	Equivalent
Et	Ethyl
FAB	Fast atom bombardment
g	Gram(s)
h	Hour(s)
HETCOR	Heteroatom correlated (NMR)
hν	Irradiation of unspecified wavelength
HMPA	Hexamethyl phosphoramide
HOMO	Highest occupied molecular orbital
HOMO NMR	Homonuclear decoupled NMR (^{1}H)
HPLC	High performance liquid chromatography
IP	Ionisation potential
IR	Infra red
λ	Wavelength
L	Unspecified ligand
lit.	Literature value
LUMO	Lowest unoccupied molecular orbital
m	Meta
m	Mutliplet
[M]	Molar concentration
M	Unspecified metal
*m*CPBA	3-Chloroperbenzoic acid
Me	Methyl
MEM	2-Methoxyethoxymethyl

mg	Milligram(s)
min	Minutes
mL	Millilitre(s)
mmHg	Millimetres of mercury
MO	Molecular orbital
m.p.	Melting point
Ms	Methanesulphonyl
NAD	Nicotinamide adenine dinucleotide
Ni-(R)	Raney nickel
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Nu	Unspecified nucleophile
[O]	Unspecified oxidant
o	Ortho
p	Para
PCC	Pyridinium chlorochromate
Pd/C	Palladium on carbon
PFTE	Poly(tetrafluoroethylene)
PMB	*p*-Methoxybenzyl
Ph	Phenyl
ppm	Parts per million
^{i}Pr	Isopropyl
PTSA	*p*-Toluenesulphonic acid
py	Pyridine
q	Quartet
R	Unspecified substituent
RDS	Rate determining step
r.t.	Room temperature
s	Singlet / second(s), as appropriate

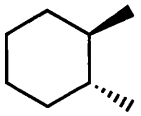
(s)	Solid
t	Triplet
t	Tertiary
TBDMS	*tert*-Butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-Tetramethylethylenediamine
TMS	Trimethylsilyl
t/o	Turnover
Tr	Trityl
TSP-d_4	2,2,3,3-Tetradeuterio-4,4-dimethyl-4-silapentanoic acid sodium salt
UV	Ultra violet (irradiation)
w.r.t.	With respect to

Stereochemical Conventions

The stereochemistry of compounds is illustrated graphically following the conventions of Maehr.[1] Thus bold type is used to represent bonds towards the observer relative to the page, and dashed type to represent bonds away from the observer. Diastereomeric compounds are represented using bold and dashed lines when racemic, and bold and dashed wedges when homochiral.



Racemic

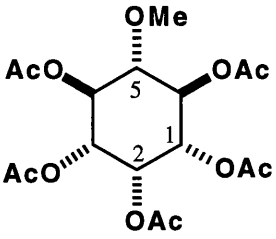


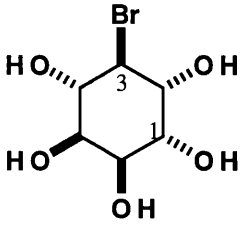
Homochiral

Nomenclature and Numbering

The inositols and their derivatives in chapters 2 and 3 are named according to Angyal.[2] The inositols and conduritols and their derivatives are numbered according to the following rule:

> 'The larger consecutive number of functional groups on one side of the plane of the hexagon shall be described by the lowest possible number'





Acknowledgements

To Professor Willie Motherwell, for providing such an interesting area of research! Thank you for all the animated arguments we had over osmate esters, the government and the Swiss centime. Your help over the last three years has been invaluable.

I would also like to thank my contemporaries: Tim, Mila and Caroline, for providing a working environment from which we all benefited (although I came last in the race!). Thanks also to the other members of the lab: Donogh and Lewis for writing up even more slowly than I did; Richard for being competent at all things; Pete for changing projects nearly as often as I did and helping me out in Cambridge, July 1995; Adrian for being the Joker and singer that he is; Rodney, the junior post-doc, for sharing the view that there *is* life outside England; Simon and Martin for providing proof that there are normal people in Oxford too; Jean-Marc and Fred for being 'foreigners' to complain with and Phil for having an answer to every question. To the newer members of the WBM group, 'Polymer' Ellen, Kamal, Matt and Sylvain: good luck. To the past members of the group: Sarah, Dave, Fez, Lisa, Ian, Sheena and my fellow Perkinites: Lisa, Man-Tat and Mark: thank you for your hospitality. Last but not least, to Kit and Ash for being friends and thanks, Ash, for providing Irina and I with hours of quality entertainment.

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To BP Research for very generous funding and my apologies to Dr Dave Griffiths for all the organic chemistry we presented to him!

Finally, I would like to thank my parents for their love and support, both moral and financial during all of my education.

To Irina

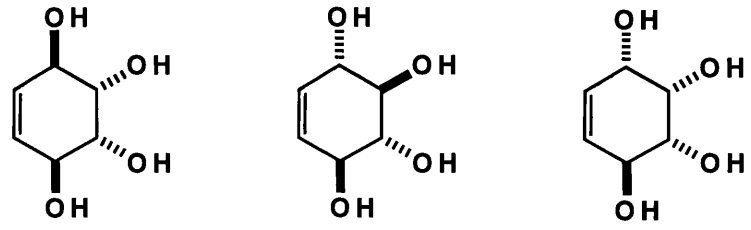
'The simplest explanation is probably the correct one'

Lisa Simpson

CHAPTER ONE

1.1 Introduction

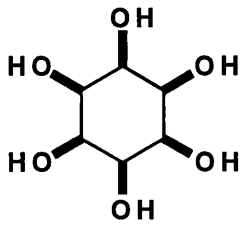
The work presented in this thesis details the development of a new catalytic method for aromatic oxidation, by which, in a one-step procedure a variety of arenes are oxidised to conduritols, inositols and related derivatives. In order to put this new methodology in context, this short introductory chapter will present some of the more frequently utilised routes to these compounds which have appeared in the literature. Reviews on conduritol and inositol syntheses have been published recently but are nearly all end-product oriented.[3-6] The purpose of the present review is to place emphasis on the starting materials used for such syntheses. The somewhat non systematic nomenclature which has evolved for these cyclitol derivatives is best encapsulated in the layout below.



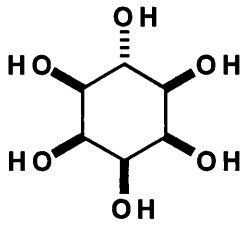
Conduritol A | Conduritol B | Conduritol C

Conduritol D | Conduritol E | Conduritol F

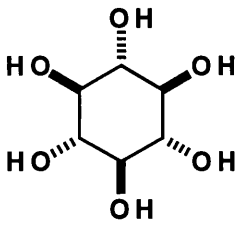
The Conduritols



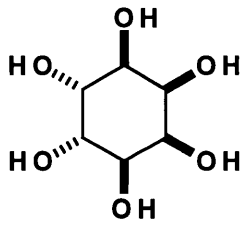
cis-Inositol



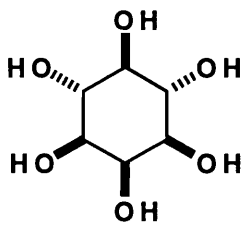
epi-Inositol



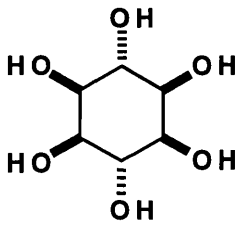
scyllo-Inositol



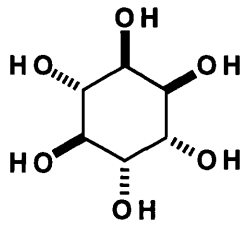
allo-Inositol



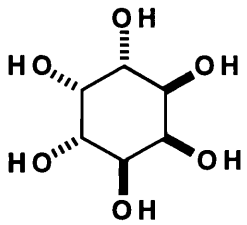
myo-Inositol



muco-Inositol



chiro-Inositol



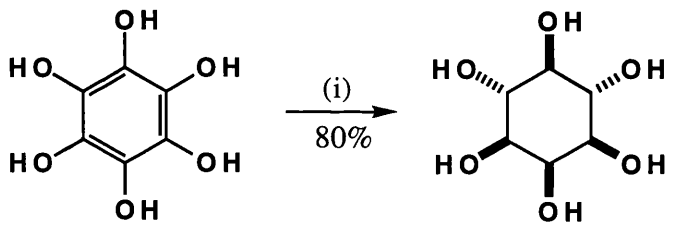
neo-Inositol

The Inositols

1.2 The synthesis of conduritols and inositols

1.2.1 Syntheses from aromatic compounds

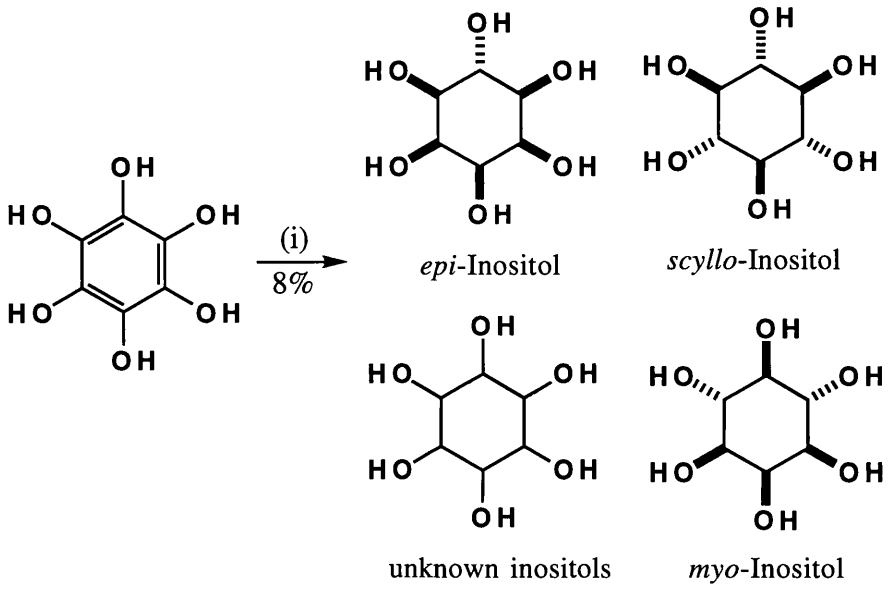
Wieland and Wishart reported the first inositol synthesis in 1914 by the catalytic hydrogenation of hexahydroxybenzene,[7] as shown in **scheme 1.1**.



Reagents: (i) Pd (cat), H_2 1 atm. r.t.

Scheme 1.1

They obtained *myo*-inositol in 80% yield which represents a highly stereospecific reaction but unfortunately attempts to repeat this reaction by several other groups failed. The reaction was re-investigated using Raney-nickel under harsher conditions and was then found to give a mixture of mainly *scyllo*-inositol but also *myo*-inositol, *epi*-inositol and two further then unknown inositols in low yields.[8]



Reagents: (i) Raney-Ni, H_2, 100 atm, 100-125 °C.

Scheme 1.2

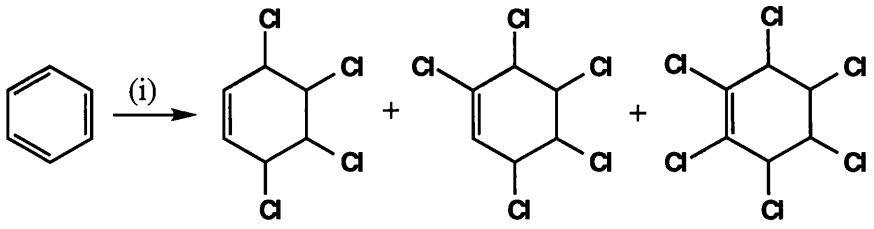
Angyal repeated both procedures and showed that palladium on carbon was also able to effect the desired reaction.[9] Interestingly, the major inositol of the various hydrogenation reactions was catalyst dependent. It was hence postulated that the substrate was able to desorb from the catalyst surface at any point during the hydrogenation process, undergo various reversible rearrangements, to finally yield the thermodynamically more stable inositols (*scyllo* and *myo*) containing a greater number of equatorial hydroxyl groups as the major products, **table 1.1**. The possibility that acid or based catalysed keto-enol tautomerisation of intermediates could also cause equilibration does not appear however to have been discussed.

Inositol	Pd, 1 atm, 20 °C	Ni-(R), 150 atm, 120-140 °C	Pd-C, 1 atm, 20 °C
myo-	17.2%	1.9%	7.5%
cis-	1.7%	4.7%	20.0%
scyllo-	1.2%	0.1%	1.0%
epi-	0.2%	1.8%	0.3%
chiro-	2.9%	-	0.05%
neo-	-	0.05%	-
allo-	-	0.1%	-
others*	6.75%	10.6%	0.45%

* a mixture of inosose, pentols, tetrols, triols and unknowns.

Table 1.1 Inositol products isolated from the hydrogenation of hexahydroxybenzene.[9]

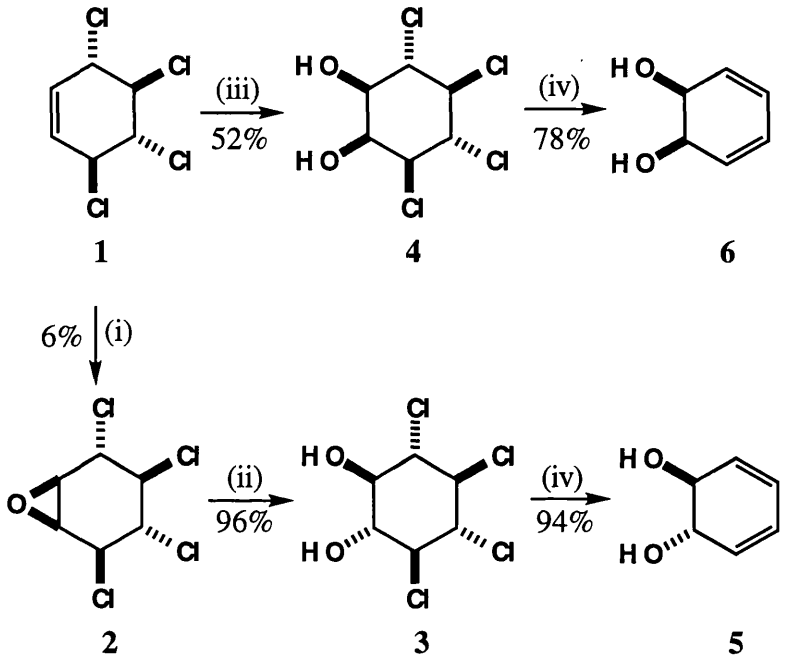
The lack of stereospecificity in the hydrogenation of hexahydroxybenzene lead Nakajima to develop a synthesis of inositols from benzene in which all the hydroxyls were introduced in a stereocontrolled fashion. Iodine catalysed photolysis of benzene with chlorine gave a mixture of chlorinated products from which tetrachlorocyclohexene could be distilled.[10-12]



Reagents: (i) I_2 (cat), Cl_2, hν.

Scheme 1.3

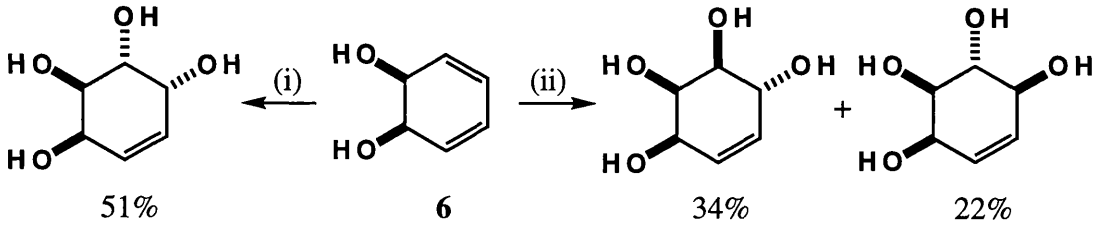
By treatment of the α-isomer of tetrachlorocyclohexene, **1**, with chromic acid the epoxide **2** was isolated as a very minor product and this was then opened to the *trans*-diol **3** through the addition of sulphuric acid.[13] Similarly treatment of **1** with potassium permanganate gave the *cis*-diol **4**.[14] Both **3** and **4** were then subjected to reductive dechlorination with zinc dust to give the *trans*-**5**[15] and *cis*-**6**[14] diene diols.

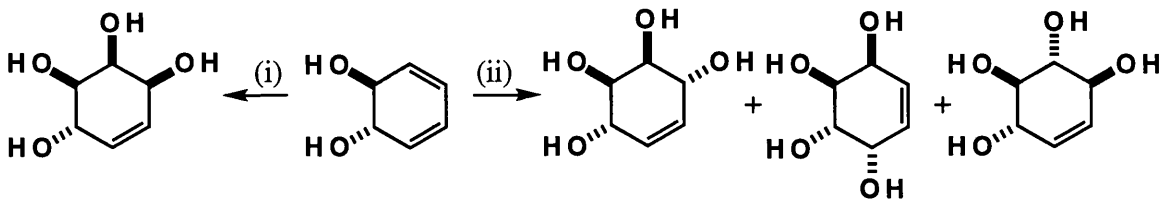


Reagents: (i) H_2CrO_4; (ii) H_2SO_4; (iii) $KMnO_4$; (iv) Zn.

Scheme 1.4

Both **5** and **6** and their acetates were then used as starting materials for the syntheses of five of the six conduritols using sequences involving *cis*- and *trans*-hydroxylation,[14,16,17] **scheme 1.5**.





24% 5 40% 25% 6%

Reagents: (i) $KMnO_4$; (ii) CH_3COOOH then H_2SO_4.

Scheme 1.5

Finally, seven out of the eight inositols were then synthesised from these conduritols using the same strategy,[17] **table 1.2**.

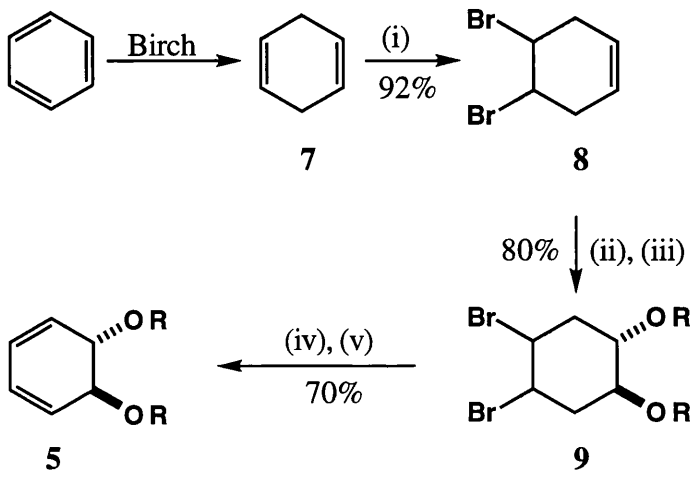
	% inositol product						
Conduritol	*chiro*	*scyllo*	*muco*	*myo*	*neo*	*allo*	*epi*
A	59 (ii)	-	60 (i)	-	-	-	-
B	44 (ii)	3 (ii)	-	65 (i)	-	-	-
C	-	-	-	3 (ii)	20 (i)	54 (ii)	4 (i)
E	27 (ii)	-	-	-	44 (ii)	45 (i)	-
F	69 (i)	-	15 (ii)	-	-	-	-

Reagents: (i) $KMnO_4$; (ii) CH_3COOOH then H_2SO_4.

Table 1.2 Inositol synthesis from conduritols.[17]

The diene diols **5**, and especially **6**, have become the substrates of choice in recent years for the synthesis of conduritols and inositols and their analogues. The routes to these starting materials have changed very considerably however.

The *trans*-diol **5** is now available in 51% overall yield from 1,4-cyclohexadiene **7**, the product of the Birch reduction of benzene,[18] **scheme 1.6**.

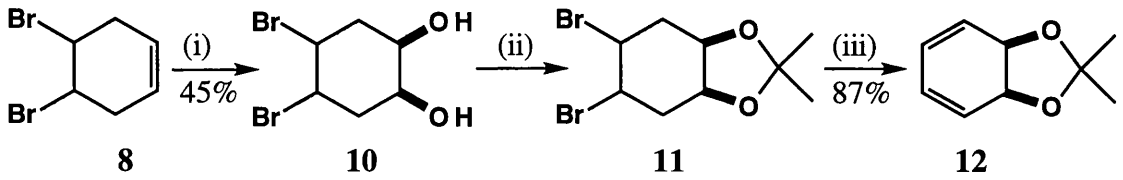


Reagents: (i) Br_2; (ii) H_2O_2, HCOOH then PTSA, R=H;

(iii) AcCl, py, R=Ac; (iv) LiCl, Li_2CO_3, R=Ac; (v) $LiAlH_4$, R=H.

Scheme 1.6

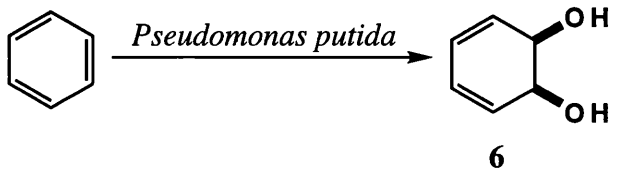
The *cis*-diol **6** can be synthesised in a similar fashion whereby the dibromide **8** is first subjected to *cis*-hydroxylated with potassium permanganate, and the resulting diol **10** then protected as an acetonide **11**. DBU mediated dehydrobromination then furnishes the required protected diol **12**,[19] **scheme 1.7**.



Reagents: (i) $KMnO_4$; (ii) DMP, H^+; (iii) DBU.

Scheme 1.7

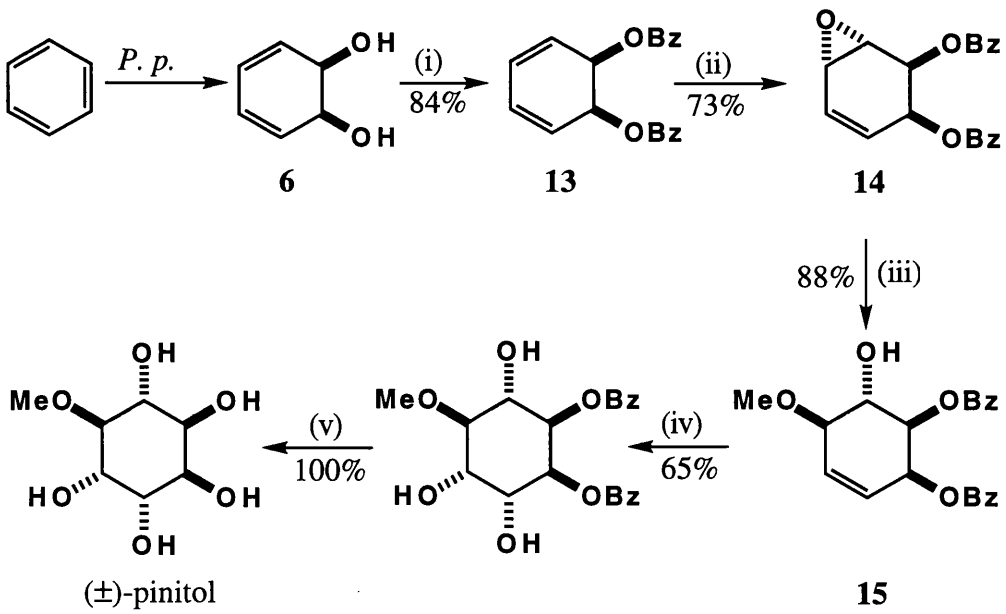
In 1968, a highly significant observation was made by Gibson,[20] who showed that certain strains of *Pseudomonas putida* were able to *cis*-dihydroxylate benzene, **scheme 1.8**. This enzymatic reaction later proved to be a cornerstone for much of the research in recent years.



6

Scheme 1.8

Thus, Ley and coworkers were the first to make use of this microbial oxidation to synthesise the 3-*O*-methyl ether of *chiro*-inositol, (±)-pinitol, in six steps from benzene,[21] **scheme 1.9**.

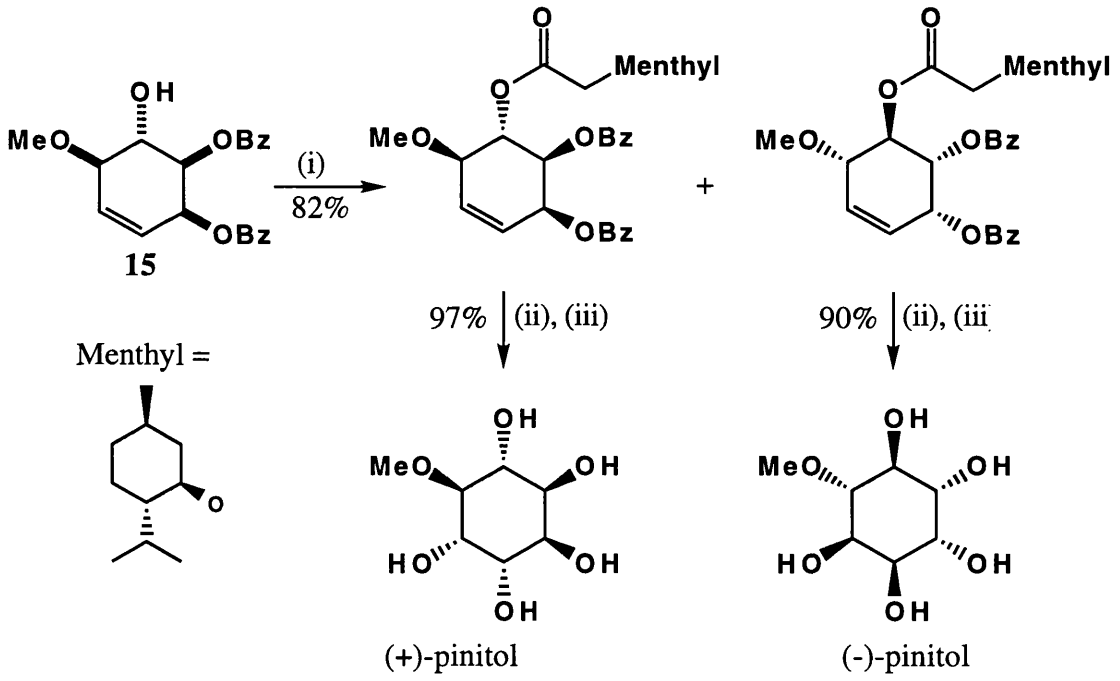


Reagents: (i) BzCl, py, DMAP; (ii) *m*CPBA; (iii) MeOH, CSA;

(iv) OsO_4, NMO; (v) Et_3N, MeOH, H_2O.

Scheme 1.9

The strategy employed involved protection of the diene diol **6** followed by epoxidation to give the epoxide **14** as the major product (14% of β-epoxide also detected). Ring opening of the epoxide **14** with methanol under acidic conditions then gave the protected conduritol-F **15** which on osmium tetroxide catalysed dihydroxylation gave the inositol which, on subsequent debenzoylation, furnished (±)-pinitol. Through the use of the menthyl moiety as a chiral auxiliary, the intermediate **15** could be resolved using HPLC. This then allowed the synthesis of both optical antipodes of pinitol,[22] **scheme 1.10**.

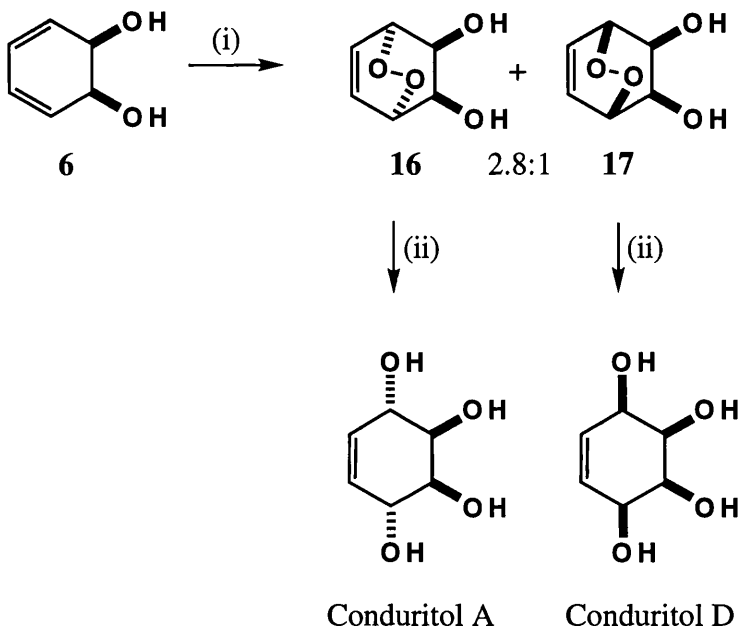


Reagents: (i) $Cl_2(CO)_2$, menthoxyacetic acid then **15**;

(ii) OsO_4, NMO; (iii) Et_3N, MeOH, H_2O.

Scheme 1.10

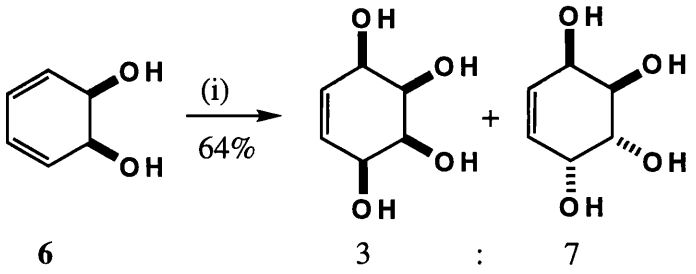
The use of epoxidation to insert *trans-diols* and osmylation to insert *cis*-diols is the methodology of choice for building conduritols and inositols from the diene diol **6**. Several groups have also made use of singlet oxygen with a thiourea work-up to obtain a 1,4-*cis*-diol from **6** and hence a short route to conduritols A and D,[23,24] **scheme 1.11**.



Reagents: (i) $^1O_2$; (ii) thiourea; 95-100% yield.

Scheme 1.11

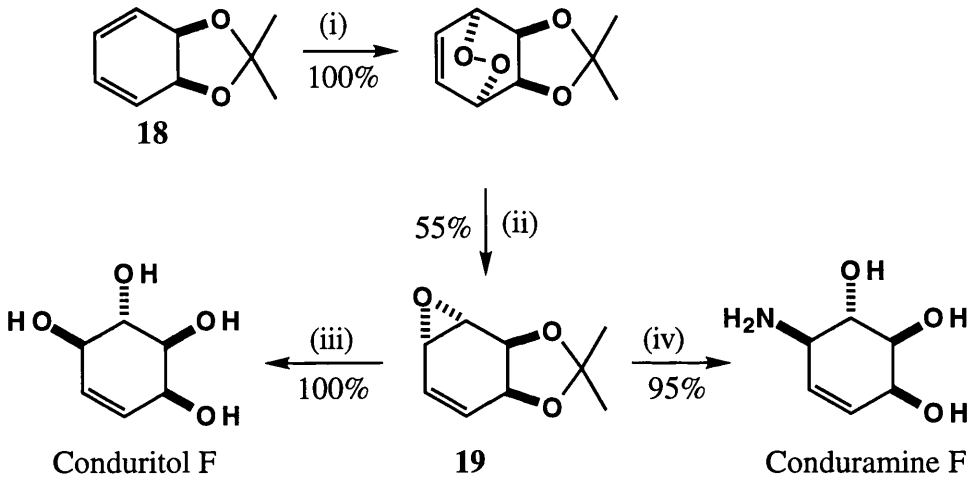
Through subsequent epoxidation (followed by hydrolysis) and osmylation the synthesis of *muco-*, *chiro-*, *allo-* and *epi*-inositol from the conduritols A and D is possible.[24] Osmylation of the diene diol **6**, **scheme 1.12**, yields a mixture of conduritols E and D.[25]



Reagent: (i) OsO_4, 1 eq NMO.

Scheme 1.12

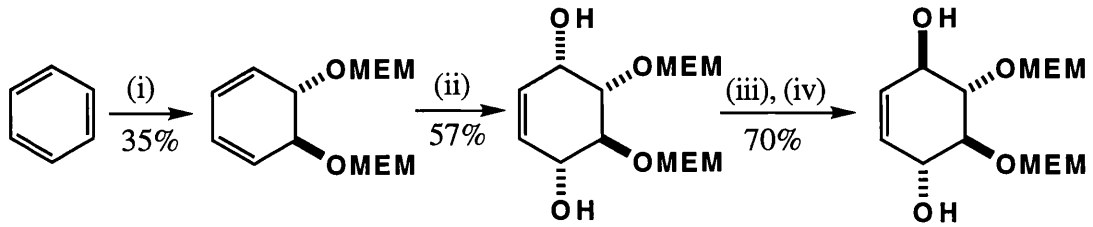
The synthesis of conduritol and conduramine F from the isopropylidene derivative **18** *via* a sequence of singlet oxygen addition, rearrangement to the epoxide **19** and opening to either conduramine F with ammonia or conduritol F under acidic conditions has also been demonstrated,[26] **scheme 1.13**.



Reagents: (i) $^1O_2$; (ii) $POEt_3$; (iii) H_2SO_4; (iv) NH_3.

Scheme 1.13

The use of an epoxide intermediate to synthesise substituted conduritols and inositols has been similarly used in the syntheses of the methylated *chiro*-inositol, (±)-quebrachitol,[24] and the phosphorylated inositols, (+) and (-)-1,4,5-IP_3 and analogues,[27,28] from **6**. A new approach to the phosphorylated inositols was presented by Carless starting with the MEM protected *trans*-diene diol **20**.[29] The reaction of **20** with singlet oxygen followed by thiourea work-up provided the protected conduritol F **21**. Oxidation to the enedione and its subsequent reduction led to the conduritol B **22, scheme 1.14**.

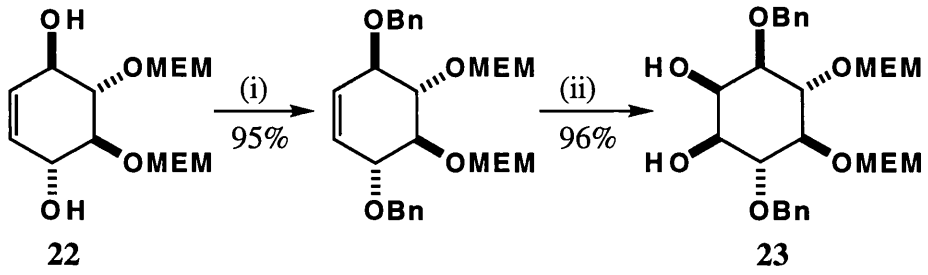


20 **21** **22**

Reagents: (i) 7 steps; (ii) $^1O_2$ then thiourea (2 steps); (iii) PCC, 3 eq; (iv) $NaBH_4$, $CeCl_3$.

Scheme 1.14

Dibenzylation of **22** followed by osmylation gave the *myo*-inositol **23**, **scheme 1.15**. This intermediate, **23**, was then used to synthesise the trisphosphorylated inositols 1,4,5-IP_3 and 2,4,5-IP_3 the bisphosphorylated 4,5-IP_2 and the tetraphosphorylated 1,2,4,5-IP_4 through selective protection and deprotection followed by phosphorylation.



22 **23**

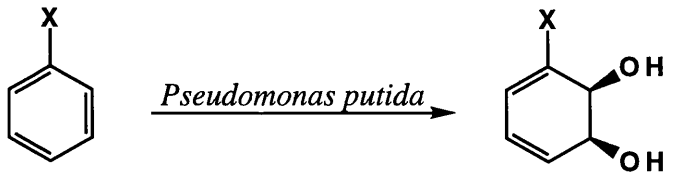
Reagents: (i) BnBr, NaH; (ii) OsO_4, NMO.

Scheme 1.15

In a similar sequence of steps **21** has been used to prepare (±)-*chiro*-inositol 2,3,5-trisphosphate.[30]

A considerable drawback in the use of the diene diol **6** for the synthesis of naturally occurring inositols and conduritols is its *meso*-symmetry. The introduction of chirality therefore calls for the use of chiral auxiliaries as used by Ley for the syntheses of (+) and (-)-conduritol F,[31] (+) and (-)-1,4,5-IP_3, and (+) and (-)-pinitol as already seen.[22,28] Alternatives have involved enzymatic transformations as demonstrated by Vandewalle[32] in the synthesis of (-)-conduritols C, E and F and by Johnson[33] in his synthesis of (+) and (-)-conduritol C and (+) and (-)-conduramine C.[34,35] The use of the AD-Mix[36] for an enantiocontrolled synthesis of conduritol E[37,38] and F[39] has also been reported.

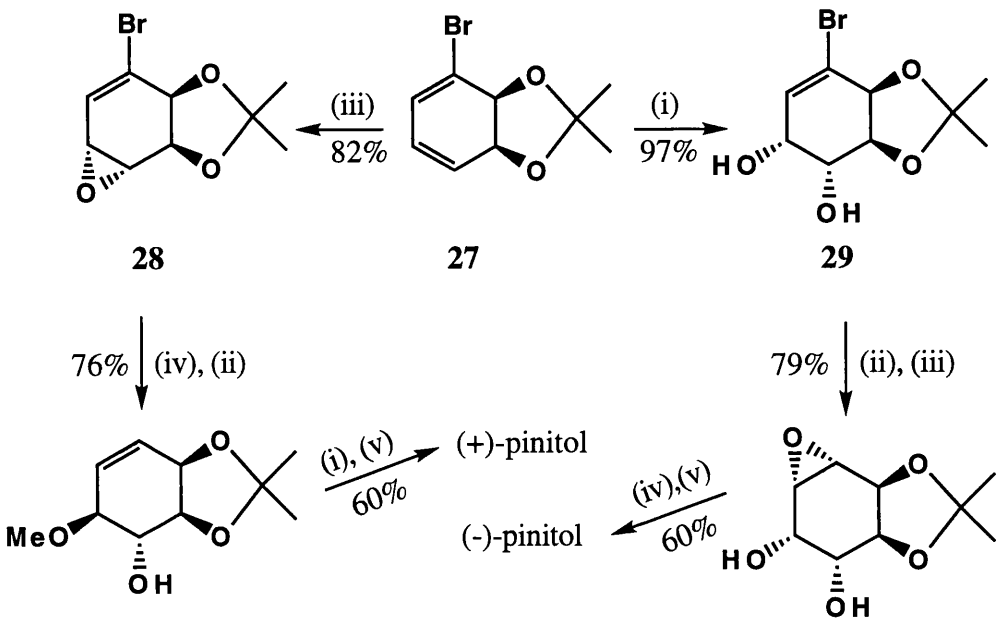
A more recent development is the availability of chiral diene diols **24-26, scheme 1.16**, which has allowed the synthesis of homochiral inositols and conduritols without the need for a resolution step. The enzyme system is however unable to produce high yields of optically pure product when disubstituted arenes such as halotoluene derivatives are used.



X=Br **24**, Cl **25**, F **26**.

Scheme 1.16

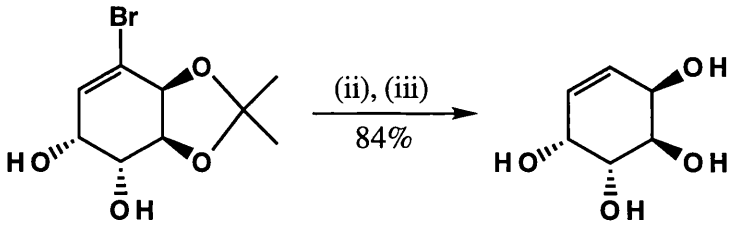
Hudlicky showed that the synthesis of both antipodes of pinitol was possible from the same starting bromo-diene diol **27**. His approach was based on using the symmetry of pinitol and, through inverting the order of the dihydroxylation and epoxidation stages of the homochiral starting material, (**scheme 1.17**), the (+) and (-) enantiomers were both successfully prepared.[40,41]



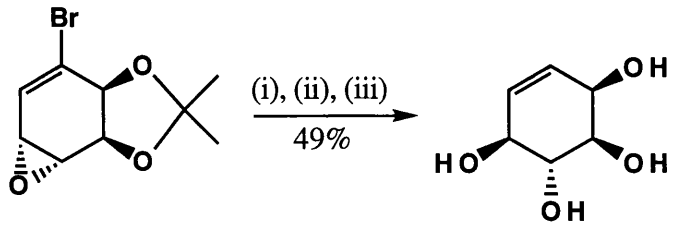
Reagents: (i) OsO_4, NMO; (ii) $LiAlH_4$; (iii) *m*CPBA; (iv) MeOH, Al_2O_3; (v) HCl

Scheme 1.17

With substrates **24-26** the ability to introduce *cis* diols *via* osmylation and *trans* diols *via* epoxidation followed by ring opening with complete *anti*-stereocontrol is possible with the use of the isopropylidene protecting group on the diol of **24-26**. Total regio control of these electrophilic oxidations is also possible through the electron withdrawing effect of the halogen. Thus both intermediates **28** and **29**, which are available stereospecifically from **27**, are perfect for the synthesis of (-)-conduritol E and (-)-conduritol F[42-44] respectively, **scheme 1.18**. A synthesis of conduramine-A from **27** has also been described.[44,45]



29 (-)-conduritol E

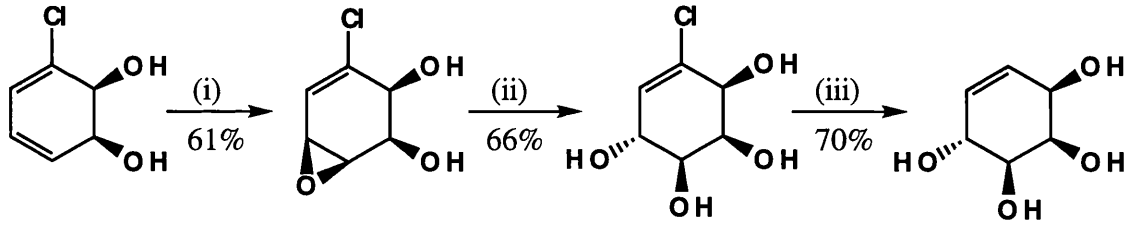


28 (-)-conduritol F

Reagents: (i) KOH, H_2O; (ii) Bu_3SnH, AIBN, *hv*; (iii) HCl, H_2O or AcOH, THF, H_2O.

Scheme 1.18

By way of contrast, *m*CPBA epoxidation of the unprotected chloro-diol **25** yields the *cis*-epoxide **30** with greater than 95% stereoselectivity. Acid hydrolysis of the epoxide followed by reductive dechlorination then led to (-)-conduritol C,[46] **scheme 1.19**.



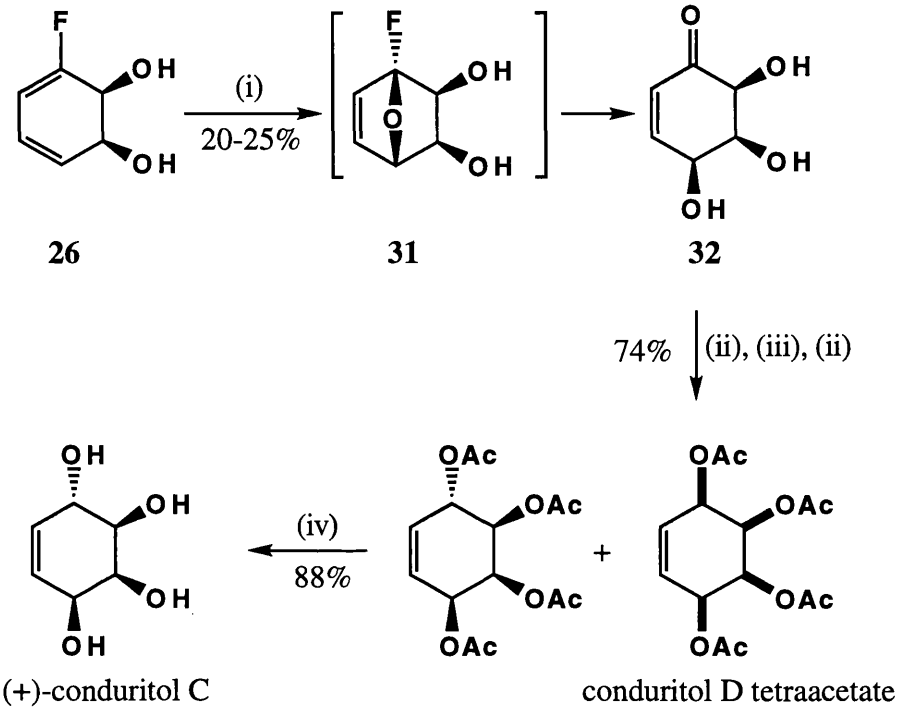
25 **30** (-)-conduritol C

Reagents: (i) *m*CPBA; (ii) TFA, H_2O; (iii) Na/NH_3.

Scheme 1.19

A synthesis of the antipode of (-)-conduritol C was achieved using the following sequence[47]: *m*CPBA epoxidation of the fluoro-diol **26** in the presence of TFA led, in one step, to the eneone **32**, *via* the bicyclic haloether **31**. Acetylation of **32** followed by

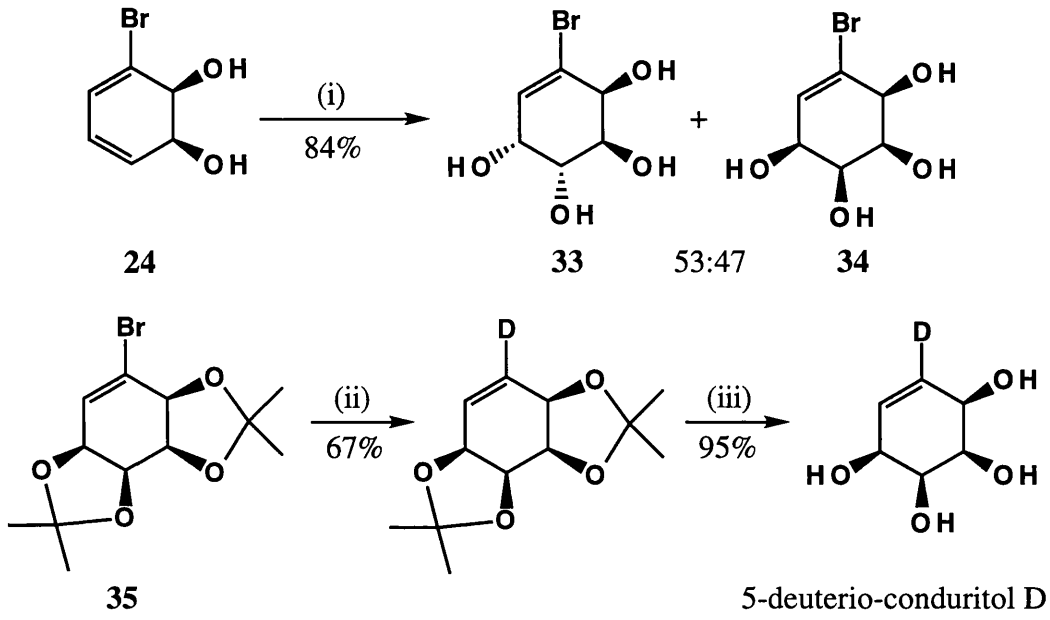
sodium borohydride/cerium trichloride reduction and acetylation of the alcohol thus produced, gave a mixture of conduritol D and (+)-C tetraacetates in a 2:1 ratio respectively. Separation of the isomers by column chromatography and deacetylation of the conduritol C isomer provided (+)-conduritol C in six steps from fluorobenzene, **scheme 1.20**.



Reagents: (i) *m*CPBA, TFA; (ii) Ac_2O, py; (iii) $NaBH_4$, $CeCl_3$; (iv) K_2CO_3, MeOH.

Scheme 1.20

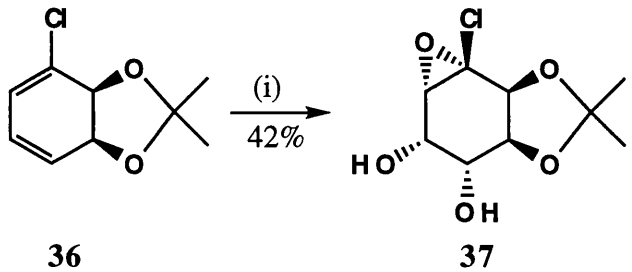
Partial *syn*-osmylation of **24** and **25** is observed leading to a mixture of halo-conduritols E **33** and the least accessible of the conduritols, conduritol D **34**, **scheme 1.21**. Protection of **33** and **34** as bis-isopropylidene derivatives allows separation of the two conduritols by column chromatography. Debromination and deprotection of **35** then provides a convenient route to isotopically labelled and chiral conduritol D.[48]



Reagents: (i) OsO_4, NMO; (ii) Bu_3SnD, *hv*; (iii) AcOH-H_2O.

Scheme 1.21

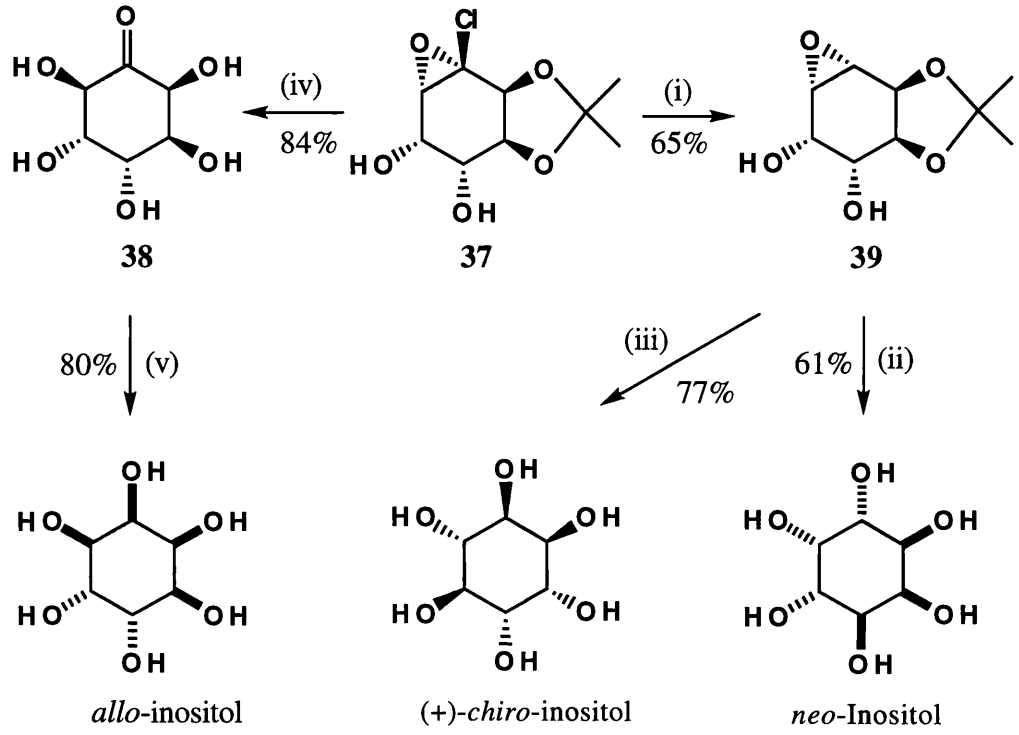
The enantiocontrolled synthesis of inositols is possible *via* osmylation and epoxidation (followed by hydrolysis) of the conduritols obtained from the microbial oxidation of the halobenzenes. A more direct route has recently been reported which uses the conduritol-halo epoxide **37** as a key intermediate.[49] **37** is available in a one step synthesis from the protected chloro-diol **36**,[50-52] **scheme 1.22**.



Reagent: (i) $KMnO_4$, H_2PO_4, tetraethylammonium chloride.

Scheme 1.22

Hydrolysis of **37** with basic alumina gave the inosose **38** which was hydrogenated to give *allo*-inositol. Aqueous hydrolysis of the dechlorinated epoxide **39** gave *neo*-inositol (as a 30-40% mixture with (+)-*chiro*-inositol). Basic hydrolysis of **39** proved to be more selective and furnished (+)-*chiro*-inositol in >95% purity,[53] **scheme 1.23**.



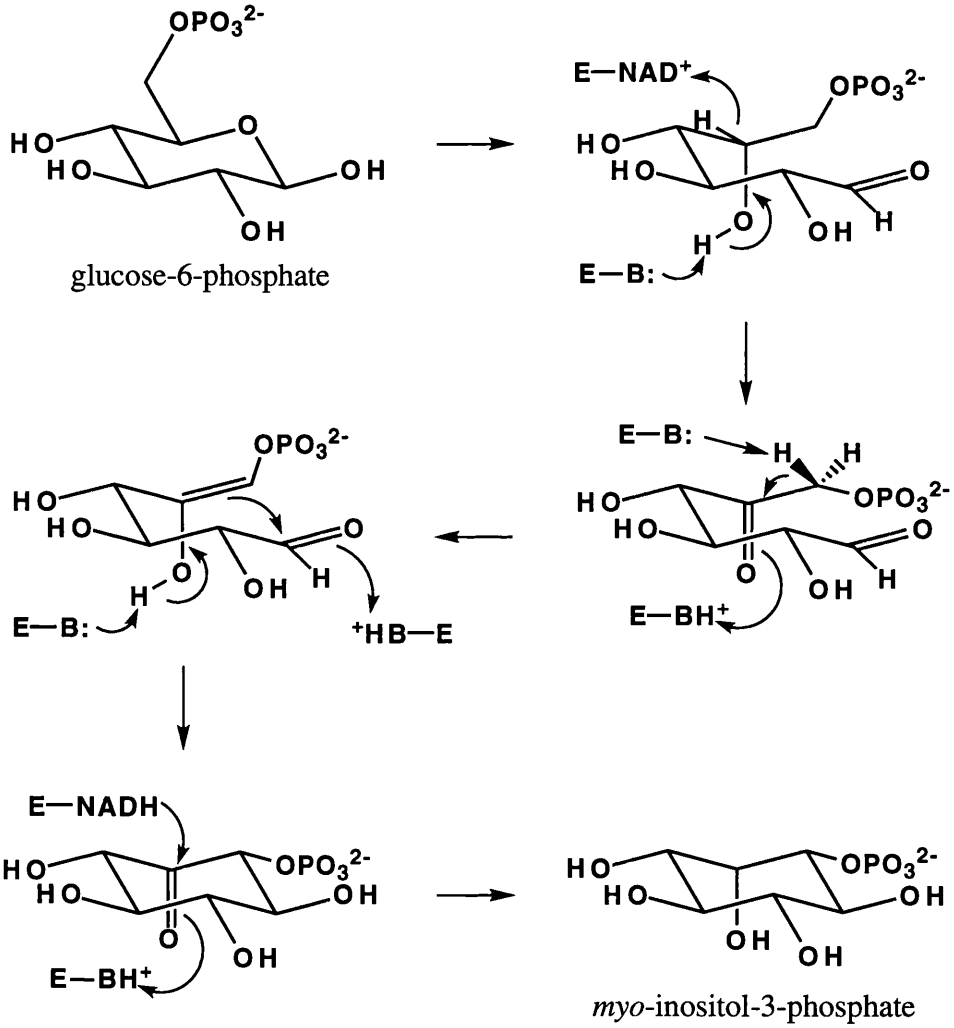
Reagents: (i) Bu_3SnH, AIBN; (ii) H_2O;

(iii) PhCOONa, H_2O; (iv) Al_2O_3, H_2O; (v) Ni-(R), H_2.

Scheme 1.23

1.2.2 Synthesis from carbohydrates

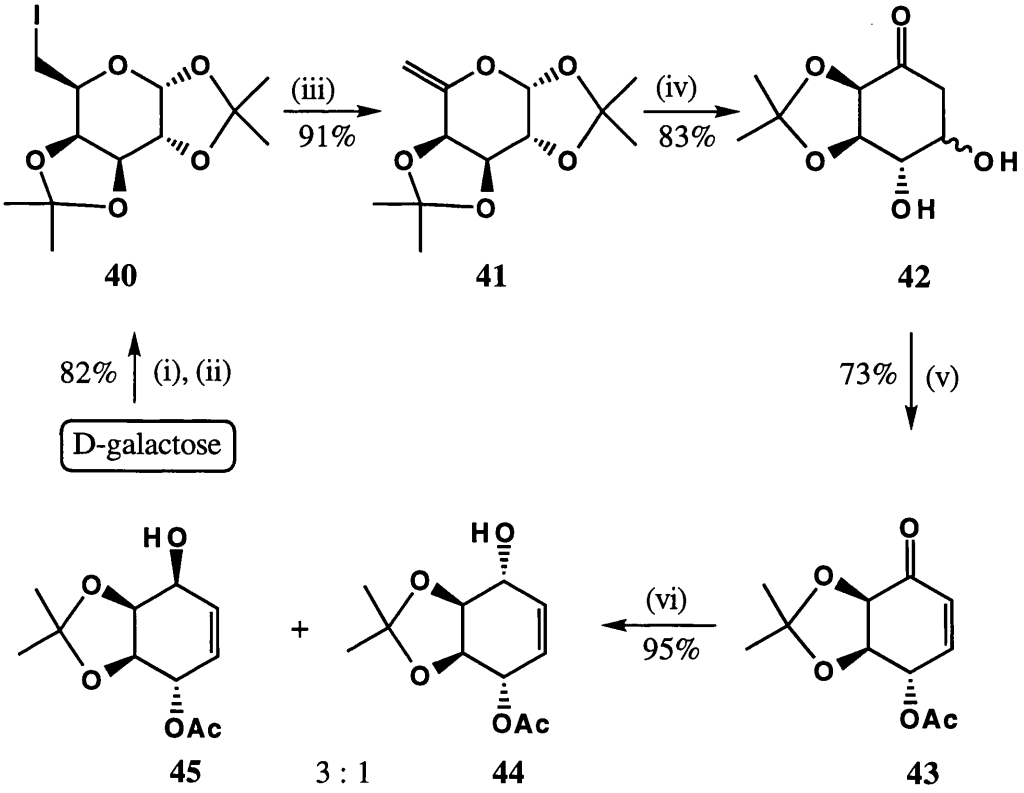
Carbohydrates are also logical precursors for the synthesis of inositol (and conduritols) as the are emperically identical. Indeed the biosynthesis of *myo*-inositol involves the enzyme *myo*-inositol-3-phosphate synthase which converts glucose-6-phosphate into (+)-*myo*-inositol-3-phosphate,[54] **scheme 1.24**.



Scheme 1.24

The key step in this transformation involves a stereospecific intramolecular aldol reaction providing the carbocyclic framework of the nascent inositol. Recent chemical routes employ two general ring closure strategies: (i) the Ferrier rearrangement[55] and (ii) the reductive coupling of a dialdehydic precursor (pinacol coupling).

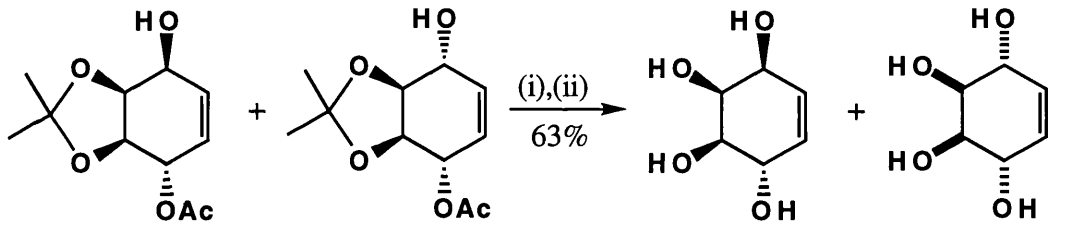
The work by Mereyala[56] is representative of the use of the Ferrier transformation for the synthesis of conduritols from carbohydrates. Thus, in a multistep route from D-galactose conduritols A, (+)-C and (-)-C are available as shown in **scheme 1.25**.



Reagents: (i) Acetone, H_2SO_4; (ii) Ph_3P, I_2, imidazole; (iii) NaH, HMPA; (iv) $Hg(OAc)_2$; (v) Ac_2O, py, DMAP; (vi) $NaBH_4$, $CeCl_3$.

Scheme 1.25

Bis-isopropylidene protection and iodination of D-galactose provided the iodide **40**. Reaction of **40** with sodium hydride gave the Ferrier enol ether precursor **41**. Reaction of **41** with catalytic amounts of mercury acetate then gave the carbocyclic diol **42**, which, through a subsequent acetylation step provided the enone **43**. Reduction of the enone **43** with sodium borohydride-cerium trichloride gave a 1:3 mixture of the protected conduritols A **44** and C **45** respectively. Deacetylation of the **44** and **45** mixture allowed the separation of the isomers by column chromatography, which, when treated with acid furnished conduritol A and (+)-conduritol C as shown in **scheme 1.26**.

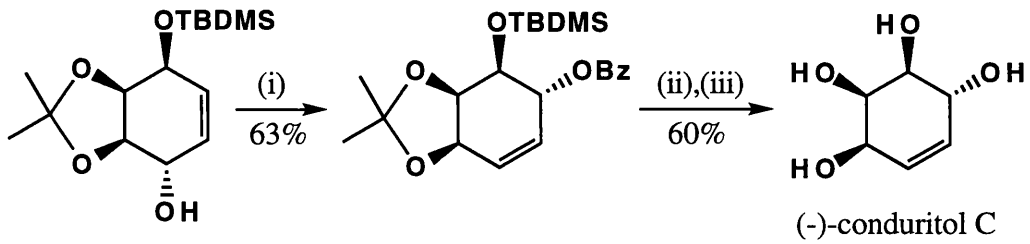


45 3 : 1 **44** (+)-conduritol C conduritol A

Reagents: (i) NaOMe, MeOH then column chromatography; (ii) HCl, MeOH.

Scheme 1.26

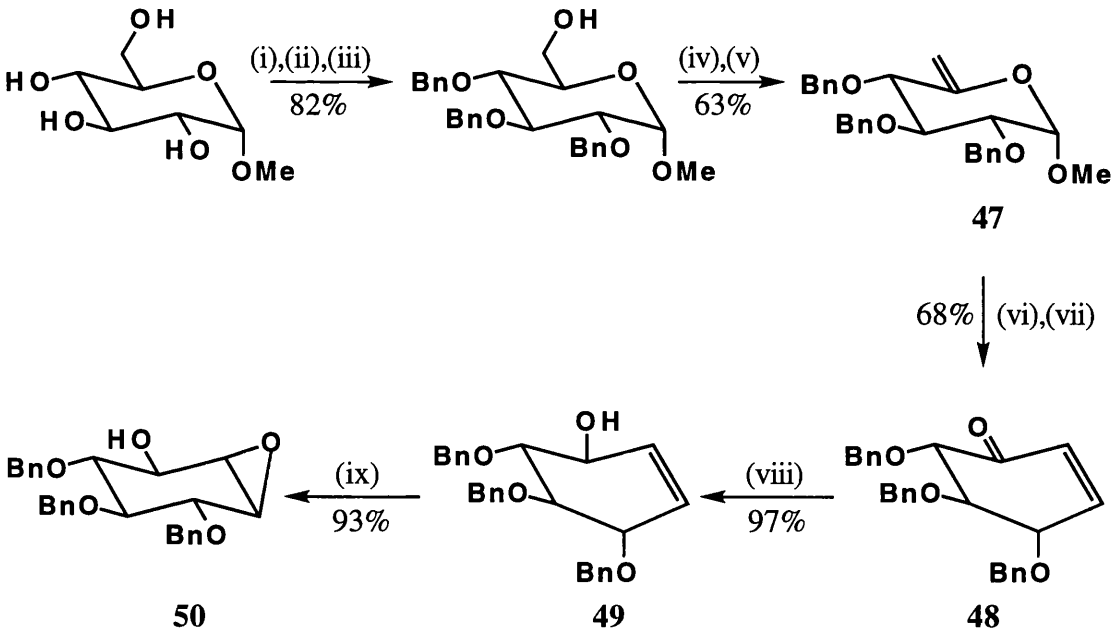
Silylation of **44** and **45** gave the fully protected conduritols, which could be separated by column chromatography. Deacetylation of **46** followed by the Mitsunobu reaction and multiple deprotection gave (-)-conduritol C, **scheme 1.27**.



Reagents: (i) Ph_3P, $PhCO_2H$, DEAD; (ii) NaOMe, MeOH; (iii) HCl, MeOH

Scheme 1.27

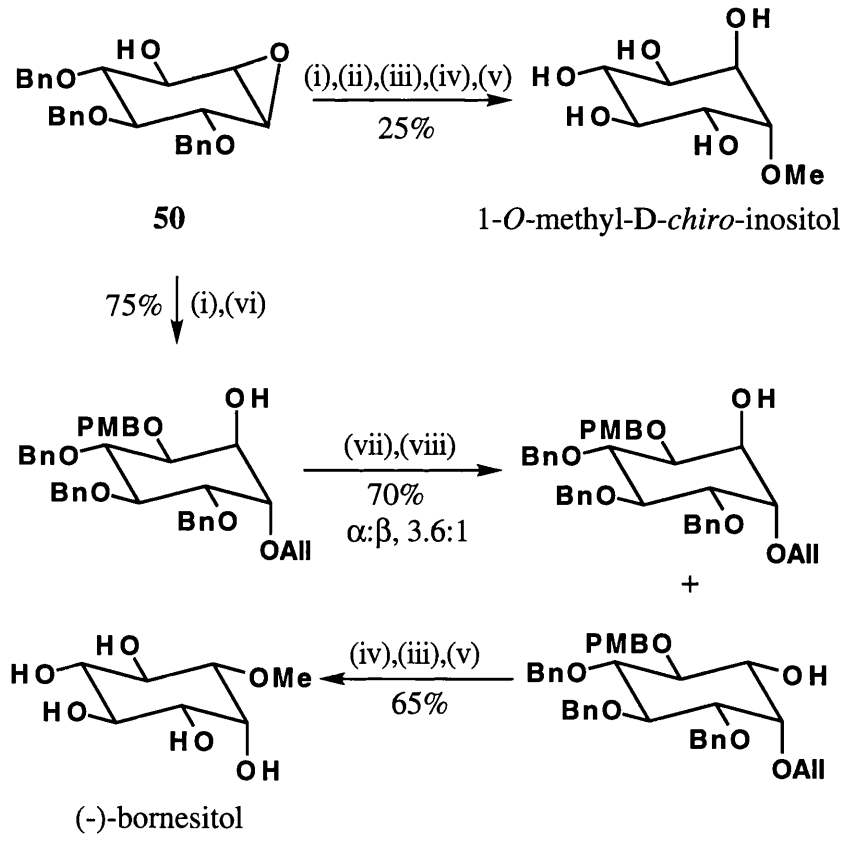
Inositols are available from carbohydrates *via* the Ferrier rearrangement in much the same way as the conduritols are obtained. By definition, the cyclisation precursor, an exocyclic enol ether, is required and hence all the syntheses have common initial steps. As an illustrative example of inositol synthesis from carbohydrates the recent work of Martín-Lomas[57] is shown in **schemes 1.28** and **1.29**.



Reagents: (i) TrCl 1.3 eq, py, DMAP; (ii) NaH, BnBr 6 eq; (iii) PTSA; (iv) Ph_3P, CI_4, py; (v) NaH; (vi) $HgCl_2$; (vii) MsCl, py, DMAP; (viii) $NaBH_4$, $CeCl_3$; (ix) *m*CPBA.

Scheme 1.28

In a multitude of steps D-glucose is transformed to the enol ether **47**, **scheme 1.28**, which undergoes the Ferrier rearrangement. Mesylation leads, *in situ*, to the eneone **48** which following borohydride reduction yields the protected conduritol B **49**. Epoxidation of **49** afforded the β-epoxide **50**[58] which was further elaborated to give 1-*O*-methyl-D-*chiro*-inositol and 1-*O*-methyl-L-*myo*-inositol ((-)-bornesitol), **scheme 1.29**.



Reagents: (i) allyl alcohol, $BF_3 \cdot Et_2O$; (ii) NaH, BnBr;

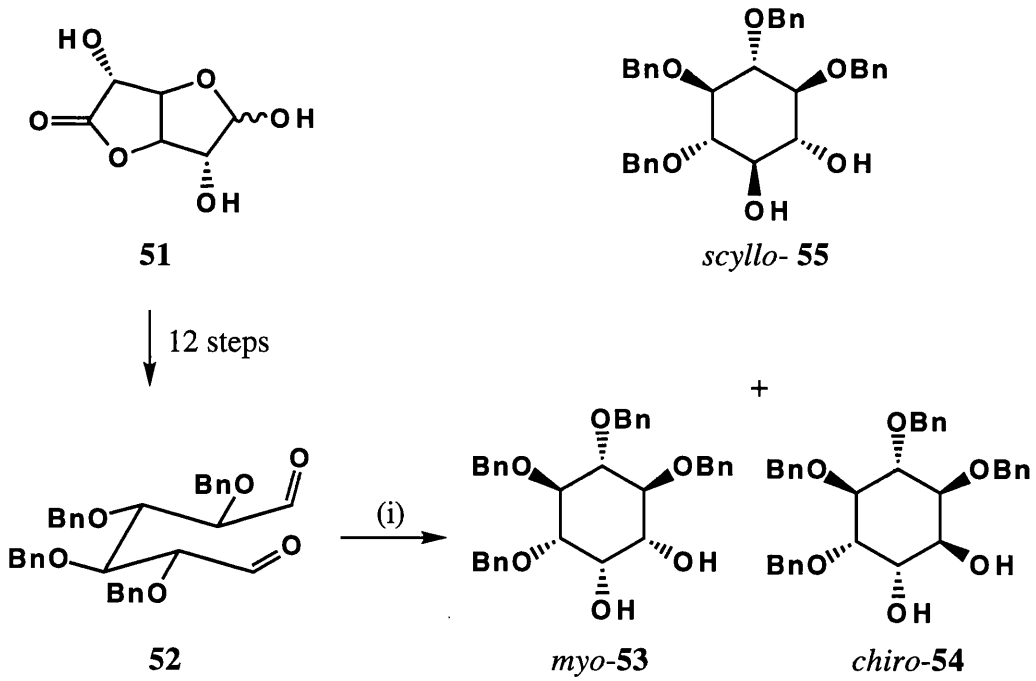
(iii) 10% Pd/C, PTSA (cat), EtOH; (iv) NaH, MeI; (v) 10% Pd/C (cat), H_2;

(vi) PMBCl, 3-Å sieves; (vii) PCC; (viii) (*R*)-Alpine hydride.

Scheme 1.29

The Ferrier rearrangement of D-glucose has also been used for the preparation of 2,3,6-tri-*O*-benzyl-D-*myo*-inositol,[59] P-1 tethered IP_4,[60] (-)-laminitol (4-*C*-methyl-*myo*-inositol) and mytilitol (4-*C*-methyl-*scyllo*-inositol)[61] other protected D-*myo*-inositols.[54]

The reductive coupling of a dialdehyde (pinacol coupling) to form the carbocycle of an inositol from a carbohydrate precursor was first used by Ozaki,[62] **scheme 1.30**. The C_2 symmetrical dialdehyde **52** was constructed from D-glucurono-6,3-lactone **51**. Reductive coupling with low valent titanium species gave the expected protected *myo*-inositol **53** but also the products of *trans* coupling *chiro*-**54** and *scyllo*-**55** in a 30:27:9 ratio respectively.



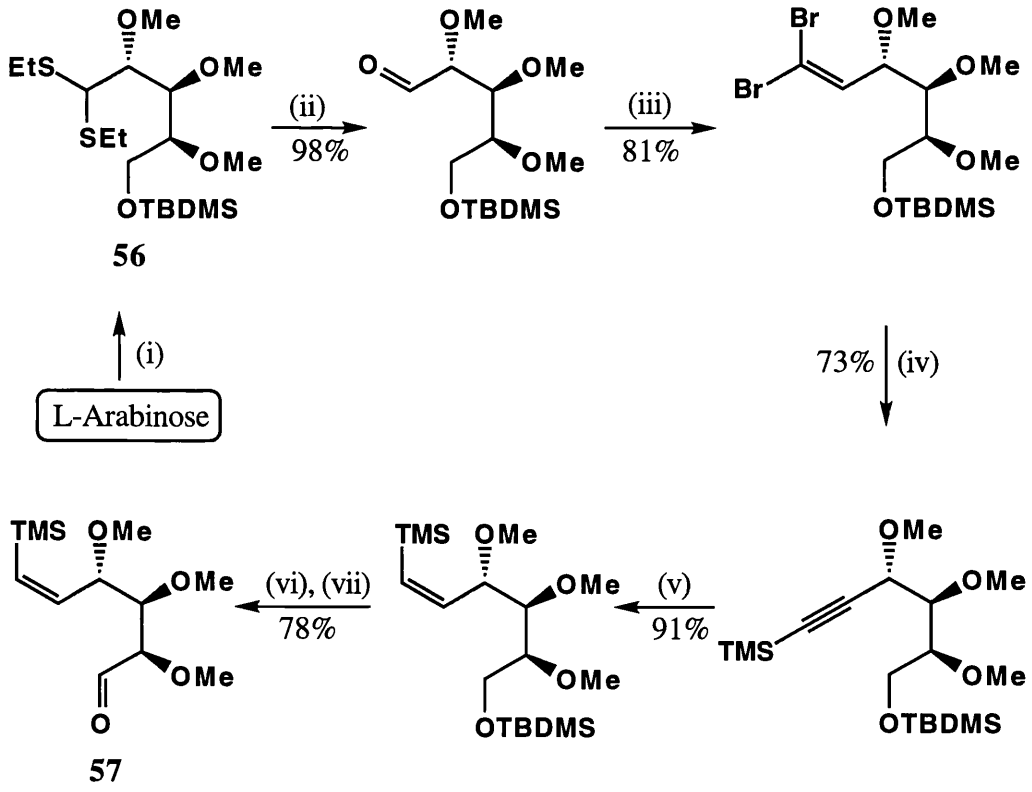
Reagent: (i) $TiCl_4$, Zn/Cu. **53**:**54**:**55**, 30:27:9, 66%;

OR (i) SmI_2, **53**:**54**:**55**, 14:1:1, 56%

Scheme 1.30

It was later shown that samarium diiodide was able to couple **52** with greater *cis*-selectivity giving a **53**:**54**:**55** ratio of 14:1:1 in 56% yield.[63] Using the same key cyclisation step a synthesis of L-*chiro*-inositol and (-)-conduritol F has also been achieved from D-sorbitol.[64]

The chemical synthesis most resembling the biosynthetic path is that elaborated by Weinreb[65] for the synthesis of conduritols A and C.



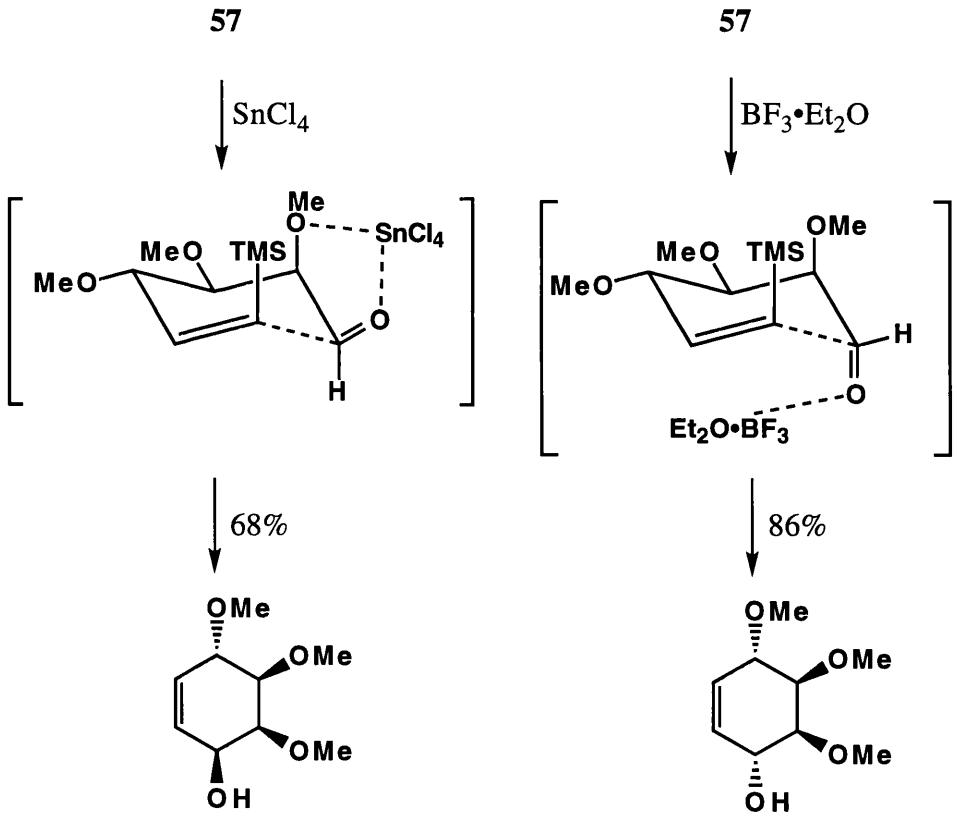
Reagents: (i) three steps; (ii) HgO, $HgCl_2$; (iii) ^tBuOK, PPh_3, $CHBr_3$;

(iv) ^nBuLi, TMEDA then TMSCl; (v) $Pd/BaSO_4$, H_2, py;

(vi) $AcOH\text{-}H_2O$; (vii) $(COCl)_2$, DMSO, Et_3N.

Scheme 1.31

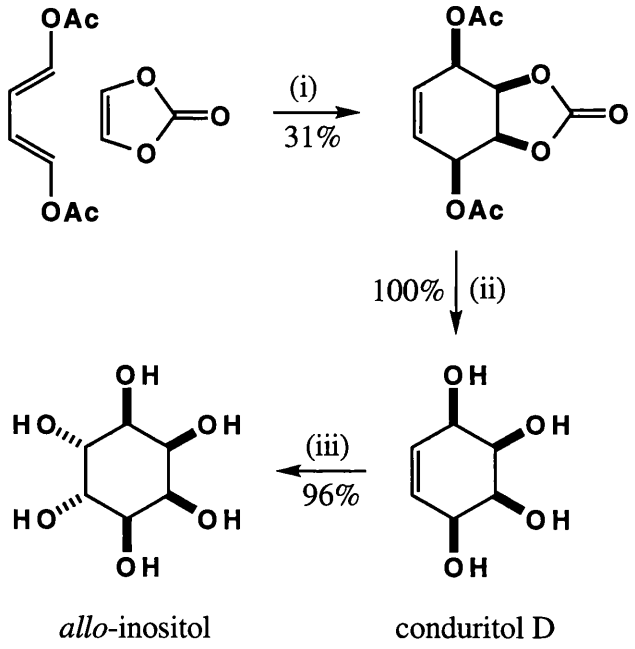
The dithioacetal trimethyl ether **56**, available in 3 steps from L-arabinose, is transformed in a multistep sequence to the vinylsilane aldehyde **57**, **scheme 1.31**. Cyclisation of **57** with BF_3•Et_2O then gave the tri-*O*-methyl conduritol A in >30:1 isomeric purity. By contrast, treatment of **57** with $SnCl_4$ gave the tri-*O*-methyl conduritol C, also in >30:1 isomeric purity. Both cyclisations are presumed to go *via* a chairlike transition state, with the difference in chelation of both Lewis acids being responsible for the selectivity of the reactions, **scheme 1.32**.



Scheme 1.32

1.2.3 Syntheses *via* Diels-Alder reactions

The construction of mono-unsaturated six-membered rings *via* the Diels-Alder reaction is a powerful tool in organic synthesis and has also found its application in the synthesis of cyclitols. In 1957 Criegee[66] accessed conduritol D through the electronically more unusual Diels-Alder reaction of *trans*, *trans*-diacetoxybutadiene and vinylene carbonate, **scheme 1.33**.

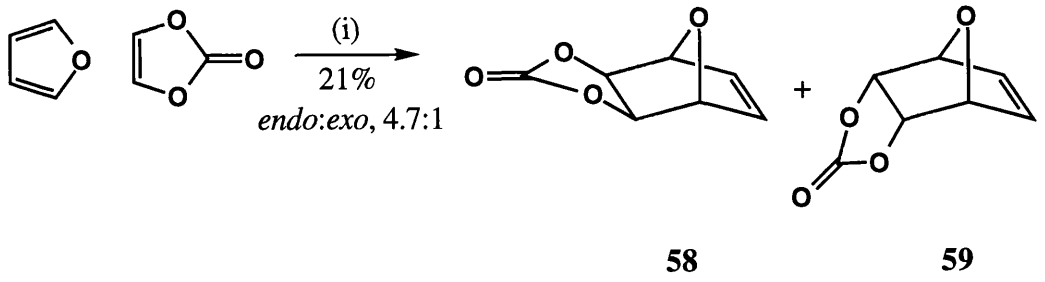


allo-inositol conduritol D

Reagents: (i) 205-210 °C, bomb; (ii) $Ba(OH)_2$; (iii) OsO_4, py.

Scheme 1.33

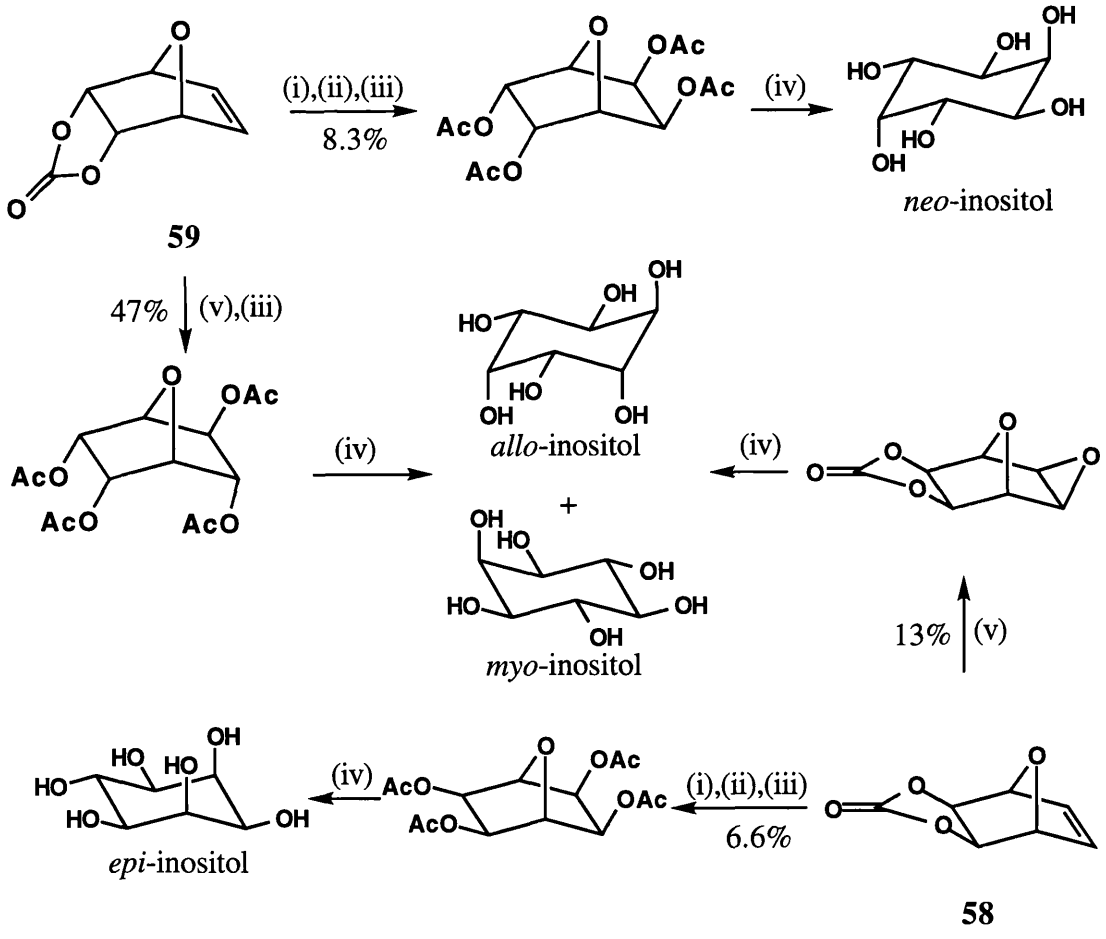
Osmylation of the conduritol provided *allo*-inositol in excellent yield. The synthesis of *myo*-, *allo*-, *neo*- and *epi*-inositol from the products of the Diels-Alder reaction of furan and vinylene carbonate has been described.[67] The *endo*-**58** and *exo*-**59** products obtained were transformed *via* osmylations, epoxidations and hydrolyses to the desired products as shown in **schemes 1.34** and **1.35**.



58 **59**

Conditions: (i) Sealed tube, 120 °C.

Scheme 1.34

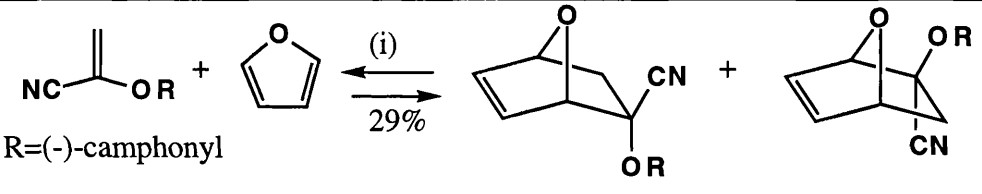


Reagents: (i) OsO_4, $NaSO_3$; (ii) NaOH; (iii) Ac_2O;

(iv) AcOH, H_2O, H_2SO_4; (v) AcOH, H_2O_2, H_2SO_4.

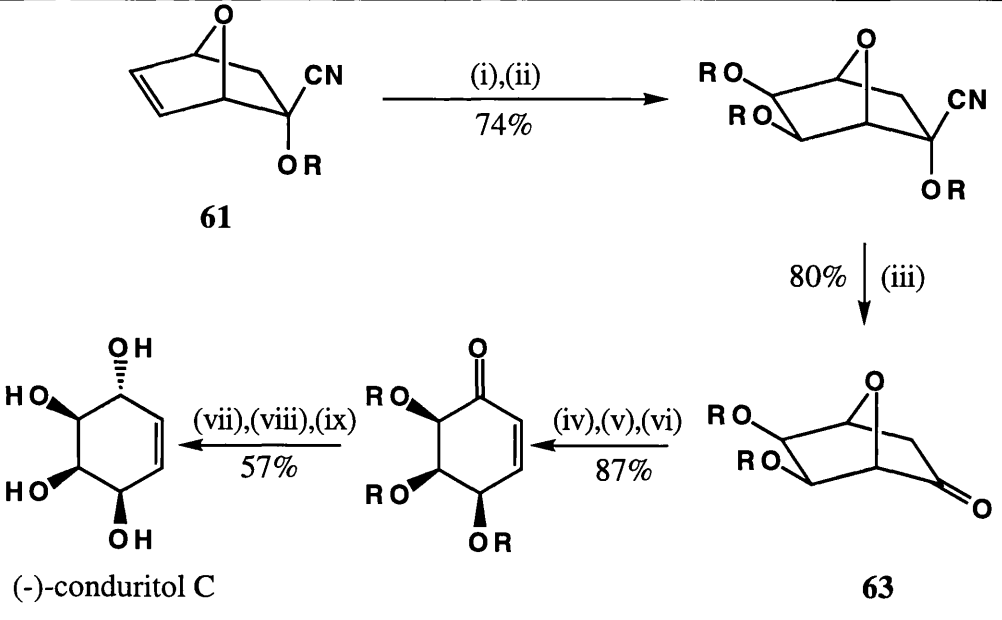
Scheme 1.35

Recently, Vogel has described the synthesis of (-)-conduritol C,[68] (-)-conduritol B and (+)-conduritol F[69] using his 'naked sugar' approach. The Diels-Alder reaction between furan and (-)-1-cyanovinyl camphanate **60** gave **61** and **62** in a 1:1 ratio from which **61** could be isolated in moderate yield.[70] Saponification of **61** and **62** then gave the corresponding ketone (eg **63** from **61**) and liberation of the chiral auxiliary. **61** was then elaborated in standard fashion to yield the desired chiral conduritols as outlined in **scheme 1.36** (in three parts below).



60 **61** **62**

Reagent: (i) $ZnCl_2$.

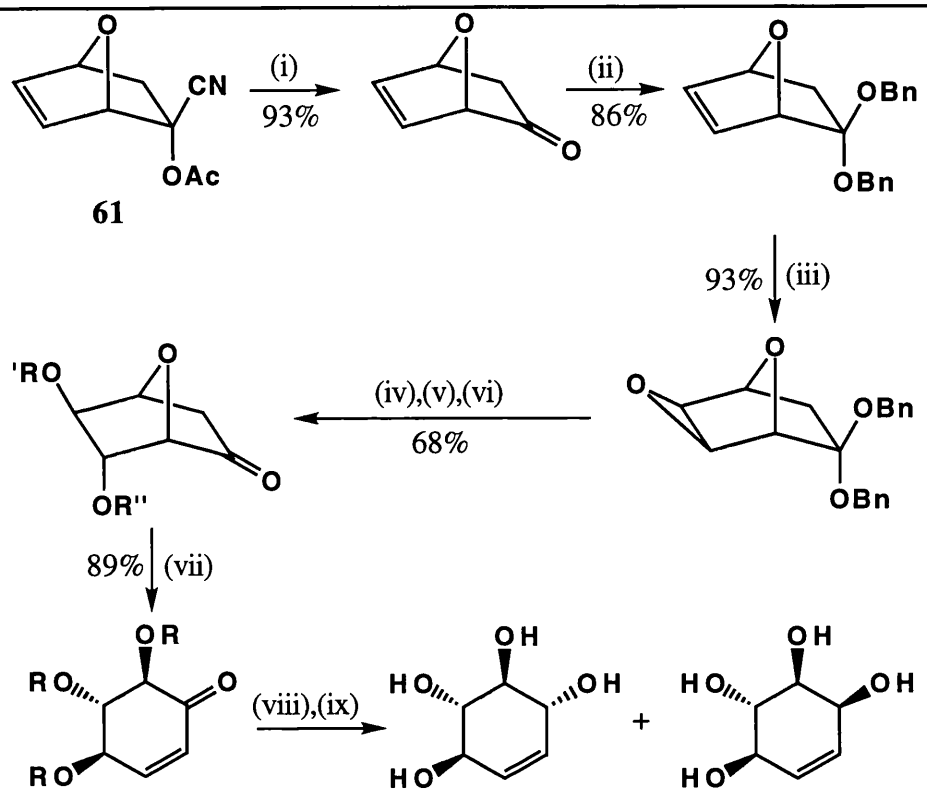


61

(-)-conduritol C

63

Reagents: (i) OsO_4, H_2O_2; (ii) TBDMSCl, imidazole; (iii) H_2CO (aq), K_2CO_3; (iv) TMSOTf, Et_3N; (v) MeOH, H_2O, HF; (vi) Ac_2O, py, DMAP; (vii) $NaBH_4$, $CeCl_3$; (viii) DEAD, Ph_3P, $PhCO_2H$; (ix) $BuNF_4$ then MeONa.



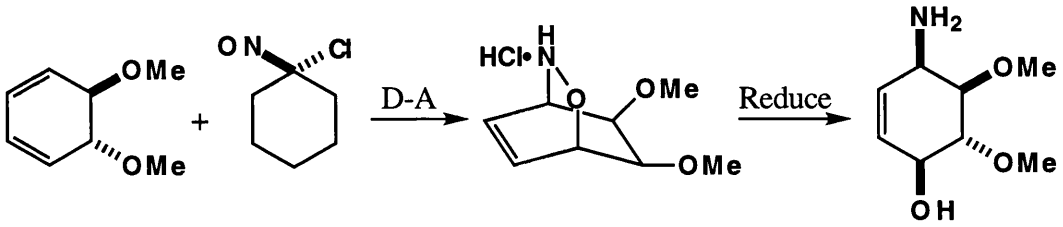
DIBAH	5.3	:	1	70%
$NaBH_4$, $CeCl_3$	1	:	2.5	84%

Reagents: (i) MeONa, formaldehyde; (ii) BnOTMS, TMSOTf (cat); (iii) *m*CPBA; (iv) BnOH, HSO_3F, R'=H, R''=Bn ; (v) Pd, H_2; (vi) TBDMSCl, imidazole; (vii) TBDMSOTf, Et_3N, R=TBDMS; (viii) reducing agent in scheme; (ix) HF.

Scheme 1.36

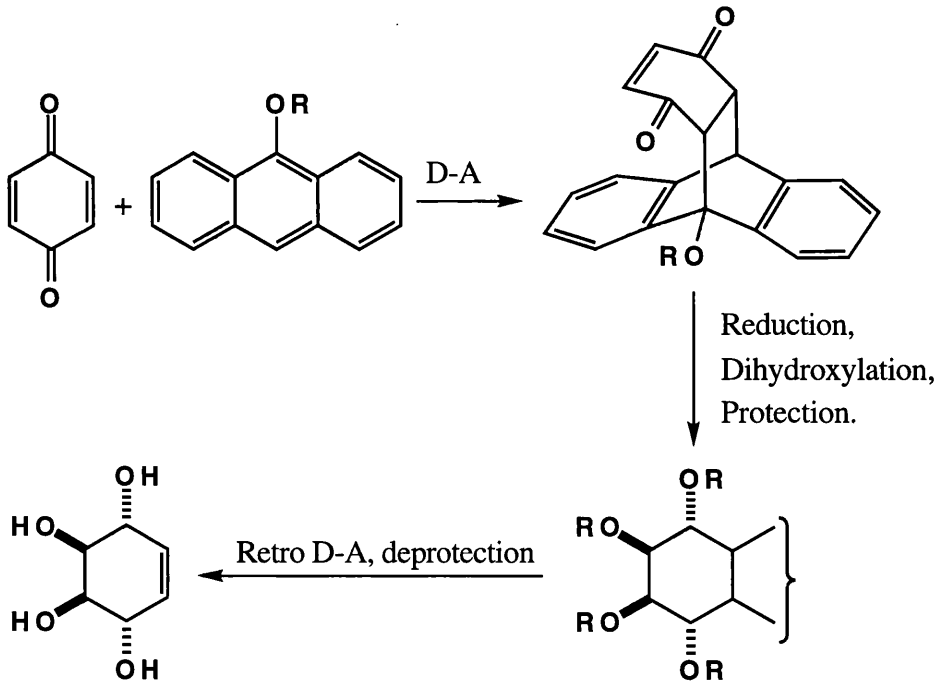
More recently **61** has been used to prepare (-)-conduramine C.[71] The versatility of the 'naked sugar' approach to homochiral conduritols and inositols lies in the ability to synthesise both antipodes using an identical synthetic route by simply choosing the required (+) or (-)-camphanic acid at the outset. Other syntheses of cyclitols which

involve Diels-Alder reactions but which do not however involve construction of the carbocycle, have also been a popular methods for the synthesis of conduritol A and C and conduramine A and C derivatives. **Schemes 1.37-1.38** exemplify such approaches.



Scheme 1.37[72,73]

In a conceptually similar fashion, the Diels-Alder reaction between the *meso*-isopropylidene protected *cis*-diene diol **6** and an α-chloronitroso derivative of D-mannose yielding chiral conduramines has also been reported.[74,75] The use of a Diels-Alder adduct as an alkene protecting group has been exemplified in a short synthesis of conduritol A from *p*-benzoquinone by Knapp[76] and Rutledge.[77]



Scheme 1.38

1.3 Conclusions

At present, the most efficient route by far to chiral cyclitols is *via* the products of the microbial oxidation of the halobenzenes. Through a protocol of stepwise oxygenation either *via* dihydroxylation or epoxidation and hydrolysis all inositols and conduritols have been synthesised. The introduction of various protecting groups as the cyclitol is built up allows for the selective 'manipulation' of practically all of the hydroxyl groups in a particular cyclitol. This strategy has made the synthesis of naturally occurring and biologically active conduritols and inositols possible in a short, linear, fashion.

The use of carbohydrates as starting materials for the synthesis of the desired products has the advantage of in-built chirality. However the lengthy transformations of the starting material to viable cyclisation precursors and the, as yet, low product specificity in the cyclisation reaction makes this strategy less desirable.

The 'naked sugar' approach developed by Vogel is again a multistep operation but has the benefit of relying on a chiral auxiliary which is readily available in both antipodal forms. Thus *via* the same synthetic sequence, it should be theoretically possible to synthesise both enantiomers of any active cyclitol.

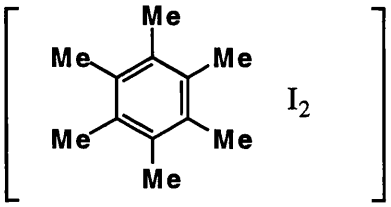
All of the foregoing synthetic approaches have involved strategic planning and tactical use of selective methods for regio- and stereocontrolled introduction, differentiation and manipulation of hydroxyl group and olefinic functionality. As we shall see, our approach is somewhat different, inasmuch as it involves an element of discovery and a posteriori rationalisation as opposed to prediction.

CHAPTER TWO

2.1 Introduction

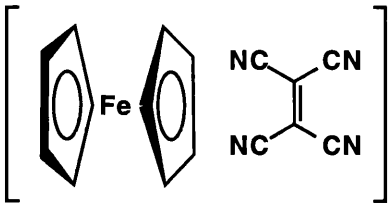
2.1.1 Electron acceptor-electron donor interactions[78]

Electron acceptor-electron donor interactions, EDA or CT (Charge Transfer) complexes were first described by Pfeiffer[79] in 1927. These typically highly coloured species arises from the non-bonding interactions of electron donor with electron acceptor molecules or elements. The type of interactions found in CT complexes, in valence-bond terms, is the result of a mixture of dispersion, dipole and covalent dative interactions in which an electron has been transferred from the donor to the acceptor. In an MO treatment the interaction is described as the transition of an electron between the HOMO of the donor to the LUMO of the acceptor. Examples of CT complexes are shown below, **scheme 2.1**, along with the characteristic physical data that arises only from the CT interactions.

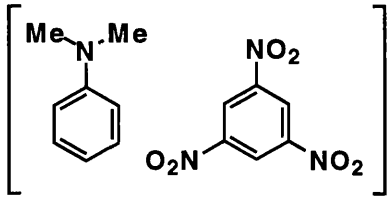


Physical characteristic of CT interaction

Absorbance 375 nm[80]



Absorbance 10,000 cm^{-1} [81]



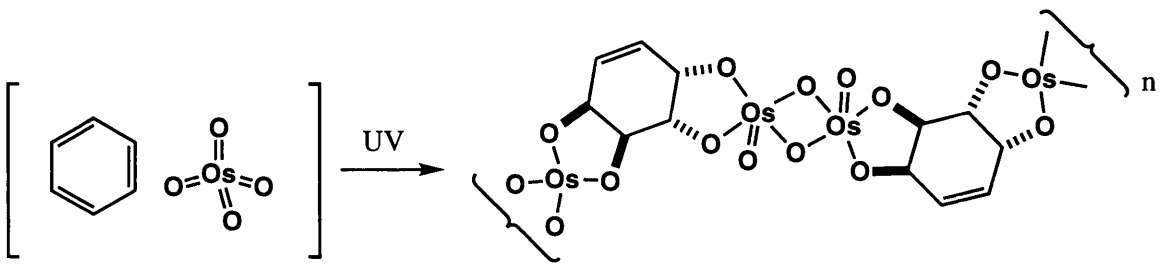
Dark violet solid, m.p. 110-111° C[82]

Scheme 2.1

In 1971 Hammond and Lake[83] showed that on the mixing of osmium tetroxide and benzene, neat or in inert solvents (cyclohexane, carbon tetrachloride) a yellow 1:1 CT complex was formed. This complex was shown to be stable at room temperature. The heat of formation of the CT complex, -525 cal mol^{-1}, is within the expected values for π-σ CT interactions. The UV spectrum for the complex revealed an absorption maxima at 380-400 nm (later measured at 328 nm[84]) which is absent in the UV spectrum of benzene and osmium tetroxide alone. This absorption is hence that of the CT interaction, and is called the CT band.

2.1.2 Stoichiometric CT osmylation of benenzoid hydrocarbons

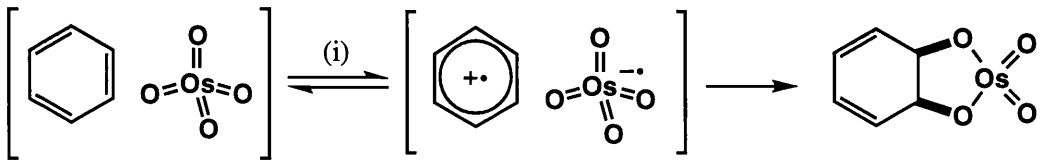
In 1988 Kochi and Wallis[85,86] re-examined Hammonds finding and were able to show that when the CT complex between benzene and osmium tetroxide **64** was irradiated with a UV source emitting at a frequency greater than or equal to that of the CT band, osmylation of benzene occurred, **scheme 2.2**. Control experiments were carried out to show that only the CT band required stimulation for the osmylation to take place. The resulting adduct, a brown amorphous solid insoluble in organic solvents, was identified as the polymeric bis-*anti*-osmate ester **65**. By treatment of **65** with pyridine, tetra-pyridyl monomers **69** were isolated as micro crystals **schemes 2.2-2.4**.



64 **65**

Scheme 2.2

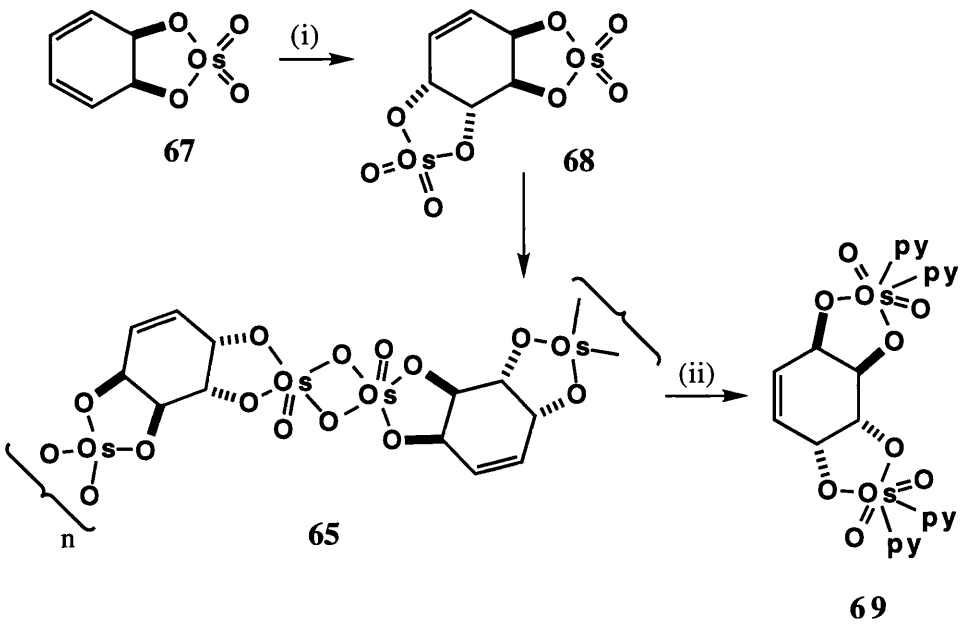
Yields for this stoichiometric CT osmylation were of the order of 10% (based on osmium), although no attempt to optimise the reaction was made. The mechanism for the reaction was shown to go *via* an arene cation radical resulting from the complete transfer of the CT electrons from benzene to osmium tetroxide upon UV irradiation. The radical ion pair formed upon irradiation can, as shown in **scheme 2.3**, decay in two ways. The primary route for this decay is back to the CT complex and accounts for the fate of 99% of the radical ion pairs formed. The secondary route of decay is one of chemical reaction in the form of cycloaddition (henceforth termed 'primary osmylation') to yield the diene diol osmate ester **67**. With concurrent loss of aromaticity, the nascent diene diol osmate ester **67** is prone to further thermal *anti* osmylation ('secondary osmylation') to the bis-*anti*-osmate ester **68, scheme 2.4**. All attempts to stop the CT osmylation after the primary osmylation through changes in reagent ratios were unsuccessful. The coordinatively unsaturated osmium(VI) centres in species of type **67** and **68** are prone to 'mutual association'[87] which leads to the polymeric osmate ester **65**.



64 **66** **67**

Reagent: (i) UV 328 nm

Scheme 2.3



Reagents: (i) OsO_4, (ii) py.

Scheme 2.4

CT osmylation of polynuclear aromatic systems (naphthalene, phenanthracene, anthracene, methoxy and methylated derivatives thereof) was also undertaken. It was found that the wavelength of the CT band increased in a linear fashion with a decrease in the ionisation potential (IP) of the aromatic. In essence, the easier it is to remove an electron from the donor of a CT complex, the less energy is required to do so which translates to a longer CT band frequency. This has a pronounced effect on the colour of the CT complex: benzene and osmium tetroxide gave a yellow colouration, naphthalene and anthracene gave orange and mauve complexes respectively, corresponding to CT bands of 426 and 532 nm. A simple correlation is possible between the ionisation potential (IP) of any given aromatic and its subsequent CT band wavelength, **equation 2.1**. **Table 2.1** shows selected physical data for the given CT complexes.[85]

Aromatic	IP(eV)	CT band (nm)	CT colour
Benzene	9.23	328*	Yellow
Mesitylene	8.42	389	Orange
Hexamethylbenzene	7.71	476	Red

Benzene	9.23	328	Yellow
Naphthalene	8.12	426	Orange
Anthracene	7.55	532	Mauve

* ref[84]

Table 2.1 Physical data for selected CT complexes with OsO_4

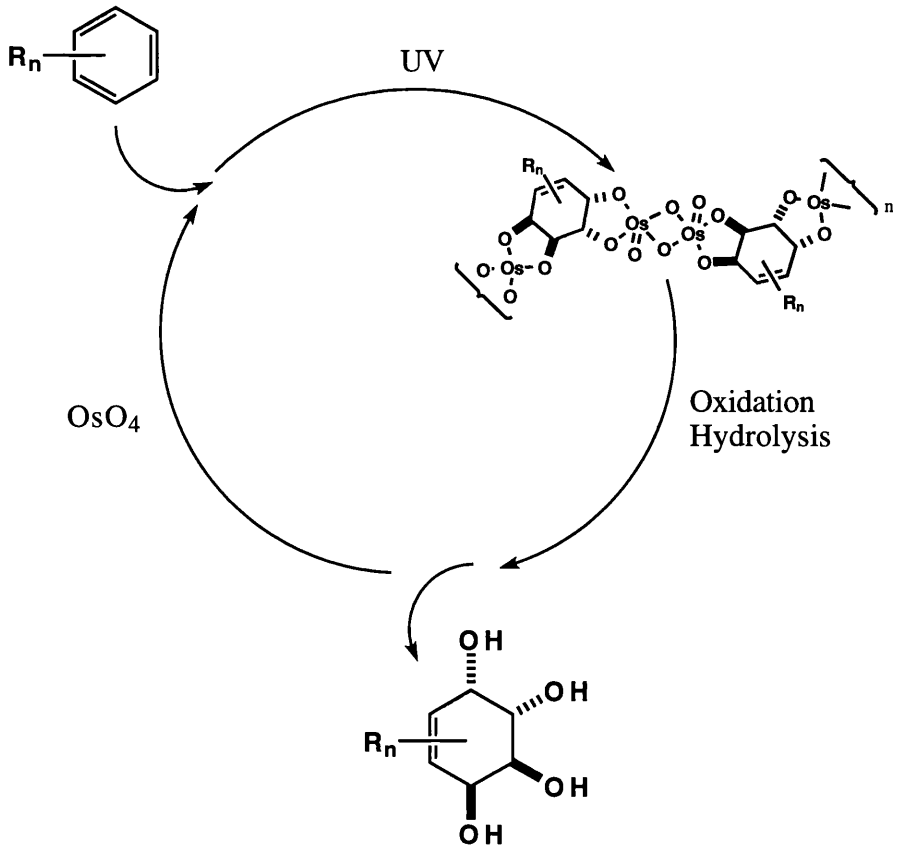
$$h\nu_{\text{CT band}} = 0.85(\text{IP}) - 3.92$$

Equation 2.1 Correlation between IP and CT band energy in eV.

CT osmylation of the polynuclear aromatics was shown to proceed with yields comparable to the benzene case. However it was found that on the irradiation of the CT complex with anthracene no osmylated product was isolated, anthraquinone and osmium dioxide being the only tractable product along with unreacted anthracene.

2.1.3 Aim

The discovery of the foregoing stoichiometric osmylation of aromatics by Kochi and Wallis (**2.1.2**) laid the fundamental groundwork from which we intended to develop a synthetically useful cyclitol synthesis. In the first instance, our primary objective was to address the necessity for a system which was catalytic in osmium, and secondly to probe the potential scope of such a catalytic CT osmylation process (hereafter termed 'photoosmylation'). **Scheme 2.5** outlines our aims.



R_n=alkyl, heteroatom, halo; n=0-6

Scheme 2.5

We envisaged that through the selection of an appropriate oxygen transfer reagent (reoxidant) and solvent system, oxidative hydrolysis of Kochi's bis-*anti*-osmate ester **65** would liberate, in the case of benzene, conduritol E, and osmium tetroxide to complete a catalytic cycle reminiscent of conventional olefin dihydroxylation. In the first instance we elected to limit our investigations to benzene and mono-substituted aromatics with a particular focus of interest in the position of primary osmylation in the latter case. On a more challenging note, and inspired by the elegant work of Sharpless, the development of a chiral photoosmylation procedure would always, however, be borne in mind.

***

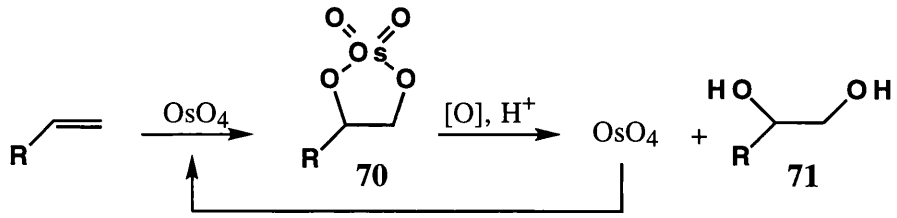
2.2 Development of a catalytic CT osmylation reaction: Photoosmylation

Foreword

From the outset, it is important to realise that, as in all scientific investigations, at any one time during this work different interwoven threads of investigation were being concurrently pursued. Whilst every attempt has been made to display the results of this work in a logical manner, it does not necessarily follow a strict chronological order. Accordingly, developments mentioned in earlier sections of chapter 2 may not always apply to later sections.

2.2.1 Selection of an oxygen atom transfer reagent (reoxidant)

The catalytic dihydroxylation of olefins with osmium tetroxide was pioneered by K. A. Hofmann[88] in 1912 with the use of stoichiometric chlorate salts as the oxygen atom transfer reagent. In its simplest form reductive addition of osmium tetroxide to an olefin to form the osmate(VI) ester **70** is followed by oxidative hydrolysis using an aqueous solution of chlorate to yield the diol **71** with concomitant liberation of osmium tetroxide thereby completing the catalytic cycle, **scheme 2.6**.



[O] = $MClO_3$, H_2O_2, ^tBuOOH, NMO, $K_3Fe(CN)_6$.

M = K, Na, Ba, Ag.

Scheme 2.6

Since this initial report no less than 4[87,89,90] other oxygen atom transfer reagents have been regularly employed for both the standard and for the modified chiral dihydroxylation,[36] and a further 3[91-93] have been found in the literature which report successful catalytic turnover. The most important criterion which we had to bear in mind in order to select an appropriate reoxidant however, was how it might adversely interfere with the CT complex. Hammond had measured the strength of the osmium tetroxide-benzene CT complex at 0.5 kcal mol^{-1} and whilst this is reasonably strong for any given π-σ CT interaction, it is almost negligible when compared to other non-bonding interactions such as H-bonding which can typically range from 3-8 kcal mol^{-1}. A reoxidant was required which would not coordinate to either the aromatic substrate or the osmium tetroxide in any way, and hence disrupt the fragile CT complex. Moreover, the by-products formed after the oxygen atom transfer had occurred were also required to be inert.

A simple test was devised to determine the suitability of any given reoxidant. A CT complex of osmium tetroxide and anthracene was made up in a solution of dichloromethane. The resulting pink-mauve solution was then treated with a variety of reoxidants and the effect on the CT complex, as monitored through changes in the colour, was then recorded, **table 2.2**. Although we were not investigating the development of a photoosmylation protocol for polynuclear aromatics, the distinctive colour of the anthracene CT complex allowed for easier monitoring. Indeed the most common colour for OsO_4 adducts is yellow[94] hence precluding the use of the benzene osmium tetroxide CT complex as a standard.

	Reoxidant	Effect on colour of CT complex
1	$KClO_3$*	Retained
2	H_2O_2*	Retained†
3	^tBuOOH	Retained
4	*N*-methyl morpholine-*N*-oxide*	Retained
5	$K_3Fe(CN)_6$*	Retained

* In aqueous solution † Violent effervescence (O_2) on mixing

Table 2.2 Effects of various reoxidants on the CT complex Anthracene-OsO_4

Much to our delight and surprise, all of the reoxidants tested had no influence on the CT complex. The effervescence of oxygen in the case of aqueous hydrogen peroxide is due to a metal catalysed decomposition of the peroxide[90] and was hence no longer retained as a possible reoxidant for our photoosmylation. We were also aware that a biphasic system in which the reactive CT complex resides in the organic phase and the reoxidant in the aqueous phase, as employed for entries 1, 4 and 5, was not ideal for any catalytic activity. Perusal of the literature on the catalytic dihydroxylations of olefins indicated that the use of a co-solvent could overcome any such phase problems. A study of suitable solvents was therefore undertaken.

2.2.2 Co-solvents and initial results. Photoosmylation of toluene

In the same way as reoxidants were tested for compatibility with the CT complex between anthracene and osmium tetroxide a range of typical co-solvents was also screened for effectiveness, **table 2.3**.

	Co-solvent	Effect on colour of CT complex
1	Acetone*	Discharged
2	Pyridine*	Discharged
3	^{t}BuOH	Discharged
4	*N*-methyl morpholine	Discharged
5	Water	Retained

* Ref[85]

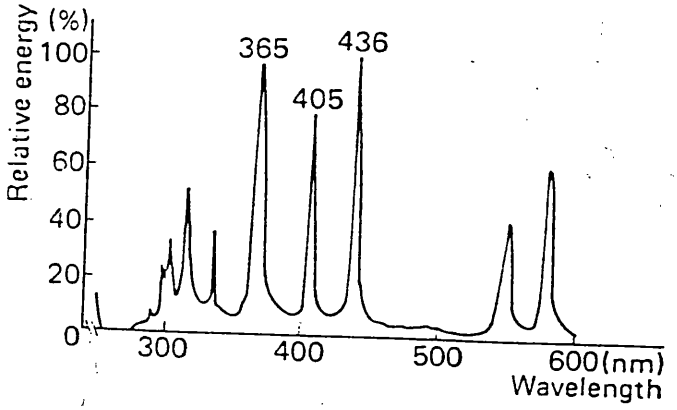
Table 2.3 Effects of co-solvents on the CT complex Anthracene-OsO_4

To our disappointment, we were to discover that virtually any solvent with a lone pair of electrons made for a better donor to osmium tetroxide than anthracene and upon mixing disrupted the CT complex. Water, it was presumed, had no such adverse effect simply due to its immiscibility with the phase containing the CT complex. The reduced forms of two of our previously considered reoxidants, namely ^{t}BuOH and *N*-methyl morpholine, were also tested (entries 3 and 4) and lead to disruption of the CT complex.

Faced with these results reasoned that a vigorously stirred biphasic system should be used as an initial experiment to test our premise. Given the literature precedent[36] that potassium ferricyanide had been previously used in such a way for catalytic dihydroxylation it was chosen as the first of the reoxidants to be screened. Its mode of oxidation was reported to operate *via* an outer sphere, electron-transfer mechanism.[95]

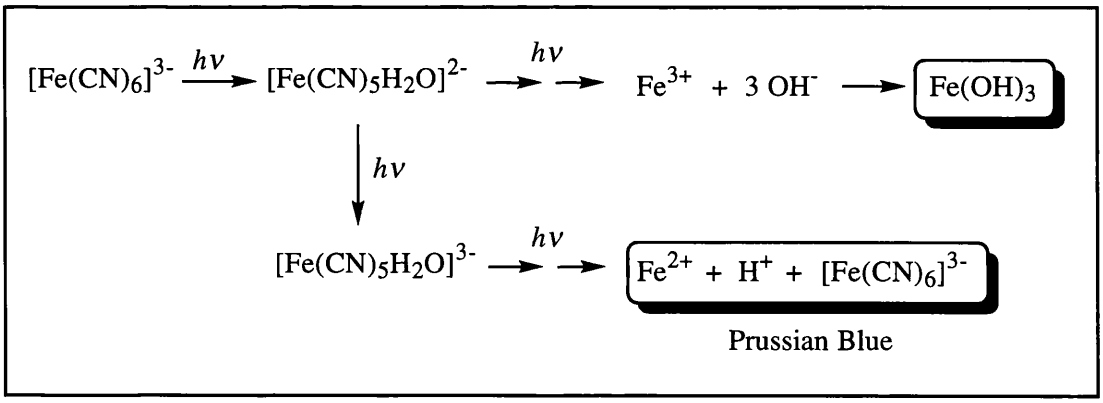
Unlike the other aforementioned reoxidants, which operate via direct attack of oxygen, this mode of oxidation was thought to be ideal for the oxidative cleavage of the sterically encumbered bis-*anti*-osmate polymer **65**. In selecting toluene as our first substrate, we intended to kill two birds with one stone by performing a catalytic CT osmylation on an aromatic substrate which had not even been oxidised in a stoichiometric manner!

Our source of irradiation was a 400W medium pressure Hg vapour lamp which, as shown from its emitance spectrum below, **graph 2.1**, possesses strong spectral lines in the UV band coinciding with the CT wavelengths of benzene and slightly more electron rich aromatic complexes.[96] The choice of glassware for the experiment posed some initial problems. It was predicted that the immense heat emitted from the lamp would vaporise the osmium tetroxide. A simple reflux condenser was considered too large to effectively condense catalytic amounts of osmium tetroxide, hence a small scale Pyrex sublimation unit fitted with a water cooled cold finger was used (reaction vessel O). Much to our delight, the UV absorption of Pyrex starts at around 303 nm to reach a maximum at ca. 250 nm, so cutting out any hard UV responsible for unwanted aromatic π–π^* transitions.



Graph 2.1[96]

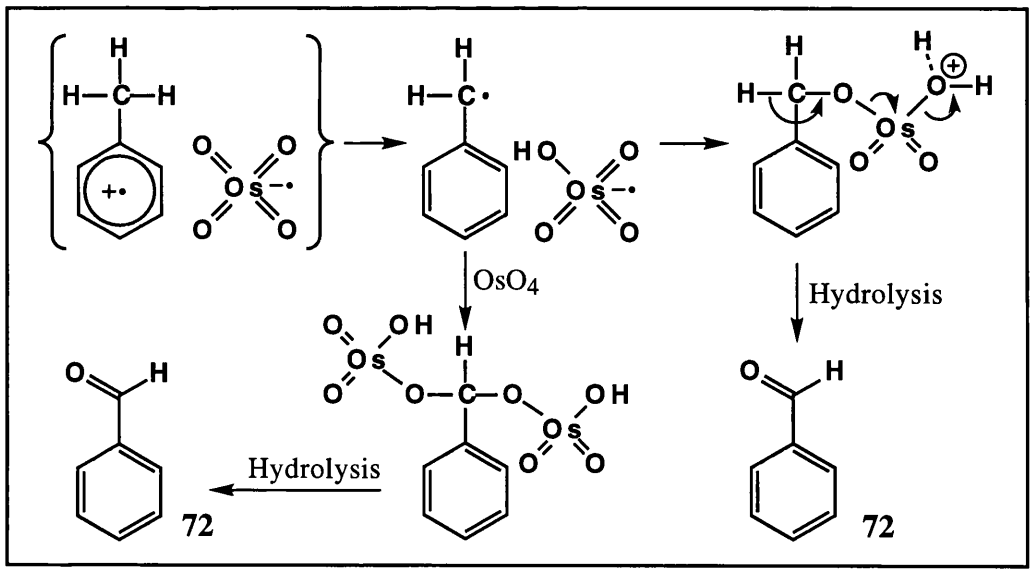
A 400 W medium pressure Hg lamp photoosmylation of toluene containing 2.6 mol% of osmium tetroxide as catalyst with respect to toluene in an aqueous solution of excess potassium ferricyanide and potassium carbonate, was therefore carried out with vigorous stirring. After 14 h of irradiation, the osmium residues were reduced with sodium sulphite and the reaction mixture reduced to dryness. Due to the water soluble nature of conduritols their isolation was performed by prior conversion to their acetates: the remaining salts were taken up in methanol, filtered, reduced further and acetylated with acetic anhydride under basic conditions. No acetylated product could be detected from this reaction mixture and it was evident that no catalytic system had been achieved. At this point however, it became apparent that the reason for our failure lay in the photochemical reactivity of potassium ferricyanide,[97] as shown in **scheme 2.7**.



Scheme 2.7

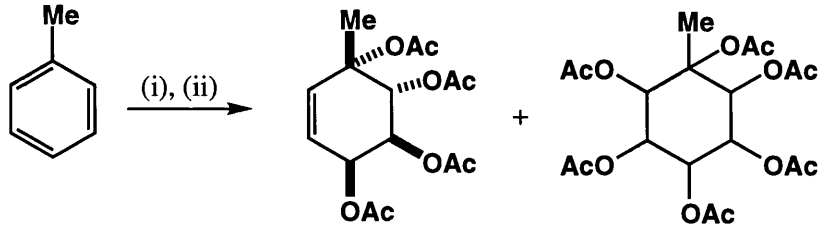
A standard solution of potassium ferricyanide darkened over a period of several days when left exposed to ordinary light in a volumetric flask. It was subsequently found that photochemical reactions of the ferricyanide anion in an aqueous medium were qualitatively independent of the wavelength of irradiation, and ultimately gave iron (III) hydroxide and Prussian Blue.[97]

Our second selection involved the use of chlorate anion which was tried under the same reaction conditions. Irradiation of a solution of osmium tetroxide (1.3mol% osmium tetroxide w.r.t. toluene) using an aqueous solution of excess potassium chlorate (2.5 eq w.r.t. toluene) was carried out as before. After 91 h, extraction of the aqueous phase gave rise to the isolation of benzaldehyde **72** in a low yield (1.6%). This may well be formed by a mechanism similar to that of the Étard reaction[98] which proceeds with chromyl chloride to oxidise toluene to benzaldehyde. Osmium tetroxide can be imagined to operate *via* a similar mechanism. It is not inconceivable however, in the case of osmium that an alternative pathway involving the collapse of a simple mono osmate ester can also give benzaldehyde, **scheme 2.8**.



Scheme 2.8

To our delight evaporation of the aqueous phase followed by acetylation gave two products (tlc) which after isolation by column chromatography were determined to be 1-*C*-methyl conduritol E acetate **73** (0.5%) and a mixture of *C*-methyl inositol acetates **74** (0.9%), **scheme 2.9**.



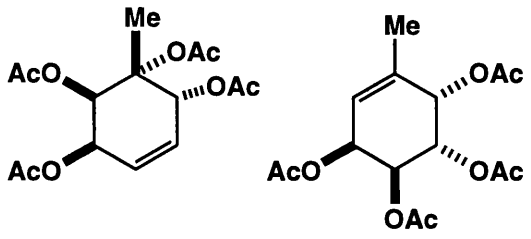
73 **74**

Reagents: (i) OsO_4 (cat), $KClO_3$ (aq), UV; (ii) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2

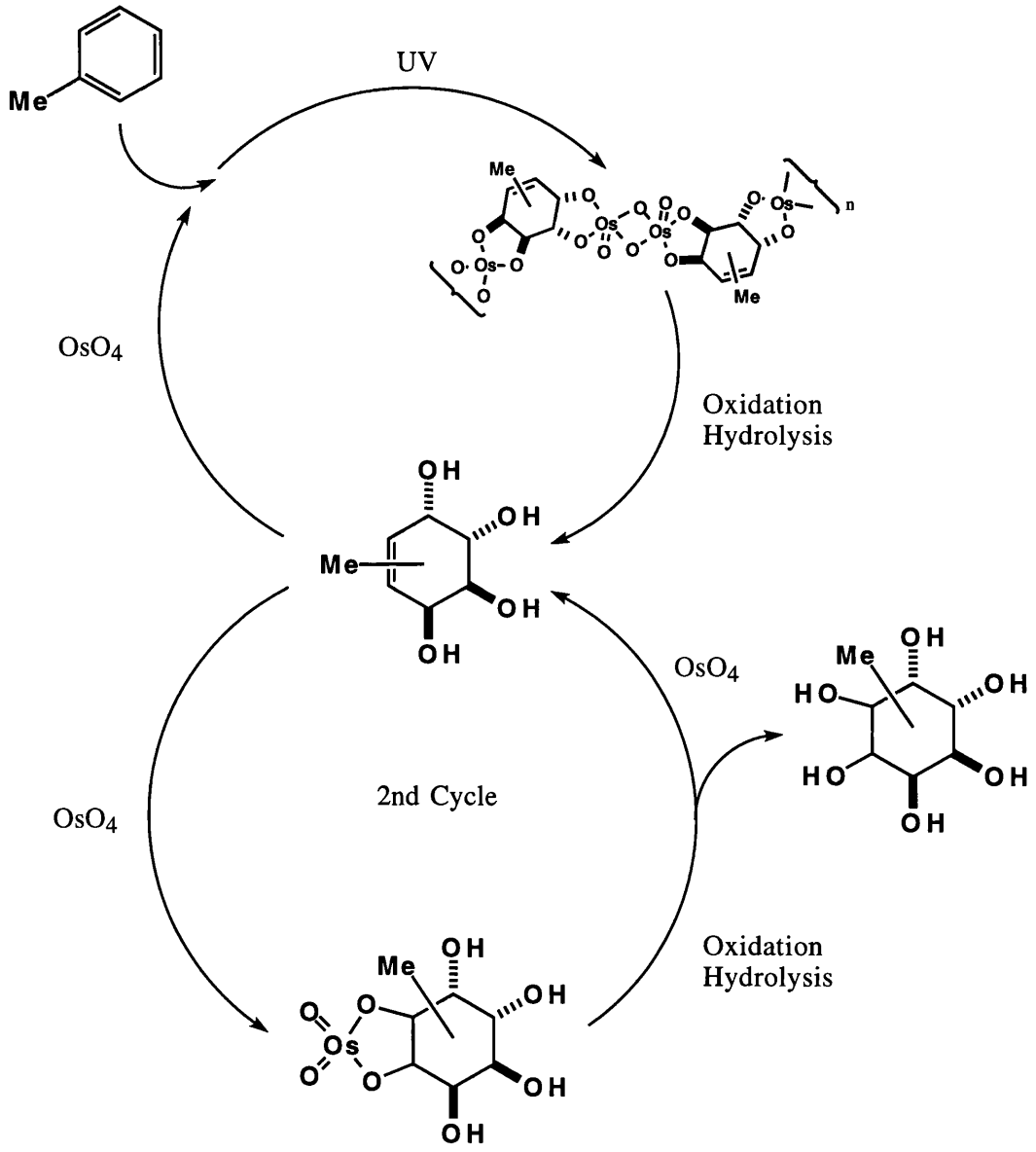
Scheme 2.9

In the first instance, the isolation of an inositol derivative came as a surprise to us. We had anticipated that in the presence of only 1.3 mol% of osmium tetroxide, oxidative hydrolysis would compete efficiently with any further normal thermal osmylation and that the arene diol could well be liberated into the aqueous phase. In practice however, the observed formation of a black residue during the reaction was taken as evidence (*vide infra*) that the bis-*anti*-osmate polymer **65** had been formed. Once again, oxidative hydrolysis might have been assumed to liberate the water soluble 1-*C*-methyl conduritol E. However, it appeared that although the solubility of osmium tetroxide in water is low (41 times more soluble in CCl_4 than water),[99] enough was present in the aqueous phase or at the interface to oxidise the tetrol and set up a further catalytic cycle which we will hereafter refer to as 'tertiary osmylation', **scheme 2.10**.

The relative stereochemistry of the conduritol product was established by ^1H and ^{13}C NMR and confirmed by X-ray crystallography (appendix A). As reported by Kochi and Wallis, *anti* secondary osmylation had been observed exclusively and to our surprise none of the other possible *C*-methyl conduritol E isomers **75** and **76** were detected.

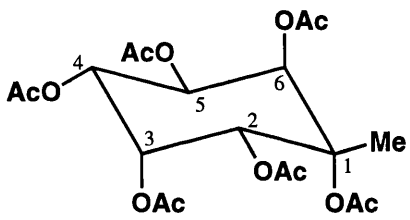


75 **76**


Me
UV
OsO4
Oxidation
Hydrolysis
OH
Me
2nd Cycle
OsO4
OsO4
Oxidation
Hydrolysis
HO

Scheme 2.10

Careful inspection of the ^{1}H NMR of the mixture of *C*-methyl inositols **74** showed the presence of only 3 isomers, as established by identifying the *C*-methyl singlets in the range 1.5-1.8 ppm. Attempts to give an approximate ratio of these isomers however was thwarted due to the severe thermodynamic broadening of one of the peaks. Fortuitously, trituration of the oil with methanol induced crystallisation and upon careful recrystallisation a single isomer was obtained. Through extensive ^{1}H HOMO NMR decoupling experiments and high temperature NMR experiments, structural elucidation of this isomer as 1-*C*-methyl *allo*-inositol hexaacetate **77** was eventually possible.



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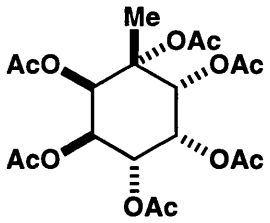


77

Although catalytic photoosmylation had been achieved, the low catalytic turnover of just 2.8 left much room for improvement. Accordingly, our efforts were first directed towards a modified experimental procedure and setup.

2.2.3 Photolysis equipment. Photoosmylation of benzene.

In an attempt to find an explanation for the low yield and the implicit low catalytic turnover for the reaction, simple inspection of the reaction glassware provided important information. Parts of the cold finger which were not immersed in the reaction mixture were covered with a black-brown insoluble material **78** which could catalyse the decomposition of hydrogen peroxide. Control experiments showed that osmium was the only component in the reaction which effected this decomposition, hence confirming its presence in **78**. We therefore deduced that reduced forms of osmium were 'escaping' from the reaction mixture and were consequently incapable of reaction with the aqueous phase containing the reoxidant.

The same photoosmylation reaction of toluene was then undertaken but on this occasion in a hydrogenation flask fitted with a cold finger. It was hoped that the increased spherical shape of this flask compared to the sublimation flask would aid mixing of the biphasic reaction mixture and reduce evaporation of the volatile organic phase. Our reasoning was proven correct inasmuch as a total yield of 6.5% of cyclitol product was achieved, translating to a catalytic turnover of 12.4. Although the cold finger still revealed the presence of osmium residues these were visibly less than in the first experiment. Other photolysis vessels were then designed which are shown in appendix C and are described below:

O) Sublimation unit fitted with cold finger

A) Hydrogenation flask fitted with cold finger

B) Florentine flask with ground-glass stopper

C) Florentine flask fitted with a Young's Teflon tap

D) Florentine flask fitted with a Young's Teflon tap and cooling jacket

E) Florentine flask fitted with a Young's Teflon tap extra thick

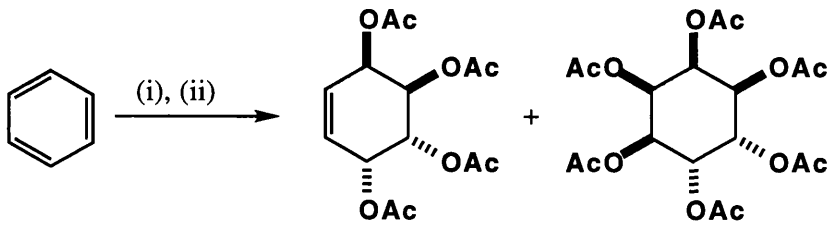
Table 2.4 shows the total yield and catalytic turnover for the photoosmylation of toluene in the given reaction vessel. It was found that the greater the volume of liquids in the reaction vessel, the greater the turnover and yield. At this point the use of barium chlorate as the standard reoxidant was introduced following reports in the early literature of its increased efficiency over the group one chlorate salts.[87,100] Of all the possible permutations (vessel and reoxidant) the use of barium chlorate and vessel B gave the best results.

Reaction Vessel	(O)*	(A)*	(B)**
Total Yield	1.4%	6.5%	13%

*Using $KClO_3$ **Using $Ba(ClO_3)_2$

Table 2.4 Photoosmylation of PhMe; yield vs reaction vessel.

Using reaction vessel type A, photoosmylation of benzene was attempted, using barium chlorate as the oxygen transfer reagent. After acetylation and workup as before, a crude crystalline product was isolated and was shown to consist of a mixture of conduritol E tetraacetate **79** and *allo*-inositol hexaacetate **80, scheme 2.11**. These highly crystalline acetates were separated by simple flash column chromatography and obtained in 1.5 and 8.7% yield respectively.



79 **80**

Reagents: (i) OsO_4 (cat), $Ba(ClO_3)_2$ (aq), UV; (ii) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2

Scheme 2.11

It was again evident from the photoosmylation products that a second catalytic cycle of tertiary osmylation was in operation to furnish the inositol product. With the availability of these two, easy to handle, crystalline products from the photoosmylation of benzene efforts were accordingly directed towards optimising the reaction conditions with benzene as the standard substrate.

As already noted in the earlier photoosmylation reactions with toluene our best results were obtained in reaction vessel B, where any black insoluble osmium species is always in contact with the aqueous reoxidant containing phase. It was found however that osmium containing residues were still able to 'creep' up the glass ground joint, even when coated with PTFE tape or high vacuum grease. This undesirable effect was stopped by replacing the groundglass joint with a Young's Teflon tap i.e. reaction vessel C. As vessels B and C gave higher yields and more reliable and reproducible results than vessel A, these were subsequently chosen for optimisation experiments, **table 2.5**.

Reaction Vessel	(A)	(B)	(C)
Total Yield (t/o)	10.2%	36%	32%

Table 2.5 Photoosmylation of PhH; yield vs reaction vessel.

A further modification involving a reductive work-up of the chlorate containing reaction mixture was added at this stage after the powdering of the dried aqueous phase was shown to be prone to detonation. Treatment of the crude photolysed aqueous reaction mixture by portionwise addition of approximately 2 eq of sodium metabisulphite ($Na_2S_2O_5$) w.r.t. chlorate ($[ClO_3^-]$) over a 10-15 min period reduces both the chlorate to chloride and osmium tetroxide to insoluble hydrate $Na_4[Os(SO_3)_3]$.

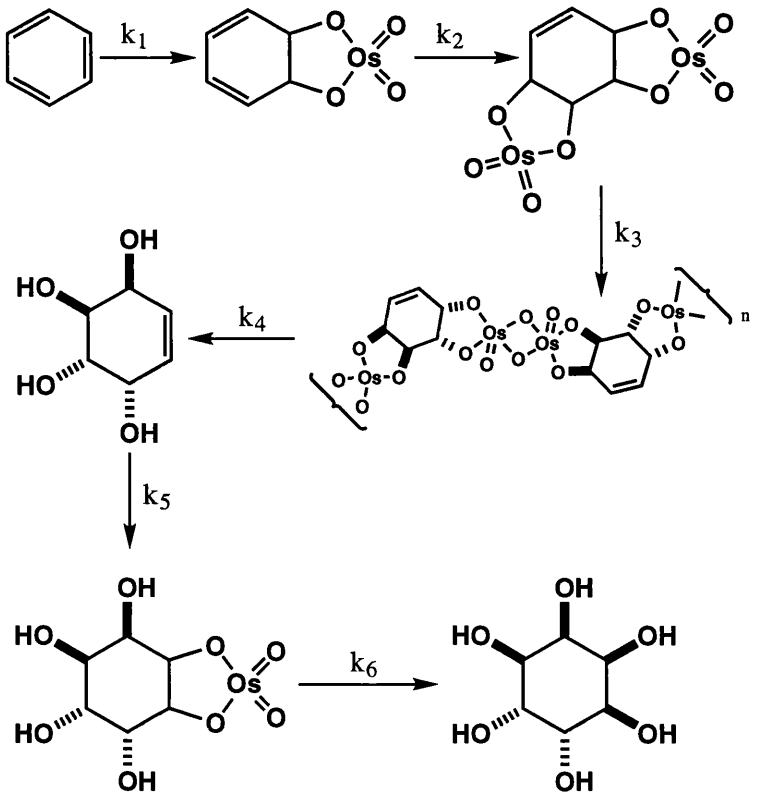
***

2.3 Optimisation

At this stage we had demonstrated that catalytic CT osmylation of toluene and benzene was possible albeit in low yield and with a low catalytic turnover to furnish conduritols and inositols as products. In the present section we outline the approach taken to ascertain the rate determining step (RDS) of the overall reaction sequence and our attempts to increase catalytic turnover.

2.3.1 Determination of the RDS

In order to attempt optimisation it was considered of importance to identify the slow step of the reaction and hence it was first necessary to catalogue all the various reactions. Based on Kochis stoichiometric observations and our own initial results, **scheme 2.12** shows our understanding of the reaction at this stage.



Scheme 2.12

k_1: Rate of primary osmylation (CT osmylation)

k_2: Rate of secondary osmylation

k_3: Rate of polymerisation

k_4: Rate of oxidative hydrolysis (osmate ester polymer)

k_5: Rate of tertiary osmylation

k_6: Rate of oxidative hydrolysis (osmate ester monomer)

These six different reaction steps fall into two distinct classes *viz*, the photochemical reaction (k_1) and secondly the catalytic dihydroxylation reactions (k_2, k_4-k_6). We initially thought the photochemically mediated primary osmylation, k_1, to be the RDS. The low quantum yield for this process reported by Kochi coupled with the fact that we were irradiating a partially opaque biphasic mixture appeared to give us good intuitive grounds for such reasoning. As shown in **equation 2.2**, the rate of primary osmylation k_1, is influenced by four factors. We therefore intended to find a simple test to alter the rate of k_1.

$$k_1=[\text{photons at } \lambda_{CT}][\text{EDA complex}][\text{Quantum yield}][\varepsilon_{CT}].$$

Equation 2.2

An easily changed variable in equation 1 is the number of photons at a given wavelength λ [photons at λ_{CT}]. The spectrum of a 400W medium pressure Hg bulb, **graph 2.1**, shows variable intensity against wavelength with peaks of great intensity listed below, **table 2.6**.

nm	Relative energy
312	50%
334	40%
365	100%
405	80%
436	100%
areas in-between peaks	5-10%

Table 2.6 Spectrum of a medium pressure Hg lamp in 312-436 nm range.[96]

By the selection of specifically substituted aromatics which would give CT bands coinciding with peaks of high and low relative energy the rate of primary osmylation should increase and decrease accordingly. Thus the following substrates were chosen for this comparative rate experiment: benzene, toluene and *o*-xylene. **Table 2.7** shows the IP's for these three aromatics and their measured CT band wavelengths. The rate of primary osmylation is expected to be approximately 10 times faster for *o*-xylene than benzene and toluene as its CT band falls in an area of high intensity of photons. Benzene and toluene will receive less of the required photons to achieve primary osmylation over the same period of irradiation than *o*-xylene hence a lower yield for these is expected if primary osmylation, k_1, is the RDS.

Aromatic in CT	IP	Calculated CT band*	Photoosmylation %†
	9.23	328 nm	36%
	8.82	345 nm	13%
	8.56	364 nm	~1%

† Total yield of product mixtures

* λ_{max} see ref[84]

Table 2.7 Photoosmylation yield *vs* CT band wavelength.

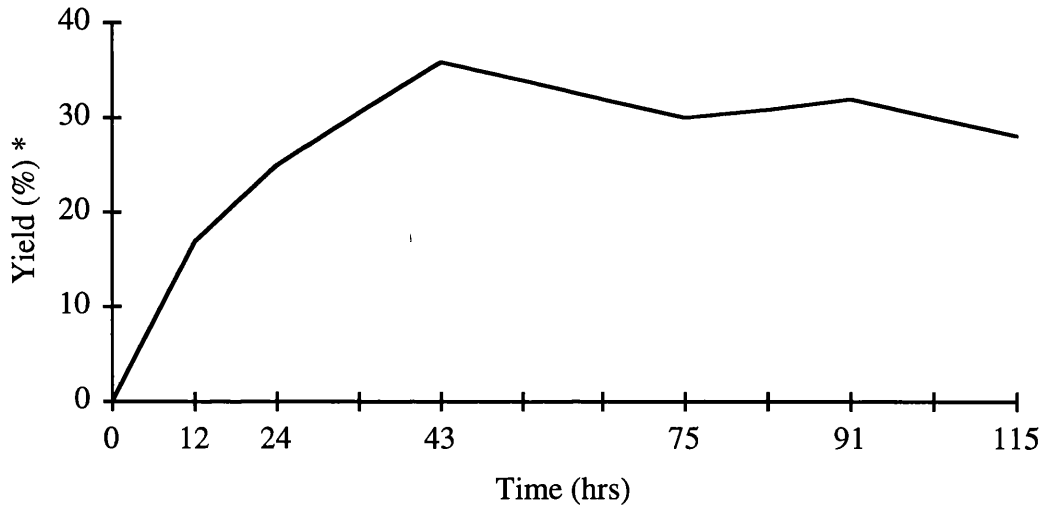
The other three variables which influence k_1 in **equation 2.1**, [EDA complex][Quantum yield][ε_{CT}] are all similar in value for the given aromatics.[85] A standard photoosmylation reaction (43 h irradiation, $Ba(ClO_3)_2$ [0.22 M], 50 mL) was therefore carried out for the three aromatics and the total isolated yields calculated for each case. The yields, **table 2.7**, clearly demonstrate that primary osmylation is not the RDS. Indeed, the expected higher yield for *o*-xylene compared to toluene and benzene is reversed with yields dropping off for those CT complexes in photochemically better wavelength regions. It can of course be argued that the RDS in the overall sequence could well change as a function of the substrate used. Thus for the xylene, it may well be that oxidative hydrolysis of a tetrasubstituted osmate ester of the arene diol becomes impossibly slow and hence dominates while such factors do not intervene at all in the case of benzene.

Other observations also convinced us that primary osmylation was not the RDS. Primary osmylation is a radically mediated reaction and might therefore be affected by the presence of oxygen. Yields for the photoosmylation of benzene in deoxygenated water *vs* normal water (10^{-3} M O_2)[101] are given in **table 2.8**. The similarity in yield could be interpreted in two ways. Either that oxygen had no effect on primary osmylation or primary osmylation was not the RDS.

Deoxygenated water	33%
Normal water	36%

Table 2.8 Yields of photoosmylation of PhH in de-ionised waters.

Photoosmylation of benzene *vs* time is shown in **graph 2.2** below. Yields of cyclitol products increase uniformly up to reaction times of 43 h after which yields decrease.

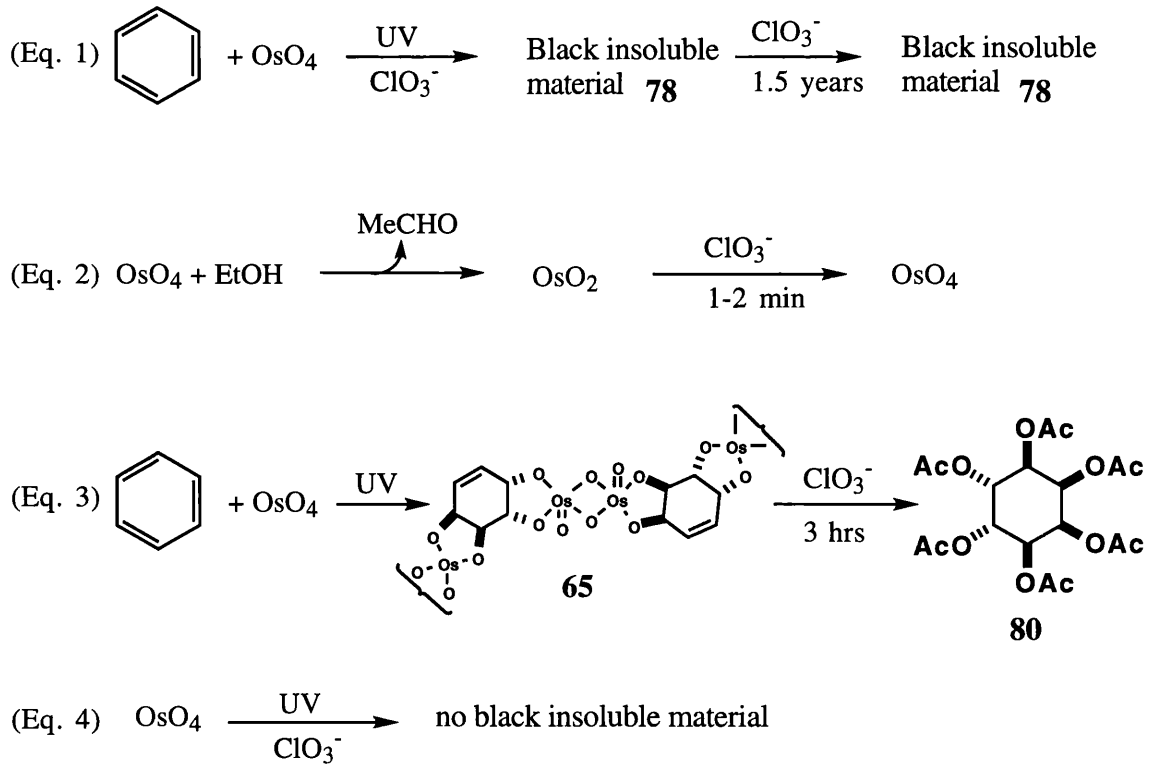


* Total yield of cyclitol products.

Graph 2.2 Yield of photoosmylation of PhH vs time

The physical appearance of the reaction mixture was also noted to change over time. At 12 h the yellow CT band was still clearly visible. At 24 h the intensity of the CT band had diminished and a black insoluble material **78** on the stirrer bead and Teflon tap could be seen. After 43 h, and likewise for 75 and 115 h, the organic phase appeared colourless and the amount of **78** had increased.

Kochi[85] had noted the formation of some black insoluble material in the stoichiometric osmylation of anthracenes which he identified as osmium dioxide. Our own black material **78** gave a positive reaction with hydrogen peroxide but **78** was not oxidatively hydrolysed by a [0.22 M] solution of chlorate even after 1.5 years, **scheme 2.13** (Eq. 1), compared to a reaction time of 1-2 min for the reoxidation of an authentic sample of osmium dioxide (Eq. 2). Furthermore, placing a sample of bis-*anti*-osmate polymer **65** in a [0.22 M] solution of chlorate effected dissolution within 3 h to yield *allo*-inositol hexaacetate **80** after acetylation (Eq. 3). As a control (Eq. 4), it was shown that in the absence of benzene formation of the black material **78** did not occur implying that benzene was required for its formation.



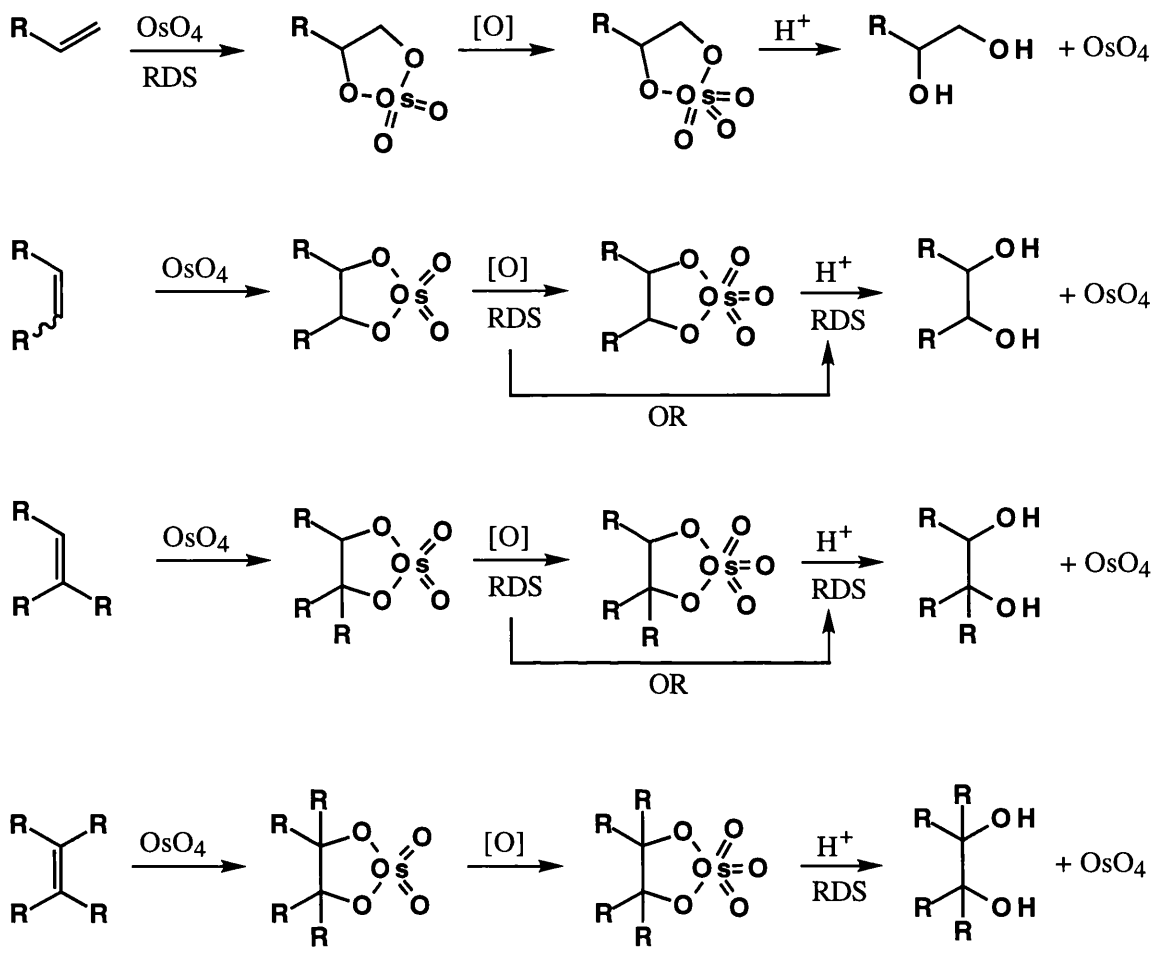
Scheme 2.13

Treatment of **78** with pyridine did not give rise to any crystalline derivative again indicative that it was not the bis-*anti*-osmate ester **65**. **78** was in fact insoluble in every solvent except 6N nitric acid.

These observations all seemed to indicate that the primary photochemical osmylation was not the RDS in the overall reaction scheme. It appeared that as the reaction proceeded, catalysis was progressively inhibited by the formation of an unknown **78** shown to contain osmium and possibly an 'organic' moiety. We now judged that the success of the reaction would depend on finding conditions which would inhibit the build-up of **78**. As benzene, or some subsequent derivative derived from it, was required for the formation of **78** we reasoned that **78** could contain hydrolytically stable osmate esters (see **scheme 2.15**). In an attempt to discover the exact composition of **78** we therefore decided to turn our efforts into the second class of reaction present, namely: catalytic dihydroxylation, representing steps k_2 and k_4-k_6 (**Scheme 2.12**).

The recent literature is abound with rate studies for this reaction. Unfortunately most of these are in the presence of amines and chiral amines in which the RDS is not the same as in the absence of amines. Zelikoff performed a rate study on the osmium tetroxide catalysed oxidation of fumaric and maleic acids (disubstituted double bonds) in the presence of potassium chlorate.[102] He showed that three independent events took place in a catalytic dihydroxylation: addition of osmium tetroxide to the double bond, hydrolysis of the osmate ester and oxidation of osmium (VI) to osmium (VIII).

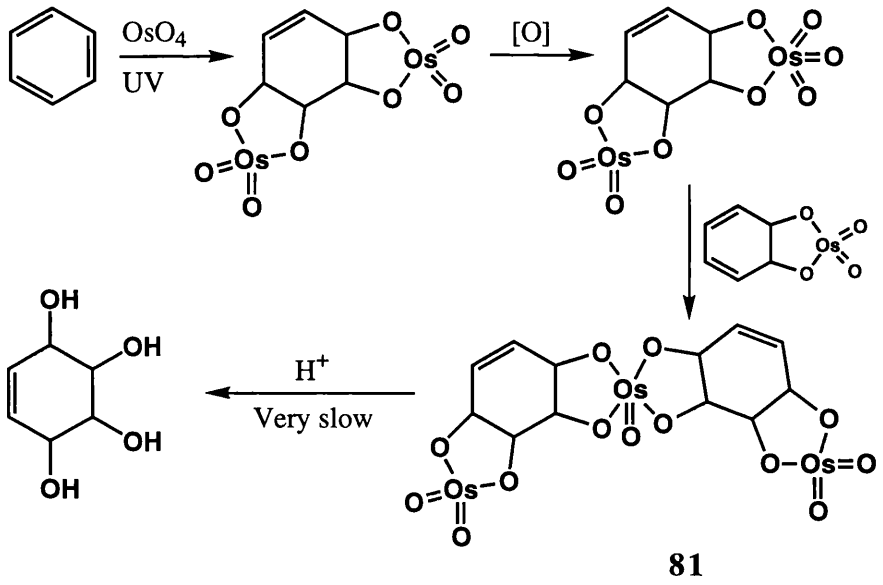
The RDS was the addition of osmium tetroxide to the double bond with the concentration of chlorate, water and co-solvent (dioxane) having no effect on the rate. Matteson[103] reinvestigated the reaction with cyclohexene and α-pinene with trimethylamine *N*-oxide as the reoxidant and demonstrated that the RDS is substrate dependent. Most importantly, he showed that the order of events in a catalytic dihydroxylation were: (i) osmium-olefin addition; (ii) oxidation; (iii) hydrolysis (**scheme 2.14**).



Scheme 2.14

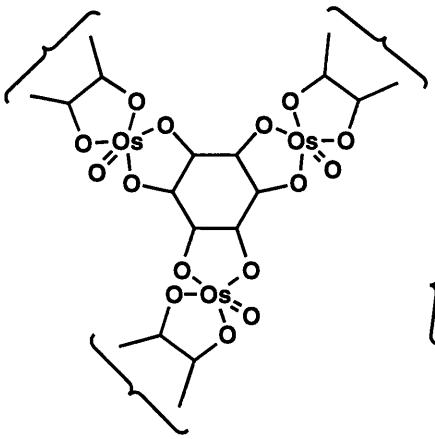
For both cyclohexene and α-pinene, oxidation of osmate(VI) ester to osmate(VIII) ester is the RDS. This contrasts with Sharpless' findings that during the catalytic dihydroxylation of tri and tetrasubstituted olefins with either chlorate or hydrogen peroxide the hydrolysis of such esters is the RDS.[104] Finally for mono-substituted olefins such as styrene the reductive addition of osmium tetroxide on to the olefin was found to be the RDS,[105] **scheme 2.14**. From the reports cited it would appear that the RDS is influenced by both the substrate and reoxidant and hence a direct comparison of the various rate results is not possible.

However, applying this mechanistic information to the photoosmylation reaction of benzene we argued that, at any one time in steps k_2 and k_4-k_6 only a disubstituted osmate ester was produced. It was therefore necessary to accelerate either the hydrolysis or the oxidation of the reaction in order to increase catalytic turnover. The trend of product yields for benzene, toluene and *o*-xylene in **table 2.7** seemed to confirm that the oxidation and/or hydrolysis was the RDS as yields drop with increasing substitution. These results are paralleled in the dihydroxylation of normal olefins.

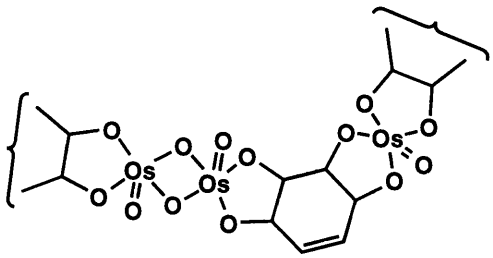


Scheme 2.15

The black insoluble osmium containing material **78** could therefore be an ester of type **81** resulting from a conventional second cycle dihydroxylation[106] (**scheme 2.15**). A mixed osmate ester of the type **82** could also be envisaged,[107] if the difference in the rate of hydrolysis versus the rate of oxidation were very great, even polymeric osmate diester esters of type **83** could be formed in the reaction mixture and have been shown to be sterically viable.[85]

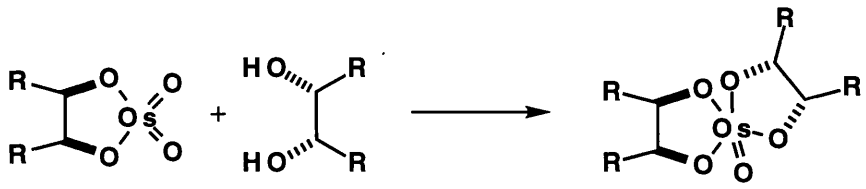


83



82

The formation of diesters has been shown by Criegee[107] to occur without the need for an osmate(VIII) ester as a precursor, **scheme 2.16**. He showed that reaction of an osmate(VI) ester with a *cis* diol gave rise to quantitative yields of **84**. Such structures require brutal conditions for hydrolysis to occur (refluxing alcoholic acetic acid).



84

Scheme 2.16

The following sections are an account of our attempts to increase the rate of turnover through variation in the 'oxidative hydrolysis' step.

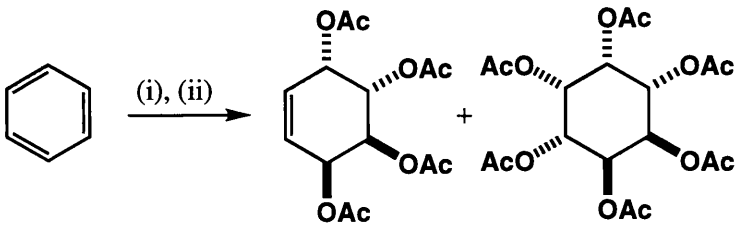
2.3.2 Attempts to increase the rate of hydrolysis

Sharpless introduced the use of tetraethylammonium hydroxide (Et_4NOH),[104] tetraethylammonium acetate (TEA)[108] and methane sulphonamide ($MeSO_2NH_2$)[109] as accelerators for hydrolysis of sterically encumbered substrates. These weak nucleophiles are reported to increase turnover rates for catalytic dihydroxylations of up to 50 fold. The compatibility of these additives with our test CT complex was determined as before, **table 2.9**.

	Hydrolysis aide	Effect on colour of CT complex
1	Et_4NOH	Discharged
2	Et_4NOAc (TEA)	Retained
3	$MeSO_2NH_2$	Retained
4	$^nBu_4NOAc$	Retained
5	KOH	Discharged
6	CTAB	Retained

Table 2.9 Effect of hydrolysis aides on the CT complex Anthracene-OsO_4

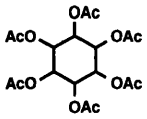
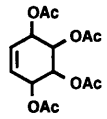
Only the very basic hydroxides were incompatible with the CT complex. In the case of tetraethyl ammonium hydroxide the purple CT band turned yellow instantly. The addition of potassium hydroxide solution led to the precipitation of the known dark green potassium osmate salt, K_2-*trans*-$[OsO_4(OH)_2]$.[110] The results for a series of standard photoosmylation reactions on benzene, **scheme 2.17**, carried out in the presence of these additives are given in **table 2.10**.



Reagents: (i) OsO_4 (cat), $Ba(ClO_3)_2$ (aq), hydrolysis aide, UV;

(ii) Ac_2O, Et_3N, DMAP (cat).

Scheme 2.17

	Hydrolysis aide	Equiv.	 **80**	 **79**	Yield	t/o
1	Et_4NOAc	1	50	50	14%	26.7
2	Et_4NOAc	4	46	54	11%	20.9
3	Et_4NOAc	8	55	45	8%	14.9
4	$MeSO_2NH_2$	1	91	9	17%	36.9
5	$^nBu_4NOAc$	1	100	0	8%	19.2
6	CTAB	CMC			14%*	32.7
7	-	-	86	14	36%	76.9

* Combined yield of inositol and deoxy-chloro inositol products

Table 2.10 Effect of various hydrolysis catalysts on the yield and product distribution for the photoosmylation of benzene.

Entries 1, 2 and 3 show that the effect of tetraethylammonium salts is detrimental to the photoosmylation reaction with yields approximately halved in the presence of 1 eq and down to one-fifth with 8 eq as compared to the standard reaction without any added additive, (entry 7). Interestingly the ratio of conduritol E **79** *vs allo*-inositol **80** approaches 1:1 for these cases, compared to 1:6 for entry 7. This seemed to indicate that the tetraethylammonium salt might be slowing the rate of the second cycle of tertiary dihydroxylation. A possible explanation, at this stage, was that an ionic interaction between the tetraethylammonium cation and lone pair of electrons on oxygen of the conduritol was present. This would sterically mask the remaining double bond to tertiary osmylation giving the 1:1 ratio, **figure 2.1**.

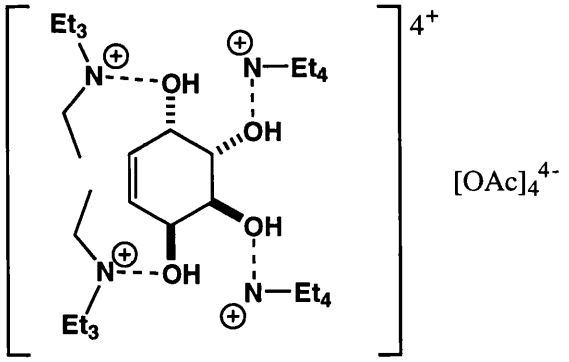
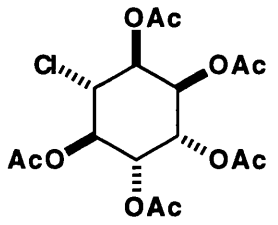


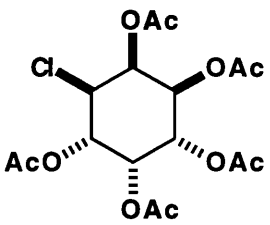
Figure 2.1

However at a later stage experiments with $^{n}Bu_4NOAc$ gave only *allo*-inositol instead of the expected greater ratio of conduritol versus inositol and it was some considerable time before this irreproducibility was traced to a temperature effect which was entirely independent of the phase transfer catalyst (*vide infra*). Likewise the addition of methane sulphonamide had a detrimental effect on turnover and had no effect on the product ratios. As the use phase transfer catalysts, weak and hard nucleophiles did not improve hydrolysis a micellar catalysed hydrolysis was attempted. The use of micelles in aqueous

phase arene reductions and alkene epoxidations gave grounds for using such a reagent in our reaction. We had hoped that the black insoluble material **78** would solubilise in a micellar environment and be more prone to hydrolysis. Photoosmylation of benzene in a solution of CTAB at the critical micellar concentration gave a total yield of 14% oxidised product corresponding to a turnover of 32.7, which was again much less than the control reaction of 77 turnovers. It was most intriguing to note that along with *allo*-inositol hexaacetate **80** (10%) two chlorinated products were isolated: 3-deoxy-3-chloro-*chiro*-inositol pentaacetate **85** and 1-Deoxy-1-chloro-*neo*-inositol pentaacetate **86** in a 1:1 ratio (^{1}H NMR) in 4%. The formation and consequences of these halo-inositols will be discussed in detail later (see section 2.4.1).



85



86

Unfortunately none of the hydrolysis agents were able to eliminate the build-up of the unknown **78**. Their detrimental effect could not be explained but an increased yellow colouration of the reaction mixtures was observed possibly affecting the rate of primary osmylation. As attempts to increase the rate of hydrolysis of our problematic osmate esters did not hold the key to better catalytic turnover we decided to examine other oxygen transfer reagents. As already discussed, the rate of oxidation of osmate esters in the catalytic dihydroxylation of olefins can be a rate limiting step. It seemed sensible to investigate this.

2.3.3 Attempts to increase the rate of oxidation

As we had already noted, hydrogen peroxide was able to hydrolyse and oxidise the osmate polymer **78** obtained from the photoosmylation of benzene and would consequently appear to be the reoxidant of choice were it not for its' decomposition to liberate oxygen in the presence of osmium. The use of reaction vessels B and C were incompatible with the evolution of any gaseous products. An attempted photoosmylation of benzene in reaction vessel O with the barium chlorate as reoxidant and with slow addition of hydrogen peroxide to turnover the polymer trapped osmium was largely unsuccessful however giving a total yield of 3.2% consisting of *allo*-inositol hexaacetate **80** (2.2%), 3-deoxy-3-chloro-*chiro*-inositol pentaacetate **85** and 1-deoxy-1-chloro-*neo*-inositol pentaacetate **86** (1.0%).

Milas, who pioneered the use of hydrogen peroxide as the oxygen transfer reagent for osmium tetroxide catalysed dihydroxylation reactions, was able to use this reoxidant successfully by extracting the peroxide from its aqueous solution into ^{t}BuOH.[90] Under anhydrous conditions hydrogen peroxide did not decompose to oxygen and water on the addition of osmium tetroxide. Although ^{t}BuOH had already been shown to be incompatible with our CT complex we were made aware of the possibility of extracting hydrogen peroxide into ethers.[111] We reasoned that the alkyl portion of a suitably bulky ether might screen the lone pairs of electrons sufficiently for them not to disrupt the crucial CT interaction, **table 2.11**.

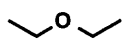
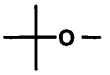
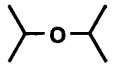
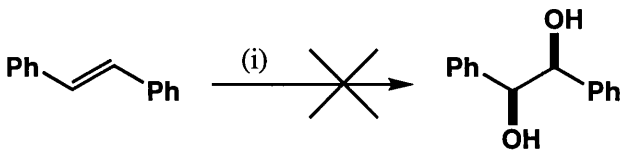
Ether	Effect on colour of CT complex
	Discharged
	Discharged
	Discharged

Table 2.11 Effect of various ethers on the CT complex Anthracene-OsO_4

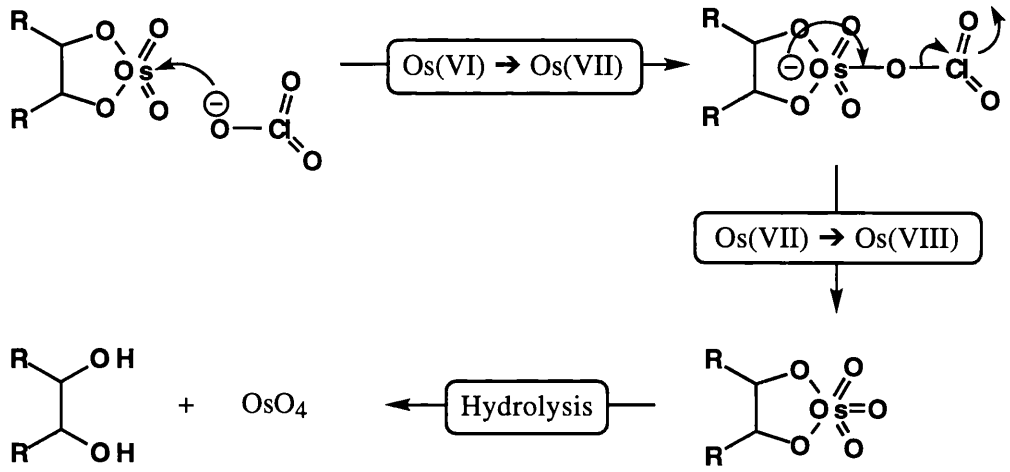
To our frustration however, none of the commercially available ethers were sufficiently unreactive and research into the use of hydrogen peroxide as an alternative reoxidant was discontinued. Reports in the literature[36,112] that solutions of potassium persulphate had been used as the reoxidant in osmium catalysed dihydroxylations in conjunction with potassium ferricyanide prompted us to try this, and related Oxone, as possible reoxidants. Before attempting any photoosmylation reactions however, these reoxidants were first tested to see if they would participate effectively in the dihydroxylation of *trans*-stilbene, **scheme 2.18**. Unfortunately in both cases 92-97% of the starting stilbene was recovered.



Reagents: (i) OsO_4 (cat.), H_2O, $(CH_3)_2CO$ and (a) $K_2S_2O_8$ or (b) Oxone

Scheme 2.18

We next considered oxidants which chemically resembled the chlorate anion. As the mode of oxidative hydrolysis of osmate(VI) esters of disubstituted olefins has been reported to go in a stepwise fashion *via* the osmate(VIII) ester and hydrolysis we scrutinised the mechanism of the Os(VI) to Os(VIII) oxidation. A mechanistic route had been proposed by Sharpless[113] for the asymmetric dihydroxylation reaction with NMO and may be in turn adapted to the chlorate system, **scheme 2.19**.



Scheme 2.19

The two principle features of this oxidation are (a) nucleophilic attack of the chlorate anion on Os(VI) and (b) cleavage of the oxygen chlorine bond to form the Os(VIII) ester. Factors which would influence the rate of this oxidative process are therefore the nucleophilicity of the oxygenating species and the strength of the oxygen-chlorine bond. We hoped to be able to influence the nucleophilicity and bond strength by the level of oxidation of the halide and by varying the halide itself. **Table 2.12** displays the various oxy-halides considered as other reoxidants for the photoosmylation reaction.

	Oxy-halide	Action on **78**	Reaction to the addition of OsO_4	t/o (%)
1	NaOCl	Dissolve	light yellow solution darkened	0
2	$NaClO_2$	Dissolve	instant yellowing	-*
3	$Ca(OCl)_2$	Dissolve	instant yellowing	-*
4	$NaBrO_3$	-	none	49 (29.1)†
5	$NaIO_3$	-	none	11.9 (5.3)
6	$Ba(ClO_3)_2$	-	none	76.9 (36)

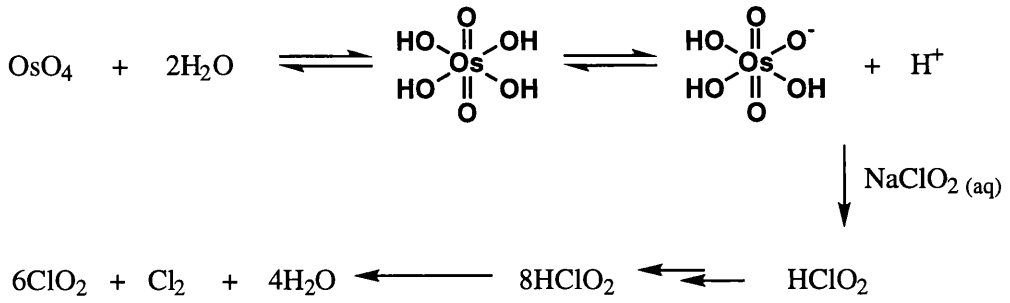
* No reaction was attempted for entries 2 and 3

† Total yield of cyclitol and deoxy-bromo-cyclitols.

Table 2.12 Survey of potential reoxidants for the photoosmylation reaction

Bleach, entry 1, was an exciting choice as it had already featured as a reoxidant for the catalytic dihydroxylation of unsaturated fatty acids[92] and was, shown by Kochi, to be able to dissolve and oxidise osmium dioxide. On addition of the black insoluble matter **78** to a solution of bleach instantaneous dissolution occurred. To our profound vexation however, we found that when a solution of osmium tetroxide was added to bleach the light yellow solution darkened considerably and the absorbance of this coloured solution inhibited photoosmylation.

Similar observations were made for entries 2 and 3. Although they were able to solubilise our unknown osmate **78** when a fresh sample of osmium tetroxide was added to their aqueous solutions instant yellowing occurred with the evolution of a gas whose smell was chlorine-like. A rational for these observations is given in **scheme 2.20** with sodium chlorite as an example.[114]

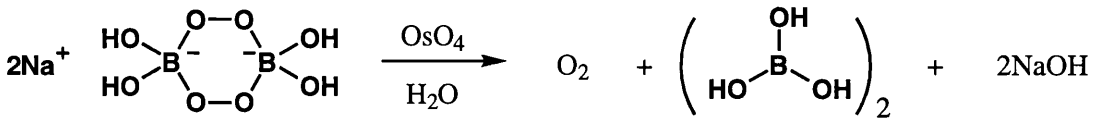


Scheme 2.20

Aqueous solutions of osmium tetroxide are acidic (osmic acid, pH 6).[115] Acidic solutions react with sodium chlorite to give chlorine dioxide and chlorine as decomposition products. Chlorine dioxide is yellow, soluble in water, and decomposes to HCl and chloric acid ($HClO_3$) which will further dictate the fate of the sodium chlorite.[116] The UV spectrum for these yellow solutions revealed peaks (λ_{max}) at 405 nm and a continuous nondescript peak from 360 nm to the far UV and were hence not considered suitable reoxidants for photoosmylation.

Such an instant yellowing was not seen in the case of the iodate, bromate and chlorate salts although after irradiation of a chlorate driven photoosmylation the aqueous phase is invariably yellow (for an exception see section 2.3.6). The results for the photoosmylation of benzene with bromate are included here for comparison although the evaluation and utility of this reoxidant will be discussed in much more detail at a later stage (see section 2.4.2). The standard reaction with sodium iodate[117] however only gave *allo*-inositol hexaacetate **80** in a disappointing 5% yield, (catalytic turnover 11). We had hoped, due to the increasing bond length and weakness, that the rate of oxidation of transient osmate esters by the bromate and iodate salts would increase. As a possible RDS we hoped such an increase in rate could have influenced the overall rate of the photoosmylation reaction.

Attempts to turn away from the empirical formula MXO_3 (X=halogen, M=main group metal) and use oxy-halides of lower oxidation states failed due to their incompatibility with the acidic reaction medium. Two other reoxidants were considered: sodium perborate,[118] **scheme 2.21** and peracetic acid. The borate, like hydrogen peroxide, decomposed in the presence of osmium tetroxide:



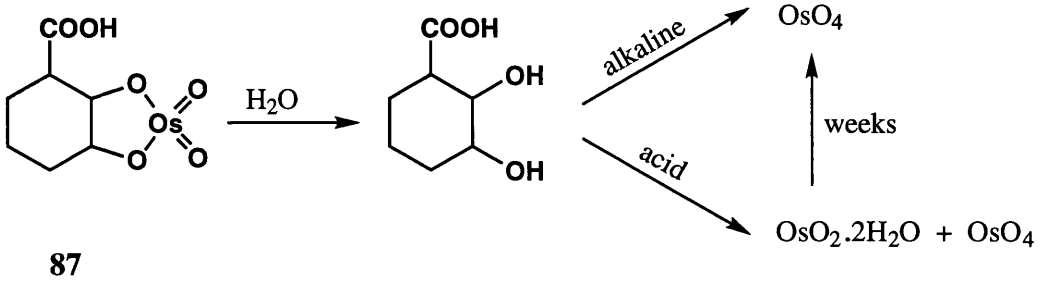
Scheme 2.21

The decomposition of peracetic acid was found to be rapid under our photochemical conditions[119,120] and was not tried as a possible reoxidant.

From the information gathered so far we were able to demonstrate, more through observation than experimentation, that the most likely RDS in the photoosmylation reaction of benzene was the oxidative hydrolysis of the unknown **78**. We reasoned that if it were possible to find the correct reaction conditions that inhibited the formation of our putative osmate polymers or oligomers, if indeed **78** was such a structure, a more efficient system would be developed.

2.3.4 Buffered reactions. The effect of pH

A study on the effect of pH on the rate of hydrolysis of osmate esters[101] has shown that hydrolysis is catalysed by both acid and by alkali to give the expected diol. The nature of the osmium containing hydrolysis products does however differ with pH (**scheme 2.22**). At pH 10 (carbonate buffer) and 5.6 (phosphate buffer) the hydrolysis of the osmate ester of 3-cyclohexenecarboxylic acid **87** was approximately twice as fast than at pH 6.85 and 7.8. Under basic conditions the hydrolysed osmium(VI) was oxidised to osmium tetroxide within 24 h by the action of the dissolved oxygen in water. Under acidic conditions disproportionation of the osmium residue occurred with ~30% recovery of osmium tetroxide the remainder of the osmium was found as osmium dioxide dihydrate. This dihydrate was found to oxidise to the tetroxide only after several weeks.



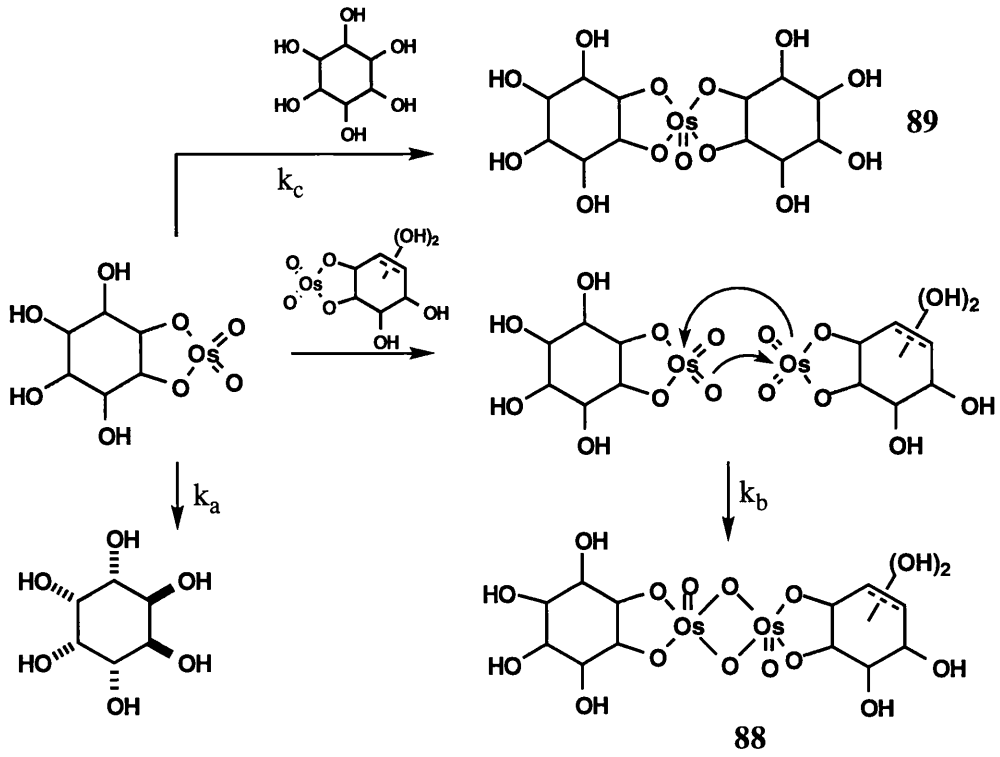
87

Scheme 2.22

Criegee,[107] in his pioneering work on the elucidation of the intermediates of catalytic dihydroxylation reactions found that the osmate(VI) esters of type **81** and **82** are *only* hydrolysed under acidic conditions. Refluxing alcoholic acetic acid and alcoholic hydrochloric acid was required to liberate the diol from these esters. Treatment of these esters with base did not induce hydrolysis but gave salts. The rate of osmium tetroxide

catalysed dihydroxylation of styrene with iodate was shown to be pH independent; a source of H^+ in the reaction medium had no affect on the overall rate.[117] In contrast the rates of oxidation of fumaric and maleic acids were found to be pH dependent,[102] alkaline conditions increased rates by up to 180% whereas the addition of HCl slowed the chlorate driven dihydroxylation reaction by 30%. Other reports by Sharpless[104] and Gopalakrishnan[121] also give evidence of alkaline conditions increasing the rate of osmium tetroxide catalysed reactions. The AD reaction[36] itself is best performed at pH 12.2, at lower pH the reaction is inhibited from turning over, and similar results are reported by Cairns's[122] osmium tetroxide catalysed oxidation of olefins to acids using molecular oxygen. Best reaction rates were found at pH 11 with marked decreases in rate at pH's above 12.5 and below 8. Similar to the case of the 3-cyclohexenecarboxylic acid osmate(VI) ester **87**, a decrease in the alkalinity of the reaction medium left regenerated osmium tetroxide reduced to a black insoluble solid which was resistant to reoxidation and presumed to be osmium dioxide.

The majority of communications uphold the view that alkaline conditions are most favourable for osmium tetroxide catalysed reactions by enhancing the rate of hydrolysis. Although some work points to an acid catalysed process this also leads to a 'corruption' of the osmium catalyst. From our standpoint we wanted reaction conditions which would inhibit the polymerisation of osmate esters. In view of the total lack of any literature precedent for the hydrolysis of such polymers, but a wealth of information available on the acid-base catalysed hydrolysis of monomeric osmate esters, we therefore undertook a pH profile of the photoosmylation reaction, **table 2.13**. We hoped that at a certain pH the rate of osmate ester hydrolysis (k_a) would be sufficiently fast to compete with the rate of polymerisation, both to the mono **88** (k_b) and diester **89** (k_c), **scheme 2.23**.



Scheme 2.23

Due to the incompatibility of the photoosmylation reaction with strong acids (decomposition of chlorate) and strong base (reaction with osmium tetroxide) reactions were carried out in a buffered medium (phosphate buffer) with sodium chlorate.

	Buffer	Photoosmylation yield**
1	pH 3.776	5.4%
2	No buffer (from pH 7 to pH 4)	15.4%
3	pH 7.2	2.5%
4	pH 9.18	1.4%
5	pH 9.93*	3.2%

*Carbonate buffer; **_allo_-inositol hexaacetate **80**

Table 2.13 pH profile on the photoosmylation reaction of benzene.

Table 2.13 charts the results of yield *vs* pH. All buffers remained at constant pH during the period of irradiation, only entry 2, the control, became acidic as expected. Overall the presence of the phosphate buffer was detrimental to the reaction. Entries 3 and 1 mimic the pH of the control reaction, 2, from start to finish respectively. Their yields, however, did not mimic that of the control hence the constitution of the buffer is the cause of the low yield and not the pH. Alkaline conditions faired even worse. It occurred to us that a 'salting out' effect might have been at the root of these disastrous yields. The highly increased ionic concentration of the aqueous phase due to the buffer would decrease the solubility of any osmate ester and this would reduce the rate of both oxidation and hydrolysis.

2.3.5 Effect of reagent ratios

The idea that the ionic strength of the aqueous phase could play an important role in the RDS of the photoosmylation reaction led us to perform a multitude of reactions in which the following variables were changed:

a) Molarity of the aqueous phase

b) Volume of the aqueous phase

c) Mole % of catalyst

Changes in variables a) and b) would allow us to examine the effect of ionic strength and the importance of the surface area of the aromatic-aqueous interface (see 2.4.1). Changes in the amount of catalyst, c), would allow us to monitor the overall catalytic efficiency of the photoosmylation reaction or indeed the enhanced formation of osmate polymers/ oligomers. **Table 2.14** gives a selection of results showing yield *vs* chlorate molarity ($Ba(ClO_3)_2$).

	Molarity of reoxidant*	Yield
1	[0.024]	8%
2	[0.18]	27%
3	[0.22]	36%
4	[0.36]	22.5%
5	[0.55]	8.1%**

*Effective molarity of ClO_3^- is double

mixture of **80 and deoxy-chloro inositols (see 2.4.1)

Table 2.14 Effect of molar concentration of chlorate on yield

Table 2.14 shows that the rate of the reaction appears to be dependent on the molarity of the reoxidant if the volume of benzene and water are not changed. However increased ionic strength does not have a defined influence on the reaction; the best yield was obtained with [0.22 M] $Ba(ClO_3)_2$. Above [0.36 M] chlorination of the cyclitol becomes an important side reaction (see section 2.4.1) and yields drop.

As shown in **table 2.15**, increasing the mol% of the catalyst did not cause an increase in yield. With 2.6 mol% a 27% yield was recorded, with 0.65 mol% the yield dropped to a low of 13%. Scale-up (x2) did not furnish twice as much cyclitol (**table 2.16**).

	mol% OsO_4	Yield (t/o)*
1	0.65	13% (30)
2	1.3	36% (77)
3	2.6	27% (31)

* Total yield of cyclitol products **80** and **79**.

Table 2.15 Effect of mol% catalyst on yield

	H_2O	OsO_4	$Ba(ClO_3)_2$*	PhH	Yield**
1	50 mL	25 mg	3 eq	0.65 mL	1.099 g (2.6 mmol)
2	100 mL	50 mg	3 eq	1.3 mL	0.851 g (2.0 mmol)

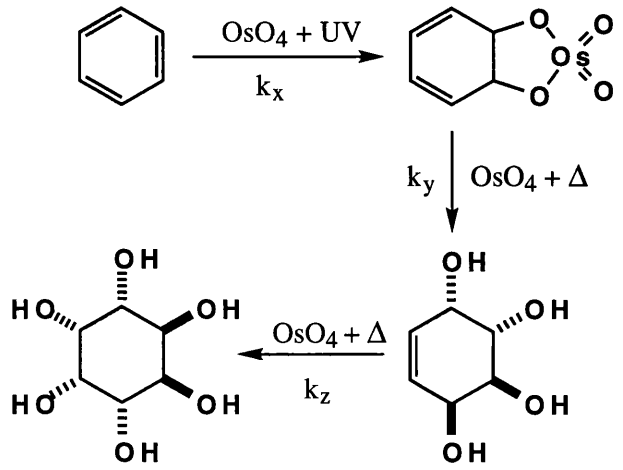
* Equivalents in ClO_3^- to PhH.

** Total mass of cyclitol products **80** and **79**.

Table 2.16 Scale-up results

2.3.6 Effect of Temperature

The last variable which we thought could possibly have an effect on the RDS was the operating temperature of the reaction. Since the introduction of the vessel C no cooling of the reactions was required as the escape of osmium residues was controlled by the design of the vessel. It had become apparent to us, that since the introduction of the water cooled vessels O and A where the conduritol : inositol ratios were approximately 1:1, this ratio had shifted towards 6:1 and 100% inositol products with the use of vessel C. Vessels O and A were used in Spring when the average water temperature was 15-18 °C. Vessels B and C, which only received fan cooling, would operate at temperatures varying between 30 °C and 54 °C depending on the rate of ventilation of the fume cupboard. The implication of these albeit empirical observations was that the effect of a temperature rise was to shift the conduritol:inositol ratio towards the inositol. The explanation for this observation can be made by assessing the photoosmylation reaction in terms of temperature dependent and temperature independent reactions for the two discrete types of reactions which are involved *viz.*, CT osmylation and catalytic dihydroxylation (**Scheme 2.24**).



Scheme 2.24

Since the photochemical reaction is an adiabatic reaction its rate is not affected by temperature. On the other hand catalytic dihydroxylation is an endothermic process, and hence temperature increases are followed by an increase in reaction rate.[101,102]

Scheme 2.24 shows a simplified reaction sequence for the photoosmylation of benzene. At any temperature the rate of primary osmylation (CT osmylation) effectively remains the same (the extinction coefficient increases by 18% from 40 to 0 °C). Secondary osmylation, however is extremely fast and is then followed a slower, more temperature dependant, tertiary osmylation. A decrease in temperature therefore slows tertiary osmylation to a more appreciable extent than secondary osmylation. At low temperatures, the RDS of the photoosmylation reaction becomes tertiary osmylation as borne out by the temperature variable experiments displayed in **table 2.17**.

	Temperature	(**79**):(**80**)	Yield
1	45 °C	**80** only†	21%
2	30 °C	1: 6.2	36%
3	15 °C	1: 5.4*	27%
4	02 °C	1: 1.4*#	10%

† By ^{1}H NMR.

* Carried out in reaction vessel D. # Reaction mixture clear after photolysis.

Table 2.17 Effect of temperature on 79:80 ratio.

As expected for a reaction where the catalytic dihydroxylation reaction is the RDS overall yields fall with a fall in temperature. As temperature increases so does the rate of tertiary osmylation and the conduritol : inositol ratio gets larger. Finally at 45 °C tertiary osmylation is now no longer the RDS as practically only *allo*-inositol hexaacetate **80** is isolated. The reason for the fall in yields at higher temperatures is not clear, however this could be attributed to an increase in the rate of polymerisation or oligomer formation of the various osmate esters at these higher temperatures.

Although we were able to affect the rate of tertiary osmylation with varying temperature we still were unable to increase oxidative hydrolysis without decreasing the rate of osmylation itself. Nevertheless a reproducible method for increasing the conduritol ratio of the photoosmylation products had been achieved. From a simple preparative standpoint, the ability to produce a reaction mixture of which almost 40% was the conduritol, as opposed to the inositol was satisfying, albeit in only 10% yield. In addition, these experiments finally laid to rest the ghost of the misleading phase transfer catalyst saga.

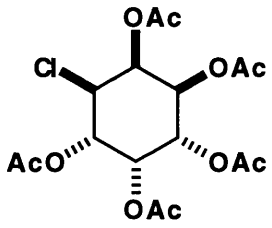
***

At this stage, our most efficient reaction for the conversion of benzene to *allo*-inositol involved the use of 1.3 mol% catalyst with 50 mL of a [0.22 M] barium chlorate solution representing a 36% yield with a catalytic turnover of 77 for osmium tetroxide. The optimisation studies, although not achieving a spectacular success have nevertheless allowed us to collect important pieces of information pertaining to the design of an optimised reaction. It was clear that efficient mixing of the two phases was important. The addition of additives, inorganic or organic, was detrimental. The RDS under the standard conditions for benzene was the oxidative hydrolysis of some unknown osmium containing material **78**. The pH of the reaction goes from neutral to acidic, from clear to yellow; attempts to influence the pH of the reaction are detrimental to it. Scale up did not seem to be a straightforward procedure and increasing the mol% catalyst did not afford greater conversion of benzene into cyclitol products. Temperature can be used to influence conduritol : inositol ratios and at higher chlorate concentrations the first detectable amounts of deoxy-chloro-inositols were formed. This was to pave the way for future developments.

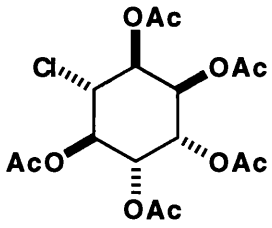
2.4 Deoxy-chloro and deoxy-bromo cyclitols

2.4.1 Deoxy-chloro cyclitols

As we have briefly indicated, during our attempts to optimise the photoosmylation reaction certain sets of experimental conditions led to the isolation of deoxy-chloro-inositols, **85** and **86**, as minor by-products.



1-Deoxy-1-chloro-*neo*-inositol pentaacetate **86**

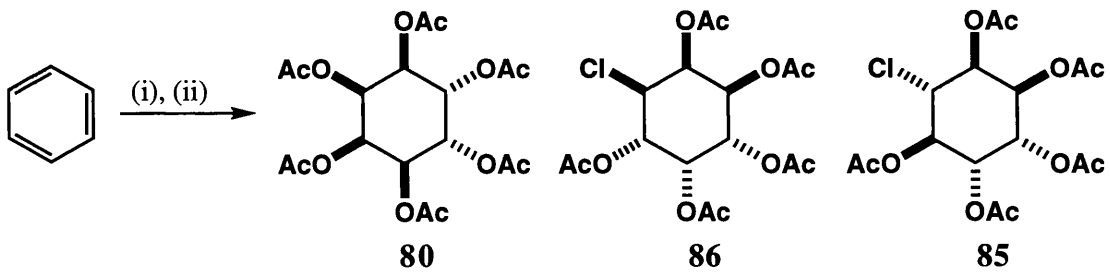


3-Deoxy-3-chloro-*chiro*-inositol pentaacetate **85**

Their formation presumably comes from the addition of hypochlorous acid (HOCl) on to the double bond of an unsaturated cyclitol intermediate. As we have seen this well established reaction represented a considerable drawback for the chlorate driven dihydroxylation reaction and fuelled extensive research for new reoxidants.[104] Eventually however, this side reaction was not significant under our typical reaction conditions of [0.22 M] chlorate concentration and was only detected under micellar and higher ([0.55 M]) chlorate concentrations, **scheme 2.25**.

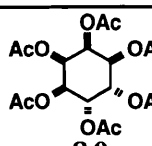
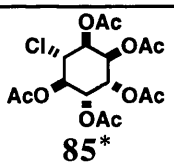
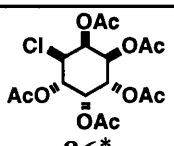
Nevertheless, the synthetic utility of compounds **85** and **86** *vis-a-vis* the *meso allo*-inositol hexaacetate **80** is considerable. The *chiro* stereochemistry is found in many naturally occurring inositols and the presence of the chlorine atom allows for further chemical differentiation of nearly all the hydroxyl groups in both the *neo* and *chiro* diastereomers. It was therefore of interest to find reaction conditions which would yield

a significant increase in the ratio of deoxy-chloro-inositols **86** and **85** as opposed to *allo*-inositol **80**.



Reagents: (i) OsO_4 (cat), UV, see table; (b) Ac_2O, Et_3N, DMAP.

Scheme 2.25

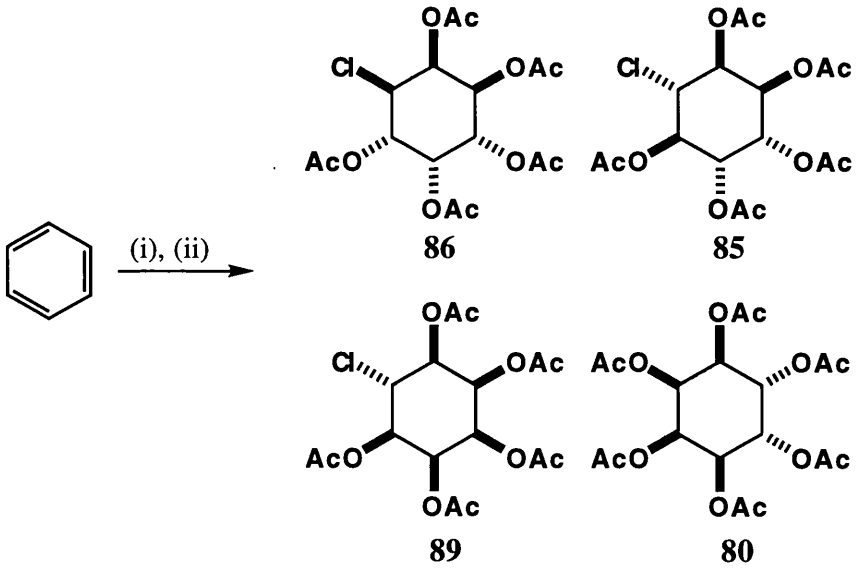
	Reaction conditions	 **80**	 **85***	 **86***	Ratio **80:85+86**
1	CTAB	10.1%	2%	2%	1.4:1.0
2	[0.55 M]	6.1%	1%	1%	4.1:1.0
3	Cl_2 added, [0.55 M]	2.4%	2%	1.3%	1.0:1.4

* ^1H NMR ratio

Table 2.18 Photoosmylation leading to deoxy-chloro-inositols

Entries 1 and 2 of **table 2.18** are those results found during the attempted optimisation of the reaction. Our first attempt to increase the amount of deoxy-chloro-inositols was to pre-treat the aqueous phase of the reaction with chlorine. The HOCl so generated would complement the HOCl formed from the reduction of the chlorate during the course of the reaction. Although a higher deoxy-chloro-inositol : *allo*-inositol ratio was obtained the yield had been adversely affected.

It was later found that by operating at 45 °C, increasing the chlorate concentration to [1.10 M] and the volume of the aromatic phase from the usual 0.65 mL (7.3 mmol) to 15 mL gave excellent conditions both for the synthesis of deoxy-chloro-inositols and *allo*-inositol, **scheme 2.26**. Using this 'formulation' 1.12 g of *allo*-inositol hexaacetate **80** together with three deoxy-chloro-inositols, **85**, **86** and 6-deoxy-chloro-*epi*-inositol pentaacetate **89**, as a minor isomer were isolated. 495 mg of **85** and **86** were obtained in a 1:1 ^{1}H NMR ratio. Preparative HPLC separation of **85** and **86** confirmed the ^{1}H NMR ratio. The minor isomer **89** was obtained in 121 mg. Overall the catalytic output of the photoosmylation reaction had significantly improved to a rate of 108 turnovers for osmium tetroxide, a 40% increase over the previous best of 77.

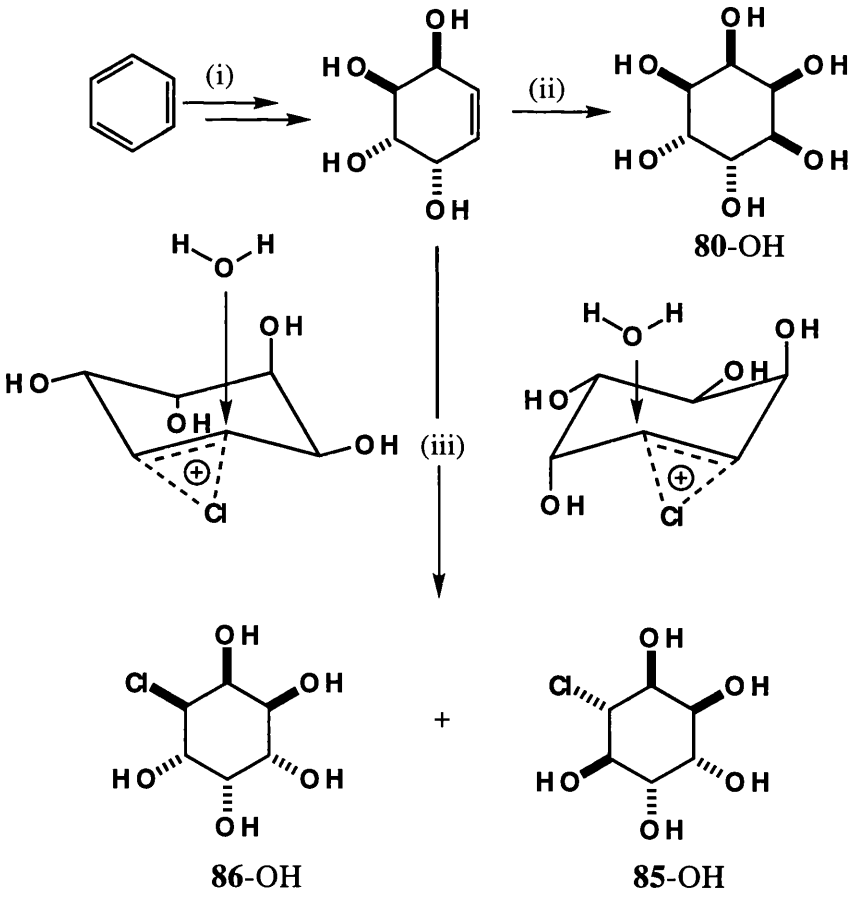


Yields: **86+85** (495 mg, 0.7%), **89** (121 mg, 0.2%), **80** (1.12 g, 1.5%).

Reagents: (i) OsO_4 (cat), UV, $Ba(ClO_3)_2$ [1.10 M], 45 °C; (b) Ac_2O, Et_3N, DMAP.

Scheme 2.26

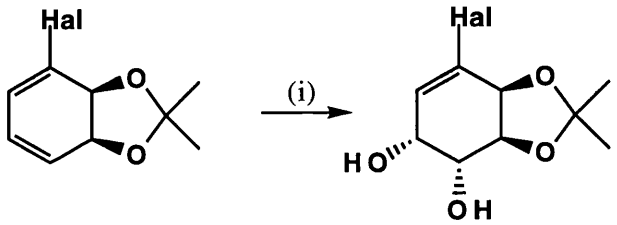
Due to the huge increase in the number of moles of benzene used, the 'yield' for the reaction was minimal (2.4%). However in terms of mmols of cyclitol product this reaction was up to ten times more efficient than any of the previously used conditions (see **table 2.19**). The isolation and identification of **89** gave a considerable amount of information on the mechanism of the photoosmylation reaction. The formation of **85** and **86** can be explained using the same mechanistic route put forth by Kochi for his stoichiometric CT osmylation reaction. Primary osmylation is followed by fast *anti*-secondary osmylation; tertiary osmylation is then in competition with the addition of HOCl to give *allo*-inositol **80**-OH or the deoxy-chloro-inositols **85**-OH and **86**-OH respectively, in a 1:1 ratio[123] **scheme 2.27**.



Reagents: (i) OsO_4, UV, H_2O; (ii) OsO_4, H_2O; (iii) HOCl, H_2O

Scheme 2.27

The *epi*-inositol **89**, however, could not be obtained by this route. The stereochemistry of **89** revealed that a *syn*-dihydroxylation had occurred. For this scenario, three routes could be considered. Firstly that secondary osmylation has occurred *syn* to the diene osmate ester. This seems extremely unlikely for steric reasons and is certainly not observed in the stoichiometric reaction. It has been shown that for case of protected diene diols **27** that dihydroxylation occurs solely *anti* to the protecting group, **scheme 2.28**.[124] The osmium moiety of the diene diol osmate ester **67** would conceivably have an even larger steric bulk and also favour *anti* dihydroxylation.

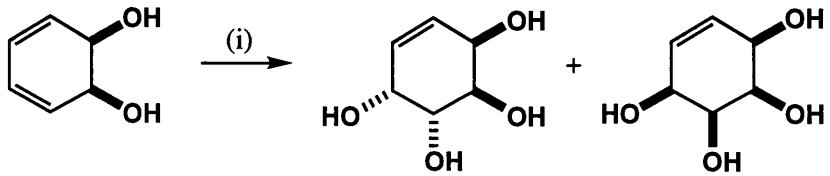


27

Reagents: (i) OsO_4 (cat), NMO; Hal=Br

Scheme 2.28

The dihydroxylation of the diene diol, **6** does afford a mixture of conduritol D and E as already seen, with a relatively consistent ratio as reported by two different groups, **scheme 2.29**.

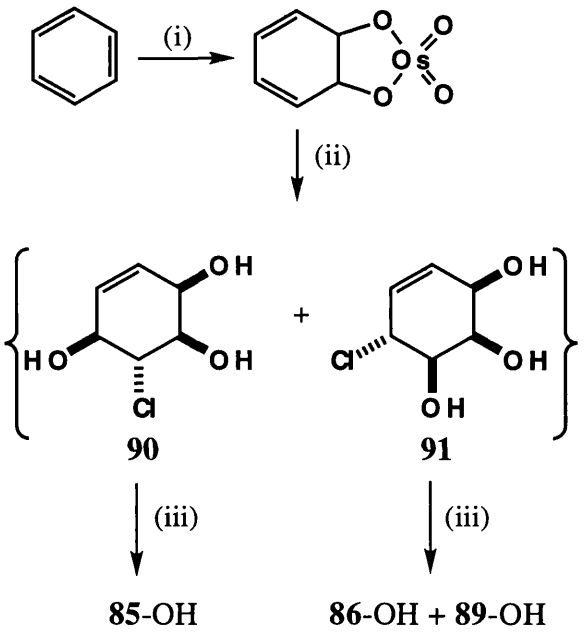


6	71	:	29	(64%)[48]
	64	:	36	(88%)*[25]

Reagents: (i) OsO_4 (cat), NMO; * Isolated as tetraacetate

Scheme 2.29

The presence of a diene diol **6** in our photoosmylation reaction would require a faster rate of hydrolysis of the diene osmate ester **67** than secondary osmylation, which is unlikely, even though this was seen in the case of the halobenzenes (see section 2.5.2). Finally, we considered the rate of addition of HOCl to the diene osmate ester to be in competition with secondary osmylation, taking us *via* a deoxy-chloro-conduritols **90** and **91, scheme 2.30**, *via* 1,2 or 1,4 addition.[125] Such conduritols could according to Kishis' rules[126,127] and reports by other groups[25,128] give **85** and **86** and a minor amount of **89** after dihydroxylation and acetylation.

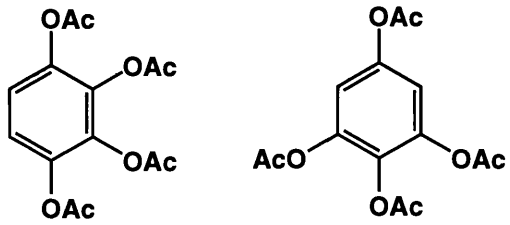


Reagents: (i) OsO_4, UV; (ii) HOCl, H_2O; (iii) OsO_4, H_2O.

Scheme 2.30

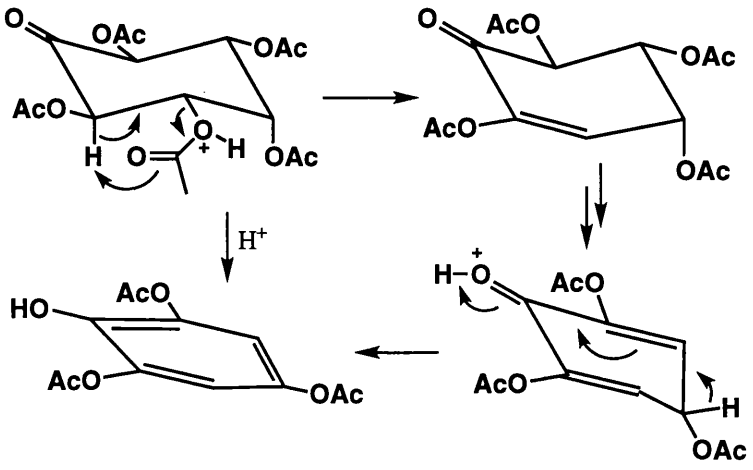
We sought to test the feasibility of such a mechanistic path by carrying out the same reaction that gave us **89** but at a lower temperature. We hereby hoped to isolate the deoxy-chloro-conduritols by slowing down tertiary dihydroxylation.

Photoosmylation of 15 mL of benzene in 10 mL barium chlorate solution ([1.10 M]) at 18 °C gave, after acid catalysed acetylation, a rewarding 1.195 g of allo-inositol hexaacetate and 537 mg of a 1:1 mixture of **85**:**86**. No **89** could be detected in the reaction mixture nor was there any sign of deoxy-chloro-conduritol products. Also isolated from the reaction mixture were two aromatic products of similar polarity to **80**. After careful chromatography and several recrystallisations pure samples of apionol tetraacetate **92** and 1,3,4,5-tetraacetoxybenzene **93** were obtained (^{1}H NMR yields: 156 mg and 593 mg respectively).



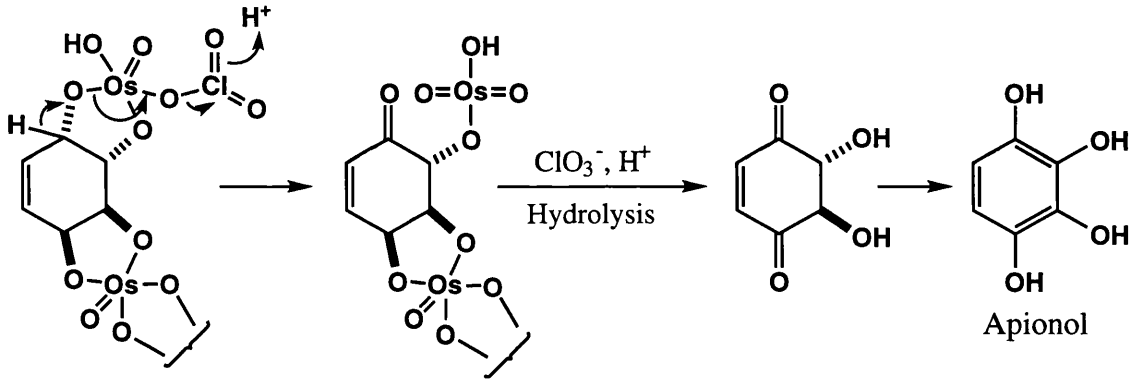
92 **93**

Their presence was at first puzzling until literature precedent[129,130] was discovered showing that when inosose (pentahydroxycyclohexanone) was treated with sodium acetate and acetic anhydride 1,3,4,5-tetraacetoxybenzene **93** was obtained, **scheme 2.31**.



Scheme 2.31

The formation of inososes under our reaction conditions is understandable given the wealth of information[87,104] pertaining to chlorate driven dihydroxylation reactions which give ketols as side product. Even under the milder ^{t}BuOOH catalysed reactions, up to 36% yields of ketol have been isolated.[131] The ability of a deoxy-chloro-inosose to undergo the equivalent reaction should also be emphasised although no chloroaromatic was detected in this case. A mechanism[131] for the formation of apionol could be considered as one of bis-ketol formation from the oxidative hydrolysis of the *anti*-osmate polymer, **scheme 2.32**. Such a mechanism is 'supported' by the reported synthesis of apionol tetraacetate **92** by the dihydroxylation of quinone followed by acetylation.[132-134]



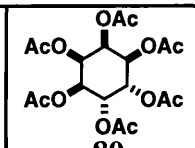
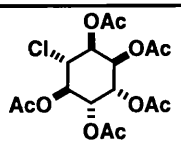
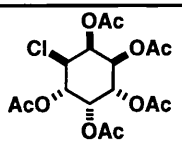
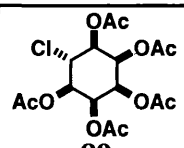
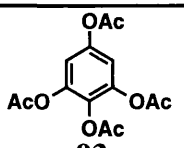
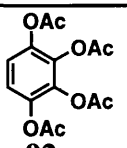
Scheme 2.32

In catalytic terms these new masses of isolated product amounted to 177 turnovers of osmium tetroxide, assuming that the aromatic compounds originated from inososes and conduritol as described previously. These two results raised more questions which were difficult to answer. The absence of the aromatic compounds, **92** and **93**, from the photoosmylation performed at 45 °C and the absence of deoxy-chloro-conduritols **90**, **91** and indeed **89** from the photoosmylation performed at 18 °C seemed puzzling and seemed to negate the proposed pathway to **89**. A possible theory to account for these observations was proposed. At 45 °C, the decomposition of the chlorate[116]

would be faster than at 18 °C, producing a greater steady-state concentration of HOCl. This would effectively be able to compete with secondary osmylation, yielding deoxy-chloro-conduritol intermediates hence **89**. At 18 °C the chlorate decomposition would be slower giving rise to a lower concentration of HOCl whose addition to an unsaturated cyclitol intermediate could only compete with tertiary osmylation. Why lower temperatures favour the oxidative hydrolysis of osmate esters to form ketols remains unclear however.

Reactions were also carried out with sodium chlorate, as literature reports had indicated that sodium and potassium chlorates led to greater yields of chlorohydrin by-products. Photoosmylation of 15 mL of benzene in [2.2 M] sodium chlorate (10 mL) at 17 °C gave, after acetylation, 441 mg of *allo*-inositol hexaacetate **80**, 261 mg of the 1:1 mixture (^{1}H NMR) of **85** and **86**, and 484 mg of the aromatic acetates, **92** and **93**, as a 1:1 mixture (^{1}H NMR).

Experiments in which the volume of the aqueous phase was further reduced, and the chlorate concentration and benzene volume increased, did not follow the trend of increased chlorination. A 2.1 mL saturated solution [10.5 M] of sodium chlorate in 23 mL of benzene only delivered 165 mg of *allo*-inositol hexaacetate and 57 mg of a 1:1 mixture (NMR) of **85**:**86**. This result vindicated the need for good phase interaction to facilitate oxidative hydrolysis. **Table 2.19** summarises this sections' results.

Entry	Conditions*	 **80**	 **85**	 **86**	 **89**	 **93**	 **92**	Overall t/o
1	CTAB	0.73 mmol	0.15 mmol	0.15 mmol	-	-	-	28.1
2	[0.55 M]	0.45 mmol	0.08 mmol	0.08 mmol	-	-	-	16.3
3	Added Cl_2	0.18 mmol	0.15 mmol	0.09 mmol	-	-	-	10.2
4	15 mL, 45° C	2.59 mmol	0.61 mmol	0.61 mmol	0.30 mmol	-	-	107.8
5	15 mL, 15° C	2.77 mmol	0.65 mmol	0.65 mmol	-	1.91 mmol	0.50 mmol	176.6
6	$NaClO_3$ [2.2 M]	1.02 mmol	0.32 mmol	0.32 mmol	-	0.78 mmol	0.78 mmol	82.4
7	$NaClO_3$ [10.5 M]	0.38 mmol	0.07 mmol	0.07 mmol	-	-	-	14.2

* General conditions: 0.1 mmol OsO_4 (25 mg), 43 hrs irradiation, ca. 30 °C; **85** and **86**; **92** and **93** are NMR ratios

1, **2** and **3**: 50 mL H_2O, 0.65 mL PhH, [0.22 M] $Ba(ClO_3)_2$ unless otherwise stated

4 and **5**: 10 mL H_2O, 15 mL PhH, [1.10 M] $Ba(ClO_3)_2$

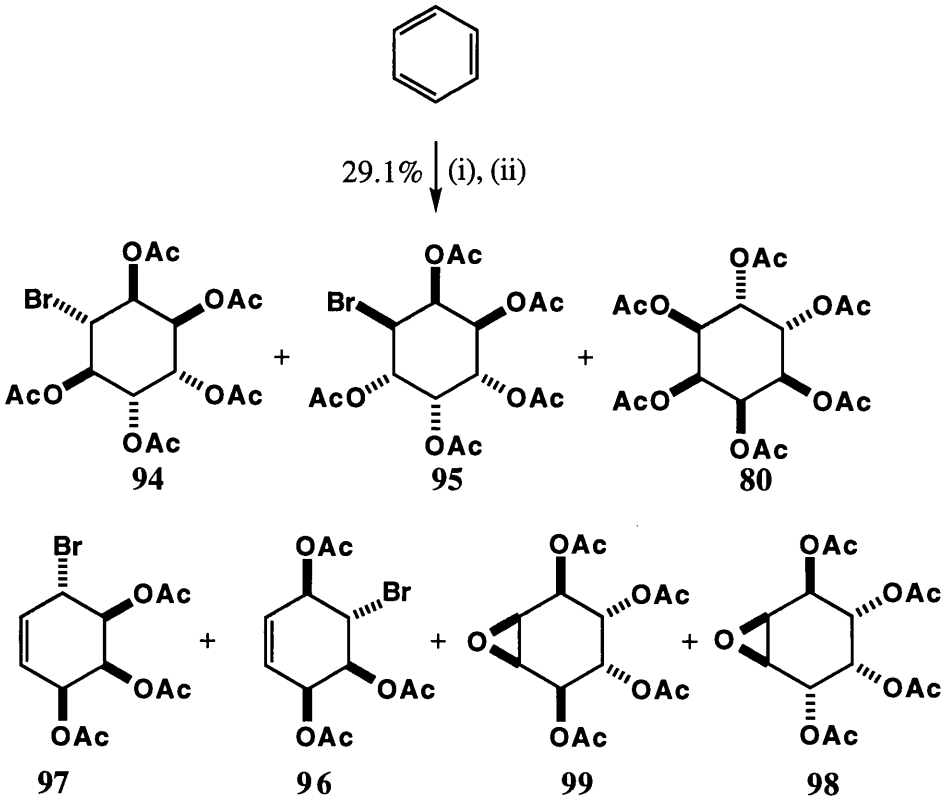
6: 10 mL H_2O, 15 mL PhH

7: 2.1 mL H_2O, 27 mL PhH

Table 2.19. Experimental conditions giving rise to deoxy-choro-inositols and aromatic acetates.

2.4.2 Deoxy-bromo cyclitols

Encouraged by the exciting isolation of deoxy-chloro inositol derivatives, it was an obvious step to suggest that the inherently weaker oxygen bromine bonds in bromate could give even higher yields of the analogous bromo derivatives. In the event, the use of sodium bromate as an alternative reoxidant to turn over the photoosmylation reaction led to a moderately good total yield of 29.1%. Amongst the products isolated were the acetates of deoxy-bromo-inositols **94** and **95**, deoxy-bromo-conduritols **96** and **97**, anhydro-inositols (epoxy-conduritols) **98** and **99** and the expected conduritol E **79** and *allo*-inositol **80**, **scheme 2.33**

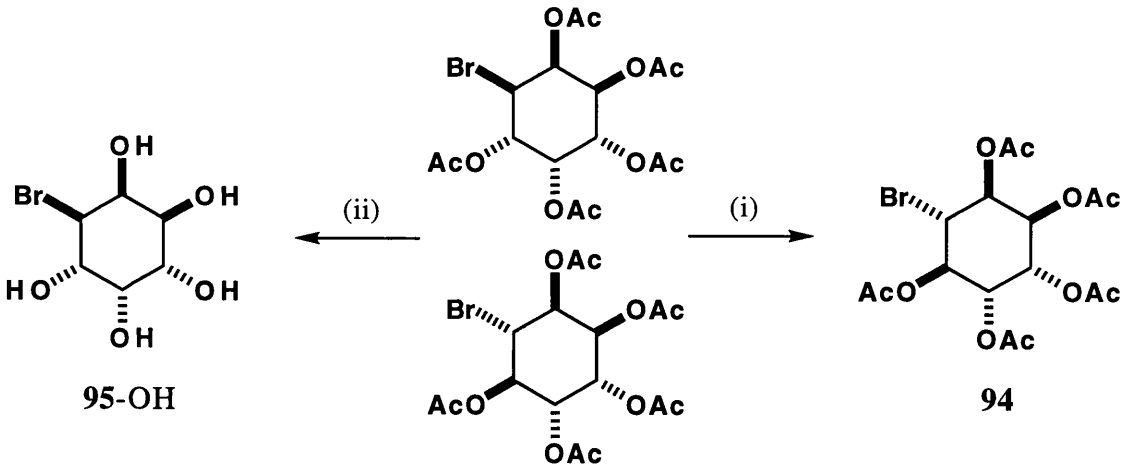


Yields: **94+95** 13.8% (2.9:1); **98+99** 4.5% (4.7:1); **96+97** 2.3% (4.7:1); **80** 7.7%

Reagents: (i) OsO_4 (cat), UV, $NaBrO_3$ [0.24 M], 30° C; (b) Ac_2O, Et_3N, DMAP.

Scheme 2.33

The fact that the two major bromo inositols, **94** and **95** provided a 14% (and later 19%) yield fully vindicated our hopes in the selection of bromate. The relative stereochemistry of these products was determined by ^{1}H NMR HOMO decoupling experiments and HETCOR (^{1}H-^{13}C) NMR coupling experiments for **96** and **97**, and X-ray crystallography in the case of **94** (see appendix A). As for their chloro-analogues, **94** and **95** were isolated as a mixture of diastereomers after column chromatography, the use of HPLC being required to effect separation. It was subsequently found that in cases where **94** was the major isomer a single recrystallisation from ethanol at r.t. would furnished pure **94**, **scheme 2.34**. Acid catalysed deacetylation of mixtures of **94** and **95** in methanol led to the precipitation of clean deprotected **95**-OH in good yield, irrespective of the **94**:**95** ratio and hence is a simple practical operation. The relative insolubility of *neo*-inositol has been reported.[135]



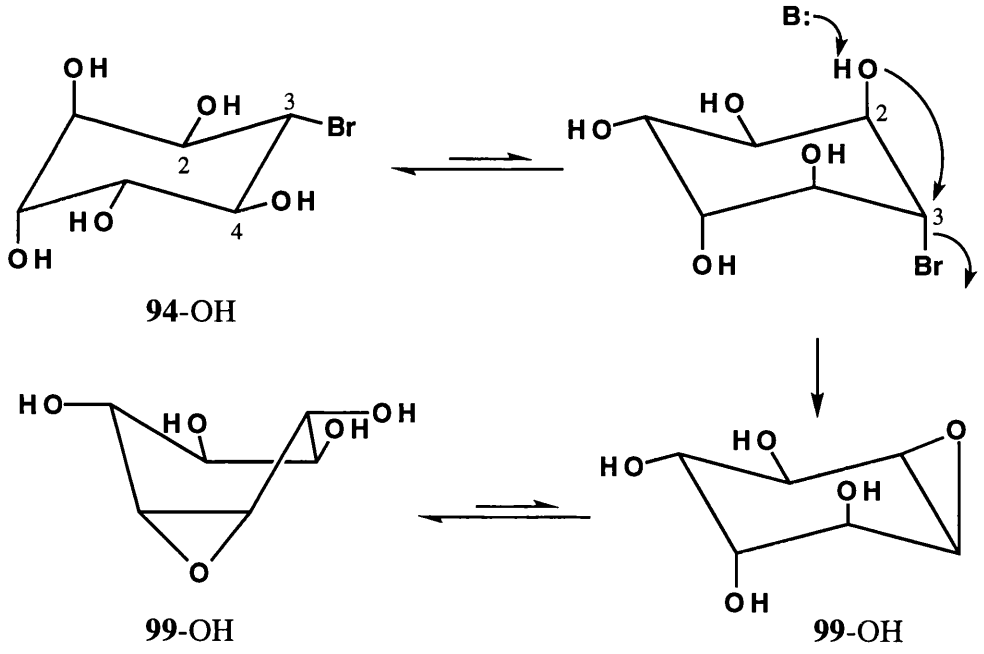
Reagents: (i) Ethanol, r.t., 80-90%; (ii) MeOH, HCl (cat), 71-79%.

Scheme 2.34

Likewise deoxy-bromo-conduritol **96** could be separated from **97** through room temperature recrystallisation. Epoxy-conduritols **98** and **99** (and later **100**) were only

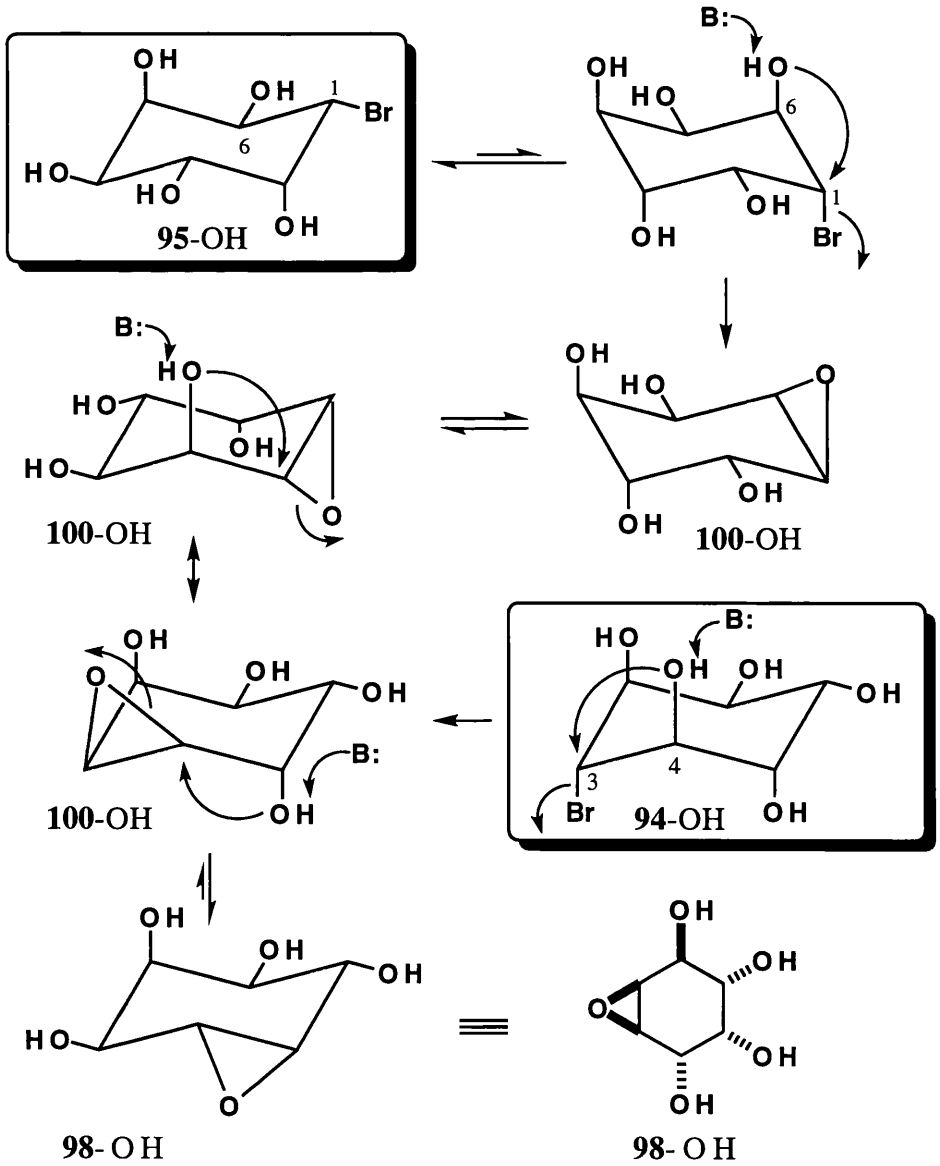
separated after HPLC. The synthetic route to **94** and **95** could be explained using the same rational as for **85** and **86** *viz.*, the addition of HOBr across the double bond of an unsaturated cyclitol intermediate. The isolation and elucidation of deoxy-bromo-conduritols **96** and **97** was proof that the addition of HOX could compete with secondary osmylation supporting, to some extent, our mechanistic path for the formation of **89**. The formation of bromo-cyclitols at bromate concentrations corresponding to those at which no chloro-cyclitols were formed in the analogous chlorate reactions could be explained by the expected increase in the rate of decomposition of bromate *vs* chlorate.[116]

The formation of epoxides **98** and **99** was the result of the basic conditions used in the acetylation step, **scheme 2.35**. *Trans*-diaxial attack of the hydroxyl at C-2 on the bromine bearing carbon of **94**-OH yields the *meso* **99**-OH. The preferred boat conformation of acetylated **99** is borne out by both ^{1}H NMR and molecular modelling studies.



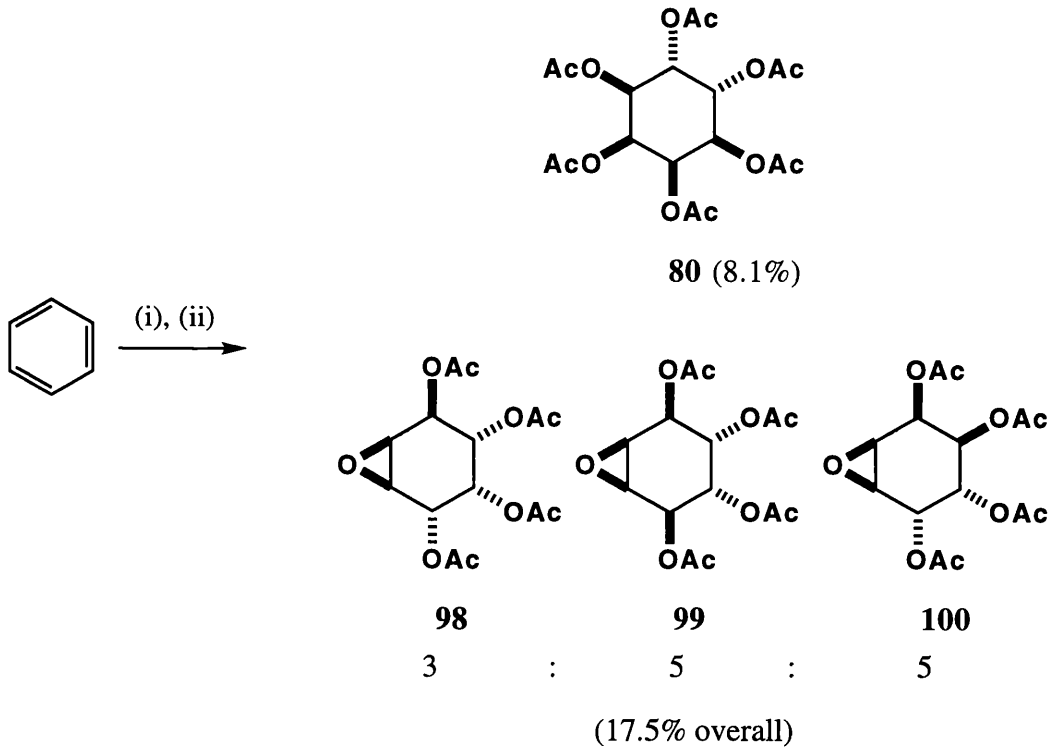
Scheme 2.35

Similar attack of the C-4 hydroxyl on C-3 of **94**-OH and the C-6 hydroxyl on C-1 of **95**-OH would give **100**-OH, **scheme 2.36**. **100**-OH then undergoes a reversible Payne rearrangement to the thermodynamically more stable **98**-OH.[136] This end product has only one axial hydroxyl group when compared to the intermediate **100**-OH. The treatment of deoxy-bromo-inositols with a solution of triethylamine-water was later found to be a literature procedure for the formation of epoxy-conduritols.[137]



Scheme 2.36

Due to the considerable interest in epoxy-conduritols as irreversible glycosidase inhibitors[58,137] the one-pot synthesis of such compounds is desirable. To demonstrate the use of the photoosmylation reaction as an efficient means of obtaining epoxy-conduritols, a reaction mixture, prior to acetylation, was treated with triethylamine at 50 °C for 17 h. As expected, most of the deoxy-bromo-inositols were then transformed into epoxides, **scheme 2.37**.

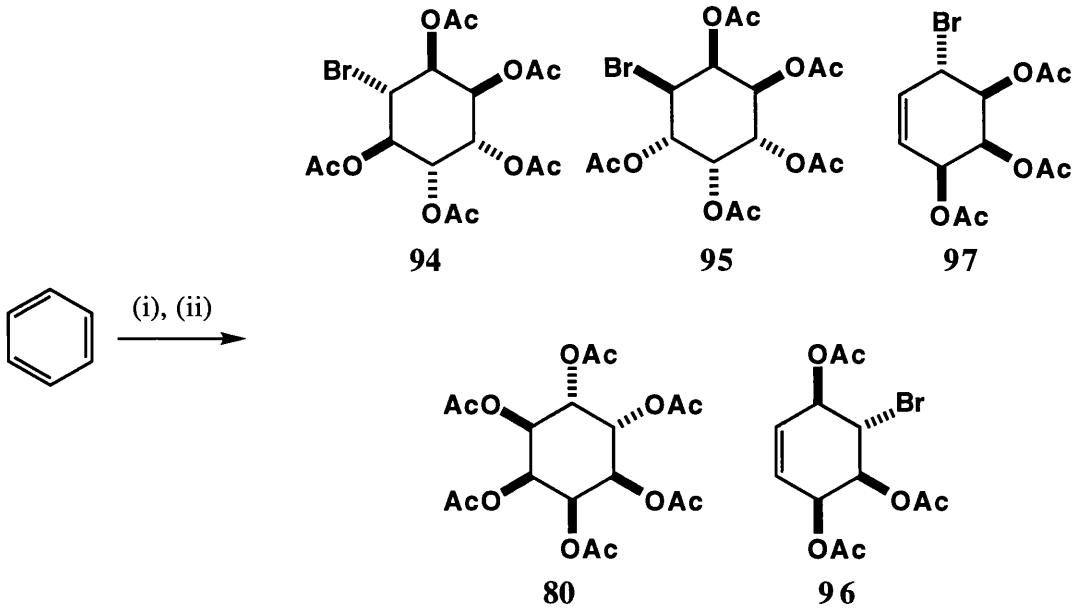


Reagents: (i) OsO_4 (cat), UV, $NaBrO_3$ [0.22 M], 52° C;

(ii) Et_3N, 50° C 17 h then Ac_2O, DMAP.

Scheme 2.37

From a preparative standpoint, it was also useful to note that epoxide formation could be suppressed by using the acid catalysed acetylation protocol, hereby providing access to the bromo derivatives themselves for further transformations such as deoxygenation, **scheme 2.38**.

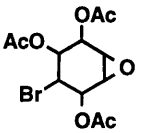
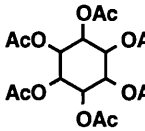
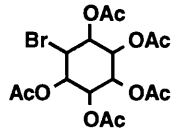


Yields: **94+95** (5.1:1) 18.8%; **96+97** (5:1) 2.3%; **80** 7.7%

Reagents: (i) OsO_4 (cat), UV, $NaBrO_3$ [0.22 M], 30° C; (ii) Ac_2O, AcOH

Scheme 2.38

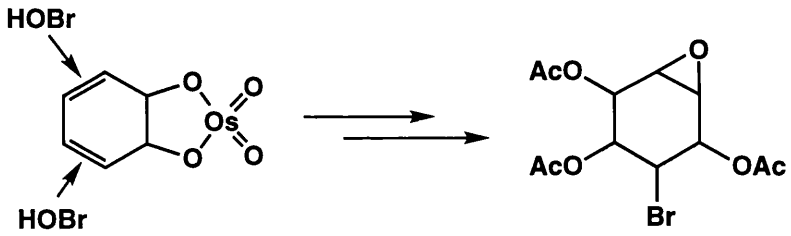
The use of similar conditions to those which gave deoxy-chloro-inositols in the chlorate system did not lead to an increased in the yield of **94, 95** and **80** in the bromate system. However small amounts of the bromo-epoxy-triacetate **101** could be isolated when working at concentrations of [0.44 M] and above, representing a primary osmylation followed by two successive HOBr additions, **scheme 2.39** and **table 2.20**.

	[M]	 **101**	 **80**	 **94+95**	Yield
1	[0.44]	0.9%	11.2%	17.3%*	29.4%
2	[2.65]	1.5%	13.8%	14.0%*	29.3%

* Combined yield of **94, 95, 98, 99** and **100**.

Table 2.20 Reaction conditions leading to epoxy-bromo-triacetates.

This was a noteworthy finding as at no point in the synthesis of **101** could osmate ester oligomerisation have taken place leading to catalytic shut-down, **scheme 2.40**. Unfortunately the mechanistic path leading to **101** only represents between 3-5% of the products in any particular high bromate concentration reaction.

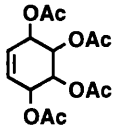
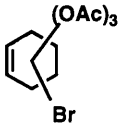
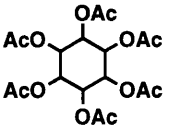
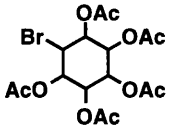


101

Scheme 2.40

Whilst investigating the effect of bromate concentration on **94+95** : **80** ratios it was found that at 20 °C and [0.12 M] bromate concentration significant amounts of conduritol products could be isolated. We assumed that the low temperature was slowing down both tertiary dihydroxylation and bromate disproportionation and hence leading to a 1:2 conduritol:inositol ratio (see experimental). We were also aware that our reductive quench of the bromate residues provided perfect conditions for the synthesis of halohydrins from olefins.[138] Hence the perceived ratio could indeed have been even higher in the absence of transient HOBr developed after the photolysis reaction.

A new work-up protocol was therefore adopted making use of a sacrificial olefin. After irradiation, the photoosmylation reaction was treated with 20 mL of cyclohexene and the reaction mixture homogenised using a 1:1 mixture of ^{i}PrOH:acetone. This was followed by slow addition of a solution of sodium metabisulphite at 0 °C which would then reduce the bromate and generate HOBr which would, we hoped, preferentially react with the large excess of cyclohexene present.[138]

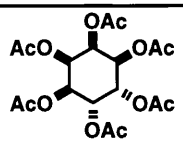
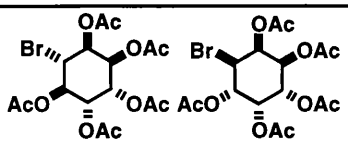
	Temp	 **79**	 **96:97**	 **80**	 **94+95**	Ratio Conduritol : Inositol	Total %
1	02° C	8.6%	4.1%, 4:1	5.3%	6.2%*	52 : 48	24.2%
2	10° C	5.9%	2.7%, 3:1	8.5%	9.2%*	33 : 67	26.3%
3	15° C	6.0%	2.7%, 4:1	7.8%	12.5%*	30 : 70	29.0%
4	45° C	0.4%	-	4.4%	11.1%*	3 : 97	15.9%

* Combined yield of **94**, **95**, **98**, **99** and **100**.

Table 2.21 Bromate photoosmylation with cyclohexene work-up

Table 2.21 shows the results of a variable temperature study using the modified cyclohexene work-up. At low temperature, the conduritol yields (**79**, **96** and **97**) were equal to the inositol yields (**80**, **94**, **95**, **98**, **99** and **100**). As expected the rate of decomposition of bromate and the rate of tertiary dihydroxylation are both sufficiently slow to push the conduritol:inositol ratio up to approximately 1:1. The ratio of **79**:**96+97** is always around 2:1 at low temperature, indicating that secondary osmylation is favoured over HOBr addition under such conditions. As the temperature increases the rate of tertiary dihydroxylation and bromate decomposition both increase and yields of conduritol product drop to reach ca. 0% at 45 °C. The deoxy-bromo-inositol:*allo*-inositol ratio is also affected by temperature. At 2 °C the ratio is approximately 1:1 and rises to 2.5:1 at 45 °C. Since the synthetic path to deoxy-bromo-inositols can go either *via* conduritol E, **79**-OH, or deoxy-bromo-conduritols, **96**-OH and **97**-OH, it was not possible to tell whether the increase in temperature had predominantly favoured the rate of tertiary dihydroxylation or bromate decomposition.

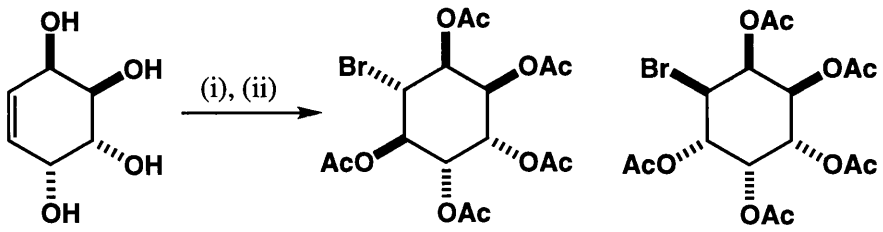
This particular mechanistic problem was clarified through the use of a temperature variable photoosmylation reaction using an acid catalysed acetylation, **table 2.22**.

	Temp	 **80**	 **94:95**	Total %*
1	2° C	5.1%	12.6%, 1:2	17.7%
2	15° C	7.4%	16.3%, 1:1	23.7%
3	30° C	7.7%	18.8%, 5:1	26.5%
4	45° C	5.7%	16.4%, 5:1	22.1%

*Not including yields of **96** and **97** in all cases < 2.3% (not shown in table).

Table 2.22 94:95 ratio as a function of temperature

Without the use of the sacrificial olefin work-up, **table 2.22** seemed to show that temperature had little effect on the ratio of deoxy-bromo-inositols:*allo*-inositol. However, having now eliminated the conversion of **94** and **95** to epoxy-conduritols, the real ratio of **94**:**95** could be established. This ratio was shown to be temperature dependant with the *neo* diastereomer **95** predominant at low temperature and the *chiro* diastereomer **94** predominant at high temperature. This trend could be explained after an independent experiment showed that the treatment of a solution of conduritol E with sodium bromate and sodium metabisulphite gave chiefly the *neo* diastereomer, **scheme 2.41**.



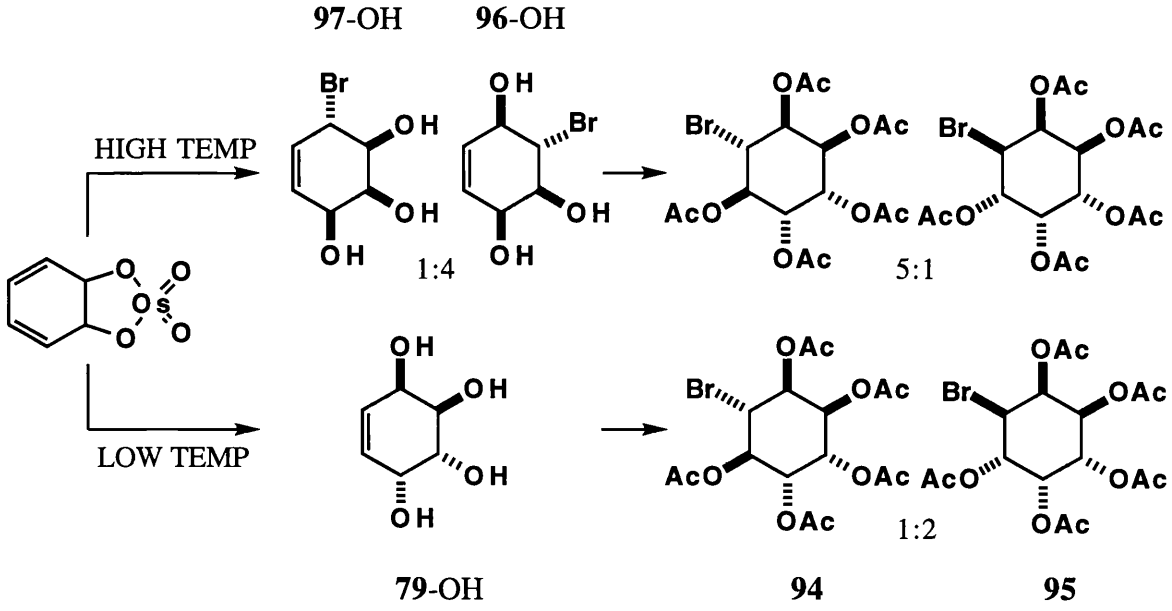
1 : 6.3

79-OH **94** **95**

Reagents: (i) $NaBrO_3$, $Na_2S_2O_5$; (ii) Ac_2O, AcOH; 72%

Scheme 2.41

As our experimental evidence (**table 2.21**) showed that at any given temperature the ratio of deoxy-bromo-conduritols **96** and **97** was always approximately 4:1, the only way in which a 2:1 ratio of **95**:**94** could arise was through the addition of HOBr on conduritol E (**79**-OH). At high temperature the 1:5 ratio of **95**:**94** could then only arise from the dihydroxylation of the major deoxy-bromo-conduritol **96**-OH, **scheme 2.42**:



79-OH **94** **95**

Major route to deoxy-bromo-inositol formation as a function of temp.

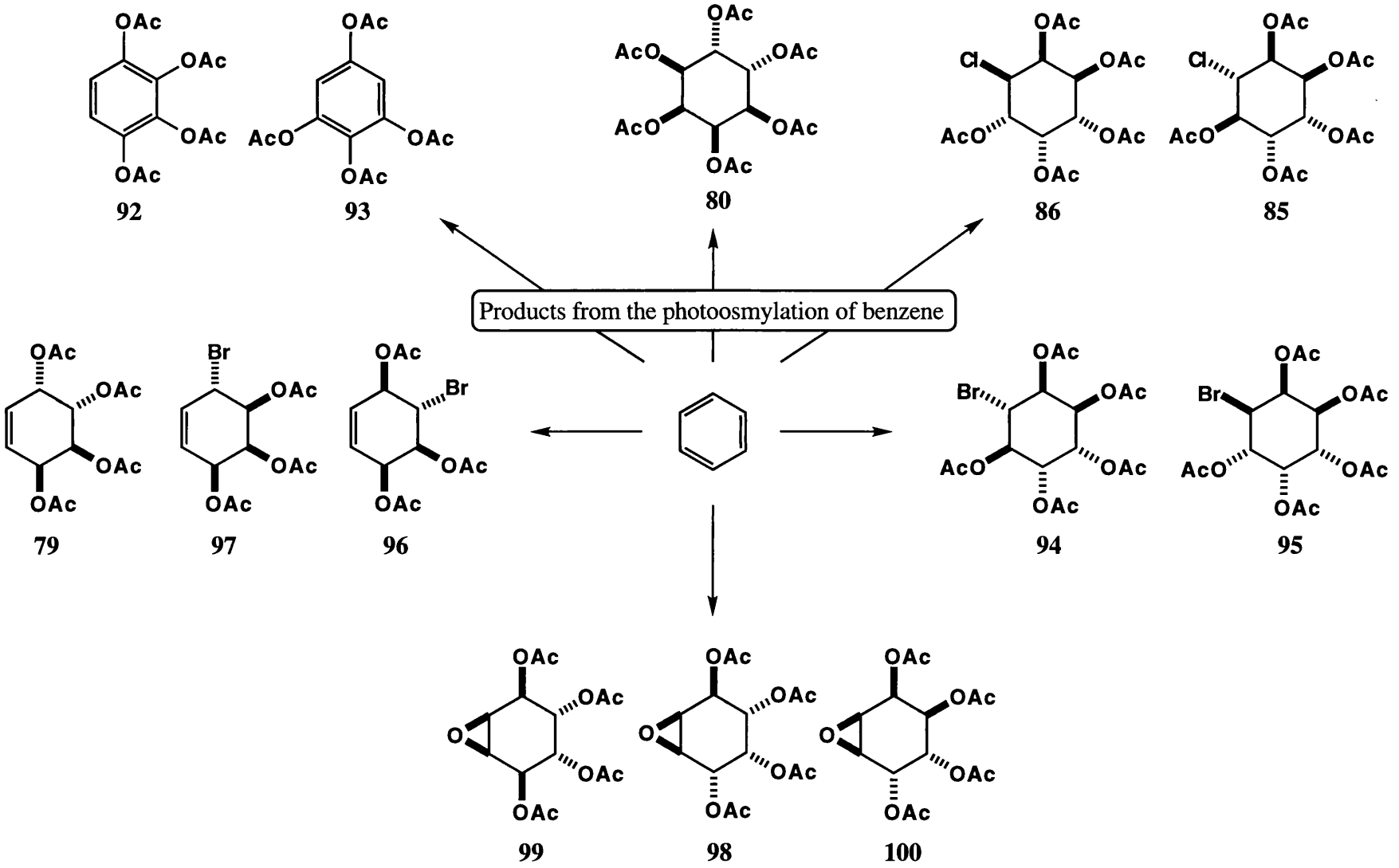
Scheme 2.42

Although we had previously seen that low temperatures favoured secondary osmylation over HOBr addition (**table 2.22**), it was now clear that at high temperature this order had reversed.

As for the case of the deoxy-chloro-inositols attempts were made to increase the overall yield of **94** and **95** through the judicious addition of various sources of 'HOBr' prior to irradiation. Unfortunately, addition of NBS and bromine both inhibited the photoosmylation reaction and no cyclitol product was isolated.

Nevertheless, from a simple practical standpoint, this section too revealed that a considerable degree of control can be exercised in the highly stereoselective introduction of 5 hydroxyl groups and a bromine around the cyclohexane ring and that, through judicious choice of experimental conditions and work-up procedures, good routes are available especially to **94, 95, 79, 80** and **96**.

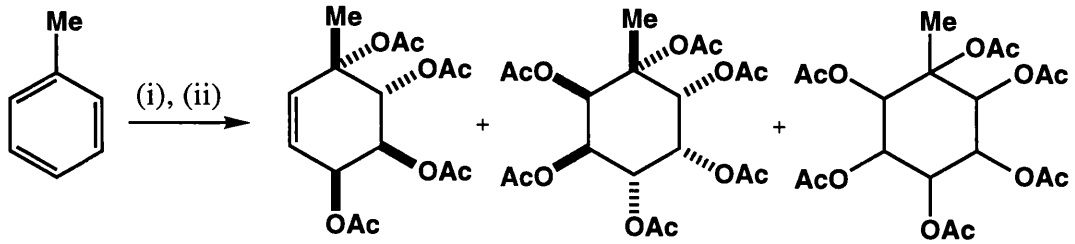
***


Products from the photoosmylation of benzene
92
93
80
86
85
79
97
96
94
95
99
98
100

2.5 Scope

2.5.1 Alkyl benzenes-Toluene

Following on from our studies with benzene, further development of the photoosmylation reaction was largely carried out with toluene due to our interest in the possibility of regioselectivity arising from the methyl group. Photoosmylation using the standard conditions gave the single *C*-methyl conduritol E **73** in 2.2% yield and a mixture of *C*-methyl inositols in 10.8% yield, **scheme 2.43**. Careful crystallisation of the mixture allowed the isolation of ^{1}H NMR pure **77**. Inspection of the 1.5-1.8 ppm ^{1}H NMR region of the mixture revealed that in all three *C*-methyl inositols had been formed.

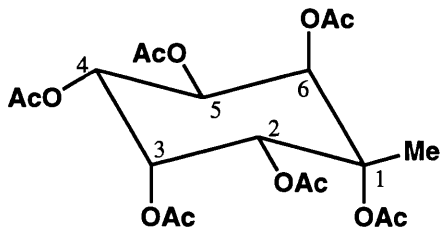


73 **77** **74**

Yields: **73** 2.2%; **77+74** 10.8%

Reagents: (i) OsO_4 (1.3 mol%), UV, $Ba(ClO_3)_2$ [0.22 M]; (ii) Ac_2O, Et_3N, DMAP

Scheme 2.43



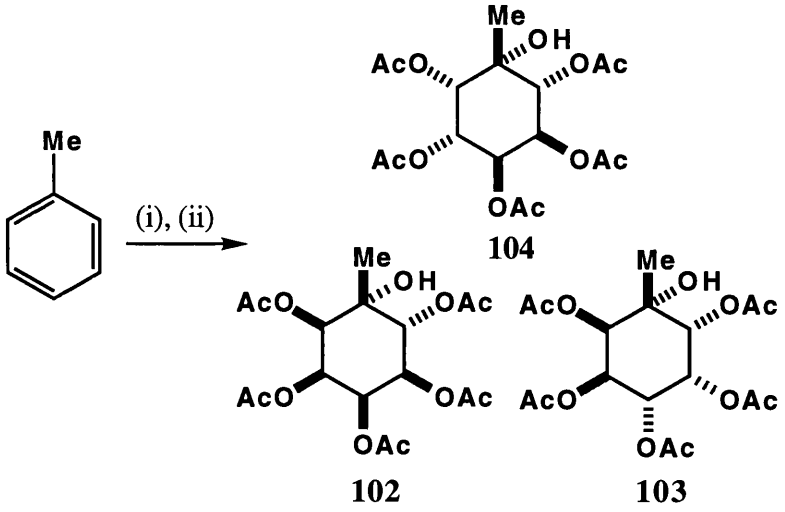
77

Distinguishing spectral features

^{1}H NMR signals for H-2, 6 and Me at C-1 are broad at r.t.. Me at C-1, 1.51 ppm

$J_{4,5}$=10.6 Hz, $J_{2,3;3,4}$=3.7 Hz.

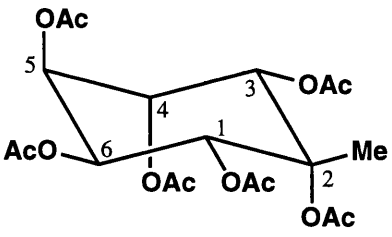
The separation of the other two isomers proved to be very problematic even with the use of HPLC. Fortuitously, it was found that by changing the solvent and reducing the temperature of the acetylation step it was possible, through careful column chromatography, to isolate all three *C*-methyl inositols as their hydroxy pentaacetates, **scheme 2.44**.



Yields: **104** 3.9%; **102** 2.0%; **103** 1.9%

Reagents: (i) OsO_4 (1.3 mol%), UV, $Ba(ClO_3)_2$ [0.22 M]; (ii) Ac_2O, py, r.t..

Scheme 2.44

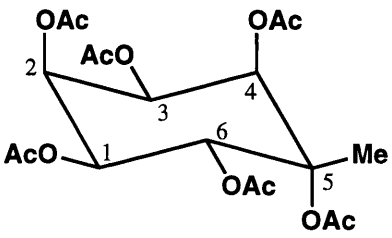


105

Distinguishing spectral features

No temperature variable phenomenon.

Me at C-2, 1.74 ppm



106

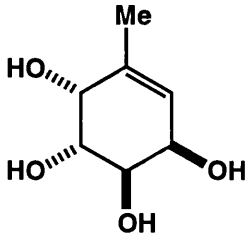
Distinguishing spectral features

No temperature variable phenomenon.

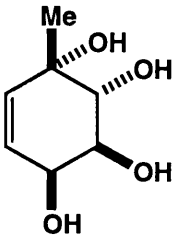
Me at C-5, 1.54 ppm. $J_{1,6}$=10.6 Hz

'W' coupling: $J_{2,4}$=1.3 Hz

The slightly higher temperature used ensured the synthesis of inositols only and the ratio of **102**:**103**:**104** was found to be 1:1:2. The presence of **103** indicated that *C*-methyl conduritols other than **73** were formed in the reaction but probably underwent a faster dihydroxylation explaining their absence from the reaction mixture from the lower temperature experiment. It would be expected, considering previous findings,[139] that due to the presence of a more electron rich double bond, **107** would dihydroxylate faster than **73**-OH to give **103** and **102**.

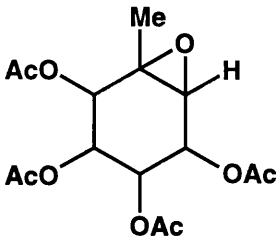


107



73-OH

Photoosmylation of toluene using bromate and basic acetylation gave a complicated mixture of products, **table 2.23**. The major product was a mixture of three epoxy-*C*-methyl inositols. The basic skeleton for these was determined from ^{1}H NMR to be the tri-substituted epoxides **108**, **109** and **110**.



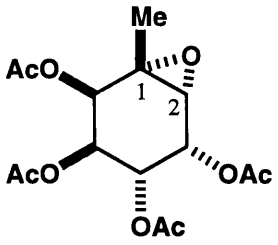
Epoxy-*C*-methyl-inositols

^{1}H: 3.4 ppm, d, 56%, **108**

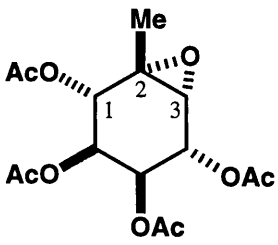
3.1 ppm, d, 32%, **109**

3.0 ppm, d, 12%, **110**

Preparative HPLC followed by several recrystallisations allowed for the isolation of the epoxides **108** and **109**, which were shown to have the 1,2- and 2,3-anhydro-*allo*-inositol stereochemistry through the use of ^{1}H NMR HOMO decoupling experiments. Unfortunately, due to the various methods of HOBr addition (1,2 and 1,4) at the diene stage and (1,2) at the conduritol stage it was not possible to establish the site of primary osmylation. However, under the acetylation conditions used, no tertiary hydroxyls were acetylated which does suggest that prior to epoxide formation the bromine was bonded to C-2 as in **108** and C-3 as in **109**; epoxide formation resulting from the attack of the unprotected tertiary hydroxyl. This would of course be the expected regioselectivity from Markovnikov addition to the trisubstituted alkene.

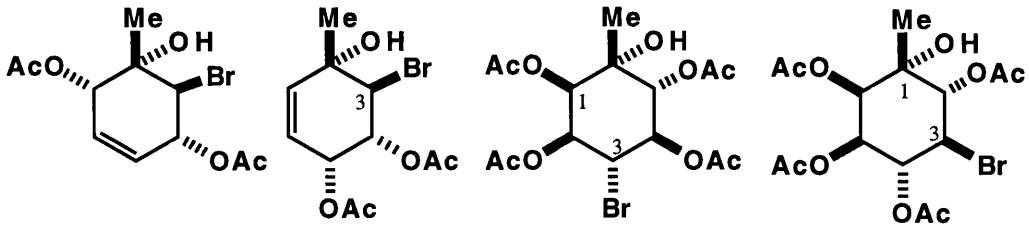


108



109

This would give a deoxy-bromo-*chiro* precursor which, in the case of benzene, was found to be the major diastereomer for brominated cyclitols in high temperature experiments. The isolation of **111** as the only conduritol product from the reaction validates the aforementioned site as C-2 for the bromine atom leading to **108**.



114 **111** **112** **113**

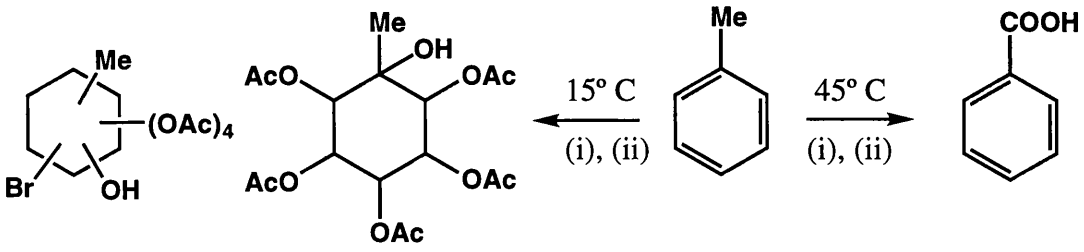
Also isolated from the mixture were the deoxy-bromo-*chiro*-inositols **112** and **113** in minor quantities along with **102** and **104**. **Table 2.23** summarises our results:

	108	**109**	**110**	**111**	**112**	**113**	**102**	**104**	Other*	t/o
mmol	0.93	0.52	0.20	0.50	0.05	0.04	0.33	0.29	0.45-0.47	ca. 70

* Unidentified material containing epoxy and bromo cyclitols and **103**.

Table 2.23 Bromate photoosmylation of toluene; products.

The reproducibility of the bromate photoosmylation reaction was called into question after a repeat reaction using the standard 7.3 mmol of aromatic conditions at 45 °C gave only 132 mg (approximately 0.3 mmol) of crude cyclitol products with the major portion of the product isolated as benzoic acid,[140] **scheme 2.45**. At lower temperatures (15-18° C) this benzylic oxidation could be surpressed and using acid acetylation conditions a mixture of *C*-methyl inositol pentaacetates **102**, **104** and **103** was isolated (0.4 mmol, 5.5%) along with 0.8 mmol (10.9%) of a mixture of unidentified deoxy-bromo-*C*-methyl inositol pentaacetates which contained **112** and **113**. Unfortunately, **114** was the only compound which could be cleanly isolated (2.3%).



Reagents: (i) OsO_4 (1.3 mol%), UV, $NaBrO_3$ [0.22 M]; (ii) Ac_2O, AcOH.

Scheme 2.45

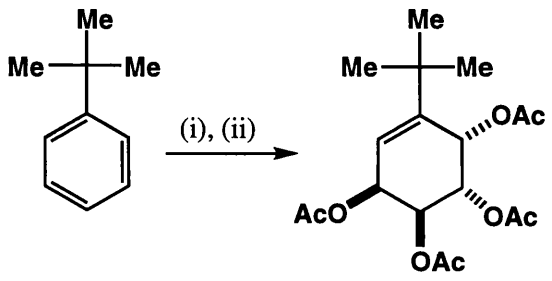
Overall however, it is significant to note that many of the above products could not be simply prepared from the diene diol derivative of toluene produced by *Pseudomonas putida*. In this respect, our chemistry is complementary in terms of furnishing 'unnatural' conduritol and inositol derivatives.

-*o*-Xylene

The photoosmylation of *o*-xylene met limited success. Although it had the perfect energy profile for primary osmylation the presence of a tetrasubstituted double bond and the consequent problem of the slow rate of the subsequent oxidative hydrolysis steps meant that only ca. 1% of protected cyclitol was isolated from a 43 h reaction. The ^{1}H NMR of the crude acetylated reaction mixture showed considerable aromatic product of a similar polarity (by tlc) to benzoic acid, and hence no further work was undertaken with this substrate.

- ^{t}Butylbenzene

In this case a single conduritol product, **115**, was isolated in 1.4% yield, **scheme 2.46**. Unlike the case of toluene where the methyl group had no apparent directing effect, the *tert*-butyl was sufficiently large to provide steric protection of the conduritol double bond from tertiary osmylation.



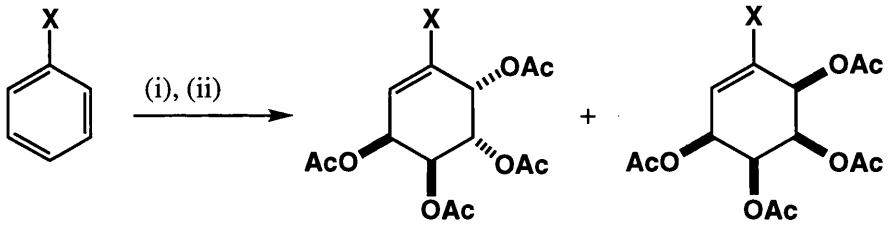
115

Reagents: (i) OsO_4 (1.3 mol%), UV, $Ba(ClO_3)_2$ [0.22 M]; (ii) Ac_2O, Et_3N, DMAP.

Scheme 2.46

2.5.2 Halobenzenes

The photoosmylation of the halobenzenes gave the halo vinylic-conduritols E and D, **scheme 2.47**. The low reactivity of the vinylic halide to dihydroxylation can be attributed to its electron deficiency,[139] thus explaining the absence of inositol products.



E D

Reagents: (i) OsO_4 (1.3 mol%), UV, $Ba(ClO_3)_2$ [0.22 M]; (ii) Ac_2O, Et_3N, DMAP.

	Ratio of Conduritol Isomers				
X	E : D	E : D	Yield	t/o	λ_{max}**
F	**116 : 117**	4.4 : 1	0.6%	>1*	283 nm
Cl	**118 : 119**	5.0 : 1	3.4%	5.0	295 nm
Br	**120 : 121**	5.5 : 1	2.6%	3.8	301 nm

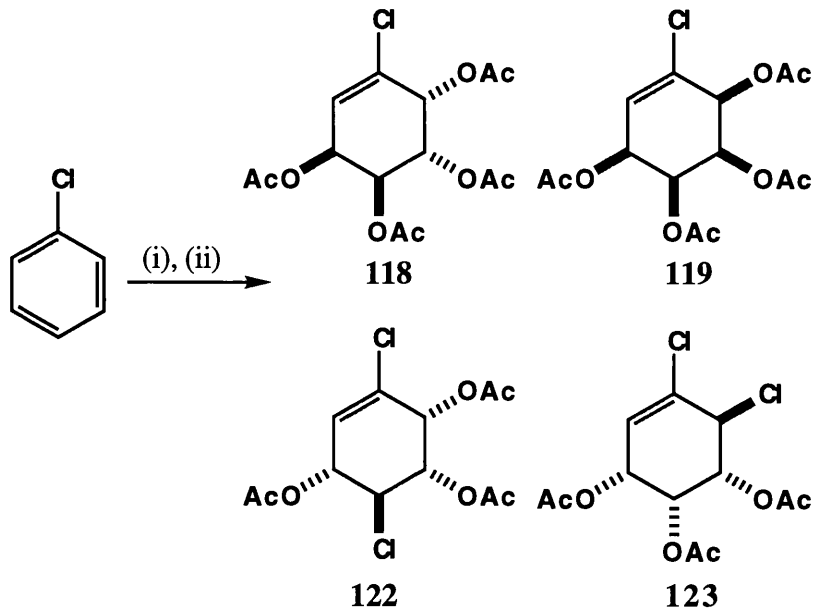
* 2.6 mol% OsO_4 used.

** Calculated using **equation 2.1** and IP's from ref[141]

Scheme 2.47 and Table 2.24 Photoosmylation of the halobenzenes.

The low yields and catalytic turnovers are most probably a function of the relatively high IP of these substrates. The calculated λ_{max} values are within the absorption spectrum of Pyrex and hence most of the charge transfer would have been the result of irradiation at the 'tail end' of the CT spectrum, **table 2.24**.

Photoosmylation of chlorobenzene using the conditions which led to the synthesis of deoxy-chloro-cyclitols with benzene did give rise to trace quantities of the interesting deoxy-chloro-conduritols **122** and **123**, **scheme 2.48**.

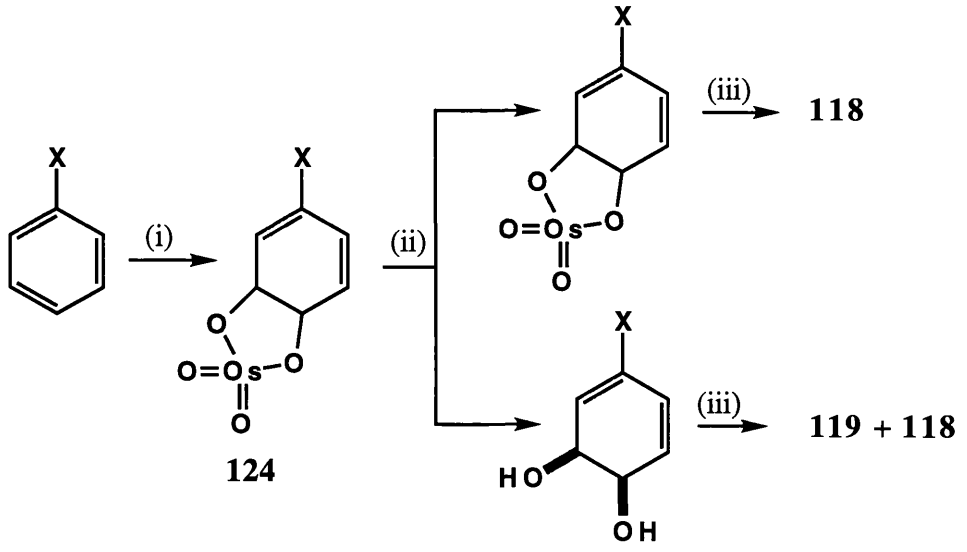


Yields: **118** (6 mg, 0.002 mmol), **119** (1 mg, 0.0003 mmol),
122 (8 mg, 0.0025 mmol), **123** (10 mg, 0.003 mmol).
Reagents: (i) OsO_4 (cat), UV, $Ba(ClO_3)_2$ [1.10 M]; (b) Ac_2O, Et_3N, DMAP.

Scheme 2.48

The approximately equal quantities of the deoxy-chloro-conduritols **122** and **123**, indicated that there was in fact no preferential site of primary osmylation. We were perplexed by the isolation of conduritol D isomers which appeared to indicate a faster rate of hydrolysis than secondary osmylation. This finding put into doubt our previous mechanistic routes which relied on a common intermediate of conduritol E type stereochemistry as proposed by Kochi.[85] However we had already learnt that the

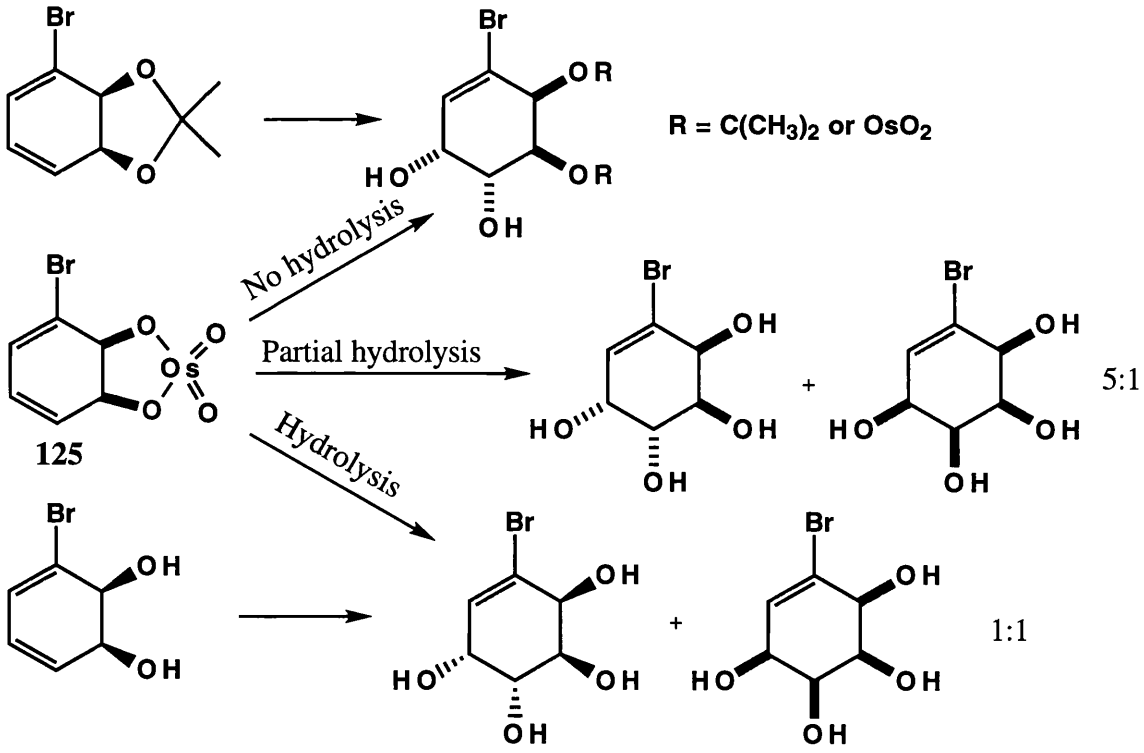
intricate mechanistic routes to the cyclitol products from the aromatic parent were substrate dependant and since oxidative hydrolysis appeared relatively fast here this did not necessarily translate to other cases. A possible reason for this apparent increase in the rate of oxidative hydrolysis was probably due to the overall electron deficient nature of a halodiene intermediate. As shown by experiment, half of the primary osmylations took place at the 3,4 position. Compared to benzene and the alkylbenzenes, the resulting diene **124** is relatively electron poor due to the electronegative halogen. This would slow the rate of secondary osmylation hereby making it perhaps competitive with oxidative hydrolysis, **scheme 2.49**. As the electronegativity of the halogen decreases, the rate of secondary osmylation increases and, as supported by our experimental evidence, conduritol E isomers are then produced in 'higher' yield.



Reagents: (i) OsO_4, UV; (ii) H_2O, ClO_3^-; (iii) OsO_4, H_2O, ClO_3^-. X=Halogen

Scheme 2.49

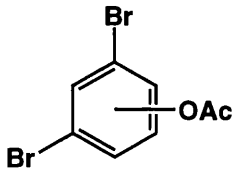
The 2,3-osmate ester diene **125** has a similarly electron deficient system but, due to the position of the halogen in this case, the effect on the rate difference would be smaller. A study carried out by Carless[48] showed that osmylation of the 2,3-diol diene obtained through microbial oxidation of bromobenzene gave an approximately 1:1 mixture of conduritol D and E products, **scheme 2.50**. In contrast, Hudlicky[124] showed that the isopropylidene protected diol gave exclusively conduritol E type products, as Kochi had found with the diene diol osmate ester **67** from benzene. To explain our D:E ratio stemming from the 2,3 intermediate, secondary dihydroxylation on a significant amount of hydrolysed 2,3 intermediate must be taking place. Nevertheless, the 5:1 ratio which is approximately observed for all the halobenzenes is preparatively useful and significant.



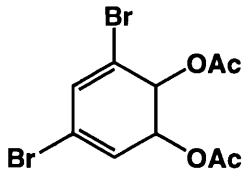
Product distribution for the reaction of various dienes with OsO_4

Scheme 2.50

The ability of halovinylic olefins to resist osmylation led us to attempt the photoosmylation of 1,3-dibromobenzene. The calculated CT band wavelength (IP 9.10 eV,[141] CT wavelength 325 nm) showed that such a process was feasible under our reaction conditions and theoretically should have given a diene diol product. Photoosmylation under the usual conditions did lead to a darkening of the aromatic phase of the reaction mixture which is normally attributed to the formation of an osmate ester. After the standard quench and base catalysed acetylation and work up, 23 mg of a crude product was isolated which showed UV active spots (on tlc) of similar polarity to diacetoxybenzene. The appearance of new peaks in the 5-7 ppm and 2-2.5 ppm region of the ^{1}H NMR lead us to believe that photoosmylation had taken place. Unfortunately however, mass spectrometry showed no M^+ or fragmentation patterns which contained a bromine pattern consistent with any of the expected products **126** or **127**.



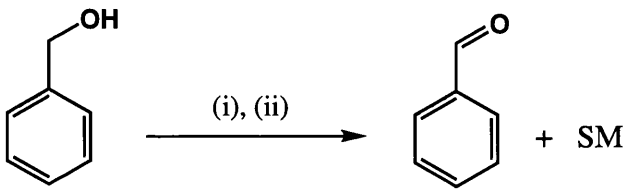
126



127

2.5.3 Benzylic systems

Photoosmylation of benzyl alcohol, **scheme 2.51**, under the standard conditions furnished a mixture of starting material and benzaldehyde **72**, the latter being isolated from the aqueous phase prior to acetylation. Acetylation of the dried aqueous phase did not reveal any conduritol or inositol products.



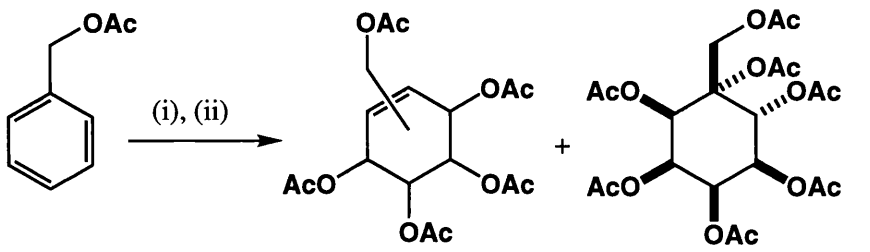
72

Reagents: (i) OsO_4 (cat), UV, $Ba(ClO_3)_2$ [0.22 M], **72**:SM 1:5, 47%.

Scheme 2.51

Benzylic oxidation came as no surprise since toluene had suffered the same fate under similar reaction conditions. However, the total lack of aromatic oxidation was surprising as it seemed to indicate that the benzylic hydroxyl was quenching the CT interaction, even though on mixing the aromatic and osmium tetroxide a stable yellow colouration developed. We reasoned that a suitably protected hydroxyl would eliminate benzylic oxidation and reduce any unwanted oxygen-osmium tetroxide interaction. Photoosmylation of benzyl acetate did indeed give traces of conduritol (0.5%) and inositol (2.1%) products, **scheme 2.52**. Unfortunately routine column chromatography did not effect separation of any of the conduritol or inositol diastereomers identified by ^1H NMR of the crude acetylated reaction mixture. Crystallisation of the inositol containing fractions allowed the isolation of 5-*C*-hydroxymethyl-*allo*-inositol heptaacetate **128** (0.6%). The remainder of the diastereomers, as well as the conduritol diastereomers were inseparable by HPLC. The

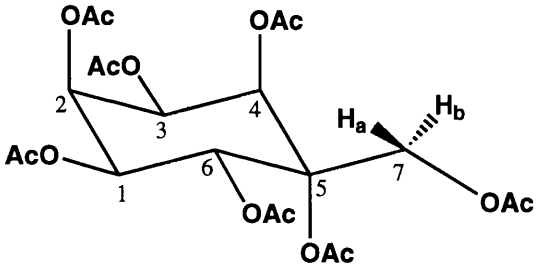
relative configuration of **128** was determined through the use of ^1H NMR HOMO decoupling and was further confirmed by the shift of the benzylic protons H-7_a and H-7_b.



129 (0.5%) **128** (0.6%)

Reagents: (i) OsO_4 (1.3 mol%), UV, $Ba(ClO_3)_2$ [0.22 M]; (ii) Ac_2O, Et_3N, DMAP.

Scheme 2.52



128

Distinguishing spectral features

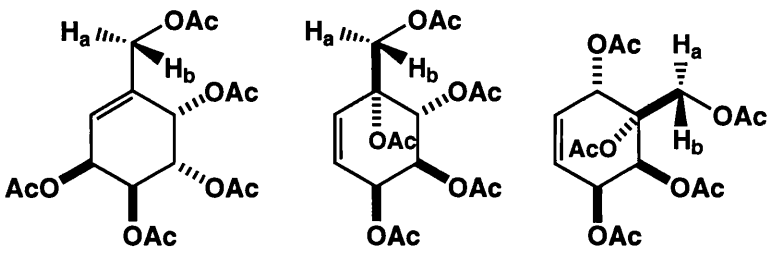
$H_{a/b}$: 4.79 ppm, $J_{a,b}$=12.3 Hz

$H_{a/b}$: 4.53 ppm, $J_{a,b}$=12.3 Hz

$J_{6,1}$=10.6 Hz, $J_{2,3;3,4}$=3.6 Hz

'W' coupling: $J_{2,4}$=1.2 Hz

The difference in chemical shift between H_a and H_b was 0.26 ppm indicating a substantially different electronic environment. This difference in environment could only arise from the two β-acetoxy groups being in different orientations: α and β. Although models could not distinguish which proton was being deshielded to a greater extent, this difference in shift did help to confirm the α,β arrangement of the β-acetoxys. The ^1H NMR of the mixture of conduritol diastereomers **129** showed a similar pattern of shifts (H_a-H_b ppm), the shift of H-7 for one diastereomer at 0.44 ppm, for another at 0.27 ppm and for the third at 0.09 ppm which could arise from the following structures:

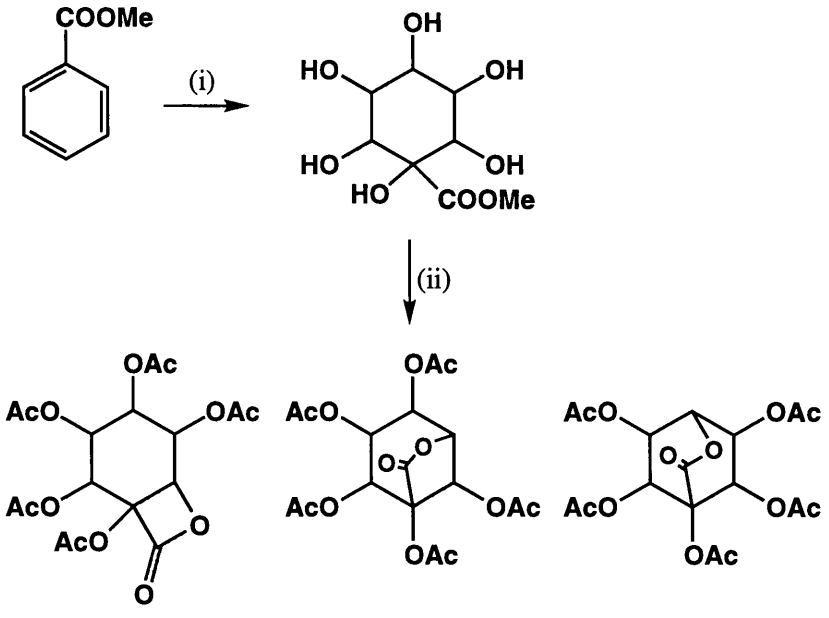


Assignment of any one of these isomers based solely on its' H-7 protons is not however possible and further work is clearly required to enhance the yield and direct the hydroxylation pattern in a benzylic substrate.

2.5.4 Heterosubstituted aromatics and others

-Methyl benzoate

The photoosmylation of methyl benzoate under the usual reaction conditions proceeded to give, after base catalysed acetylation, a mixture from which two main compounds could be isolated, **130** and **131** in 1.1 and 1.2% yield respectively. Both compounds showed five signals in the 4.5 to 6.5 ppm region of the ^{1}H NMR and no olefinic resonances in the ^{13}C NMR, thus indicating that both were inositols. The presence of five acetoxy methyl singlets in the ^{1}H NMR conflicted with the ^{13}C NMR which showed six ester carbonyl signals. Furthermore, the IR spectrum revealed two distinct carbonyl stretches in both compounds; the expected strong acetoxy ester resonance at 1759 cm^{-1} and 1760 cm^{-1} but also a weaker bands at the unusually high values of 1820 cm^{-1} and 1801 cm^{-1}.

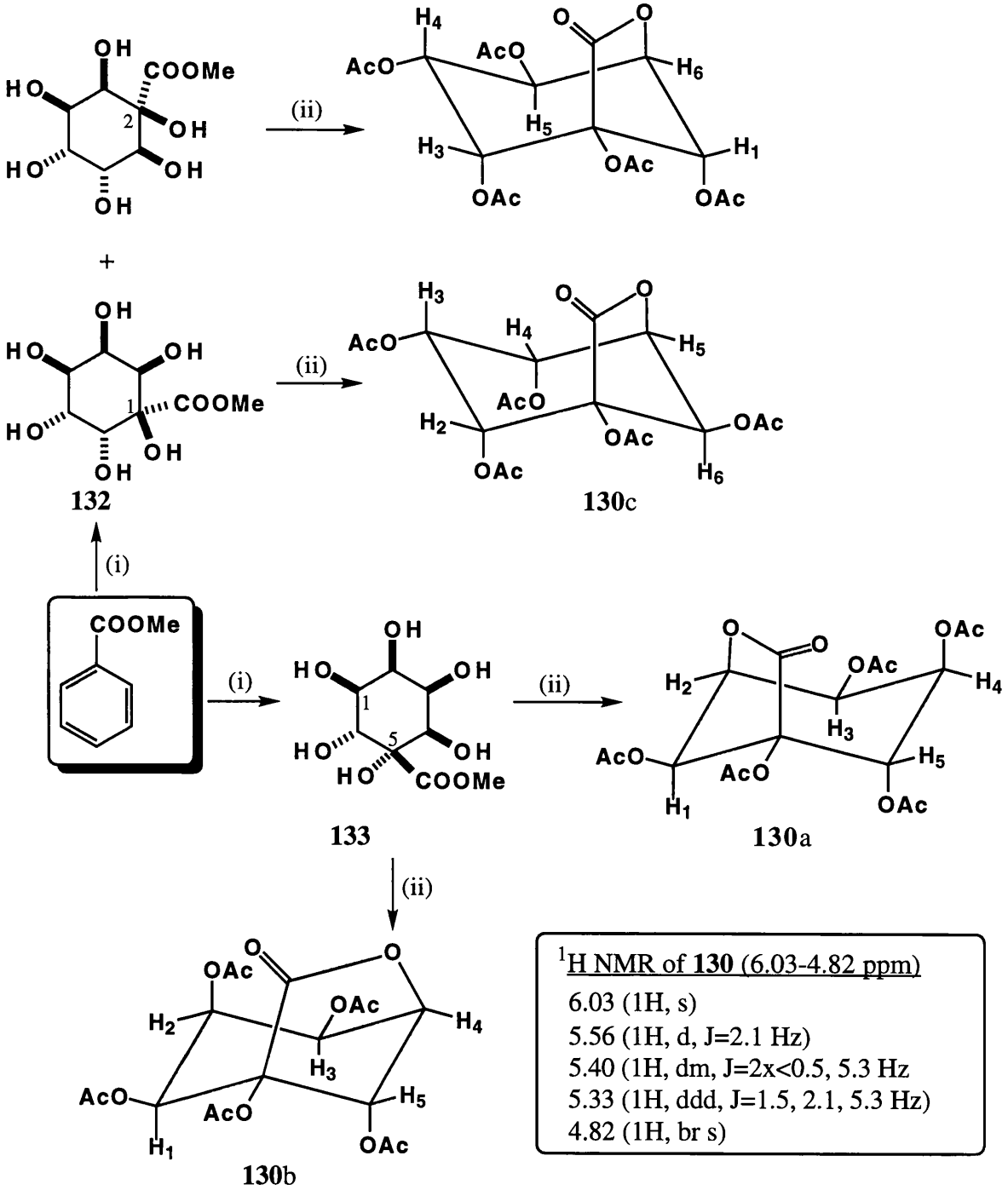


β-lactone γ-lactone δ-lactone

Reagents: (i) Photoosmylation; (ii) Base catalysed acetylation.

Scheme 2.53

Inspection of this spectral evidence led us to assign, very tentatively, both compounds as bicyclic systems containing an inositol ring and a lactone. This idea was further supported by mass spectroscopy **scheme 2.53**.

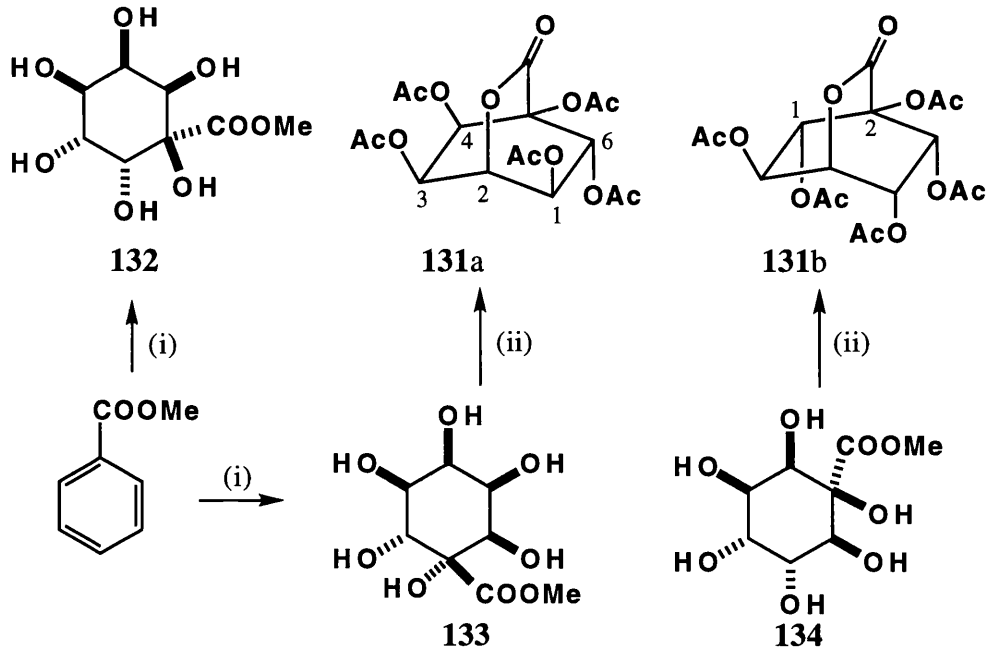


^{1}H NMR of **130** (6.03-4.82 ppm)
6.03 (1H, s)
5.56 (1H, d, J=2.1 Hz)
5.40 (1H, dm, J=2x<0.5, 5.3 Hz
5.33 (1H, ddd, J=1.5, 2.1, 5.3 Hz)
4.82 (1H, br s)

(i) OsO_4 (cat), UV, $Ba(ClO_3)_2$ [0.22 M]: (ii) Ac_2O, Et_3N, DMAP

Scheme 2.54

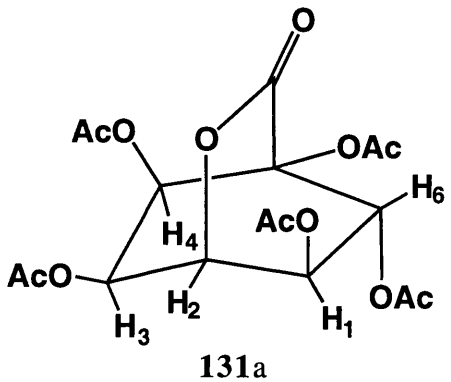
Of the three lactones theoretically available (β, γ, δ), the β-lactone, although fulfilling the IR criteria, was discarded as a possibility due the known thermal instability of such products. In one case, **130**, the data collected points strongly to a γ-lactone of structure (**130**a-c), **scheme 2.54**. Its ^{1}H NMR gave one of the inositol ring protons as a double triplet (on ^{1}H HOMO decoupling it was found to be a ddd J=1.5, 2.1 and 5.3 Hz). This splitting pattern is possible through two ^3J couplings split by a ^4J coupling ('W' coupling). In a cyclohexane ring such a splitting pattern is encountered with an array of protons in an equatorial, axial, equatorial, axial disposition. The γ-lactones (**130**a-c), a product from the intramolecular lactonisation of the 5-*C*-hydroxymethyl-*allo*-inositol (**133**) and of the 1-*C*-hydroxymethyl-*allo*-inositol (**132**) gives rise to this disposition. Only the stretching frequency of the lactone itself (1819 cm^{-1}) is not consistent with this structure. The γ-lactone stretch of bridged cyclohexanes have a reported[142] stretching frequency at around 1790 cm^{-1}. However, the extra strain induced by the five acetoxy groups of the inositol moiety might be responsible for the higher value observed for the recorded lactone stretch in **130**a-c.



(i) OsO_4 (cat), UV, $Ba(ClO_3)_2$ [0.22 M]: (ii) Ac_2O, Et_3N, DMAP

Scheme 2.55

The lower stretching frequency of the other lactone **131** and its remarkable ^1H NMR spectrum lead us to tentatively assign it as a δ-lactone, **scheme 2.53**. Two such lactones **131**a-b are possible candidates from the three *allo*-inositol precursors **132-134**, **scheme 2.55**. Adopting a twisted-boat conformation, **131**a displays three protons with dihedral angles approaching 90° (H_6-H_1, H_1-H_2, H_2-H_3). The ^1H NMR of **131** shows three proton resonances: a singlet, a broad singlet and a double doublet (J=0.8 and 1.5 Hz). Such small coupling constants (0-1.5 Hz) are typical of dihedral angles approaching 90°. The dihedral angle (H_3-H_4) approaches 0° for which the ^1H NMR of **131** shows a coupling of 7.9 Hz. Also, the chemical shift of the protons in the spectrum of **131** is consistent with the structure of **131**a, **table 2.25**. Again only the stretching frequency of the lactone itself (1801 cm^{-1}) is not entirely consistent with this structure. (δ-lactone bridged cyclohexane: 1770 cm^{-1}).[142]



131a

^1H NMR of **131** (4.8-6.15 ppm)	Assignment*
6.15 ppm (s)	H_6
5.82 ppm (d) J=7.9 Hz	H_4
5.31 ppm (dd) J=0.8, 8.1 Hz	H_3
4.95 ppm (dd) J=0.8, 1.5 Hz	H_2
4.80 ppm (br s)	H_1

* Tentative assignment of protons H_1-H_6 of **131**a to ^1H NMR of **131**

Table 2.25 Assignment of δ-lactone 131a

Although we have reasonable evidence to claim the formation of these lactones under the photoosmylation conditions, the given structures (**130**a-c, **131**a) must be considered with considerable caution and further comparative NMR spectra are necessary.

-1-Phenyldodecane

Photoosmylation of this long chain substrate proceeded with all the usual signs of a successful reaction. Upon irradiation the yellow CT band gave way to a black solution normally indicative of an osmate ester. After 43 hrs of irradiation the pH of the aqueous phase had dropped to 3.5 indicative that the chlorate had been reduced. Unfortunately, acetylation of the aqueous phase gave rise to the recovery of starting material only. This lack of reactivity was surprising considering that we had found success with ^{t}butylbenzene, which represents a much larger steric volume near the aromatic system. The possibility that the dodecane chain itself inhibited the formation of a CT complex is doubtful but is, at present, our only explanation for the lack of desired reactivity.

- *O*-phenyl. Diethylphenylphosphate and anisole.

Diethyphenylphosphate was synthesised from phenol and diethylchlorophospate following literature procedure.[143] The desire to photoosmylate such a compound was its potential to deliver an advanced synthetic intermediate towards the total synthesis of the important inositol phosphates and analogues. A yellow colouration developed on the addition of osmium tetroxide to the aromatic but, after 40 hrs of irradiation, the colour of the organic phase was unchanged. The pH of the aqueous phase had fallen to 1 and it was assumed that under these acidic conditions hydrolysis had occurred. The usual base catalysed acetylation gave no protected cyclitol products.

Likewise, the attempted photoosmylation of anisole failed (amber CT complex gave a measured λ_{max} of 396 nm). The reason for the failure for the photoosmylation of both diethyphenylphosphate and anisole is possibly a result of their electron rich aromatic character due to the oxygen atom α- to the ring. It can be expected that the lone pairs of electrons of the oxygen are equally good donors to the LUMO of osmium tetroxide as are

the electrons in the aromatic sextet.[85] Although n-π^* transitions are normally forbidden the presence of osmium would allow such a transition by the heavy atom effect. An alternative explanation can also be advanced; namely, that the low energy pathway for the radical pair formed by the electron transfer is simple relaxation to the CT complex, as opposed to osmate ester formation.

-*S* and *N*-phenyl. Thiophenol and Acetanilide

The photoosmylations of both thiophenol and acetanilide in dichloromethane failed. The orange-brown CT band between thiophenol and osmium tetroxide darkened rapidly only seconds after its formation to give a black opaque organic layer. Irradiation of this mixture did not lead to the isolation of any cyclitol product. Tlc examination of the organic phase showed mainly starting material and traces of slightly more polar spots which were not further investigated. Acetanilide gave an orange-yellow CT band on the addition of osmium tetroxide. After irradiation, extraction of the reaction mixture with dichloromethane gave recovered acetanilide in 89% yield, and acetylation of the dried aqueous phase gave no evidence for any cyclitol product.

The failure of the photoosmylation of thiophenol was probably due to the harsh oxidative reaction medium causing the oxidation of sulphur to sulphoxide and sulphone, which, due to the overall electron withdrawing effect of the oxygen atoms would inhibit the desired reactivity. For acetanilide the reason for failure could be the same as that for the phenolic series. The lone pair of electrons on the nitrogen, even as an amide, could be a competitive donor towards osmium tetroxide.

-Trimethylsilylbenzene

The ability of the *tert*-butyl group to control the photoosmylation reaction into yielding *tert*-butyl conduritol E tetraacetate **115** as the sole product was a result which we wished to exploit in order to develop a methodology for the synthesis of conduritol E substrates. The basic requirement called for a bulky, easily removable substituent on the benzene ring, which led us to consider commercially available trimethylsilylbenzene. Unfortunately under the usual photoosmylation conditions and after acetylation no cyclitol product was detected by ^{1}H NMR of the crude reaction mixture.

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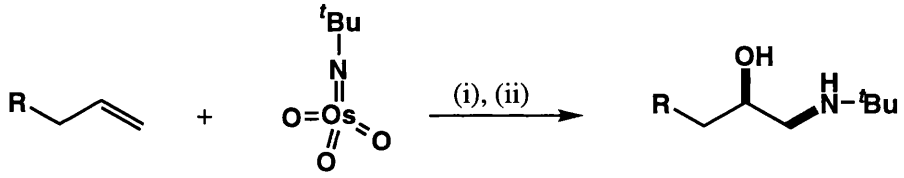
Thus this initial probing of the scope of the photoosmylation reaction has revealed a disappointing intolerance towards a large number of aromatics with a heteroatom attached directly to the ring. Alkylbenzenes photoosmylate but do suffer from benzylic oxidation under the more extreme bromate/high temperature conditions. The halobenzenes are photoosmylated, albeit in very low yield, to conduritol products only.

2.6 Attempted synthesis of amino alcohols

2.6.1 Stoichiometric reactions *via* ^{t}Bu-N=OsO$_3$

In 1975 Sharpless and co-workers[144] showed that, in coordinating solvents, trioxo(*tert*-butylimido)osmium(VIII) **135** reacted with a variety of olefins to afford amino alcohols in fair to excellent yields (20-95%), **scheme 2.56**.



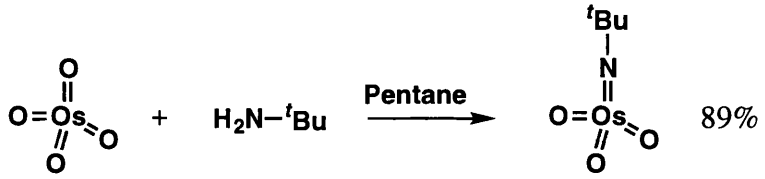
135

Reagents: (i) py; (ii) LAH

Scheme 2.56

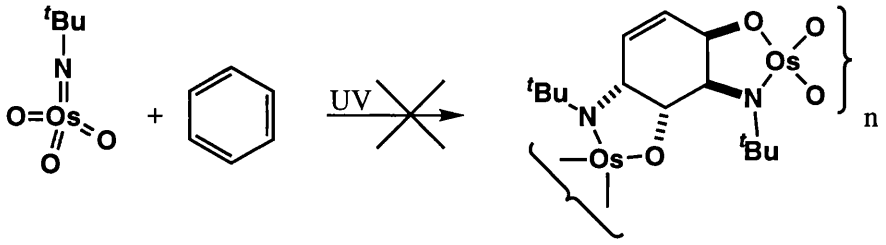
In non-coordinating solvents yields were generally lower and gave a mixture of diols and amino alcohols. The reasons for the preferential formation of a C-O and a C-N bond from an osmium reagent containing three times as many oxygen atoms as nitrogen atoms was not explained but suggested that the R-N=Os=O moiety was more electrophilic than the isoelectronic O=Os=O unit. This was of considerable interest to us as we saw the potential to develop an oxyamination reaction of aromatics using this osmium reagent. We reasoned that the apparent increased electrophilicity of **135** over osmium tetroxide would give higher CT band wavelengths for the same aromatic substrate than with osmium tetroxide. This would in turn, allow electron transfer in systems which were unreactive under the usual photoosmylation conditions.

Although **135** was reported to be a light sensitive compound we felt that the importance of a successful reaction, even in low yield, warranted an attempt. **135** was synthesised according to a literature procedure[145] in 89%, **scheme 2.57**.



Scheme 2.57 **135**

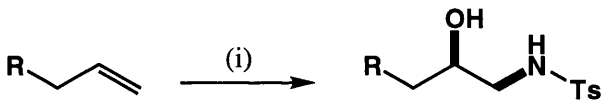
The orange crystals obtained were shown to have two main absorptions in the UV-VIS region: a shoulder at 370 nm and continuous absorption from 360 nm. The ability of **135** to form a CT band with an aromatic donor, a prerequisite for CT oxyamination, was demonstrated with 9,10-dimethylanthracene. On mixing **135** with 9,10-dimethylanthracene in dichloromethane solution a new absorption band was observed, not found in the UV-VIS spectrum of either compound on its own. This new absorption band, λ_{max} 420 nm, was considerably lower than the osmium tetroxide CT complex of 9,10-dimethylanthracene (λ_{max} 578 nm) indicating that **135** in fact had a lower EA than osmium tetroxide. Irradiation of a benzene solution of **135** lead to an unidentifiable black precipitate within seconds, **scheme 2.58**. After 10 hrs of irradiation, standard quench and work-up, no identifiable products were isolated as judged by ^{1}H NMR.



Scheme 2.58

2.6.2 Catalytic reactions using Chloramine-B.

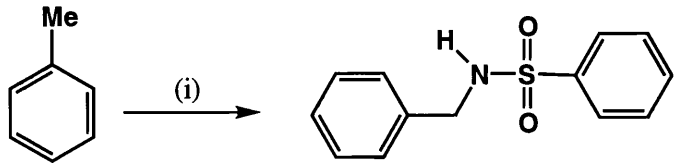
The photolytic instability of **135** with apparent decomposition obviously precluded any CT oxyamination from taking place. We reasoned that the preparation of the oxyamination reagent *in situ* would have a better prospect of delivering the desired reaction by limiting the exposure time of the nascent reagent to the UV source. Such a protocol had already been designed by Sharpless[146,147] for oxyamination of olefins employing catalytic osmium tetroxide and stoichiometric chloramine-T as the reoxidant and the source of nitrogen, **scheme 2.59**.



Reagents: (i) OsO_4 (cat), Chloramine-T, ^tBuOH, 60° C. Yields 34-96%.

Scheme 2.59

In an attempt to avoid the oxidation of the aromatic ring of the stoichiometric oxidant and increase its water solubility our test reaction called for the use of chloramine-B. The choice of toluene as our substrate was based on its lower IP than benzene and the success which we had enjoyed with it under the usual photoosmylation conditions. In the event, however, photolysis of an aqueous solution of chloramine-B with toluene and a catalytic amount of osmium tetroxide afforded benzylsulphonamide **136** in 2.3% yield, **scheme 2.60**, and no aminocyclitols were detected.



136

Reagents: (i) OsO4 (cat), Chloramine-B, H_2O; 2.3%

Scheme 2.60

***

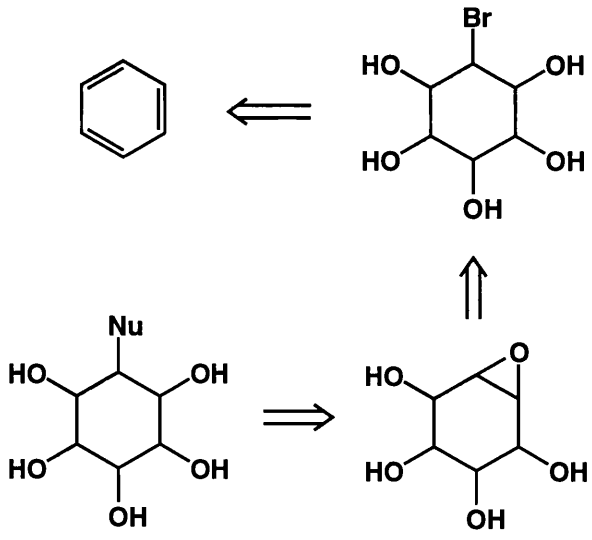
Our initial studies on the possibility of a CT oxyamination reaction of aromatics suggested that, although a CT complex could be detected between an aromatic substrate and osmium reagents of type **135**, irradiation did not lead to the desired reactivity. The photochemical instability of the reagent **135** led us to investigate a catalytic alternative in which the oxyamination reagent was produced *in situ*. Under these conditions the desired reaction was again not forthcoming, with only small amounts of product resulting from benzylic oxidation of the substrate (toluene) taking place. It was later discovered that chloramines too were liable to photochemical decomposition,[148] thus ending our attempts to oxyaminate aromatic systems under such conditions.

2.7 Synthesis of inositol *O*-methyl ethers.

This section details the use of the photoosmylation reaction as a strategy for the preparation of advanced synthetic intermediates and uses the deoxy-bromo-cyclitols **94** and **95** as precursors for a one-pot synthesis of the biologically important inositol methyl ethers.

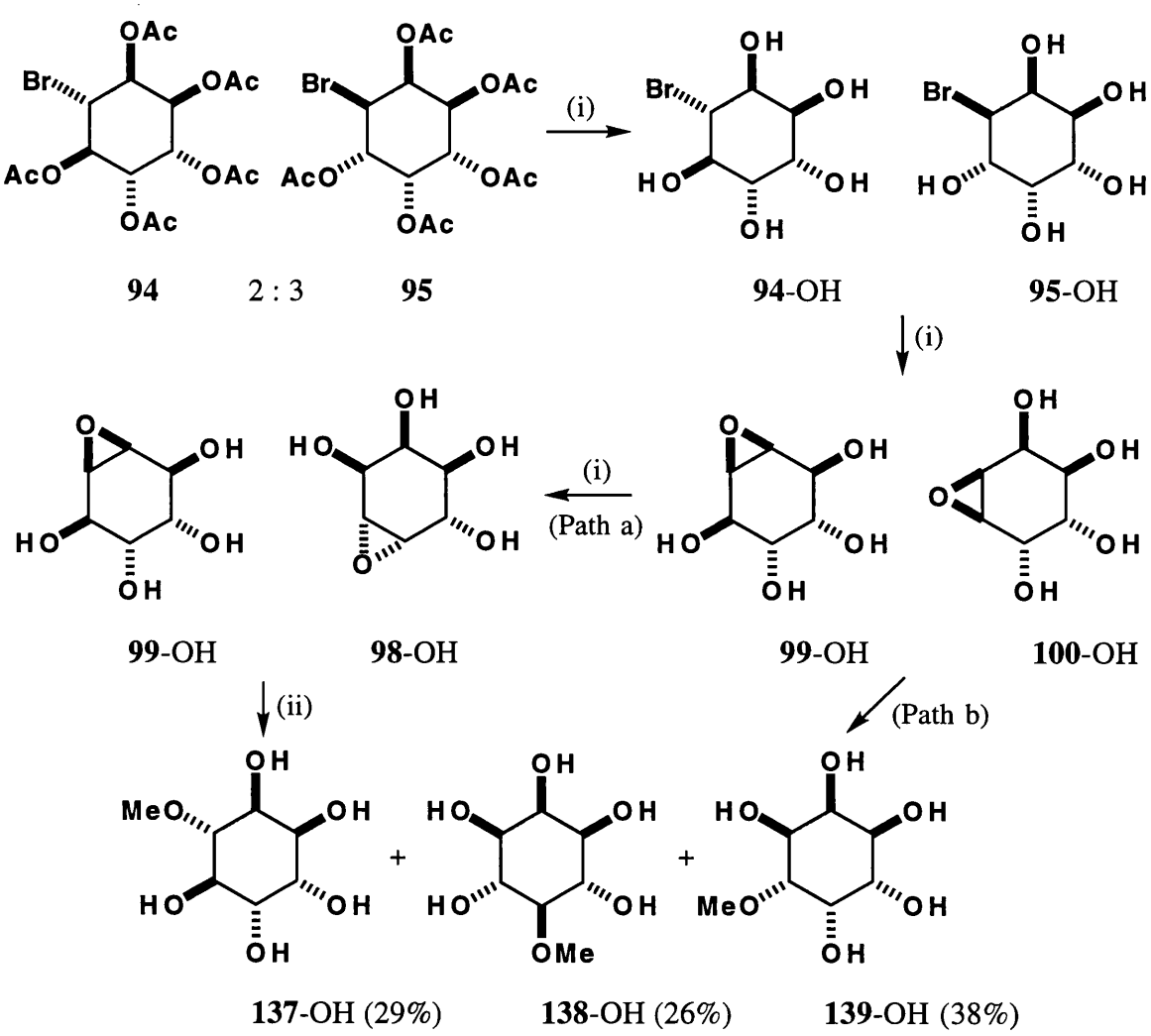
2.7.1 Pinitol, Sequoyitol and 1-*O*-methyl-*neo*-inositol.

The use of sodium bromate to drive the photoosmylation reaction of benzene gave rise to the deoxy-bromo-cyclitols **94** and **95** in up to 19% yield, representing aprox. 0.5 g of protected cyclitol for 0.025 g of osmium tetroxide. The difficulty in deprotecting these acetates using conventional basic conditions leading to epoxidation (sodium methoxide, potassium carbonate in methanol) forced us to develop an acid catalysed deprotection protocol which concomitantly separated the two diastereomers (*vide supra*). However, this 'undesirable' epoxidation reaction could also be seen as a bonus, inasmuch as it provides a route to monosubstituted inositols as indicated in the following retrosynthetic analysis, **scheme 2.61**.



Scheme 2.61

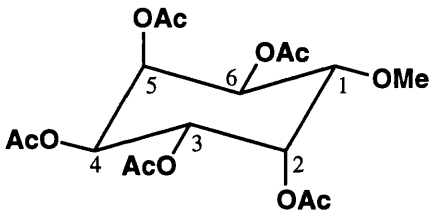
The use of conduritol epoxides as intermediates for a variety of inositol syntheses has been shown to be a popular route (see chapter 1). The nucleophile, Nu, can be oxygen or nitrogen leading to inosamines with the latter. We envisaged that with methoxide anion as the nucleophile a one-pot synthesis of inositol methyl ethers would be possible from the protected **94** and **95**. An excess of methoxide would serve as a threefold purpose reagent: firstly to deprotect the acetates, then to provide the base for epoxide ring formation and finally as a nucleophile to open the epoxide.



Reagent: (i) NaOMe, r.t., 2 h; (ii) Reflux, 4.5 h; 93%

Scheme 2.62

Such a strategy did indeed reward us with an excellent yield of the methyl ether inositols: pinitol **137**-OH 29%, sequoyitol **138**-OH 26% and 1-*O*-methyl-*neo*-inositol **139**-OH in 38%, giving an overall yield of 93% from a 2:3 mixture of the starting materials **94**:**95** as indicated in **scheme 2.62**. These polyols were separated by careful column chromatography but analytical samples of sequoyitol and 1-*O*-methyl-*neo*-inositol could only be obtained once converted to their acetates. Pinitol[22] and sequoyitol[149] were elucidated based on their ^{1}H NMR spectra (see appendix B) which corresponded with literature values. The relative stereochemistry of the third inositol methyl ether was assigned as 1-*O*-methyl-*neo*-inositol based on the ^{1}H NMR of its acetate **139**.



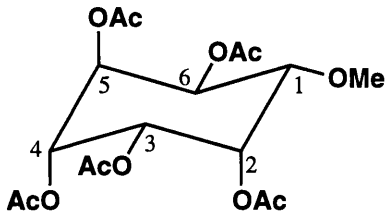
139

^{1}H NMR distinctive spectral features

4 protons with 10-11 Hz coupling

H-2, t, $J_{1,2=2,3}$=3.0 Hz

H-5, t, $J_{4,5=5,6}$=3.0 Hz



1-*O*-methyl-*allo*-inositol pentaacetate **140**

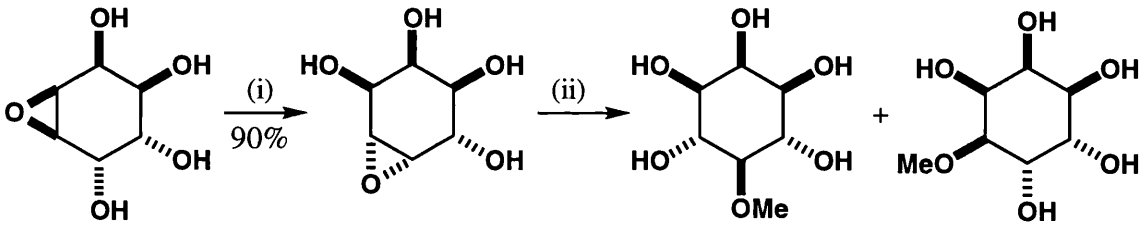
^{1}H NMR expected spectral features

2 protons with 10-11 Hz coupling

Based on path (a) of **scheme 2.62** the expected methyl ethers would have been pinitol from the methoxide ring opening of **99**-OH, sequoyitol from the opening of **98**-OH at C-2 and 1-*O*-methyl-*allo*-inositol **140**-OH from the opening of **98**-OH at C-1.[136] The ^{1}H NMR of the third methyl ether did not correspond to an *allo* configuration but in fact revealed a *neo* stereochemistry with two distinctive triplets at either end of the molecule

and four trans diaxial protons giving rise to four double doublets displaying a small (3 Hz) and large (10-11 Hz) coupling. The detection of this *neo* inositol revealed that the Payne rearrangement[136] of **100**-OH had not been complete under the reaction conditions and that methoxide anion had opened **100**-OH at C-1 to give **139**-OH (route (b)) and pinitol **137**-OH *via* attack at C-2.[123]

The apparent selectivity in the methoxide opening of the non *meso* epoxide **98**-OH was in sharp contrast with the findings of Angyal, **scheme 2.60**, who reported a 1:1.2 mixture of sequoyitol and 1-*O*-methyl-*allo*-inositol from the reaction of methoxide on **98**-OH (starting material **100**-OH, **98**-OH formed *in situ*).[136]



1 : 1.2

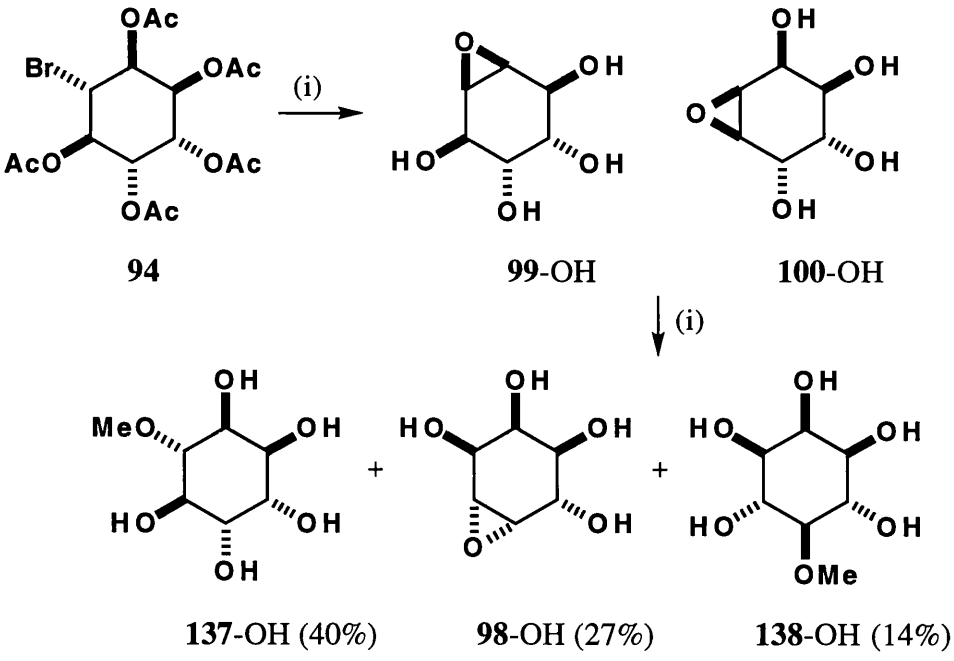
100-OH **98**-OH **138**-OH **140**

Reagents: (i) NaOMe, r.t., 24 h; (ii) Reflux, 5 h

Scheme 2.63

We sought to take advantage of the apparent slowness of the Payne rearrangement under our reaction conditions in order to increase the ratio of pinitol versus the other methyl ethers. The reaction of the single diastereomer **94** with a refluxing solution of sodium methoxide was performed, **scheme 2.64**. It was hoped that the initially formed **98**-OH would, under reflux conditions, react faster with methoxide as a nucleophile to give **139**-OH and pinitol **137**-OH rather than undergo Payne rearrangement. ^{1}H NMR analysis of

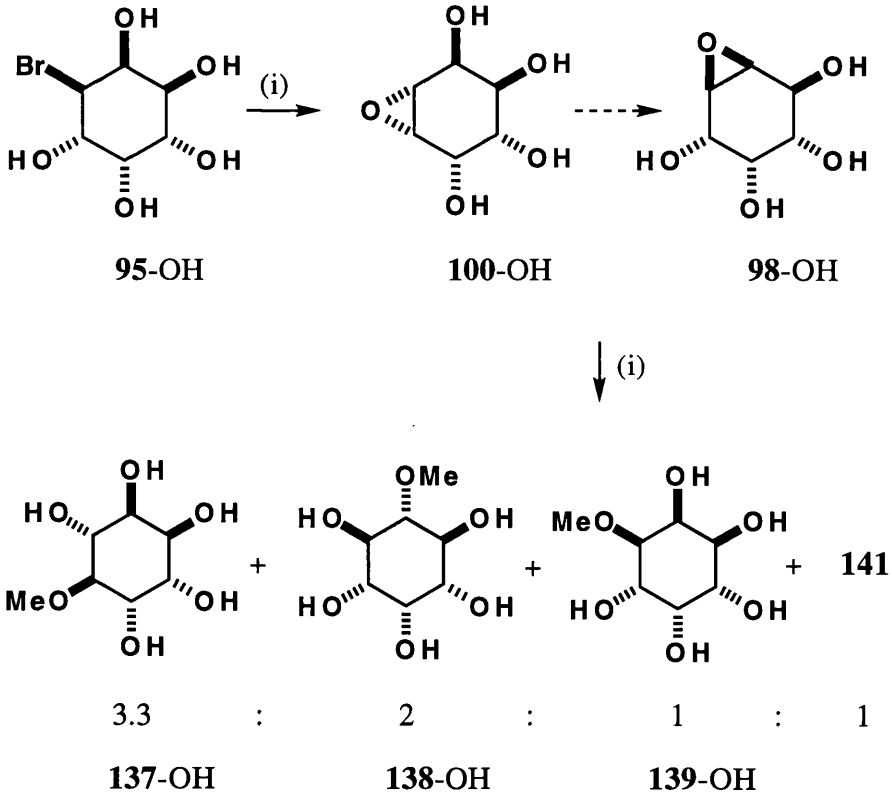
the crude reaction mixture unfortunately revealed the presence of pinitol, epoxide **100**-OH and sequoyitol in 2.2:1.6:1 ratio along with a trace of 1-*O*-methyl-*neo*-inositol **139**-OH and a new methyl ether **141**-OH. Column chromatography of the reaction mixture gave fractions of pure epoxide **98** (27%) and pinitol (40%), together with enriched sequoyitol (17% of 80% purity, remainder **139**-OH and **141**-OH) and an inseparable mixture of 1-*O*-methyl-*neo*-inositol **139**-OH and the new methyl ether **141**-OH (4%, **139**-OH:**141**-OH, aprox. 2:3). The elucidation of **141**-OH was not possible due to the overlap of peaks with **139** and the severe thermodynamic broadening of the peaks in the ^{1}H NMR making the measurements of coupling constants and hence stereochemical assignments impossible. **141**-OH was very tentatively assigned as the expected 1-*O*-methyl-*allo*-inositol **140**-OH solely based on the fact that it displayed thermodynamic broadening in the same manner as its demethylated parent inositol did!



Reagents: (i) NaOMe, Reflux, 2 h.

Scheme 2.64

The recovery of the epoxide **98**-OH showed that the reaction had not gone to completion and, from the negligible yield of **139**-OH, that the rate of the Payne rearrangement had actually increased under these reaction conditions. Again the large yield of sequoyitol indicated, as previously seen, a highly selective opening of epoxide **98**-OH. We next intended to use this result to develop a specific synthesis of sequoyitol from **95**-OH. Treatment of **95**-OH with a refluxing solution of sodium methoxide gave, after 18 h, a 3.3:2:1:1 mixture (^{1}H NMR) of pinitol, sequoyitol, 1-*O*-methyl-*neo*-inositol and the unknown methyl ether **141**-OH in 90% crude yield, **scheme 2.65**.



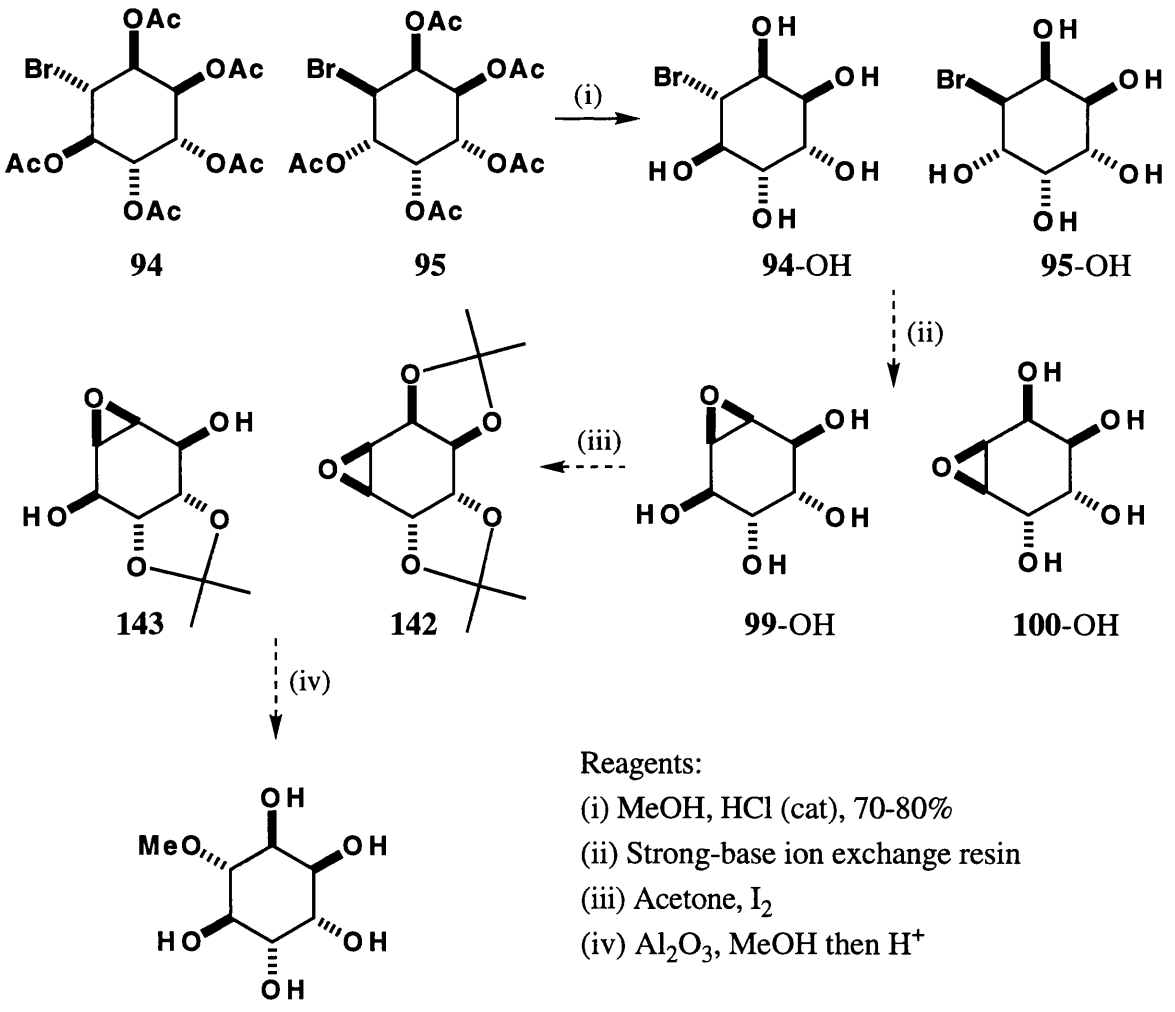
Reagents: (i) NaOMe, Reflux, 18 h.

Scheme 2.65

The low selectivity displayed by this reaction came as a surprise as it appeared that the Payne rearrangement had been slow in this case accounting for the large yield of pinitol and **139**. Although we were able to demonstrate the use of the photoosmylation products **94** and **95** for the synthesis of inositol methyl ethers the lack of selectivity displayed by these capricious reactions led us to design a selective pinitol synthesis.

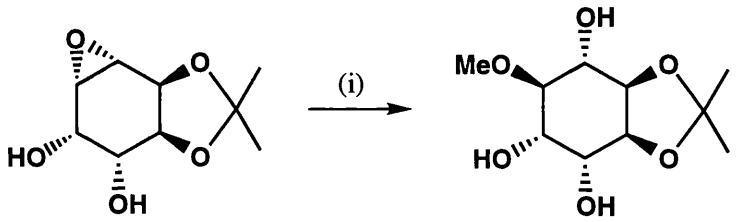
2.7.2 Studies towards a convergent synthesis of Pinitol.

As we have seen in the previous section, the treatment of **94** and **95** with methoxide anion led to the synthesis of inositol methyl ethers in high yield. Unfortunately these one pot reactions displayed very little product selectivity even when single diastereomers were used as starting materials. The following route, **scheme 2.66**, outlines a stereoconvergent synthesis of pinitol from the diastereomeric mixture of **95** and **94**.



Scheme 2.66

As we have already shown, the acid catalysed deacetylation of **94** and **95** gave **94**-OH and **95**-OH in good yield. The epoxidation of these was then considered to be possible using an ion exchange resin which has been shown to promote epoxidation but not the Payne rearrangement.[150] Protection of the epoxides **100**-OH and **99**-OH as their isopropylidene acetals with acetone and iodine would then furnish the bis and mono-protected epoxides **142** and **143**. Reaction of these with alumina in methanol would then furnish pinitol as a sole product. The precedent for **142** to only yield pinitol under these reaction conditions comes from Hudlicky's synthesis[40,41] of pinitol where, in his penultimate step, he opened the epoxide **144** to the single diastereomer **145**, **scheme 2.67**.



144 **145**

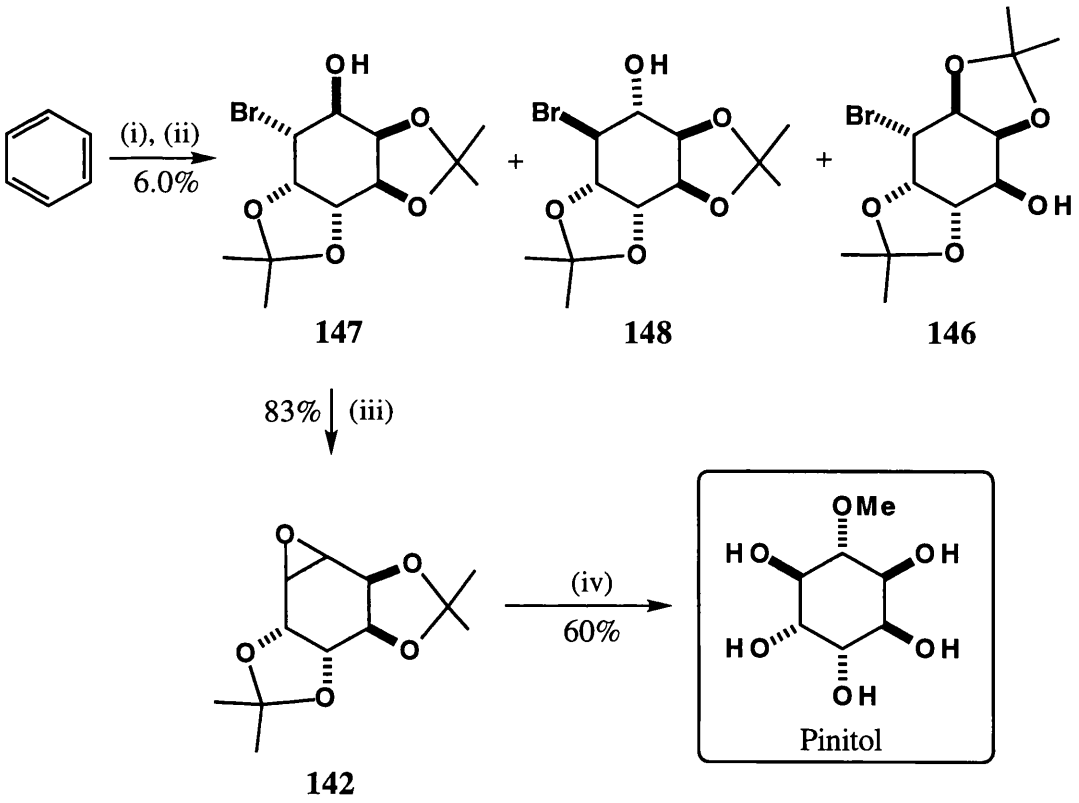
Reagent: (i) Al_2O_3, MeOH, 60%

Scheme 2.67

We reasoned that under the methanolysis conditions the meso-epoxide **143** could only give pinitol upon subsequent acid hydrolysis. The fate of the epoxide **142** under the same reaction conditions was tested and to our delight gave pinitol as the only methyl ether inositol (**scheme 2.68**).

142 was prepared in an unoptimised route shown in **scheme 2.68**. The oxidation products from a bromate driven photoosmylation of benzene were isolated as their isopropylidenes by treatment of the crude reaction mixture with acetone and iodine. Differentiation between the three bromo alcohols obtained, **146** (1.4%), **147** (3.0%) and

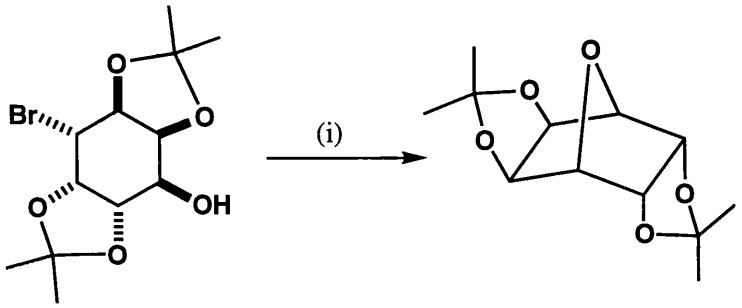
148 (1.6%) (overall yield 6%), proved difficult. However, once **147** and **146** had been converted to their anhydro-inositols, **142** and **149** respectively, a distinction between all three diastereomers could be made, (**schemes 2.68** and **2.69**). The required anhydro-inositol, **142**, was then treated to Hudlicky's methanolysis conditions and without further purification acidified to yield pinitol in 60% isolated yield.



Reagents: (i) OsO_4 (cat), UV, $NaBrO_3$ [0.24 M], 30° C; (ii) Acetone, I_2;
(iii) K_2CO_3, MeOH; (iv) Al_2O_3, MeOH, then H_2O/THF/HCl (cat).

Scheme 2.68

The symmetry of the 1,4 anhydro-inositol **149** is clearly visible by ^1H NMR and can only be formed from a 2,3;5,6-bis acetonide **146** which itself can only form from 1-deoxy-bromo-*neo*-inositol **139**-OH.



146 **149**

Reagent: (i) K_2CO_3, MeOH, 83%

Scheme 2.69

Having shown that the key step of our route to pinitol was indeed selective, this synthetic path formally represents a stereoconvergent synthesis, and comprising of only five steps would be amongst the shortest. In an unoptimised route (**scheme 2.68**) pinitol is available in three steps. Further optimisation and streamlining of this route should however be possible.

***

2.8 Conclusions and Perspectives.

2.8.1 Conclusions.

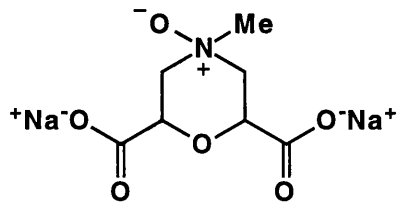
This work has demonstrated that the charge transfer induced osmylation of aromatic compounds can be made catalytic in osmium. This represents a novel reaction akin to the catalytic dihydroxylation of olefins and widens the scope of dihydroxylation chemistry.

This new methodology can be used for the preparation of *allo*-inositol from benzene in a one step procedure with good catalytic efficiency. Through changes in the reaction conditions, notably temperature, a 1:1 mixture of conduritol E and *allo*-inositol can also be obtained. Through changes in reagent ratios deoxy-chloro-inositols are obtained, as are tetrahydroxybenzenes in certain circumstances. Such conditions allowed optimal catalytic efficiency with turnover reaching 177. The use of bromate as a stoichiometric oxidant delivered two deoxy-bromo-inositols as major products in up to 19% yield. These diastereomers are easy to separate using either standard recrystallisation or deprotection methods. Their use as starting materials for the synthesis of natural and unnatural inositol methyl-ether has been shown.

2.8.2 Perspectives.

-Increased catalytic turnover

The current catalytic efficiency of the photoosmylation reaction, under specific conditions, has reached 177. Whilst this is acceptable and can be expressed as a 0.5 mol% catalyst affording 88% yield for a reaction involving only one catalytic sequence, the photoosmylation reaction requires three catalytic sequences to deliver one molecule of *allo*-inositol. Furthermore, these specific conditions call for the catalyst to be present in very low concentrations (0.0006 mol%) which results in low yields (2-3%). Although yields are not important when benzene is the starting material, and indeed no attempt has yet been made to recover the unreacted benzene, or other substrate, from a reaction, the use of this methodology for hydroxylation of tailor made aromatics would be hampered if yields could not pass the 40% mark. Increased efficiency of the 1.3 mol% catalyst reaction is hence required which entails better conditions for oxidative hydrolysis. Research into new stoichiometric oxidants is required as well as co-solvents to facilitate hydrolysis. The success of NMO in catalytic dihydroxylations of olefins might possibly suggest that the development of a water soluble equivalent **150** whose reduced form would not interfere with the CT complex is a worthwhile objective.

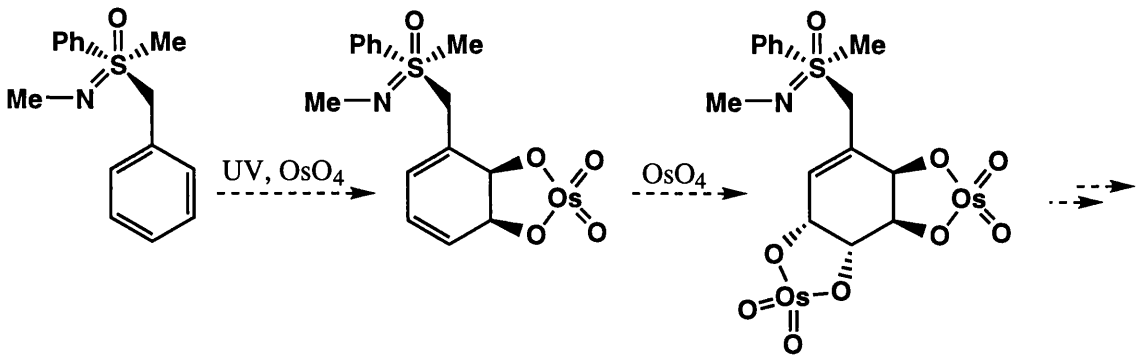


150

-Asymmetric photoosmylation, induced chirality and chiral catalysis

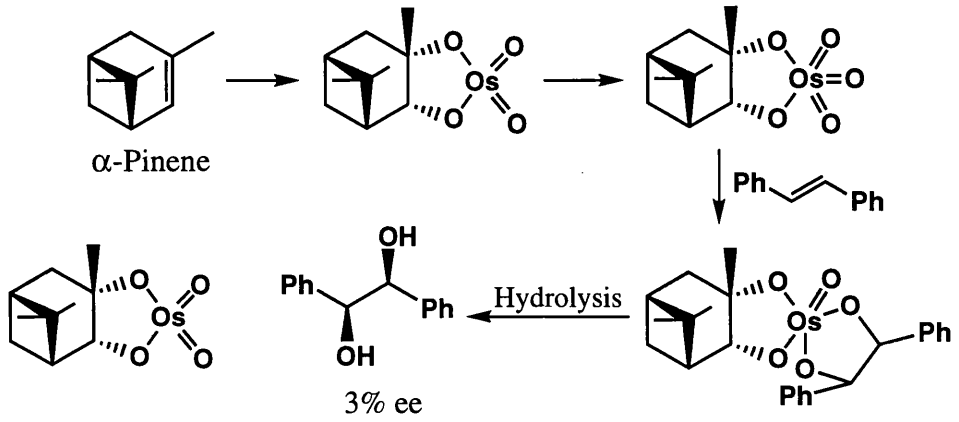
In terms of our original aims, the challenging question of an enantioselective photoosmylation remains to be addressed. The use of nitrogenous chiral ligands prevents the CT interaction for the very same reason that they afford ligand accelerated catalysis in AD reactions *viz.*, the formation of a nitrogen-osmium complex. Chiral catalysis will probably not therefore be possible unless such a coordination is less strong than the CT interaction.

Chiral induction might however be possible in an analogous fashion to the sulphoxamine-directed osmylation of cyclohexenes developed by Johnson,[151] **scheme 2.70**. Although the induction itself is the result of osmium coordinating to the nitrogen the reversibility of this coordination might allow CT and hence osmylation to occur.



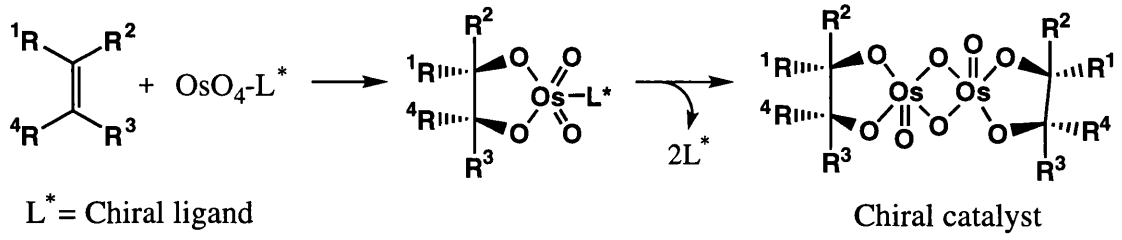
Scheme 2.70

Chiral catalysis would preferably come from a chiral moiety attached to osmium *via* oxygen. We should be able to put to use our problem of slow oxidative hydrolysis for that very purpose. Matteson has shown[103] that the osmate ester of α-pinene is oxidised to the osmate(VIII) ester before hydrolysis. Such an osmate ester can then participate in a second catalytic cycle[106] type scenario and indeed induce chirality in the dihydroxylation of a second prochiral olefin, **scheme 2.71**.

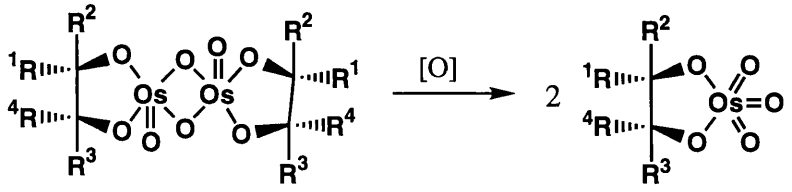


Scheme 2.71

The use of a tetrasubstituted osmate ester as the chiral catalyst in a photoosmylation reaction could then be envisaged. Using standard procedures a chiral osmate ester is available, **scheme 2.72**. Stored as a bis osmate ester **151** the active catalyst **152** would then be generated *in situ* by the action of the stoichiometric oxidant [O], **scheme 2.73**. By a judicious choice of substituents R^1-R^4 and R_n the approach of a substituted aromatic would be controlled and a chiral CT complex would result, **Scheme 2.74**.



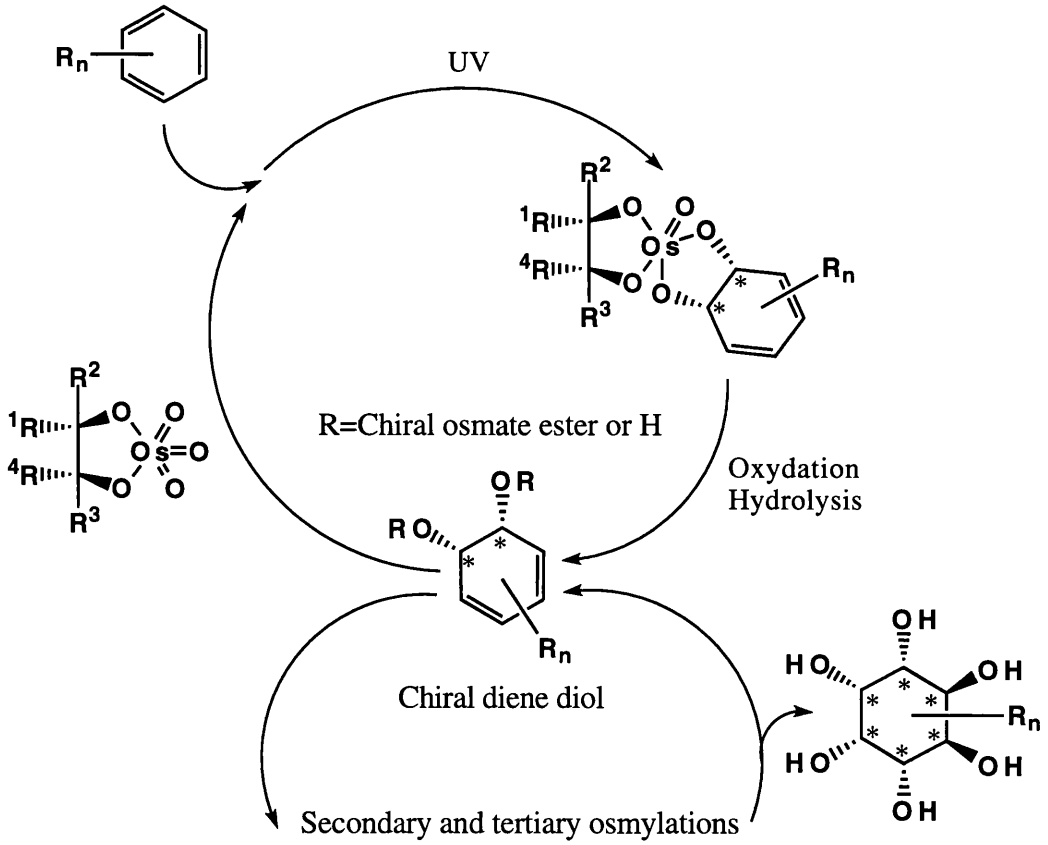
Scheme 2.72



151 **152**

Scheme 2.73

The following CT osmylation would then also be regioselective creating two new chiral centres, **scheme 2.74**. Secondary and tertiary osmylation would then furnish the final four stereocentres either *via* directed osmylation from the steric bulk of the initial osmate ester or *via* chiral osmylation of the diene diol intermediate. This approach would rely on competitive oxidative hydrolysis with the disubstituted and trisubstituted osmate esters hydrolysing in preference to the tetrasubstituted osmate ester **152** containing the chiral moiety which is usually the case. Polymeric build-up as seen in the present system would also be reduced under such a chiral photoosmylation approach.



Scheme 2.74

CHAPTER THREE

3.1 General Procedures.

^1H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz respectively on a Bruker AM 500 instrument, or at 400 MHz and 100 MHz respectively on a Varian VXR 400 instrument at RT unless stated otherwise. Spectra were recorded in the solvent specified, with chemical shifts expressed in parts per million (δ) relative to the internal standard. For $CDCl_3$ the residual protic solvent was used as the internal standard for ^1H spectra and $CDCl_3$ for ^{13}C spectra (7.26 and 77.0 ppm respectively). For D_2O, TSP-d_4 was used as the internal standard (0.0 ppm) and for acetone-d_6 the residual protic solvent for ^1H spectra and $(CD_3)_2CO$ for ^{13}C spectra (2.04 and 29.8 ppm respectively). Coupling constants 'J' are measured in Hertz (Hz) with a digital accuracy of 0.28 Hz. Mass spectra were recorded by EI or CI (ammonia) on a VG Micromass 7070 B Extended Geometry or AutoSpecQ, and by FAB on a VG ZAB SE Double Focussing machine. IR spectra were recorded on either a Perkin Elmer 943G spectrometer or a Perkin Elmer 1600 FTIR. UV-VIS spectra were recorded on a Perkin Elmer 554 UV-VIS spectrophotometer. Melting points were recorded on either a Reichert hot-stage apparatus or an Electrothermal and are uncorrected.

Petrol refers to petroleum ether (b.pt. 40-60 °C) and was distilled prior to use. Ether refers to diethyl ether. Tetrahydrofuran (sodium and benzophenone) and *tert*-butylamine (calcium hydride) were distilled under an atmosphere of nitrogen immediately prior to use. Triethylamine and pyridine (potassium hydroxide) were distilled and stored over 4Å molecular sieves under nitrogen. Osmium tetroxide and all other reagents and solvents were used as purchased without further purification.

Analytical thin layer chromatography (tlc) was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}) and visualised using acidic ammonium molybdate (IV) [concentrated H_2SO_4 (250 mL), ammonium molybdate•$4H_2O$, water (2.25 L)]. Preparative chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh). High pressure liquid chromatography was performed using a semi-

preparative 250 mm x 10 mm Partisil silica gel column on a Varian 5000 machine with an IR detector.

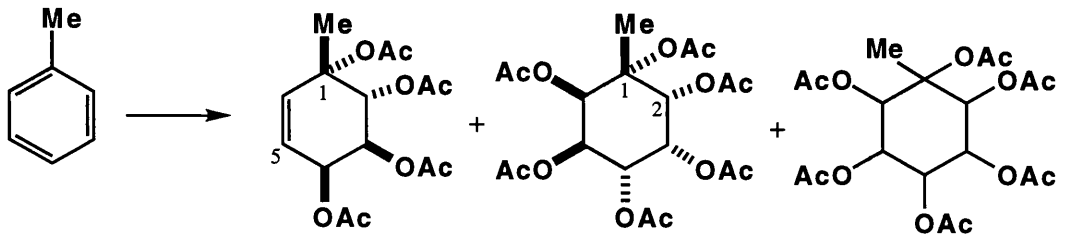
Photolyses were performed at 11 cm (middle of bulb - middle of reaction vessel) using an Osram MB/U 400W medium pressure Hg lamp. 'Fan-cooling' refers to ventilation of the lamp using a desk-fan. 'Peristaltic pump' refers to a Masterflex variable speed and reversible drive unit mounted with a Masterflex L/S pump head. 'Cryocool' refers to a RP-100-CD LabPlant variable temperature coil.

3.2.1 Experimental procedures for section 2.2

1. Compatibility test of oxidants [O] and solvents with the CT complex of anthracene-osmium tetroxide.

To a suspension of anthracene (200 mg) in dichloromethane (5 mL) was added a solution of osmium tetroxide (250 mg) in dichloromethane (2.5 mL). The resulting mauve dichloromethane solution was used as a stock CT complex solution and stored at 4 °C. The compatibility tests for reagents listed in tables 2.2, 2.3, 2.9 and 2.11 were carried out as follows: To a solution of the stock CT complex (0.5 mL) was added the reagent under investigation. Liquids were added neat (0.5 mL), solids (typically 10-15 mg) dissolved in the solvent specified (0.5 mL). The mixture was shaken and left for 2 min after which the effect on the CT complex was recorded. The 'glowing splint' test was used to confirm oxygen in the case of hydrogen peroxide, table 2.2, entry 2.

2. Photoosmylation ($KClO_3$) of toluene in reaction vessel type O: (1β,2β,3α,4α)-1α-methyl-cyclohex-5-ene tetra-*O*-acetate **73**, 1-*C*-methyl-*allo*-inositol hexa-*O*-acetate **77** and a mixture of *C*-methyl inositols hexa-*O*-acetates **74**.



73 **77** **74**

To distilled water (4 mL) in a 25 mL capacity vacuum sublimation tube fitted with a water cooled cold finger (vessel type O) was added potassium chlorate (0.77 g, 7.3 mmol). The solution was stirred and degassed by bubbling a steady stream of argon through the aqueous medium. After 15 min toluene (0.77 mL, 7.3 mmol) was added followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in dichloromethane (0.5 mL) *via* syringe. The biphasic system was then vigorously stirred, to ensure good mixing of the two layers, and irradiated (400 W, medium pressure Hg lamp) for 91 h. After irradiation the solution was treated with sodium sulphite (2 g), stirred for 2 h, diluted with water (100 mL) and transferred to a separating funnel. The aqueous layer was extracted with ether (3 x 15 mL), the combined extracts washed with brine and dried ($MgSO_4$). Evaporation under reduced pressure gave a yellow oil, which upon column chromatography (1:19 EtOAc:petrol to 2:8 EtOAc:petrol) gave benzaldehyde (12.7 mg, 1.6%) (compared to an authentic sample by tlc and ^1H NMR). Evaporation of the aqueous layer under reduced pressure gave salt residues which were freeze dried for 14 h at 0.03 mmHg. The dried salts were washed with copious quantities of methanol, filtered and the filtrate evaporated to leave a reduced white mass of salts. These salts were suspended in dichloromethane (20 mL) and treated with acetic anhydride (20 mL), triethylamine (5 mL) and DMAP (cat.) and heated to reflux for 2 h. The reaction mixture was then cooled on an ice bath and water (20 mL) was slowly added and the lot transferred to a separating funnel. The mixture was then extracted with ether (3 x 100 mL), the combined ethereal extracts washed with aqueous HCl (2 M, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), and dried over $MgSO_4$. Evaporation of then ethereal extracts under reduced pressure followed by column chromatography (4:6 to 1:1 EtOAc:petrol) gave *(1β,2β,3α,4α)-1α-methyl-cyclohex-5-ene tetra-O-acetate* **73** (12 mg, 0.5%) as a white solid and a mixture of *C-methyl inositol hexa-O-acetates* **74** as a yellow oil (30 mg, 0.9%). Trituration of **74** with methanol induced crystallisation, which on recrystallisation at -20 °C gave *1*-C-*methyl-allo-inositol hexa-O-acetate* **77** (3 mg) as colourless crystals.

(1β,2β,3α,4α)-1α-Methyl-cyclohex-5-ene tetra-*O*-acetate.

(1-*C*-Methyl-conduritol E tetra-*O*-acetate) 73

δ^1H(500 MHz, r.t., $CDCl_3$) 6.48 (1H, d, J=9.9 Hz, H-6), 5.77 (1H, dd, J=9.9, 5.0 Hz, H-5), 5.66 (1H, dd, J=4.6, 4.7 Hz, H-4), 5.44 (1H, dd, J=11.1, 4.4 Hz, H-3), 5.33 (1H, d, J=11.1 Hz, H-2) 2.13, 2.08, 2.03, 1.99 (4x3H, s, $OCOCH_3$), 1.58 (3H, s, H-7).

δ^{13}C(125 MHz, r.t., $CDCl_3$) 170.2, 170.1, 169.8, 169.6, 134.1 (C-5), 125.2 (C-6), 78.9 (C-1), 71.0, 66.9, 65.9, 21.8 (C-7), 20.7, 20.6, 20.5.

ν_{max} (CH_2Cl_2) 2921, 1745, 1433, 1371, 1227, 1163, 1057, 1019, 934 cm^{-1}.

m/z (70 eV, NH_3) 346 (27%, $[M+NH_4]^+$), 286 (5%, $[M-C_2H_2O]^+$), 269 (100, $[M-CH_3CO_2]^+$).

m.p.: 104-106 °C (ether)

Elemental analysis; calculated: C 54.88 , H 6.10; found: C 54.92 , H 6.21.

Chrystallographic determination (see appendix B).

1-*C*-Methyl-*allo*-inositol hexa-*O*-acetate 77

δ^1H(400 MHz, 70 °C, $CDCl_3$) 6.09 (1H, d, J=2.8 Hz, H-6), 5.61 (1H, t, J=3.7 Hz, H-3), 5.47 (1H, dd, J=10.6, 2.8 Hz, H-5), 5.36 (1H, dd, J=10.6, 3.7 Hz, H-4), 5.17 (1H, br d, J~2.7 Hz, H-2), 2.14, 2.11, 2.11, 2.07, 1.99, 1.97 (6x3H, s, $OCOCH_3$) 1.51 (3H, s, H-7).

δ^{13}C(100 MHz, 60 °C, $CDCl_3$) 170.0, 169.7, 169.7, 169.4, 169.1, 168.7, 81.4 (C-1), 70.5, 69.7, 68.5 , 67.1, 66.9, 22.0, 20.6, 20.5, 20.4, 20.4, 20.4, 18.6 (C-7).

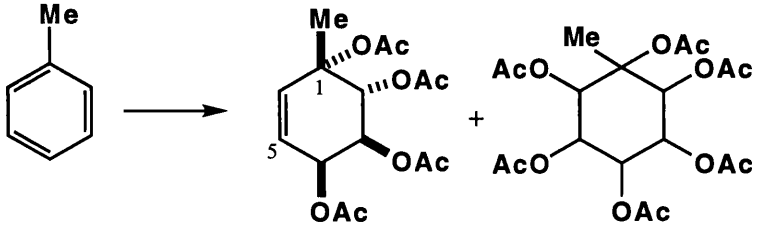
ν_{max} (CH_2Cl_2) 2958, 1750, 1436, 1372, 1224, 1123, 1079, 1060, 958, 922, 900 cm^{-1}.

m/z (70 eV, NH_3) 464 (100%, $[M+NH_4]^+$), 387 (5%, $[M-CH_3CO_2]^+$).

m.p.: 143-144 °C (methanol)

Elemental analysis; calculated: C 51.12 , H 5.87; found: C 50.67 , H 5.65.

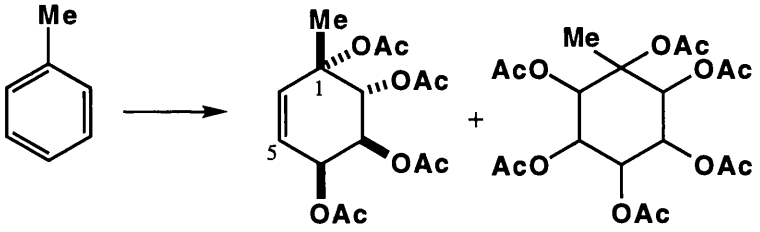
3. Photoosmylation ($KClO_3$) of toluene in reaction vessel type A: (1β,2β,3α,4α)-1α-methyl-cyclohex-5-ene tetra-*O*-acetate **73** and a mixture of *C*-methyl inositol hexa-*O*-acetates **74**.



73 **74**

To distilled water (40 mL) in a 50 mL capacity hydrogenation flask fitted with a water cooled cold finger (vessel type A) was added potassium chlorate (2.22 g, 18.25 mmol). The solution was stirred and degassed by bubbling a steady stream of argon through the aqueous medium. After 15 min. toluene (0.77 mL, 7.3 mmol) was added followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in dichloromethane (0.5 mL) *via* syringe. The biphasic system was then vigorously stirred (Teflon stirrer bar), to ensure good mixing of the two layers, and irradiated (400 W, medium pressure Hg bulb) for 91 h. After irradiation the solution was treated with sodium sulphite (2 g), stirred for 2 h and evaporated under reduced pressure. Acetylation as before yielded a yellow oil that partially crystallised on standing. Recrystallisation from ether gave **73** (12.7 mg, 0.5%) as colourless needles. Column chromatography (3:7 to 1:1 EtOAc:petrol) of the mother liquor yielded **73** (66 mg, 2.8%) as a white solid and **74** (104 mg, 3.2%) as a yellow oil.

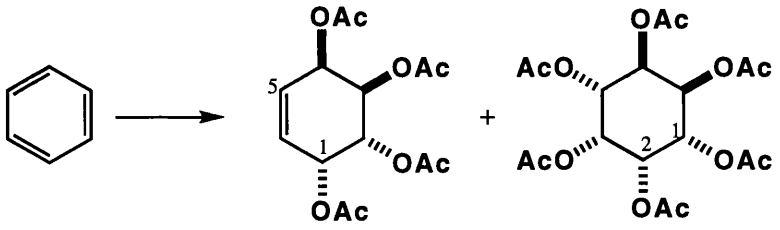
4. Photoosmylation ($Ba(ClO_3)_2$ of toluene in reaction vessel type B: (1β,2β,3α,4α)-1α-methyl-cyclohex-5-ene tetra-*O*-acetate **73** and a mixture of *C*-methyl inositols hexa-*O*-acetates **74**.



73 **74**

To a florentine shaped Pyrex flask (vessel type B) was added barium chlorate mono hydrate (2.9 g, 9 mmol) and distilled water (50 mL). The solution was stirred and degassed by bubbling a steady stream of argon through the aqueous medium. After 15 min. toluene (0.77 mL, 7.3 mmol) was added followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in dichloromethane (0.5 mL) *via* syringe. The biphasic system was then stirred vigorously, to ensure good mixing of the two layers, and irradiated (400 W, medium pressure Hg bulb) for 91 h. Upon irradiation the solution was treated with sodium sulphite (2 g), stirred for 2 h and evaporated under reduced pressure as before. Acetylation as before followed by column chromatography (4:6 to 1:1 EtOAc:petrol) gave **73** (52 mg, 2.2%) as a yellow oil and **74** (361 mg, 10.8%) as a yellow oil.

5. Photoosmylation ($(Ba(ClO_3)_2$) of benzene in reaction vessel type A: (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-inositol hexa-*O*-acetate **80**



79 **80**

To distilled water (40 mL) in a 50 mL capacity hydrogenation flask fitted with a water cooled cold finger (vessel type A) was added barium chlorate monohydrate (2.9 g, 9 mmol), benzene (0.65 mL, 7.3 mmol) and osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The biphasic mixture was stirred vigorously and irradiated for 43 h as before. The irradiated solution was then treated with sodium sulphite (2 g), stirred for 2.5 h and evaporated under reduced pressure. The remaining salts were powdered to which was added triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation under reduced pressure afforded a yellow oil that partially crystallised upon standing. Column chromatography (7:3, ether:petrol) of this material gave *(1β,2β,3α,4α)-cyclohex-5-ene-tetra*-O-*acetate* **79** (36 mg, 1.5%) as a white solid and allo-*inositol hexa-O-acetate* **80** (283 mg, 8.7%) as a white solid.

(1β,2β,3α,4α)-Cyclohex-5-ene-tetra-*O*-acetate.

(Conduritol E tetraacetate) 79

δ^1H(500 MHz, r.t., $CDCl_3$) 5.90 (2H, dd, J=1.1, 2.6 Hz, H- 5, 6), 5.67 (2H, m, H-1, 4), 5.43 (2H, dd, J=1.4, 2.2 Hz, H- 2, 3), 2.07 (6H, s, 2x$OCOCH_3$), 2.03 (6H, s, 2x$OCOCH_3$).

δ^{13}C(125 MHz, r.t., $CDCl_3$) 170.1, 169.8, 128.1 (C-5, 6), 66.6, 66.1, 20.7, 20.6.

ν_{max} (CH_2Cl_2) 1745, 1376, 1246, 1222, 1078, 1015, 943 cm^{-1}.

m/z (70 eV, NH_3) 332 (100%, $[M+NH_4]^+$), 255 (31%, $[M-CH_3CO_2]^+$).

m.p. 154-155 °C (ethanol), (lit.: 156 °C (EtOAc/hexane)[25], 152.5-153 °C (EtOH)[16]).

Elemental analysis; calculated: C 53.50 , H 5.77; found: C 53.33 , H 5.59.

***allo*-Inositol hexa-*O*-acetate 80**

δ^1H(400 MHz, 55 °C, $CDCl_3$) 5.44 (4H, m, H-2, 3, 5, 6), 5.30 (2H, m, H-1, 4), 2.05 (18H, br s, 6x$OCOCH_3$).

δ^{13}C(125 MHz, 55 °C, $CDCl_3$) 169.5, 169.3, 169.2, 67.7, 67.4, 20.6, 20.5, 20.5.

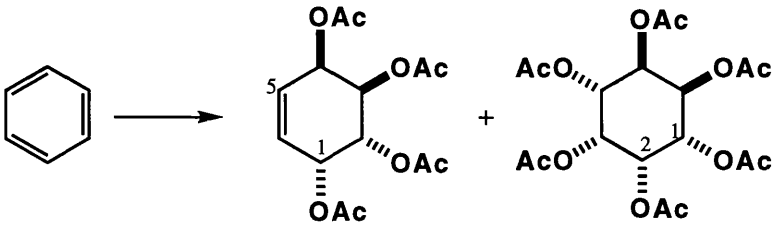
ν_{max} (CH_2Cl_2) 2960, 1752, 1372, 1228, 1078, 1051, 936 cm^{-1}.

m/z (70 eV, NH_3) 450 (100%, $[M+NH_4]^+$), 373 (12%, $[M-CH_3CO_2]^+$).

m.p. 142-142.5 °C (ethanol), (lit.[152]: 141.5-142 °C (methanol)).

Elemental analysis; calculated: C 50.00, H 5.59; found: C 49.83, H 5.67.

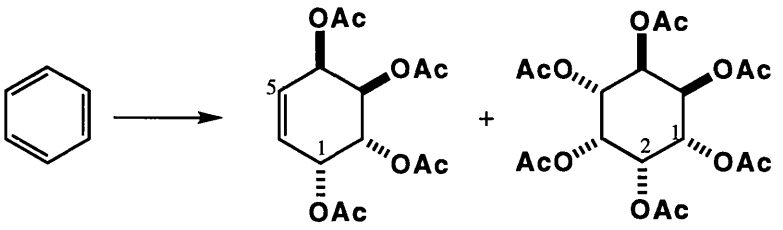
6. Photoosmylation ($(Ba(ClO_3)_2)$) of benzene in reaction vessel type B: (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-inositol hexa-*O*-acetate **80**



79 **80**

To a florentine shaped Pyrex 50 mL flask (vessel type B) was added barium chlorate mono hydrate (3.53 g, 11 mmol) and de-ionised water (50 mL). Upon solvation benzene (0.65 mL, 7.3 mmol) was added followed by a solution of osmium tetroxide (25 mg, 0.1 mmol in carbon tetrachloride 0.25 mL). The vigorously stirred mixture was then irradiated for 43 h and quenched, acetylated and worked up as in experiment 4. The yellow oil obtained was triturated with ethanol to give a crude crystalline mass which upon recrystallisation gave **80** (784 mg, 24.8%). Column chromatography (7:3, ether:petrol) of the mother liquor gave **79** (115 mg, 5.0%) as a white solid and **80** (195 mg, 6.2%) as an off-white solid.

7. Photoosmylation ($(Ba(ClO_3)_2)$) of benzene in reaction vessel type C: (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-inositol hexa-*O*-acetate **80**



79 **80**

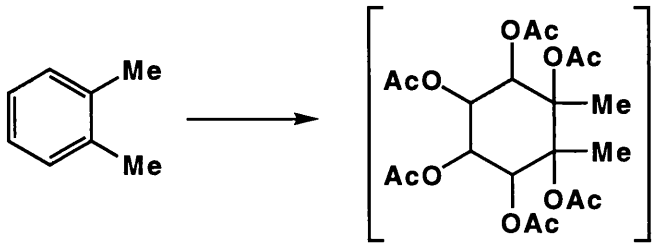
Photoosmylation of benzene using the method described in general procedure A, below, gave a brown oil. Column chromatography (7:3, ether:petrol) gave **79** (41 mg, 1.8%) as a white solid and **80** (952 mg, 30.2%) as an off-white solid.

General procedure A. Photoosmylations carried out in reaction vessel C:

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added barium chlorate monohydrate (3.53 g, 11 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt the *aromatic* was added (7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The tap was fastened and the reaction mixture stirred vigorously using a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. The operating temperature of the reaction was taken with a mercury thermometer positioned directly behind the reaction vessel, out of the direct path of irradiation. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (9 g, 47 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and concentrated under reduced pressure. The salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts washed with brine and dried over $MgSO_4$. Evaporation of the organic volatiles then affords the crude products.

3.2.2 Experimental procedures for section 2.3

1. Photoosmylation of *o*-xylene using general procedure A.



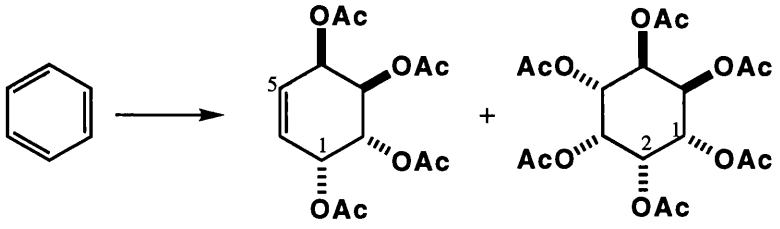
460 gmol^{-1}

Photoosmylation of *o*-xylene (0.89 mL, 7.3 mmol) was carried out using general procedure A. Column chromatography (7:3 ether:petrol to 100% ether) of the brown oil obtained gave a mixture of unidentifiable products (29 mg).

δ^1H(400 MHz, $CDCl_3$) 6-5 (m), 2.2-2.0 (m).

m/z (70 eV, NH_3) 401 (38%, $[M\text{-}CH_3CO_2]^+$).

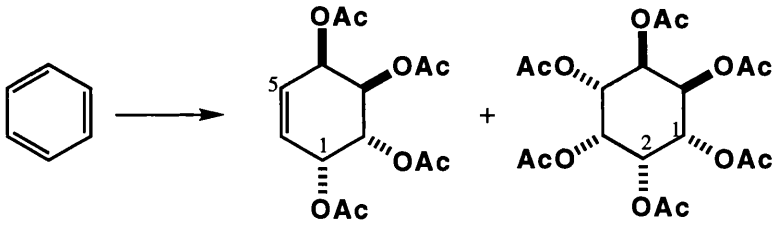
2 Photoosmylation of benzene with deoxygenated water using general procedure A: (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-inositol hexa-*O*-acetate **80**



79 **80**

Photoosmylation of benzene (0.65 mL, 7.3 mmol) was carried out using general procedure A. Prior to the addition of the benzene and osmium tetroxide the aqueous solution was degassed by bubbling a steady stream of nitrogen through it for 15 min. The yellow oil obtained was crystallised and recrystallised from ethanol to afford **80** (905 mg, 28.7%). Column chromatography of the mother liquor gave **79** (66 mg, 2.9%) and further **80** (20 mg, 0.6%) as white solids.

3. Photoosmylation of benzene using general procedure A: Yield of photoosmylation *vs* time; (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-inositol hexa-*O*-acetate **80**.



79 **80**

Photoosmylation of benzene (0.65 mL, 7.3 mmol) was carried out using general procedure A using the following irradiation times:

12 h.

Column chromatography (7:3, ether:petrol) of the dark brown oil obtained gave **79** (39 mg, 1.7%) and **80** (511 mg, 16.2%) as yellow oils that crystallised overnight.

24 h.

The yellow oil obtained crystallised on standing, recrystallisation from ethanol gave **80** (700 mg, 22.2%). Column chromatography (7:3, ether:petrol) of the mother liquor gave **79** (37 mg, 1.6%) as a white solid and **80** (13 mg, 0.4%) as an oil.

43 h.

Experiment 6. section 3.2.2.

75 h.

The dark-yellow oil obtained was triturated with ethanol which induced crystallisation. Recrystallisation afforded **80** (943 mg, 29.9%) as off-white crystals. ^{1}H NMR of the mother liquor (22 mg) showed a 1:1 mixture of **79**:**80**.

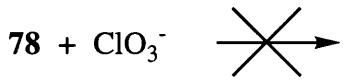
91 h.

The yellow oil obtained was triturated with ethanol which induced crystallisation. Recrystallisation afforded **80** (1.009 g, 32%) as white crystals. The composition of the deeply coloured mother liquor (15 mg) was not determined

115 h.

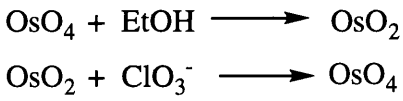
The brown oil obtained triturated with ethanol which induced crystallisation, recrystallisation afforded **80** (883 g, 28%) as yellow crystals. Column chromatography (7:3, ether:petrol) of the reduced dark brown mother liquor gave traces of **79** (<1 mg) and allo-*inositol hexa-O-acetate* **80** (31 mg, 1%) as a yellow oil.

4. Reaction of unknown **78** with an solution of barium chlorate.



The unknown **78** (21 mg) was suspended in a solution of barium chlorate (10 mL, [0.22 M]) and stirred for 15 h. After 525 days no visible change in the consistency of the reaction mixture could be seen.

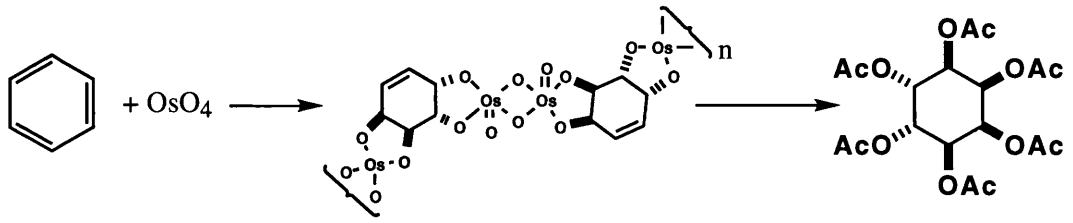
5. Preparation of osmium dioxide and reaction with barium chlorate solution.[85]



Osmium tetroxide (113 mg, 0.44 mmol) was added to a ethanol (2 mL) upon which a black precipitate formed. The mixture was stirred for a further 5 min after which the solvent was removed by passing a steady stream of nitrogen over the ethanolic solution yielding osmium dioxide as a black powder (102 mg).

Osmium dioxide (ca. 25 mg) was suspended in a solution of barium chlorate (10 mL, [0.22 M]) and stirred. The black suspension dissolved within 2-3 minutes to give a clear colourless solution.

6. Preparation of polymeric osmate ester **65** *via* stoichiometric CT osmylation of benzene[85]; reaction of **65** with a solution of barium chlorate: *allo*-inositol hexa-*O*-acetate **80**.



65 **80**

To benzene (5 mL) was added osmium tetroxide (244 mg, 0.9 mmol) in reaction vessel type O. The water cooled benzene solution was irradiated and stirred for 15 h after which a fine black precipitate had formed. The volatiles were removed by passing a steady stream of nitrogen over the benzene layer to leave **65** (22 mg) as a black powder.

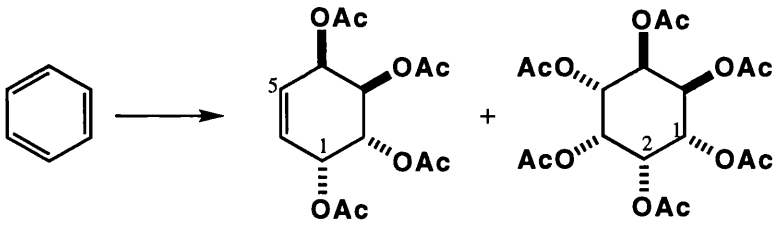
65 (22mg) was suspended in a solution of barium chlorate (10 mL, [0.22 M]) and stirred for 3 h upon which a clear colourless solution was obtained. Sodium metabisulphite (ca. 2 g) was then added to the reaction mixture and left stirring for a further 10 min. Evaporation of the aqueous layer left white salts which were treated with triethylamine (10 mL), acetic anhydride (2 mL) and DMAP (cat) and heated to 70 °C for 2 h. The mixture was then cooled on an ice-water bath and diluted with water (ca. 5 mL). The reaction mixture was then extracted with ether (2x20 mL) and the ethereal extracts dried over $MgSO_4$. ^1H NMR of the reduced ethereal extracts showed the presence of **80**. No further purification was carried out.

7. Photoosmylation in the absence of benzene.

$$OsO_4 + h\nu + ClO_3^- \not\longrightarrow$$

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added barium chlorate monohydrate (3.53 g, 11 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL) was added. The vigorously stirred solution was irradiated for 15 h after which no observed change to the clear, colourless reaction mixture could be detected.

8. Photoosmylation of benzene in the presence of hydrolysis catalysts (table 2.10): (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-inositol hexa-*O*-acetate **80**.



79 **80**

Photoosmylation of benzene (0.65 mL, 7.3 mmol) was carried out using general procedure A with the addition of the following hydrolysis catalysts prior to irradiation:

1 eq Et_4NOAc.

Tetraethylammonium acetate tetrahydrate (1.91 g, 7.3 mmol) was added to the reaction mixture prior to irradiation. The yellow oil was triturated with ether to obtain a crystalline mass (311 mg) which was shown to contain a mixture of **79** and **80**. Column

chromatography (7:3, ether petrol) of the combined crystals and reduced mother liquor gave **79** (167 mg, 7.3%) and **80** (226 mg, 7.2%) as white crystals.

4 eq Et_4NOAc.

Tetraethylammonium acetate tetrahydrate (7.64 g, 29.2 mmol) was added to the reaction mixture prior to irradiation. The yellow oil obtained crystallised on standing. Recrystallisation from ethanol gave **79** (36 mg, 1.6%) as clear colourless crystals. Column chromatography (6:4, EtOAc:petrol) of the mother liquor gave **79** (103 mg, 4.5%) and **80** (168 mg, 5.3%). A repeat experiment gave a yellow oil which upon column chromatography (7:3, ether petrol) gave **79** (24 mg, 1.0%) and **80** (353 mg, 11.2%) as white solids.

8 eq Et_4NOAc.

Tetraethylammonium acetate tetrahydrate (15.6 g, 59.7 mmol) was added to the reaction mixture prior to irradiation. The light yellow oil obtained crystallised on standing. Recrystallisation gave a mixture of **79** and **80**. Column chromatography (7:3, ether petrol) of the combined crystals and reduced mother liquor gave **79** (81 mg, 3.5%) and **80** (137 mg, 4.3%). A repeat experiment gave a yellow oil which crystallised on standing recrystallisation gave **80** (202 mg, 6.4%). The dark yellow mother liquor (5 mg) was discarded.

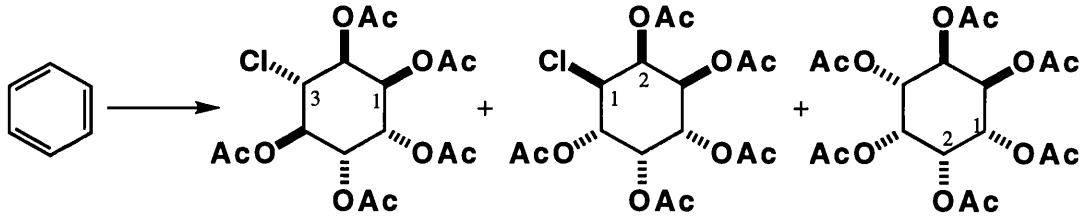
1 eq $MeSO_2NH_2$.

Methane sulphonamide (693 mg, 7.3 mmol) was added to the reaction mixture prior to irradiation. The oil obtained partially crystallised on standing. Crystallisation from ethanol gave **80** (397 mg, 12.6%) as clear colourless crystals. Column chromatography (7:3, ether:petrol) of the reduced mother liquor gave **79** (35 mg, 1.5%) and **80** (94 mg, 3.0%) as coloured oils.

1 eq $^{n}Bu_4NOAc$.

Tetra-*n*-butylammonium acetate (2.2 g, 7.3 mmol) was added to the reaction mixture prior to irradiation. The oil obtained was crystallised from ethanol to afford **80** (214 mg, 6.7%) as off-white crystals. Column chromatography (7:3, ether:petrol) of the reduced mother liquor gave further **80** (50 mg, 1.6%) as an oil.

9. Photoosmylation of benzene with CTAB (table 2.10 entry 6): 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86** and *allo*-inositol hexa-*O*-acetate **80**.



85 **86** **80**

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added barium chlorate monohydrate (3.53 g, 11 mmol) and an aqueous solution of cetyltrimethylammonium bromide at the critical micellar concentration (50 mL, [0.026 mM]). Upon solvation of the chlorate salt, benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (9 g, 47 mmol) over 15 min. The grey mixture was then neutralised with

NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (cat). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the organic volatiles afforded a yellow oil. Column chromatography (7:3, ether:petrol) of this yellow oil gave *3-deoxy-3-chloro*-chiro-*inositol penta*-O-*acetate* **85** and *1-deoxy-1-chloro*-neo-*inositol penta*-O-*acetate* **86** (122 mg, 4.1%) as a 1:1 mixture (^{1}H NMR) as a white solid and **80** (318 mg, 10.1%) as a solid. Preparative HPLC (25% EtOAc in hexane) effected separation of the diastereoisomers. Less polar: **85**, retention time 17.3 min; more polar: **86**, retention time 19.6 min.

3-Deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate 85

δ^1H(400 MHz, r.t., $CDCl_3$) 5.49 (1H, t, J=10.3 Hz, H-4), 5.36 (2H, m, J=2.9, 5.6 Hz, H-1, 6), 5.31 (1H, dd, J=2.7, 11.0 Hz, H-2), 5.21 (1H, dd, J=2.8, 10.3 Hz, H-5), 4.15 (1H, t, J=10.9 Hz, H-3), 2.00, 2.07, 2.11, 2.17, 2.20 (5x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.7, 169.3, 169.3, 169.0, 168.7, 70.8, 70.5, 69.3, 67.5, 67.1, 57.4 (C-3), 20.7, 20.6, 20.5, 20.5, 20.4.

ν_{max} (CH_2Cl_2) 2964, 1760, 1431, 1372, 1228, 1149, 1056, 932, 909, 889, 816 cm^{-1}.

m/z (70 eV, NH_3) 428/426 (100%, $[M+NH_4]^+$), 332 (5%, $[M\text{-}HCl\text{-}C_2H_3O]^+$).

m.p.: 146-147 °C (Ethanol), (lit.[153]: 144 °C).

Elemental analysis; calculated : C 47.01, H 5.18 Cl 8.67.

found : C 46.79, H 5.11, Cl 8.58.

1-Deoxy-1-chloro-*neo*-inositol penta-*O*-acetate 86

δ^1H(400 MHz, r.t., $CDCl_3$) 5.72 (1H, t, J=3.0 Hz, H-2), 5.65 (1H, t, J=3.0 Hz, H-5), 5.34 (1H, dd, J=3.0, 11.2 Hz, H-4), 5.32 (1H, dd, J=2.8, 11.2 Hz, H-6), 5.23 (1H, dd, J=3.0, 11.0, H-3), 4.34 (1H, dd, J=3.0, 11.1 Hz, H-1), 2.20, 2.16, 2.07, 2.00, 2.00 (5x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.9, 169.7, 169.6, 169.4, 169.3, 69.5, 69.4, 68.6, 68.4, 67.0, 54.7 (C-1), 20.6, 20.5, 20.4.

ν_{max} (CH_2Cl_2) 1752, 1372, 1223, 1110, 1079, 1044, 1021, 948, 900 cm^{-1}.

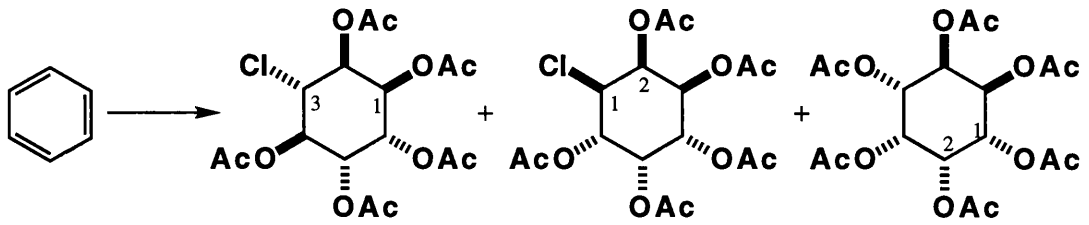
m/z (70 eV, NH_3) 428/426 (100%, $[M+NH_4]^+$), 373 (2%, $[M-Cl]^+$), 332 (4%, $[M-HCl-C_2H_3O]^+$).

m.p.: 137-139 °C (Ethanol).

Elemental analysis; calculated: C 47.01, H 5.18, Cl 8.67.

found: C 46.70, H 5.14, Cl 8.48.

10. Photoosmylation of benzene in reaction vessel type A with slow addition of hydrogen peroxide solution: 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86** and *allo*-inositol hexa-*O*-acetate **80**.

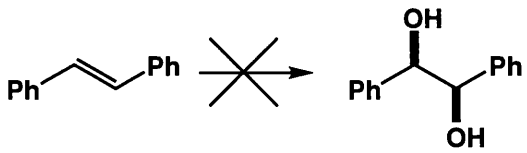


85 **86** **80**

To de-ionised water (40 mL) in a 50 mL capacity hydrogenation flask fitted with a water cooled cold finger (vessel type A) was added barium chlorate monohydrate (3.53 g, 11 mmol). Upon solvation of the chlorate salt benzene was added (0.65 mL, 7.3 mmol)

followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The vigorously stirred solution was irradiated for 43 h with concomitant addition of hydrogen peroxide (5 mL, 30% v/v, at 2.5 mL/24 h) using a syringe pump. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (9 g, 47 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the organic volatiles at reduced pressure gave a dark brown oil which upon column chromatography gave **85** and **86** (30 mg, 1.0%) as a 1:1 mixture (^1H NMR) as a yellow oil and **80** (69 mg, 2.2%) as a yellow oil.

11. Attempted catalytic dihydroxylation of *trans*-stilbene with (a) potassium persulphate and (b) Oxone.



a)

To a solution of *trans*-stilbene (718 mg, 4 mmol) in water (25 mL) and acetone (2.5 mL) was added potassium persulphate (1.61 g, 6 mmol) followed by osmium tetroxide (10 mg, 0.04 mmol) in carbon tetrachloride (0.1 mL) under a positive pressure of nitrogen. The reaction mixture was stirred for 3 days after which tlc analysis revealed no new

spots. The reaction was treated with sodium sulphite (2 g), stirred for 2.5 h and filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (2 x 20 mL), the combined extracts were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to yield *trans*-stilbene (660 mg, 92%).

b)

To a solution of *trans*-stilbene (720 mg, 4 mmol) in water (25 mL) and acetone (2.5 mL) was added Oxone (614 mg, 6 mmol) followed by osmium tetroxide (10 mg, 0.04 mmol, in carbon tetrachloride 0.1 mL) under a positive pressure of nitrogen. The reaction mixture was stirred for 3 days after which tlc analysis revealed no new spots. The reaction was treated with sodium sulphite (2 g), stirred for 2 h and filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (2 x 20 mL), the combined extracts were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure to yield *trans*-stilbene (701 mg, 97%).

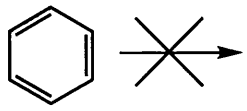
12. Action of solutions of oxy-halides in table 2.12 on (a) unknown **78** and (b) osmium tetroxide.

General procedures:

(a) To a solution of the oxy-halide (40-50 mg) in water (1 mL) was added the unknown **78** (ca. 5 mg). The mixture was shaken for several seconds and the effect on **78** recorded (table 2.12).

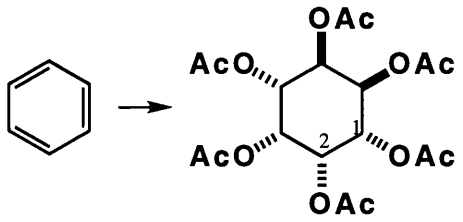
(b) To a solution of the oxy-halide (40-50 mg) in water (1 mL) was added several drops of osmium tetroxide solution ([0.4 M] in carbon tetrachloride). The mixture was shaken for several seconds and the effect on the solution recorded (table 2.12).

13. Attempted photoosmylation of benzene with bleach.



To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added sodium hypochlorite solution (ca. [0.14 M], 50 mL) and benzene (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (20 g, 47 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and evaporated. The salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (cat). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the volatile components left a brown oil (41 mg) of unidentifiable composition.

14. Photoosmylation of benzene with sodium iodate: *allo*-inositol hexa-*O*-acetate **80**.



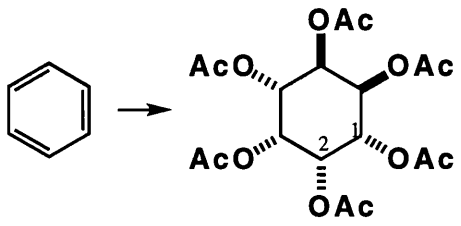
80

Using general procedure A except sodium iodate (3.92 g, 18.23 mmol) was used instead of barium chlorate. The brown oil obtained crystallised on standing, on recrystallisation from ethanol gave **80** (165 mg, 5.3%) as yellow crystals. The dark brown mother liquor (18 mg) was discarded.

15. Action of osmium tetroxide on a solution of sodium perborate.

To a solution of sodium perborate (ca. 50 mg) in water (1 mL) was added several drops of osmium tetroxide solution ([0.4 M] in carbon tetrachloride). Vigorous effervescence ensued which relit a glowing splint.

16. Photoosmylation of benzene in buffered solutions (table 2.13): *allo*-inositol hexa-*O*-acetate **80**.



80

General procedure:

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added sodium chlorate (2.33 g, 21.9 mmol) and *the buffer* (50 mL). Upon solvation of the chlorate salt, benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. Upon irradiation the pH of the aqueous phase was recorded and transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (8 g) over 15 min. The mixture was then evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of all volatiles afforded the crude cyclitol products.

pH 3.776 phosphate buffer. pH 3.8 after irradiation. The oil obtained crystallised on standing, recrystallisation from ethanol gave **80** (167 mg, 5.4%) as off-white crystals.

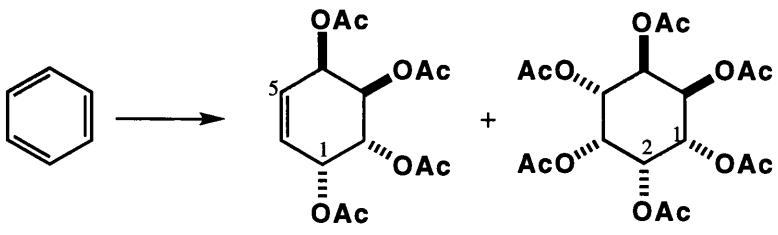
No buffer. pH 4 after irradiation. The brown oil obtained crystallised on standing, recrystallisation (twice) from ethanol gave **80** (486 mg, 15.4%) as yellow crystals. The deeply coloured mother liquor (33 mg) was discarded.

pH 7.2 phosphate buffer. pH 7.2 after irradiation. Tlc analysis of the yellow oil obtained revealed **80** as the only product (79 mg, 2.5%).

pH 9.18 phosphate buffer. pH 9.2 after irradiation. The brown oil obtained was crystallised from ethanol. Recrystallisation from ethanol gave **80** (44 mg, 1.4%) as yellow-brown crystals.

pH 9.93 carbonate buffer. pH 10.0 after irradiation. The oil obtained crystallised on standing, recrystallisation from ethanol gave **80** (69 mg, 2.2%). Column chromatography of the reduced mother liquor gave **80** (32 mg, 1.0%) as an oil.

17. Photoosmylation of benzene in varying concentrations of barium chlorate (table 2.14).



79 **80**

Using general procedure A except the following masses of barium chlorate monohydrate and sodium metabisulphite were used:

[0.024 M] .

Barium chlorate monohydrate (0.39 g, 1.22 mmol) and sodium metabisulphite (2 g). The colourless oil obtained crystallised on standing to give **80** (255 mg, 8.1%) which was shown to be pure by ^{1}H NMR.

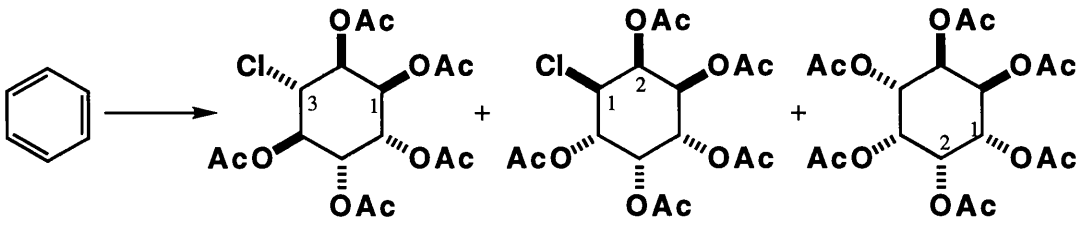
[0.18 M].

Barium chlorate monohydrate (2.90 g, 9 mmol) and sodium metabisulphite (7 g). Column chromatography (7:3, ether:petrol) of the yellow oil obtained gave **79** (41 mg, 1.8%) and **80** (801 mg, 25.4%) as white solids.

[0.22 M]. Experiment 6. section 3.2.2.

[0.36 M].

Barium chlorate monohydrate (5.8 g, 18 mmol) and sodium metabisulphite (14 g). Column chromatography (7:3, ether:petrol) of the yellow oil obtained gave **79** (62 mg, 2.7%) as an oil and **80** (624 mg, 19.8%) as an oil that crystallised on standing.

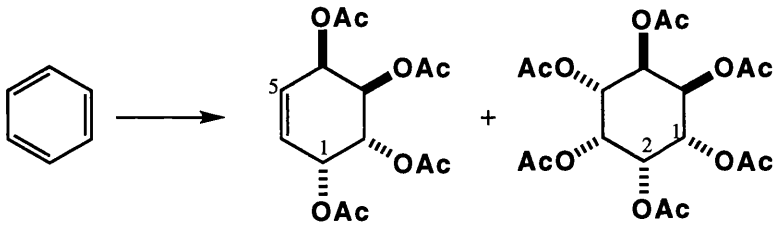


85 **86** **80**

[0.55 M].

Barium chlorate monohydrate (8.86 g, 27.5 mmol) and sodium metabisulphite (25 g as a saturated aqueous solution). Column chromatography (7:3, ether:petrol) of the partially crystallised residue gave **85** and **86** (60 mg, 2.0%) as a white solid in a 1:1 mixture as determined by ^{1}H NMR and **80** (192 mg, 6.1%) as an off-white solid.

18. Photoosmylation of benzene with varying mol% catalyst (table 2.15): (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-Inositol hexa-*O*-acetate **80.**



79 **80**

Using general procedure A except the following volumes of osmium tetroxide solution were used:

0.65 mol%.

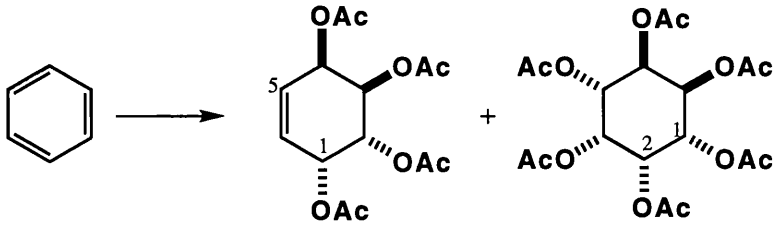
Osmium tetroxide (12.5 mg, 0.05 mmol) in carbon tetrachloride (0.125 mL). The yellow oil obtained was triturated with ethanol which induced crystallisation. Recrystallisation from ethanol gave **80** (410 mg, 13%) as clear colourless crystals. The mother liquor (12 mg) was discarded.

1.3 mol%. Experiment 6. section 3.2.2.

2.6 mol%.

Osmium tetroxide (50 mg, 0.2 mmol) in carbon tetrachloride (0.5 mL). Column chromatography (7:3, ether:petrol) of the oil obtained gave **79** (67 mg, 2.9%) and **80** (757 mg, 24%) as oils.

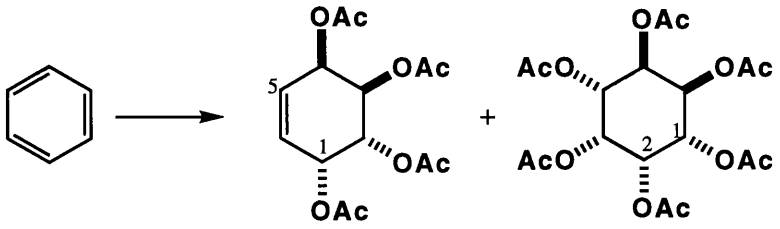
19. Attempted scale up of the photoosmylation reaction with benzene: (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-Inositol hexa-*O*-acetate **80**.



79 **80**

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added barium chlorate monohydrate (7.1 g, 22 mmol) and de-ionised water (100 mL). Upon solvation of the chlorate salt, benzene was added (1.3 mL, 14.6 mmol) followed by a solution of osmium tetroxide (50 mg, 0.2 mmol, in carbon tetrachloride 0.5 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (18 g, 94 mmol) over 15 min. The grey mixture was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (cat). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the organic volatiles afforded a yellow oil. Column chromatography (7:3, ether:petrol) of this yellow oil gave **79** (58 mg, 1.3%) as a white solid and **80** (793 mg, 12.6%) as an oil that crystallised on standing.

20. Photoosmylation of benzene at various temperatures (table 2.17): (1β,2β,3α,4α)-cyclohex-5-ene-tetra-*O*-acetate **79** and *allo*-Inositol hexa-*O*-acetate **80**.



79 **80**

At 45 °C:

Using general experimental procedure A. The reaction was heated to 45 °C by the heat of the lamp without fan-assisted cooling. Column chromatography (7:3, ether:petrol) of the brown oil obtained gave **80** (662 mg, 21.0%) as a yellow oil that crystallised on standing.

At 30 °C: Experiment 6. Section 3.2.2.

At 15 °C:

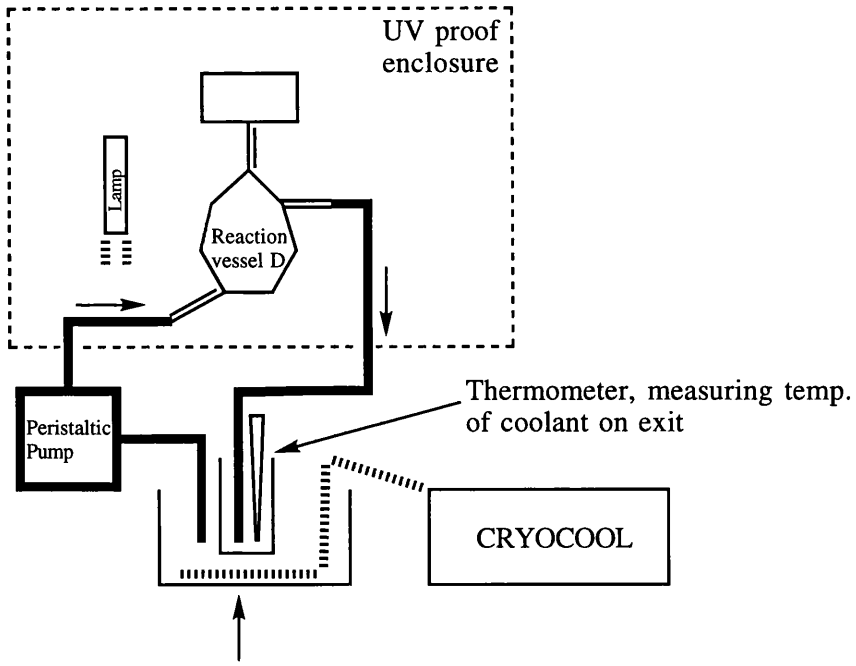
To a florentine shaped flask fitted with a Teflon tap and a glass cooling jacket (reaction vessel D) was added barium chlorate monohydrate (3.53 g, 11 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt the *aromatic* was added (7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Tap water was continuously passed through the cooling jacket at such a rate that $T_{water\ in}=T_{water\ out}$ (±1°). Irradiation of the reaction mixture was then carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was

transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (9 g, 47 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (cat). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the organic volatiles afforded an oil, which, upon column chromatography (7:3, ether:petrol) gave **79** (101 mg, 4.4%) as a yellow solid and **80** (719 mg, 22.8%) as a yellow solid.

At 2 °C:

Using general procedure for low temperature reactions B (below) and general experimental conditions A. Column chromatography (7:3, ether:petrol) of the brown oil gave **79** (96 mg, 4.1%) and **80** (192 mg, 6.1%) as yellow oils that crystallised overnight.

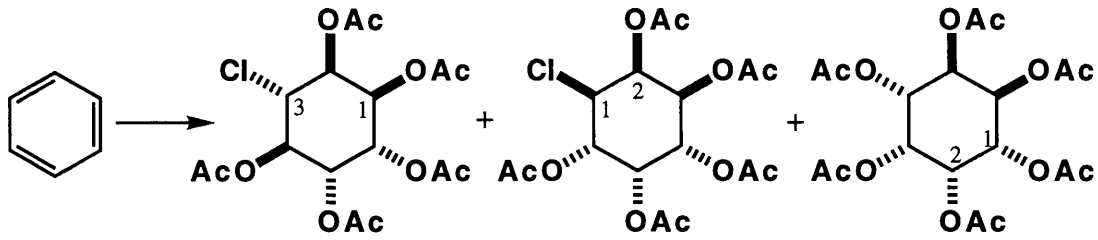
General procedure B. Photoosmylations carried out in reaction vessel D at 2 °C:



Reaction vessel D was cooled by circulating a cooled solution of ethanol/water 'coolant' (1/4, v/v) through the jacket of the vessel (diagram above). Using a cryocool the stirred coolant was cooled to ca. 2 °C in a Dewar. By means of a peristaltic pump the coolant was circulated through the vessel at such a rate that $T_{coolant\ in}=T_{coolant\ out}$ (±1°) which typically required a pump rate of ca. 1.5 $Lmin^{-1}$. The $T_{coolant\ out}$ temperature was monitored by allowing the coolant to flow into a wide-bore test tube containing a thermometer. By positioning the test tube over the Dewar the overflow of the coolant would thus be collected to be cooled and recycled.

3.2.3 Experimental procedures for section 2.4

1. Photoosmylation of benzene with addition of chlorine prior to irradiation, (table 2.18, entry 3): 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86** and *allo*-inositol hexa-*O*-acetate **80**.



85 **86** **80**

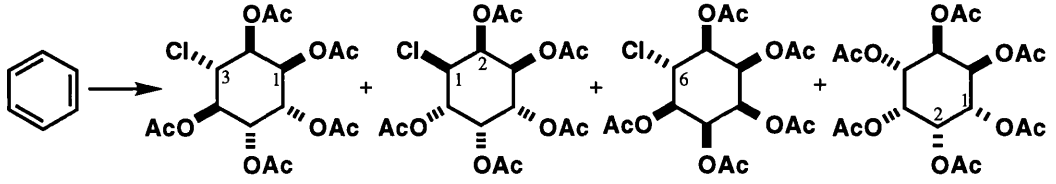
To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added barium chlorate monohydrate (8.85 g, 27.5 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt the solution was cooled on an ice-water bath and chlorine (5-10 bubbles s^{-1} through a Pasteur pipette) was bubbled through the stirred solution for 30 min. upon which the solution developed a light green coloration. Benzene was then added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 65 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (9 g, 47 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and evaporated under reduced pressure. The residue was then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture

was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts washed with brine and dried over $MgSO_4$. Evaporation of the organic volatiles afforded a yellow oil. Column chromatography (4:6 to 7:3, ether:petrol) of this oil gave **85** and **86** (100 mg, 3.4%) as a white solid as a 3:2 mixture as determined by ^1H NMR; a mixture of unidentifiable products (90 mg), and **80** (76 mg, 2.4%) as a white solid.

General procedure C. Photoosmylation at 1:1.5 aqueous:aromatic volume ratio using reaction vessel E.

To a thick walled florentine shaped flask fitted with a Teflon tap (reaction vessel E) was added barium chlorate monohydrate (3.53 g, 11 mmol) and de-ionised water (10 mL). Upon solvation of the chlorate salt the *aromatic* was added (15 mL) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. The operating temperature of the reaction was taken with a mercury thermometer positioned directly behind the reaction vessel, out of the direct path of irradiation. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, water (50 mL) was added, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (15 g, 79 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The residue was then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 100 mL) and the combined ethereal extracts washed with brine (100 mL) and dried over $MgSO_4$. Evaporation of the organic volatiles then affords the crude products.

2. Photoosmylation of benzene using general procedure C at 45 °C: 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86**, 6-deoxy-6-chloro-*epi*-inositol penta-*O*-acetate **89** and *allo*-inositol hexa-*O*-acetate **80**.



85 **86** **89** **80**

Using general procedure C without fan-assisted cooling. Column chromatography (7:3, ether:petrol) of the yellow oil obtained (crystalline at r.t.) gave **85** and **86** (495 mg, 0.7%) as a white solid as a 1:1 mixture as determined by ^{1}H NMR; *6-deoxy-6-chloro-*epi*-inositol penta-*O*-acetate* **89** (121 mg, 0.2%) as a white solid and **80** (1.120 g, 1.5%) as a white solid.

6-Deoxy-6-chloro-*epi*-inositol penta-*O*-acetate 89

δ^1H(400 MHz, r.t., $CDCl_3$) 5.37 (5H, m, H-1, 2, 3, 4, 5), 4.36, (1H, br t, J=7.3 Hz, H-6) 2.12 (3H, s, $OCOCH_3$), 2.10 (6H, s, 2x $OCOCH_3$), 2.08 (6H, s, 2x$OCOCH_3$).

δ^{13}C(100 MHz, 55 °C, $CDCl_3$) 169.2-169.0 (5xOCOMe), 71.1 (C-2, 4), 68.3 (C-1, 5), 67.7 (C-3), 54.0 (C-6), 20.6, 20.4.

ν_{max} (CH_2Cl_2) 2958, 1756, 1436, 1372, 1223, 1062, 918, 874 cm^{-1}.

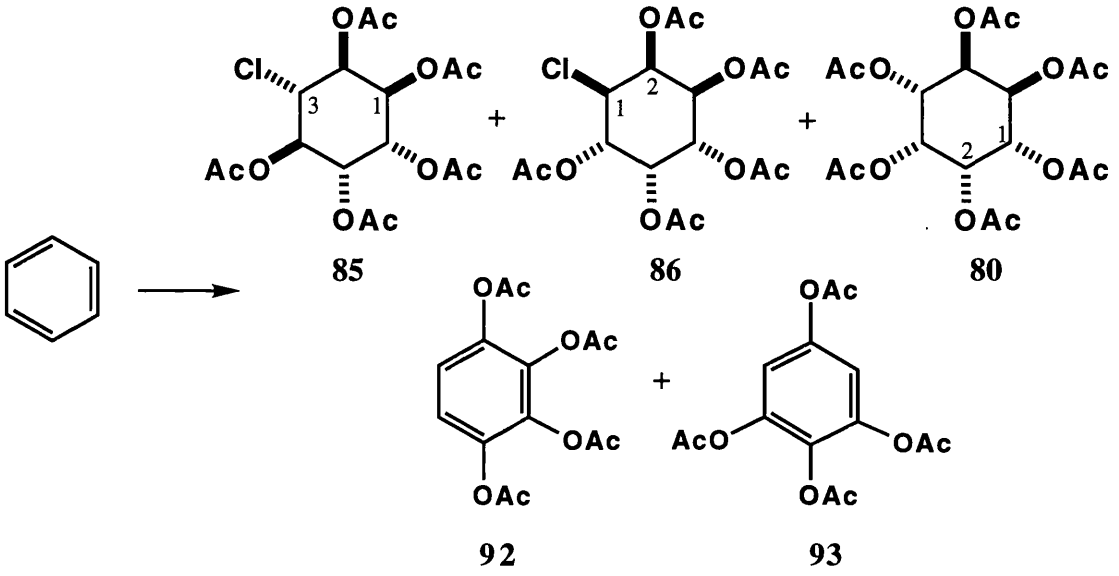
m/z (70 eV, NH_3) 428/426 (92%, $[M+NH_4]^+$), 332 (45%, $[M\text{-}HCl\text{-}C_2H_3O]^+$).

m.p.: 167-167.5 °C (ethanol), (lit.[154]: 185 °C (*iso*-propanol)).

Elemental analysis; calculated : C 47.01, H 5.18, Cl 8.67.

found : C 46.81, H 5.09, Cl 8.86.

3. Photoosmylation of benzene using general procedure C at 18 °C: 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86**, 1,2,3,4-tetraacetoxybenzene (apionol tetraacetate) **92**, 1,3,4,5-tetraacetoxybenzene **93** and *allo*-inositol hexa-*O*-acetate **80**.



To a florentine shaped flask fitted with a Teflon tap and a glass cooling jacket (reaction vessel D) was added barium chlorate monohydrate (3.53 g, 11 mmol) and de-ionised water (10 mL). Upon solvation of the chlorate salt benzene was added (15 mL, 167.8 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Tap water was continuously passed through the cooling jacket at such a rate that $T_{water\ in}=T_{water\ out}$ (±1 °C). Irradiation of the reaction mixture was then carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath, water (50 mL) added and treated portionwise with sodium metabisulphite (15 g, 79 mmol) over 15 min. The brown opaque slurry was evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with acetic acid (50 mL) and acetic anhydride (20

mL). The resulting mixture was stirred at 70-80 °C for 15 h after which it was cooled in an ice-water bath and reduced (rotary evaporator). Water (100 mL) was then added and the mixture filtered through a pad of Celite. The filtrate was then extracted with ether (3 x 100 mL) and the combined ethereal extracts washed with brine and dried over $MgSO_4$. Evaporation of the organic volatiles afforded a yellow oil, which crystallised on standing, recrystallisation from ethanol provided a batch of crystals that melted at r.t.. Column chromatography (7:3 to 8:2, ether:petrol) of the oil gave **85** and **86** (537 mg, 0.8%) as an off-white solid as a 1:1 mixture as determined by ^{1}H NMR; a mixture of **80**, *1,3,4,5-tetraacetoxybenzene* **93** and traces of *1,2,3,4-tetraacetoxybenzene (apionol tetraacetate)* **92** (1.837 g) as an oil and a mixture of **92** and **93** (162 mg) as an oil that crystallised on standing in a 4:1 ratio respectively by ^{1}H NMR. Trituration of the 1.837 g mixture with ethanol induced crystallisation which upon recrystallisation (r.t.) gave ^{1}H NMR pure **80** (889 mg) as colourless crystals. Concentration of the mother liquor followed by recrystallisation from ethanol (r.t.) gave a second batch of ^{1}H NMR pure **80** (145 mg). Column chromatography (1:1, petrol:ether) of the mother liquor gave **80** (161 mg) as an oil that crystallised on standing and a mixture of **93** and **92** and a trace of **80** (587 mg) as an oil in ca. 20:1 ratio (^{1}H NMR ratio **93**:**92**). Trituration of this oil (ethanol) induced crystallisation which upon recrystallisation gave a sample of pure **93** (99 mg). Recrystallisation (r.t.) of the 162 mg mixture of **92** and **93** from ethanol gave a sample of pure **92** (15 mg).

Overall:

85:**86** (1:1) (537 mg, isolated)

80 (1.195 g, isolated)

92 (156 mg, based on NMR ratios)

93 (593 mg, based on NMR ratios)

1,2,3,4-Tetra-*O*-acetoxy-benzene

(Apionol tetraacetate) 92

δ^1H(400 MHz, r.t., $CDCl_3$) 7.14 (2H, s, H-Ar), 2.08 (6H, s, 2x$OCOCH_3$), 2.077 (6H, s, 2x$OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 167.6, 166.5, 140.7, 135.8, 120.1 (C-5,6), 20.5, 20.0.

ν_{max} (CH_2Cl_2) 2940, 1778, 1614, 1491, 1464, 1372, 1294, 1190, 1056, 1025 cm^{-1}.

m/z (70 eV, NH_3) 328 (100%, $[M+NH_4]^+$), 268 (2%, $[M-C_2H_2O]^+$).

m.p.: 138-139 °C (ethanol), (lit.[132]: 139 °C).

Elemental analysis; calculated: C 54.19, H 4.52; found: C 53.93, H 4.39.

1,3,4,5-Tetra-*O*-acetoxy-benzene 93

δ^1H(400 MHz, r.t., $CDCl_3$) 6.99 (2H, s, H-Ar), 2.28 (3H, s, $OCOCH_3$), 2.27 (9H, s, 3x$OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 168.3, 167.4, 166.8, 147.5, 143.4, 114.3 (C-2,6), 21.07, 20.6, 20.1.

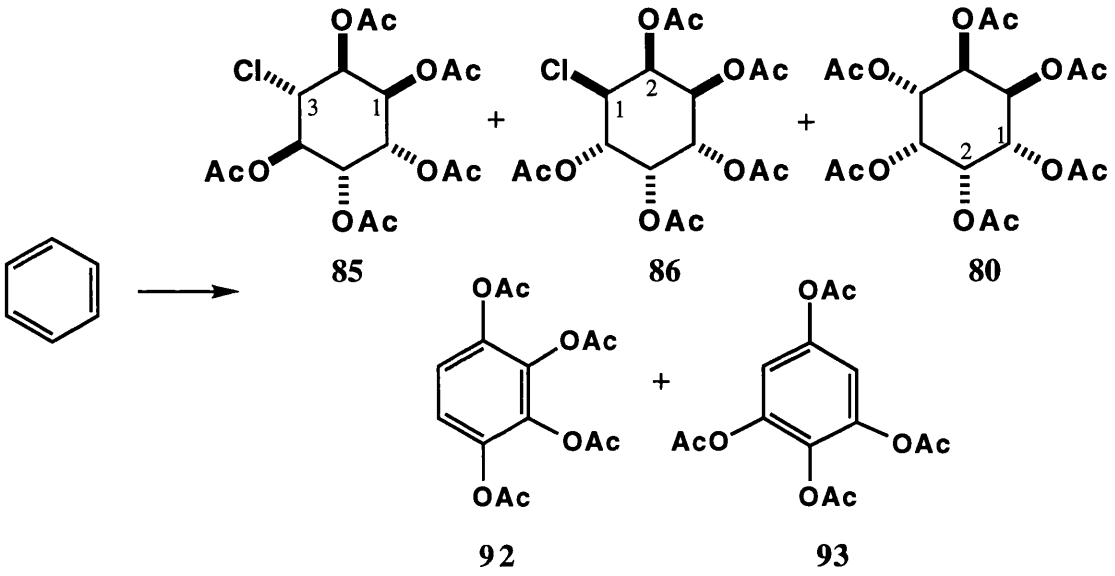
ν_{max} (CH_2Cl_2) 3056, 2964, 1779, 1723, 1420, 1266, 1189 cm^{-1}.

m/z (70 eV, NH_3) 328 (100%, $[M+NH_4]^+$), 310 (1%, $[M]^+$), 268 (6%, $[M-C_2H_2O]^+$).

m.p. 103-105 °C (ethanol), (lit.[129]: 107-108 °C (ethanol)).

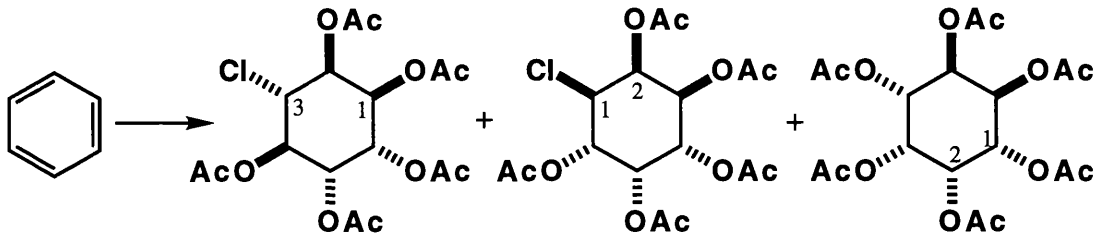
m/z (FAB, Na) $C_{14}H_{14}O_8Na$ requires: 333.0586, found: 333.0582.

4. Photoosmylation of benzene with sodium chlorate using general procedure C at 17 °C: 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86**, 1,2,3,4-tetraacetoxybenzene (apionol tetraacetate) **92**, 1,3,4,5-tetraacetoxybenzene **93** and *allo*-inositol hexa-*O*-acetate **80**.



Photoosmylation of benzene was carried out using general procedure C at 17 °C with the same experimental set-up as in the previous experiment (3.). Sodium chlorate (2.34 g, 22 mmol) was used in place of the barium chlorate. Column chromatography of the oil obtained (1:1, petrol:ether) gave **85** and **86** (261 mg) as an oil as a 1:1 mixture as determined by ^{1}H NMR; **80** and traces (<5%) of **93** (441 mg) as an oil that crystallised on standing and **92** and **93** (484 mg) as an oil as a 1:1 mixture as determined by ^{1}H NMR.

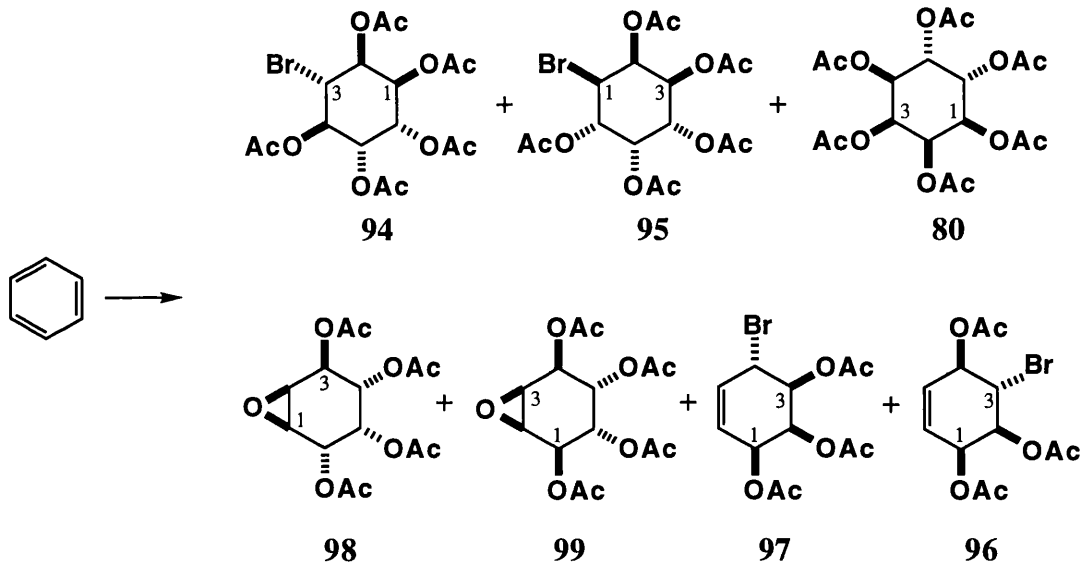
5. Photoosmylation of benzene with a saturated solution of sodium chlorate: 3-deoxy-3-chloro-*chiro*-inositol penta-*O*-acetate **85**, 1-deoxy-1-chloro-*neo*-inositol penta-*O*-acetate **86** and *allo*-inositol hexa-*O*-acetate **80**.



85 **86** **80**

To a florentine shaped flask fitted with a Teflon tap and a glass cooling jacket (reaction vessel D) was added sodium chlorate (2.33 g, 22 mmol) and de-ionised water (2.1 mL). Upon solvation of the chlorate salt benzene was added (23 mL, 257.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The reaction mixture was then irradiated, quenched and worked-up as according to the general procedure C. Column chromatography (7:3, ether:petrol) of the oil obtained gave **85** and **86** (57 mg) as an oil as a 1:1 mixture as determined by ^{1}H NMR and **80** (165 mg) as a yellow oil that crystallised on standing.

6. Photoosmylation of benzene with sodium bromate: 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**, 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95**, *allo*-inositol hexa-*O*-acetate **80**, (1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate **98**, (1β,2β,3β,4β,5α,6α)-2,3-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **99**, (1β,2β,3β,4α)-4-bromo-cyclohex-5-ene-1,2,3-tri-*O*-acetate **97** and (1β,2β,3α,4β)-3-bromo-cyclohex-5-ene-1,2,4-tri-*O*-acetate **96**.



To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added sodium bromate (2.75 g, 18.2 mmol) and de-ionised water (50 mL). Upon solvation of the bromate salt, benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (7 g, 37 mmol) over 15 min throughout which the reaction mixture turned orange, red and finally grey-black. The opaque slurry was then neutralised with NaOH (2 M) and evaporated at reduced

pressure. The residue was then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (cat). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of all volatiles under reduced pressure gave an oil. Column chromatography of this oil (5:5 to 7:3, ether: petrol) gave, in order of elution, *(1β,2β,3β,4α)-4-bromo-cyclohex-5-ene-1,2,3-tri*-O-*acetate* **97** and *(1β,2β,3α,4β)-3-bromo-cyclohex-5-ene-1,2,4-tri*-O-*acetate* **96** (56 mg, 2.3%) as a yellow oil in a 1:4.7 ratio by ^1H NMR, trituration of this oil with ethanol induced crystallisation which upon recrystallisation gave pure **96** by ^1H NMR; *3-deoxy-3-bromo*-chiro-*inositol penta*-O-*acetate* **94** and *1-deoxy-1-bromo*-neo-*inositol penta*-O-*acetate* **95** (456 mg, 13.8%) as an oil that crystallised on standing in a 1:2.9 ratio by ^1H NMR, recrystallisation from ethanol at ambient temperature gave pure **94** by ^1H NMR; *(1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetra*-O-*acetate* **98** and *(1β,2β,3β,4β,5α,6α)-2,3-epoxy-cyclohexane-1,4,5,6-tetra*-O-*acetate* **99** (108 mg, 4.5%) as a yellow oil in a 4.7:1 ratio by ^1H NMR and 016 (243 mg, 7.7%). Preparative HPLC (6.5% EtOAc in hexane, analytical column) of the reduced mother liquor of the diastereomers **97** and **96** effected separation. Less polar: **97**, retention time 31 min; more polar: **96**, retention time 32 min. Preparative HPLC (25% EtOAc in hexane) of the reduced mother liquor of the diastereomers **94** and **95** effected separation. Less polar: **94**, retention time 30.5 min; more polar: **95**, retention time 35.5 min. Preparative HPLC (30% EtOAc in hexane) of the mixture of diastereomers **98** and **99** effected separation. Less polar: **98**, retention time 27.9 min; more polar: **99**, retention time 30.9 min

(1β,2β,3β,4α)-4-Bromo-cyclohex-5-ene-1,2,3-tri-*O*-acetate 97

δ^1H(400 MHz, r.t., $CDCl_3$) 5.81 (1H, dt, J=2.3, 10.3 Hz, H-6), 5.76 (1H, dt, J=1.9 Hz, H-2), 5.73 (1H, dq, J=2.2, 9.0 Hz, H-3), 5.66 (1H, dq, J=1.9, 10.3 Hz, H-5), 5.63 (1H, m, J=2.3, H-1), 2.16, 2.14, 2.03 (3x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.2, 170.1, 169.9, 128.4 (C-6), 126.7 (C-5), 72.3 (C-2/3), 72.2 (C-2/3), 67.8 (C-1), 47.3 (C-4), 20.9, 20.7, 20.6.

ν_{max} (CH_2Cl_2) 1751, 1370, 1224, 1146, 1042, 931, 838 cm^{-1}.

m/z (70 eV, NH_3) 354/352 (100%, $[M+NH_4]^+$), 277/275 (26%, $[M-C_2H_3O]^+$), 255 (3%, $[M-Br]^+$), 196 (4%, $[M-Br-C_2H_3O]^+$).

m/z (FAB, Na) $C_{12}H_{15}O_6BrNa$ requires: 356.9950, found: 356.9954.

(1β,2β,3α,4β)-3-Bromo-cyclohex-5-ene-1,2,4-tri-*O*-acetate 96

δ^1H(400 MHz, r.t., $CDCl_3$) 5.90 (1H, ddd, J=1.6, 4.9, 9.9 Hz, H-6), 5.87 (1H, dd, J=2.0, 9.9 Hz, H-5), 5.65 (1H, br d, J=8.4 Hz, H-4), 5.60 (1H, t, J=4.2 Hz, H-1), 5.20 (1H, dd, J=4.0, 11.6 Hz, H-2), 4.32 (1H, dd, J=8.6, 11.7 Hz, H-3), 2.14, 2.09, 2.08 (3x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.9, 169.8, 169.4, 131.5 (C-5), 125.3 (C-6), 73.9 (C-4), 69.6 (C-2), 65.6 (C-1), 47.3 (C-3), 20.8, 20.8, 20.6.

ν_{max} (CH_2Cl_2) 2938, 1749, 1436, 1368, 1224, 1044, 962, 923, 836 cm^{-1}.

m/z (70 eV, NH_3) 354/352 (100%, $[M+NH_4]^+$), 277/275 (47%, $[M-C_2H_3O]^+$), 255 (14%, $[M-Br]^+$).

m.p.: 101-102 °C (ethanol).

Elemental analysis; calculated : C 43.01, H 4.51, Br 23.84.

found : C 43.06, H 4.43, Br 23.73.

3-Deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate 94

δ^1H(400 MHz, r.t., $CDCl_3$) 5.56 (1H, t, J=10.4 Hz, H-1), 5.36 (3H, m, H-1, 2, 6), 5.20 (1H, dd, J=3.2, 10.2 Hz, H-5), 4.17 (1H, t, J=10.8 Hz, H-3), 2.20, 2.17, 2.11, 2.07, 1.99 (5x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.7, 169.3, 169.2, 169.1, 168.8, 70.8, 70.6, 69.5, 67.7, 67.2, 47.9 (C-3), 20.8, 20.8, 20.6, 20.6, 20.5.

ν_{max} (CH_2Cl_2) 2964, 1755, 1431, 1371, 1223, 1145, 1052, 932, 737 cm^{-1}.

m/z (70 eV, NH_3) 472/470 (100%, $[M+NH_4]^+$), 395/393 (15%, $[M-C_2H_3O]^+$).

m.p. 157-159 °C (ethanol), (lit.[154]: 159 °C).

Elemental analysis; calculated : C 42.41, H 4.67 Br 17.63.

found : C 42.62, H 4.70, Br 17.42.

Chrystallographic determination (see appendix A).

1-Deoxy-1-bromo-*neo*-inositol penta-*O*-acetate 95

δ^1H(400 MHz, r.t., $CDCl_3$) 5.72 (1H, t, J=2.9 Hz, H-2), 5.61 (1H, t, J=3.0 Hz, H-5), 5.33 (1H, dd, J=2.6, 11.4 Hz, H-6), 5.32 (1H, dd, J=3.0, 10.9 Hz, H-4), 5.22 (1H, dd, J=2.9, 10.9 Hz, H-3), 4.36 (1H, dd, J=2.9, 11.4 Hz, H-1), 2.18, 2.14, 2.05 (3x3H, s, $OCOCH_3$), 1.98 (6H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.0, 169.6, 169.6, 169.4, 169.2, 69.7, 69.6, 68.9, 68.4, 66.9, 45.2 (C-1), 20.6, 20.5.

ν_{max} (CH_2Cl_2) 2986, 1755, 1436, 1372, 1224, 1107, 1078, 1045, 947, 900, 790 cm^{-1}.

m/z (70 eV, NH_3) 472/470 (100%, $[M+NH_4]^+$).

Elemental analysis; calculated : C 42.40, H 4.67, Br 17.63.

found : C 42.16, H 4.82, Br 17.37.

(1β,2β,3β,4α,5α,6α)-1,2-Epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate.

(1,2-Anhydro-*neo*-inositol tetra-*O*-acetate) 98

δ^1H(400 MHz, r.t., $CDCl_3$) 5.50 (1H, dd, J=2.3, 9.2 Hz), 5.44 (1H, dt, J=1.9, 3.8 Hz), 5.17 (1H, d, J=3.8 Hz), 5.03 (1H, dd, J=1.8, 9.2 Hz), 3.60 (1H, dd, J=2.4, 3.7 Hz), 3.22 (1H, dd, J=1.9, 3.7 Hz), 2.14, 2.12, 2.06, 2.00 (4x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.7, 169.9, 169.7, 169.0, 69.3, 69.3, 67.4, 66.5, 54.9, 53.9, 20.4, 20.3, 20.3, 20.1.

ν_{max} (CH_2Cl_2) 2965, 1748, 1436, 1371, 1224, 1041, 961, 932, 907, 880, 835 cm^{-1}.

m/z (70 eV, NH_3) 348 (100%, $[M+NH_4]^+$), 331 (93%, $[M+H]^+$), 271 (13%, $[M-C_2H_3O]^+$).

m/z (FAB, Na) $C_{14}H_{18}O_9Na$ requires: 353.0849, found: 353.0845.

(1β,2β,3β,4β,5α,6α)-2,3-Epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate.

(2,3-anhydro-*allo*-inositol tetra-*O*-acetate) 99

δ^1H(400 MHz, r.t., $CDCl_3$) 5.22 (4H, br s, H-1, 4, 5, 6), 3.52 (2H, br s, H-2, 3), 2.16 (6H, s, 2x$OCOCH_3$), 2.07 (6H, s, 2x$OCOCH_3$).

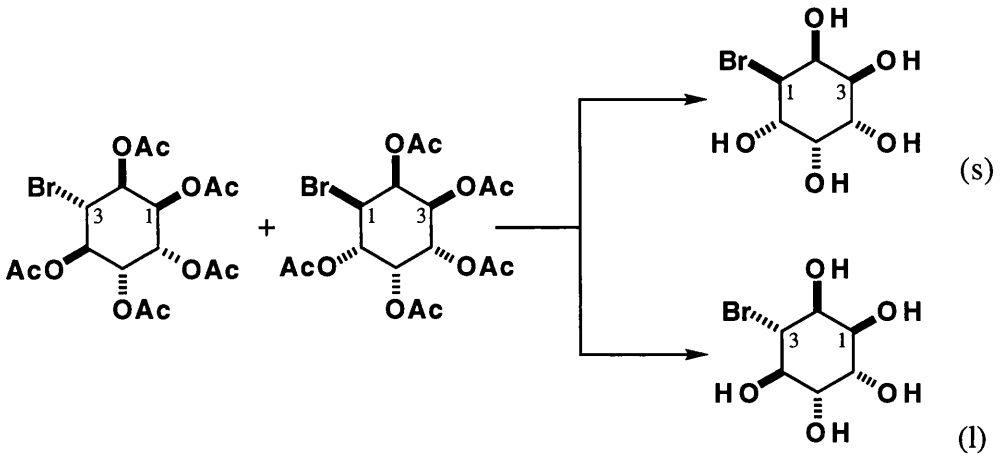
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.2, 169.5, 69.2, 68.7, 53.4 (C-2, 3), 20.8.

ν_{max} (CH_2Cl_2) 2930, 2860, 1749, 1459, 1373, 1271, 1227, 1124, 1072, 1043 cm^{-1}.

m/z (70 eV, NH_3) 348 (100%, $[M+NH_4]^+$), 331 (11%, $[M+H]^+$) 271% (3, $[M-C_2H_3O]^+$).

m/z (FAB, Na) $C_{14}H_{18}O_9Na$ requires: 353.0849, found: 353.0845.

7. Separation of **95** from **94** by means of acid catalysed deacetylation: 1-deoxy-1-chloro-*neo*-inositol **95**-OH and 3-deoxy-3-chloro-*chiro*-inositol **94**-OH.



To a solution of the *bromopentaacetates* **94** and **95** (337 mg, 0.74 mmol, 3:2 respectively) in methanol (20 mL) and dichloromethane (2 mL) was added c. HCl (10 drops). The solution was heated to reflux overnight upon which tlc (7:3, ether:petrol) showed a single baseline spot. The solution was allowed to cool to r.t. upon which a white precipitate formed. The solution was then cooled on an ice-water bath for a further 2 h and the precipitate filtered off (59 mg, 83%) and shown to be pure **95**-OH by ^{1}H NMR. The filtrate was evaporated to dryness and filtered through a short pad of silica (7:3, EtOAc:MeOH) to yield **94**-OH (74 mg, 41%) as a gum.

1-Deoxy-1-bromo-*neo*-inositol 95-OH

δ^1H(400 MHz, r.t., D_2O) 4.17 (1H, dd, J=2.6, 11.2 Hz), 4.06 (1H, t, J=2.8 Hz), 3.98 (1H, t, J=2.9 Hz), 3.77 (1H, dd, J=3.0, 11.2 Hz), 3.69 (1H, dd, J=2.6, 10.4 Hz), 3.67 (1H, dd, J=2.6, 10.4 Hz).

δ^{13}C(100 MHz, r.t., D_2O) 75.1, 75.0, 72.7, 72.3, 71.7, 57.9 (C-1).

m/z (70 eV, NH_3) 262/260 (100%, $[M+NH_4]^+$), 244/242 (16%, $[M+H]^+$).

m.p.: (decomposed) 190-195 °C (methanol).

Elemental analysis; calculated: C 29.64, H 4.53, Br 32.89.

found: C 27.80, H 5.09, Br 30.92.

calculated for $C_6H_{11}O_5Br \cdot H_2O$: C 27.59, H 4.98, Br 30.62.

3-Deoxy-3-bromo-*chiro*-inositol 94-OH

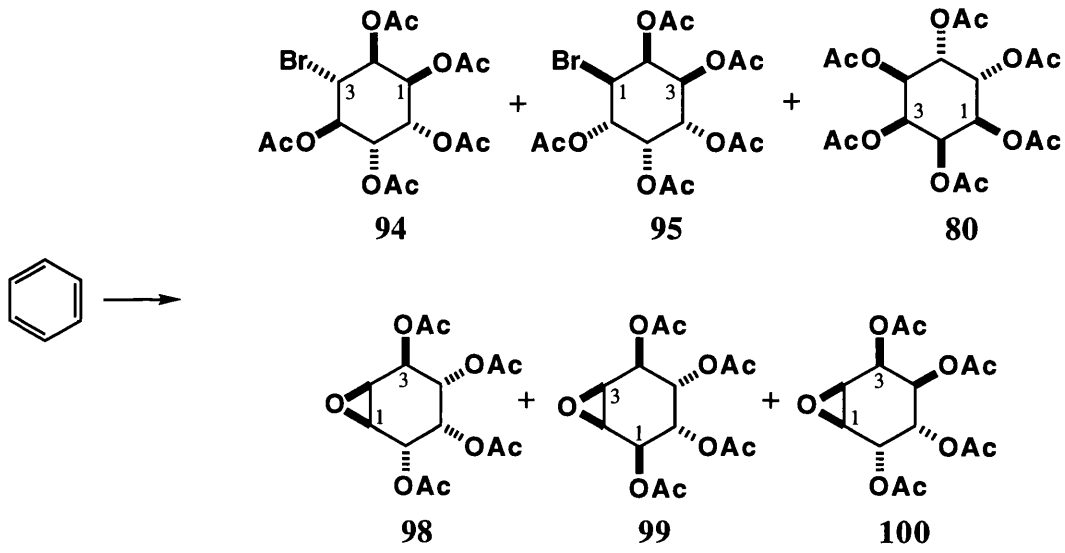
δ^1H(400 MHz, r.t., D_2O) 4.04 (4H, m), 3.82 (1H, m), 3.76 (1H, m).

δ^{13}C(100 MHz, r.t., D_2O) 75.8, 75.0, 74.0, 73.9, 73.7, 61.3 (C-3).

m/z (70 eV, NH_3) 260/262 (23%, $[M+NH_4]^+$).

m/z (CI, NH_3) $C_6H_{15}NO_5Br$ requires: 260.0134, found: 260.0130.

8. Photoosmylation of benzene with sodium bromate with basic work-up: 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**, 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95**, *allo*-inositol hexa-*O*-acetate **80**, (1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate **98**, (1β,2β,3β,4β,5α,6α)-2,3-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **99** and (1β,2β,3β,4β,5α,6α)-1,2-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **100**.



To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added sodium bromate (2.75 g, 18.2 mmol) and de-ionised water (50 mL). Upon solvation of the bromate salt the benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h without fan-assisted cooling $T_{irradiation}$=52 °C. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (7 g, 37 mmol) over 15 min throughout which the reaction mixture turned orange, red and finally grey-black. The opaque slurry was then neutralised with NaOH (2 M) and evaporated under reduced pressure. The residue was then treated with triethylamine (50

mL) heated to 50 °C and stirred for 17 h upon which acetic anhydride (20 mL) and DMAP (cat) were added. The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) added. The mixture was then filtered through a pad of Celite and the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of all volatiles under reduced pressure gave an oil. Column chromatography (7:3, ether:petrol) of this oil gave **94** and **95** (101 mg, 3.1%) as a yellow solid as a 1:1.1 mixture by ^1H NMR; **98**, **99** and *(1β,2β,3β,4β,5α,6α)-1,2-Epoxy-cyclohexane-3,4,5,6-tetra*-O-*acetate* **100** (421 mg, 17.5%) as a yellow oil in a 3:5:5 ratio by ^1H NMR and **80** (256 mg, 8.1%) as a yellow solid. Preparative HPLC (30% EtOAc in hexane) of the mixture of diastereomers **98**, **99** and **100** effected separation. Less polar: **98**, retention time 29.2 min; mid. polar: **99**, retention time 32.5 min; most polar: **100**, retention time 34.1 min.

(1β,2β,3β,4β,5α,6α)-1,2-Epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate. (1,2-anhydro-*allo*-inositol tetra-*O*-acetate) 100

δ^1H(400 MHz, r.t., $CDCl_3$) 5.70 (1H, dd, J=1.9, 3.3 Hz, H-3), 5.57 (1H, dd, J=4.3, 5.1 Hz, H-6), 5.32 (1H, J=3.3, 9.9 Hz, H-4), 5.28 (1H, dd, J=5.1, 9.9 Hz, H-5), 3.47 (1H, dd, J=3.4, 4.1 Hz, H-1), 3.32 (1H, dd, J=2.2, 3.4 Hz, H-2), 2.14 (6H, s, 2x$OCOCH_3$), 2.04, 2.02 (2x3H, s, $OCOCH_3$).

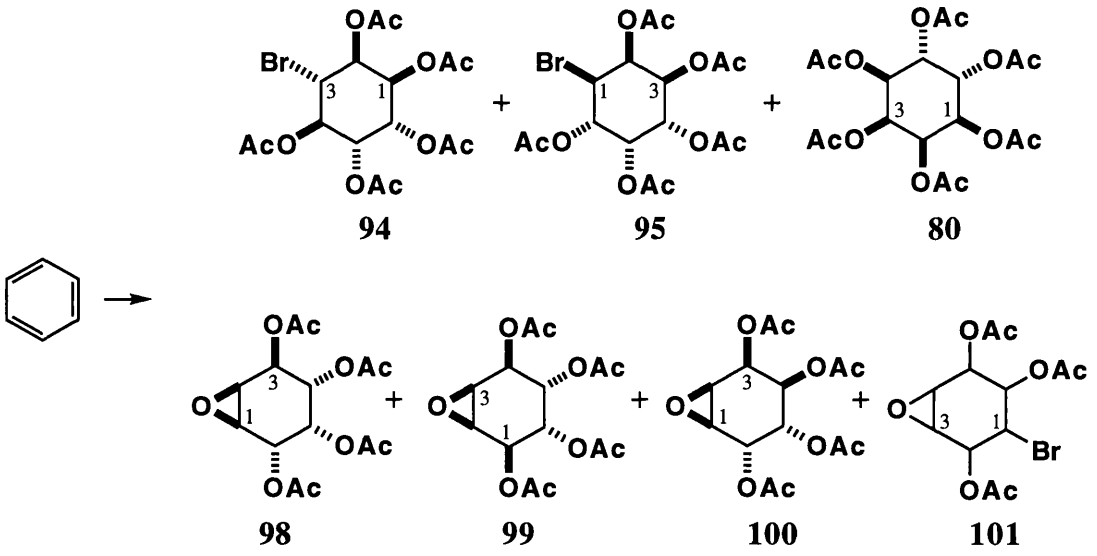
$\delta^{13}C$(100 MHz, r.t., $CDCl_3$) 170.2, 169.9, 169.7, 169.4, 66.6, 65.8, 65.7, 65.3, 53.3 (C-1/2), 51.0 (C-1/2), 20.7, 20.6.

ν_{max} (CH_2Cl_2) 2961, 2933, 1748, 1652, 1436, 1372, 1228, 1100, 1066, 896 cm^{-1}.

m/z (70 eV, NH_3) 348 (100%, $[M+NH_4]^+$), 331 (12%, $[M+H]^+$).

m/z (FAB, Na) $C_{14}H_{18}O_9Na$ requires: 353.0849, found: 353.0845.

9. Photoosmylation of benzene using sodium bromate at various concentrations (table 2.20: 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**, 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95**, *allo*-inositol hexa-*O*-acetate **80**, (1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate **98**, (1β,2β,3β,4β,5α,6α)-2,3-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **99** and (1β,2β,3β,4β,5α,6α)-1,2-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **100** and 1-bromo-3,4-epoxy-cyclohexane-2,5,6-tri-*O*-acetate **101**.



At [0.44 M].

Using the same procedure as for experiment 6., except sodium bromate (5.5 g, 36.4 mmol) was used. Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained gave *1-bromo-3,4-epoxy-cyclohexane-2,5,6-tri*-O-*acetate* **101** (23 mg, 0.9%) as a yellow oil; a mixture of **94** and **95** (440 mg, 13.3%) as a yellow solid in a 1.6:1 ratio by ^{1}H NMR; a mixture of **98**, **99** and **100** (96 mg, 4.0%) as a yellow oil in a 5:3.2:1 ratio by ^{1}H NMR and **80** (355 mg, 11.3%) as a yellow solid.

At [2.65 M].

Using the general procedure C except sodium bromate (4 g, 26.5 mmol) was used. Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained gave **101** (38 mg, 1.5%) as a yellow oil; a mixture of **94** and **95** (413 mg, 12.5%) as a yellow solid in a 3.3:1 ratio by ^{1}H NMR; a mixture of **98** and **99** (36 mg, 1.5%) as a yellow oil in a 2.1:1 ratio by ^{1}H NMR and **80** (435 mg, 13.8%) as a yellow solid.

1-Bromo-3,4-epoxy-cyclohexane-2,5,6-tri-*O*-acetate 101

δ^1H(400 MHz, r.t., $CDCl_3$)5.56 (2H, m, J=1.6, 2.0, 2.8, 3.4, 10.0 Hz, H-2, 6), 5.13 (1H, dd J=0.7, 3.4 Hz, H-5), 4.02 (1H, dd, J=1.6, 9.9 Hz, H-1), 3.53 (1H, ddd, J=0.6, 2.8, 3.7 Hz, H-3/4), 3.24 (1H, dd, J=1.9, 3.7 Hz, H-3/4), 2.18, 2.18, 2.05 (3x3H, s, $OCOCH_3$).

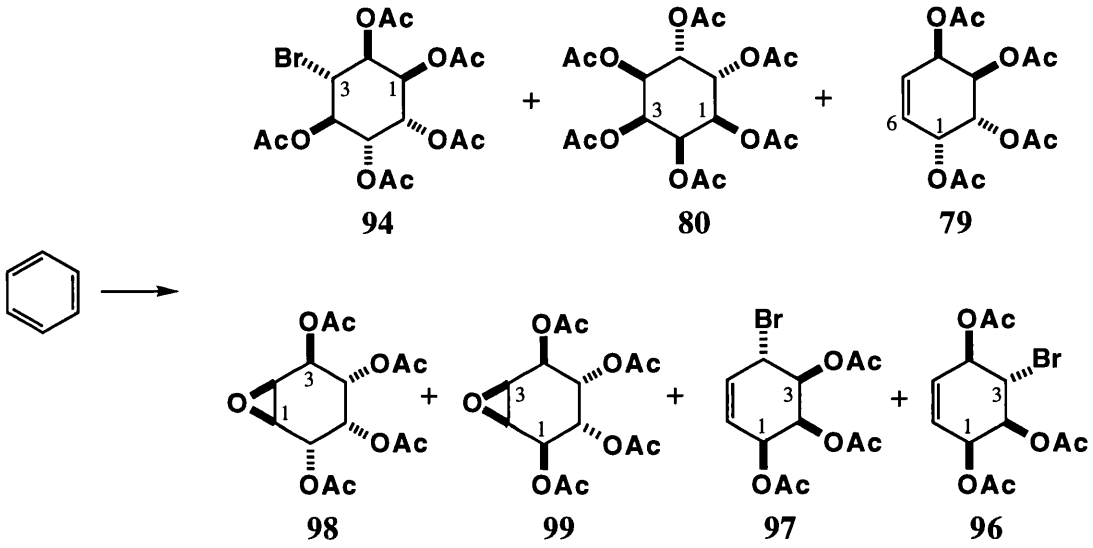
δ^{13}C(100 MHz, r.t., $CDCl_3$)170.4, 169.7, 169.1, 71.9 (C-2/6), 71.7 (C-2/6), 66.6 (C-5), 54.8 (C-3/4), 53.8 (C-3/4), 43.8 (C-1), 20.8, 20.6, 20.5.

ν_{max} (CH_2Cl_2) 2966, 1750, 1436, 1369, 1223, 1045, 918, 888, 824 cm^{-1}.

m/z (70 eV, NH_3) 370/368 (78%, $[M+NH_4]^+$), 353/351 (91%, $[M+H]^+$).

m/z (EI, H^+) $C_{12}H_{16}O_7Br$ requires: 351.0079, found 351.0074.

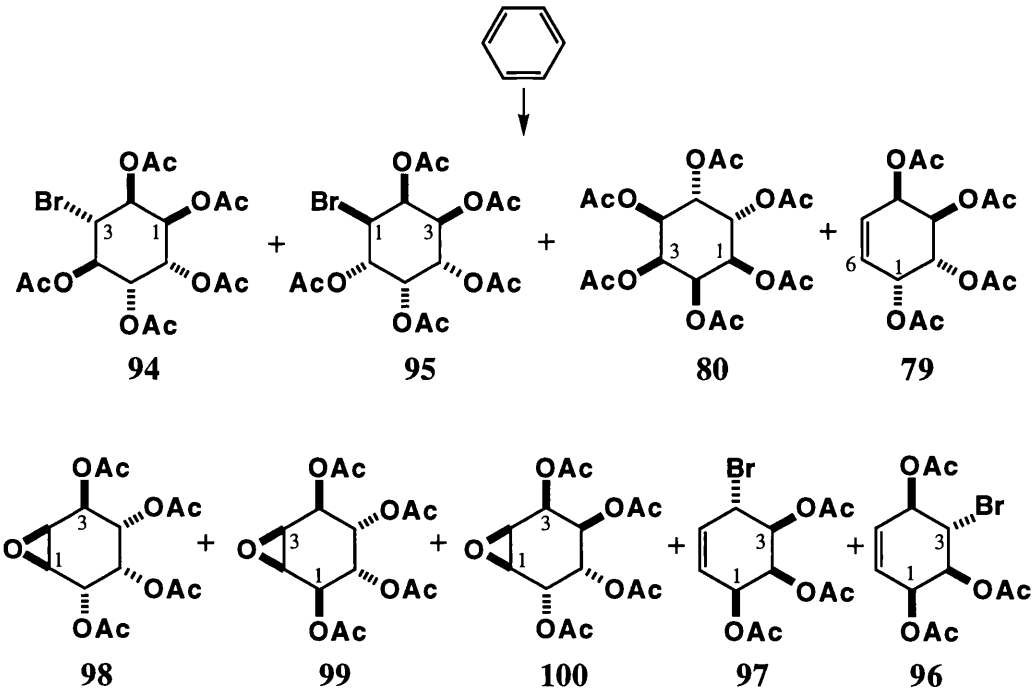
10. Photoosmylation of benzene using sodium bromate [0.12 M] at 20 °C: 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**, *allo*-inositol hexa-*O*-acetate **80**, (1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate **98**, (1β,2β,3β,4β,5α,6α)-2,3-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **99**, conduritol E tetra-*O*-acetate **79**, (1β,2β,3β,4α)-4-bromo-cyclohex-5-ene-1,2,3-tri-*O*-acetate **97** and (1β,2β,3α,4β)-3-bromo-cyclohex-5-ene-1,2,4-tri-*O*-acetate **96**.



To a florentine shaped flask fitted with a Teflon tap and a glass cooling jacket (reaction vessel D) was added sodium bromate (905 mg, 6 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Tap water was continuously passed through the cooling jacket at such a rate that $T_{water\ in}=T_{water\ out}$ (±1°). Irradiation of the reaction mixture was then carried out over 43 h with fan-assisted cooling. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath, water (50 mL) added and treated portionwise with sodium metabisulphite (2.6 g) over 15 min. The black solution was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-

45 °C). The moist salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (cat). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite, the filtrate extracted with ether (3 x 75 mL), and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the organic volatiles under reduced pressure gave a brown oil. Column chromatography (1:1 to 7:3, ether:petrol) of this oil gave **96** and **97** (60 mg, 2.5%) as a yellow oil in a 5.5:1 ratio by ^1H NMR; **94** and **79** (294 mg, 10.3%) as a yellow solid in a 1.3:1 ratio by ^1H NMR; **98** and **99** (56 mg, 2.3%) as a yellow oil in 3:1 ratio by ^1H NMR and **80** (184 mg, 5.7%) as a yellow solid.

11. Photoosmylation of benzene with sodium bromate with a sacrificial olefin work-up at variable temperatures (table 2.21): 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**, 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95**, *allo*-inositol hexa-*O*-acetate **80**, (1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetra-*O*-acetate **98**, (1β,2β,3β,4β,5α,6α)-2,3-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **99** and (1β,2β,3β,4β,5α,6α)-1,2-epoxy-cyclohexane-1,4,5,6-tetra-*O*-acetate **100**, (1β,2β,3β,4α)-4-bromo-cyclohex-5-ene-1,2,3-tri-*O*-acetate **97**, (1β,2β,3α,4β)-3-bromo-cyclohex-5-ene-1,2,4-tri-*O*-acetate **96** and conduritol E tetra-*O*-acetate **79**.



General procedure:

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C or D) was added sodium bromate (2.75 g, 18.2 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. The reaction

mixture was then irradiated at the given temperature for 43 h. Upon irradiation the reaction mixture was transferred to a 250 mL Büchi-type flask and cooled on an ice-water bath. The cooled reaction mixture was then treated with cyclohexene (20 mL) and a solution of ^{n}PrOH/acetone (1:1) until a homogeneous mixture was obtained (typically 100-120 mL of ^{n}PrOH/acetone required). A solution of sodium metabisulphite (5.7 g) in water (10 mL) was then added dropwise over 40-45 min to the stirred solution upon which it had turned black. The solution was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with triethylamine (50 mL), acetic anhydride (20 mL) and DMAP (catalytic quantity). The resulting mixture was stirred at 70-80 °C for 3 h after which it was cooled in an ice-water bath and water (100 mL) was added. The mixture was then filtered through a pad of Celite, the filtrate extracted with ether (3 x 75 mL) and the combined ethereal extracts dried over $MgSO_4$. Evaporation of the organic volatiles under reduced pressure gave the crude products.

At 2 °C:

Photoosmylation was carried out in reaction vessel D using the general procedure for low temperature reactions (general procedure B). Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained gave **96** and **97** (99 mg, 4.1%) as an oil that crystallised on standing in a 4:1 ratio by ^{1}H NMR; **79** and **94** (334 mg, 12.7%) as a yellow solid in a 2.1:1 ratio by ^{1}H NMR; **98** and **99** (50 mg, 2.0%) as an oil in a 10:1 ratio by ^{1}H NMR and **80** (168 mg, 5.3%) as a yellow solid.

At 10 °C:

Photoosmylation was carried out in reaction vessel D using water at 10 °C to cool the reaction mixture. Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained gave **96** and **97** (67 mg, 2.7%) as an oil that crystallised on standing in a 3:1 ratio by ^{1}H NMR; **79** and **94** (352 mg, 12.5%) as a yellow solid in a 1:1.1 ratio by ^{1}H NMR; **98**, **99** and **100** (63 mg, 2.6%) as an oil in a 10:2.5:1 ratio by ^{1}H NMR and **80** (268 mg, 8.5%) as a yellow solid.

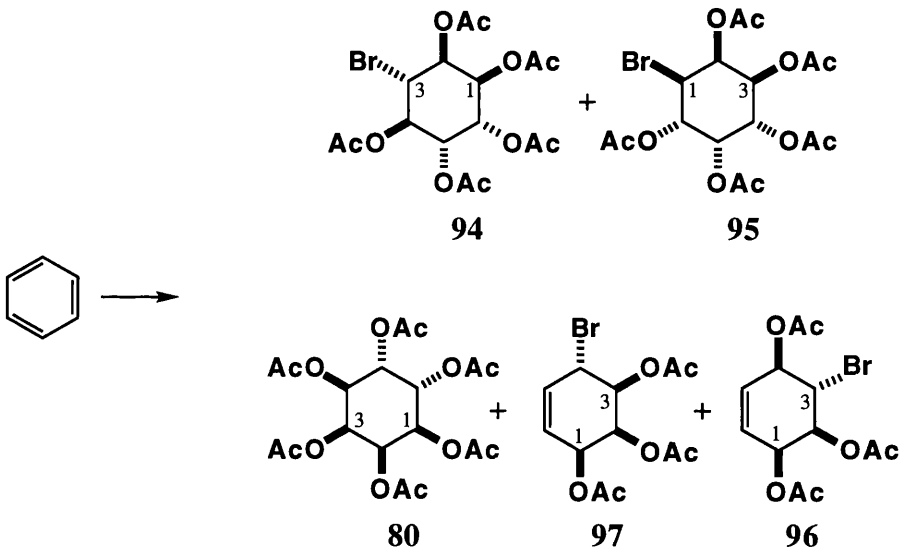
At 15 °C:

Photoosmylation was carried out in reaction vessel D using tap-water at 15 °C to cool the reaction mixture. Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained gave **96** and **97** (66 mg, 2.7%) as an oil that crystallised on standing in a 4:1 ratio by ^{1}H NMR; **79**, **95** and **94** (437 mg, 15.1%) as a yellow solid in a **79**:**95+94** ratio of 1:1.5 (**94**:**95**, 18:1) by ^{1}H NMR; **98**, **99** and **100** (83 mg, 3.4%) as an oil in a 7.7:3:1 ratio by ^{1}H NMR and **80** (246 mg, 7.8%) as a yellow solid.

At 45 °C:

Photoosmylation was carried out in reaction vessel C without fan-assisted cooling. Column chromatography (1:1 to 7:3, ether:petrol) of the dark yellow oil obtained gave **79**, **95** and **94** (308 mg, 9.5%) as a yellow solid in a **79**:**95+94** ratio of 1:22 (**94**:**95**, 5.6:1) by ^{1}H NMR; **98** and **99** (51 mg, 2.1%) as an oil in a 7:1 ratio by ^{1}H NMR and **80** (138 mg, 4.4%) as a yellow solid.

12. Photoosmylation of benzene with sodium bromate using an acid catalysed acetylation protocol (table 2.22): 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**, 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95**, (1β,2β,3β,4α)-4-bromo-cyclohex-5-ene-1,2,3-tri-*O*-acetate **97**, (1β,2β,3α,4β)-3-bromo-cyclohex-5-ene-1,2,4-tri-*O*-acetate **96** and *allo*-inositol hexa-*O*-acetate **80**.



General procedure:

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C or D) was added sodium bromate (2.75 g, 18.2 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. The reaction mixture was then irradiated at the given temperature for 43 h. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath, water (50 mL) added and treated portionwise with sodium metabisulphite (8 g) over 15 min. The black solution was then evaporated (rotary evaporator, waterbath 40-45 °C). The moist salts were then treated with acetic acid (50 mL) and acetic anhydride (20 mL). The resulting mixture was stirred at 70-80 °C for 15 h after which it

was cooled in an ice-water bath and reduced (rotary evaporator). Water (100 mL) was then added and the mixture filtered through a pad of Celite. The filtrate was then extracted with ether (3 x 100 mL) and the combined ethereal extracts washed with brine and dried over $MgSO_4$. Evaporation of the organic volatiles then afforded the crude products.

At 2 °C:

Photoosmylation was carried out in reaction vessel D using the general procedure for low temperature reactions (general procedure B). Column chromatography (1:1 to 7:3, ether:petrol) of the yellow-brown oil obtained gave **96** and **97** (55 mg, 2.3%) as an oil that crystallised on standing in a 3.3:1 ratio by ^1H NMR; **94** and **95** (417 mg, 12.6%) as an off-white solid in a 1:2 ratio by ^1H NMR and **80** (161 mg, 5.1%) as a yellow solid.

At 15 °C:

Photoosmylation was carried out in reaction vessel D using water at 15 °C to cool the reaction mixture. Column chromatography (1:1 to 7:3, ether:petrol) of the oil obtained gave **96** and **97** (26 mg, 1.1%) as an oil in a 2.9:1 ratio by ^1H NMR; **94** and **95** (539 mg, 16.3%) as an oil that crystallised on standing in a 1:1 ratio by ^1H NMR and **80** (233 mg, 7.4%) as an off-white solid.

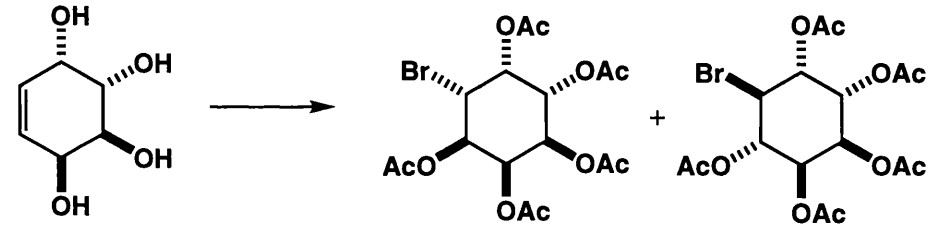
At 30 °C:

Photoosmylation was carried out in reaction vessel C at 30 °C. Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained gave **96** and **97** (56 mg, 2.3%) as an oil in a 5:1 ratio by ^1H NMR; **94** and **95** (622 mg, 18.8%) as a yellow solid in a 5.1:1 ratio by ^1H NMR and **80** (243 mg, 7.7%) as an off-white solid.

At 45 °C:

Photoosmylation was carried out in reaction vessel C at 45 °C. Column chromatography (1:1 to 7:3, ether:petrol) of the yellow oil obtained **94** and **95** (476 mg, 14.4%) as a yellow solid in a 5:1 ratio by ^{1}H NMR and **80** (240 mg, 7.7%) as an off-white solid.

13. Preparation of 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94** and 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95** from conduritol E.

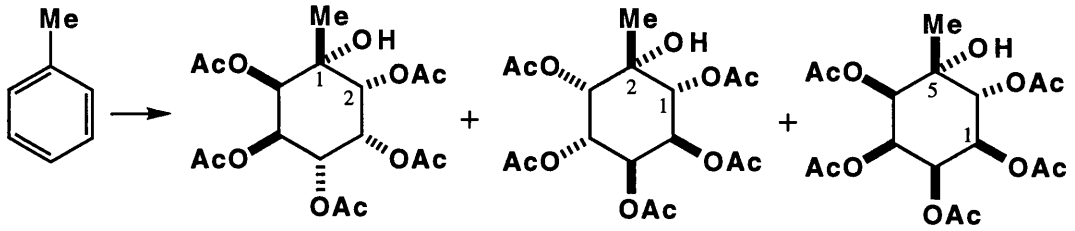


conduritol E **95** **94**

To a stirred solution of conduritol E **79**-OH (20 mg, 0.14 mmol) in de-ionised water (15 mL) was added sodium bromate (0.858 g, 5.7 mmol). The solution was cooled on an ice-water bath and sodium metabisulphite (1.76 g, 9 mmol) was added portionwise over 15 min. The clear, colourless solution turned orange and, upon addition of the final portion of metabisulphite, turned back to clear and colourless. The acidic solution was then neutralised with NaOH (2 M) and evaporated to dryness under reduced pressure. The remaining salts were treated with acetic acid (10 mL) and acetic anhydride (3 mL) and heated for 15 h at 100 °C. The reaction mixture was then cooled, concentrated, and added to water (20 mL). Extraction of this aqueous mixture with ether (3x20 mL) followed by washing of the combined ethereal extracts with brine (50 mL), drying over $MgSO_4$, and evaporation of the organic volatiles left a gummy residue. ^{1}H NMR analysis of this residue showed a mixture of **95** and **94** in a 6.3:1 ratio.

3.2.4 Experimental procedures for section 2.5

1. Photoosmylation of toluene at 45 °C using a r.t. acetylation protocol: 2-*C*-methyl-*allo*-inositol-1,3,4,5,6-penta-*O*-acetate-2-ol **104**, 1-*C*-methyl-*allo*-inositol-2,3,4,5,6-penta-*O*-acetate-1-ol **103** and 5-*C*-methyl-*allo*-inositol-1,2,3,4,6-penta-*O*-acetate-5-ol **102**.



103 **104** **102**

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added barium chlorate monohydrate (3.53 g, 11 mmol) and de-ionised water (50 mL). Upon solvation of the chlorate salt, toluene was added (0.77 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol, in carbon tetrachloride 0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 h with fan-assisted cooling. The operating temperature of the reaction was taken with a mercury thermometer positioned directly behind the reaction vessel, out of the direct path of irradiation. Upon irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled on an ice-water bath and treated portionwise with sodium metabisulphite (9 g, 47 mmol) over 15 min. The brown opaque slurry was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The remaining salts were then taken up in pyridine (50 mL) and acetic anhydride (20 mL) and stirred at r.t. for 3 days. Methanol (20 mL) was then added and the reaction stirred for a further 15 h upon which it was

concentrated under reduced pressure. Water (50 mL) was then added and the mixture extracted with ether (3 x 75 mL). The combined ethereal extracts were washed with a saturated solution of copper sulphate (2 x 100 mL), brine (100 mL) and dried over $MgSO_4$. Evaporation of the organic volatiles left a yellow oil. Column chromatography (7:3 to 1:0, ether:petrol) gave, in order of elution, 2-*C*-methyl-*allo*-inositol-1,3,4,5,6-penta-*O*-acetate-2-ol **104** (116 mg, 3.9%) as a crystalline solid; 1-*C*-methyl-*allo*-inositol-2,3,4,5,6-penta-*O*-acetate-1-ol **103** (56 mg, 1.9%) as a crystalline solid and 5-*C*-methyl-*allo*-inositol-1,2,3,4,6-penta-*O*-acetate-5-ol **102** (59 mg, 2.0%) as an oil.

2-*C*-Methyl-*allo*-inositol-1,3,4,5,6-penta-*O*-acetate-2-ol 104

δ^1H(400 MHz, 60 °C, $CDCl_3$) 5.47 (1H, dd, J=3.3, 9.8 Hz, H-6), 5.39 (1H, dd, J=3.3, 4.7 Hz, H-5), 5.30 (1H, dd, J=3.8, 4.6 Hz, H-4), 5.22 (1H, d, J=9.8 Hz, H-1), 5.10 (H1, d, J=3.8 Hz, H-3), 2.58 (1H, br s, OH, visible at r.t.), 2.12, 2.11, 2.10, 2.08, 1.96 (5x3H, s, $OCOCH_3$), 1.21 (3H, s, H-7).

δ^{13}C(100 MHz, 60 °C, $CDCl_3$) 169.8, 169.5, 169.5, 169.1, 169.0, 74.1 (C-2), 72.3, 70.8, 68.8, 67.8, 67.7, 23.1 (C-7), 20.6, 20.6, 20.5, 20.5, 20.4.

ν_{max} (CH_2Cl_2) 3484, 2961, 1751, 1431, 1372, 1228, 1070, 1044, 929 cm^{-1}.

m/z (70 eV, NH_3) 422 (100%, $[M+NH_4]^+$), 405 (1%, $[M+H]^+$), 387 (27%, $[M-OH]^+$), 345 (9%, $[M-CH_3CO_2]^+$).

m.p. 132-133 °C (ethanol).

Elemental analysis; calculated: C 50.50, H 5.98; found: C 50.21, H 6.01.

1-*C*-Methyl-*allo*-inositol-2,3,4,5,6-penta-*O*-acetate-1-ol 103

δ^1H(400 MHz, r.t., $CDCl_3$) 5.68 (1H, br t, J=3.2 Hz, H-3), 5.61 (1H, dd, J=3.1, 11.2 Hz, H-5), 5.36 (1H, d, J=3.1 Hz, H-6), 5.32 (1H, dd, J=3.4, 11.1 Hz, H-4), 5.10 (1H, d, J=3.4 Hz, H-2), 2.99 (1H, br s, OH), 2.17, 2.15, 2.11 (3x3H, s, $OCOCH_3$), 1.99 (6H, s, 2x$OCOCH_3$), 1.12 (3H, s, H-7).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 168.8, 169.6, 169.5, 169.4, 73.8 (C-1), 73.4, 70.0, 69.2, 67.1, 67.0.

ν_{max} (CH_2Cl_2) 3486, 2983, 1749, 1732, 1433, 1372, 1228, 1076, 1054, 919 cm^{-1}.

m/z (70 eV, NH_3) 422 (100%, $[M+NH_4]^+$), 387 (9%, $[M-OH]^+$), 345 (4%, $[M-CH_3CO_2]^+$).

m.p. 146-147 °C (ethanol).

Elemental analysis; calculated: C 50.50, H 5.98; found: C 50.33, H 5.66.

5-*C*-Methyl-*allo*-inositol-1,2,3,4,6-penta-*O*-acetate-5-ol 102

δ^1H(400 MHz, 60 °C, $CDCl_3$) 5.61 (1H, ddd, J=1.3, 3.3, 3.4 Hz, H-2), 5.45 (1H, t, J=3.6 Hz, H-3) 5.44 (1H, d, J=10.5 Hz, H-6), 5.40 (1H, dd, J=3.2, 10.5 Hz, H-1), 5.26 (1H, dd, J=1.3, 3.7 Hz, H-4), 2.32 (1H, br s, OH) 2.14, 2.14, 2.10, 1.97, 1.96 (5x3H, s, $OCOCH_3$), 1.21 (3H, s, H-7).

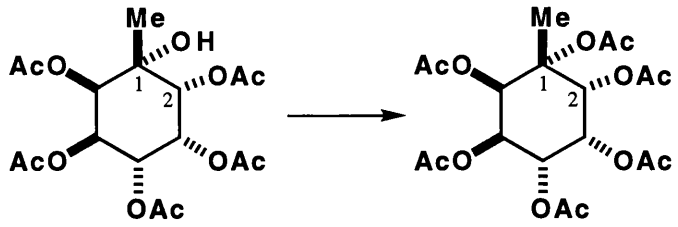
δ^{13}C(100 MHz, 60 °C, $CDCl_3$) 170.1, 170.0, 169.8, 169.7, 169.4, 73.5, 72.9 (C-5), 71.2, 69.1, 68.5, 66.0, 22.8 (C-7), 20.8, 20.7, 20.7, 20.6, 20.5.

ν_{max} (CH_2Cl_2) 3479, 2982, 1749, 1732, 1372, 1229, 1056, 975, 928, 904, 830 cm^{-1}.

m/z (70 eV, NH_3) 422 (100%, $[M+NH_4]^+$), 387 (7%, $[M-OH]^+$), 345 (4%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na) $C_{17}H_{24}O_{11}Na$ requires: 427.1216, found: 427.1212.

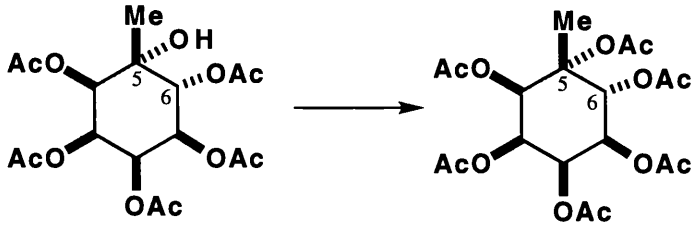
2. Preparation of 1-*C*-methyl-*allo*-inositol hexa-*O*-acetate **77**.



103 **77**

To a solution of **103** (20 mg, 0.05 mmol) in dichloromethane (1 mL) was added triethylamine (1 mL), acetic anhydride (0.5 mL) and DMAP (cat). The stirred reaction mixture was heated to reflux for 4 h. Evaporation of all volatiles at reduced pressure gave a brown gum. ^{1}H NMR analysis of this gum gave a spectrum identical with that of **77** already reported.

3. Preparation of 5-*C*-methyl-*allo*-inositol hexa-*O*-acetate **106**.



102 **106**

To a solution of **102** (36 mg, 0.09 mmol) in dichloromethane (1 mL) was added triethylamine (1 mL), acetic anhydride (0.5 mL) and DMAP (cat). The stirred reaction mixture was heated to reflux for 2.5 h. Evaporation of all volatiles at reduced pressure gave a yellow oil which was filtered through a short pad of silica with ether to afford **106** (30 mg, 75%) as a yellow oil.

5-*C*-Methyl-*allo*-inositol hexa-*O*-acetate 106

δ^1H(400 MHz, r.t., $CDCl_3$) 6.11 (1H, br d, J=2.3 Hz, H-4), 5.61 (1H, ddd, J=1.3, 3.4, 3.5 Hz, H-2), 5.55 (1H, d, J=10.6 Hz, H-6), 5.34 (1H, dd, J=3.5, 10.6 Hz, H-1), 5.15 (1H, t, J=3.5 Hz, H-3), 2.13, 2.12, 2.12, 2.10,1.98, 1.96 (6x3H, s, $OCOCH_3$), 1.54 (3H, s, H-7).

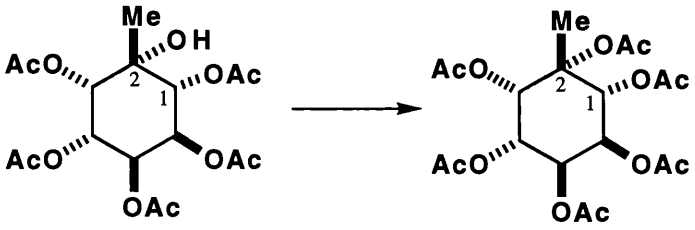
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.1, 170.1, 169.6, 169.2, 169.1, 169.1, 81.3 (C-5), 70.4, 69.1, 68.4, 67.8, 65.4, 22.0, 20.8, 20.7, 20.7, 20.5, 20.4, 18.4 (C-7).

ν_{max} (CH_2Cl_2) 2992, 1749, 1372, 1232, 1156, 1090, 1058, 953, 923 cm^{-1}.

m/z (70 eV, NH3) 464 (100%, $[M+NH_4]^+$), 404 (1%, $[M-C_2H_2O]^+$), 387 (6%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na) $C_{19}H_{26}O_{12}Na$ requires: 469.1322, found: 469.1325.

4. Preparation of 2-*C*-methyl-*allo*-inositol hexa-*O*-acetate **105**.



104 **105**

To a solution of **104** (28 mg, 0.07 mmol) in dichloromethane (0.5 mL) was added triethylamine (1 mL), acetic anhydride (0.5 mL) and DMAP (cat). The stirred reaction mixture was heated to reflux for 3 h. Evaporation of all volatiles at reduced pressure gave a yellow oil which was filtered through a short pad of silica with ether to afford **105** (21 mg, 52%) as an oil.

2-*C*-Methyl-*allo*-inositol hexa-*O*-acetate 105

δ^1H(400 MHz, 70 °C, $CDCl_3$) 5.51 (1H, dd, J=3.5, 7.3 Hz, H-4), 5.46 (1H, dd, J=3.5, 6.9 Hz, H-5) 5.41 (1H, d, J=3.0 Hz, H-3), 5.40 (1H, d, J=6.9 Hz, H-1), 5.32 (1H, dd, J=3.5, 6.9 Hz, H-6), 2.10, 2.10, 2.08, 2.07, 2.05, 2.02 (6x3H, s, $OCOCH_3$), 1.74 (3H, s, H-7).

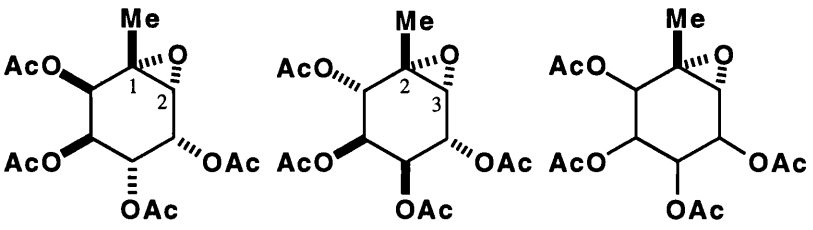
δ^{13}C(100 MHz, 60 °C, $CDCl_3$) 170.1, 169.8, 169.7, 169.6, 169.5, 168.8, 81.2 (C-2), 71.8, 70.3, 69.3, 67.5, 66.8, 20.7, 20.7, 20.7, 20.6, 20.6, 20.6, 18.6 (C-7).

ν_{max} (CH_2Cl_2) 2926, 1755, 1432, 1372, 1228, 1127, 1059, 1020, 932 cm^{-1}.

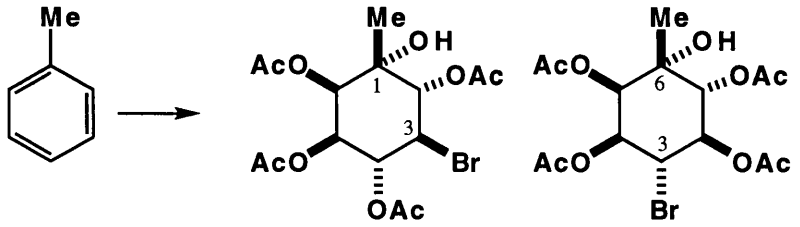
m/z (70 eV, NH3) 464 (100%, $[M+NH_4]^+$), 387 (6%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na) $C_{19}H_{26}O_{12}Na$ requires: 469.1322, found: 469.1325.

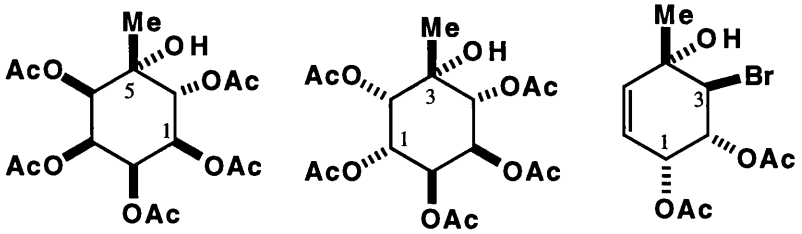
5. Photoosmylation of toluene with sodium bromate using general procedure C at 30 °C: (1α,2α,3α,4α,5β,6β)-1,2-epoxy-1β-methyl-cyclohexane-3,4,5,6-tetra-*O*-acetate **108**, (1α,2α,3α,4α,5β,6β)-2,3-epoxy-cyclohexane-2β-*C*-methyl-1,4,5,6-tetra-*O*-acetate **109**, 3-deoxy-3-bromo-6-*C*-methyl-*chiro*-inositol-1,2,4,5-tetra-*O*-acetate-6-ol **112**, 3-deoxy-3-bromo-1-*C*-methyl-*chiro*-inositol-2,4,5,6-tetra-*O*-acetate-1-ol **113**, 5-*C*-methyl-*allo*-inositol-1,2,3,4,6-penta-*O*-acetate-5-ol **102**, 2-*C*-methyl-*allo*-inositol-1,3,4,5,6-penta-*O*-acetate-2-ol **104** and (1α,2α,3β,4α)-3-bromo-4β-methyl-cyclohex-5-ene-1,2-di-*O*-acetate-4-ol **111**.



108 **109** **110**



113 **112**



102 **104** **111**

Photoosmylation of carried out according to the general procedure C. Sodium bromate (2.75 g, 18 mmol) was used instead of barium chlorate. Column chromatography (3:7 to 1:0, ether:petrol) of the yellow oil obtained gave fractions containing **111** (145 mg) as a yellow oil; a mixture of **108**, **109** and **110** (569 mg) as a yellow oil in a 4.6:2.6:1 ratio by ^{1}H NMR; a mixture of **112** and **113** (37 mg) as a yellow oil in a 1.3:1 ratio by ^{1}H NMR; **102** (132 mg) as a yellow oil that crystallised on standing and **104** (118 mg) as a yellow solid. Combining the remaining fractions provided another 189 mg of unidentified products. Preparative HPLC (25% EtOAc in hexane) of the mixture of **108**, **109** and **110** gave enriched fractions of **108** and **109**, retention times: **108** 34.8 min, **94** 39.2 min. **110** appeared as a shoulder to **108** and was not further purified. Crystallisation of **108** (ethanol) from its' enriched fraction was attempted providing a crystalline solid consisting ca. 90% **108** (3 mg). **109** was obtained in ca. 70% purity an could not be crystallised. Preparative HPLC (27.5% EtOAc in hexane) of the mixture of **112** and **113** gave, less polar: **113** as an oil, retention time 22.8 min; more polar: **112** as an oil, retention time 24.4 min.

(1α,2α,3β,4α)-3-Bromo-4β-methyl-cyclohex-5-ene-1,2-di-*O*-acetate-4-ol. 111

δ^1H(400 MHz, r.t., $CDCl_3$) 6.01 (1H, d, J=9.9 Hz, H-5), 5.68 (1H, dd, J=4.9, 9.9 Hz, H-6), 5.57 (1H, t, J=4.5 Hz, H-1), 5.19 (1H, dd, J=4.3, 11.7 Hz, H-2), 4.51 (1H, d, J=11.7 Hz, H-3), 2.31 (1H, br, OH), 2.09 (6H, s, 2x$OCOCH_3$), 1.45 (3H, s, H-7).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.1, 169.5, 138.2 (C-6), 121.7 (C-5), 73.0 (C-4), 69.2, 66.2, 59.0 (C-3), 26.3 (C-7), 20.9, 20.7.

ν_{max} (CH_2Cl_2) 3446, 2923, 2851, 1743, 1456, 1369, 1241, 1061, 1025, 964 cm^{-1}.

m/z (70 eV, NH_3) 326/324 (100%, $[M+NH_4]^+$), 308/306 (11%, $[M+H]^+$), 291/289 (50%, $[M-OH]^+$).

m/z (CI, NH_3) $C_{11}H_{19}NO_5Br$ requires: 324.0447, found: 324.0442.

(1α,2α,3α,4α,5β,6β)-1,2-Epoxy-4β-methyl-cyclohexane-3,4,5,6-tetra-*O*-acetate. (1,2-Anhydro-1-*C*-methyl-*allo*-inositol tetra-*O*-acetate) 108

d^{1}H(400 MHz, r.t., $CDCl_3$) 5.36 (1H, d, J=6.4 Hz, H-6), 5.21 (1H, dd, J=2.4, 5.0 Hz, H-4), 5.17 (1H, dd, J=2.4, 6.3 Hz, H-5), 5.15 (1H, dd, J=3.2, 5.0 Hz, H-3), 3.43 (1H, d, J=3.3 Hz, H-2), 2.16, 2.15, 2.09, 2.05 (4x3H, s, $OCOCH_3$), 1.40 (3H, s, H-7).

d^{13}C(100 MHz, r.t., $CDCl_3$) 170.3, 170.2, 169.5, 70.8, 69.5, 69.4, 68.8, 60.4 (C-1), 59.4 (C-2), 20.8, 20.7, 20.0 (C-7).

ν_{max} (CH_2Cl_2) 2977, 1749, 1436, 1372, 1225, 1040, 947, 921, 885 cm^{-1}.

m/z (70 eV, NH_3) 362 (100%, $[M+NH_4]^+$), 345 (17%, $[M+H]^+$).

m/z (FAB, Na) $C_{15}H_{20}O_9Na$ requires: 367.1005, found: 367.1000.

(1α,2α,3α,4α,5β,6β)-2,3-Epoxy-cyclohexane-2β-*C*-methyl-1,4,5,6 tetra-*O*-acetate. (2,3-Anhydro-2-*C*-methyl-*allo*-inositol tetra-*O*-acetate) 109

δ^{1}H(400 MHz, r.t., $CDCl_3$) 5.62 (1H, d, J=9.1 Hz, H-1), 5.45 (1H, ddd, J=1.8, 2.0, 4.0 Hz, H-5), 5.17 (1H, d, J=4.0 Hz, H-4), 4.98 (1H, dd, J=1.8, 9.1 Hz, H-6), 3.04 (1H, d, J=2.0 Hz, H-3), 2.17, 2.14, 2.06, 1.99 (4x3H, s, $OCOCH_3$), 1.38 (3H, s, H-7).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.6, 170.1, 170.0, 169.8, 69.3, 68.7, 66.7, 61.5 (C-3), 60.5 (C-2), 20.8, 20.8, 20.7, 20.6, 19.0 (C-7).

ν_{max} (CH_2Cl_2) 2932, 1748, 1436, 1373, 1228, 1123, 1039, 956 cm^{-1}.

m/z (70 eV, NH_3) 362 (100%, $[M+NH_4]^+$), 345 (43%, $[M+H]^+$), 285 (5%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na) $C_{15}H_{20}O_9Na$ requires: 367.1005, found: 367.1000.

3-Deoxy-3-bromo-6-*C*-methyl-*chiro*-inositol-1,2,4,5-tetra-*O*-acetate-6-ol.112

δ^1H(400 MHz, r.t., $CDCl_3$) 5.58 (1H, dd, J=9.7, 10.7 Hz, H-2), 5.56 (1H, dd, J=3.1, 11.3 Hz, H-4), 5.28 (1H, d, J=3.1 Hz, H-5), 5.11 (1H, d, J=9.7 Hz, H-1), 4.16 (1H, t, J=11.0 Hz, H-3), 2.37 (1H, br s, OH), 2.16, 2.11, 2.09, 2.05 (4x3H, s, $OCOCH_3$),1.17 (3H, s, H-7).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.8, 169.5, 169.3, 169.3, 77.1 (C-6), 74.2, 73.2, 72.7, 71.0, 48.3 (C-3), 22.7 (C-7), 20.7, 20.6, 20.6, 20.6.

ν_{max} (CH_2Cl_2) 3480, 2924, 2854, 1760, 1738, 1456, 1373, 1228, 1153, 1045 cm^{-1}.

m/z (70 eV, NH_3) 444/442 (100%, $[M+NH_4]^+$), 407/409 (20%, $[M-OH]^+$), 345 (20%, $[M-Br]^+$).

m/z (FAB, NH_3) $C_{15}H_{25}NO_9Br$ requires: 442.0713, found 442.0710.

3-Deoxy-3-bromo-1-*C*-methyl-*chiro*-inositol-2,4,5,6-tetra-*O*-acetate-1-ol. 113

δ^1H(400 MHz, r.t., $CDCl_3$) 5.54 (1H, t, J=10.5 Hz, H-4), 5.36 (1H, dd, J=3.2, 10.1 Hz, H-5), 5.34 (1H, d, J=11.0 Hz, H-2), 5.32 (1H, d, J=3.2 Hz, H-6), 4.27 (1H, t, J=10.8 Hz, H-3) 2.20, 2.20, 2.09, 1.97 (4x3H, s, $OCOCH_3$), 1.42 (3H, s, H-7).

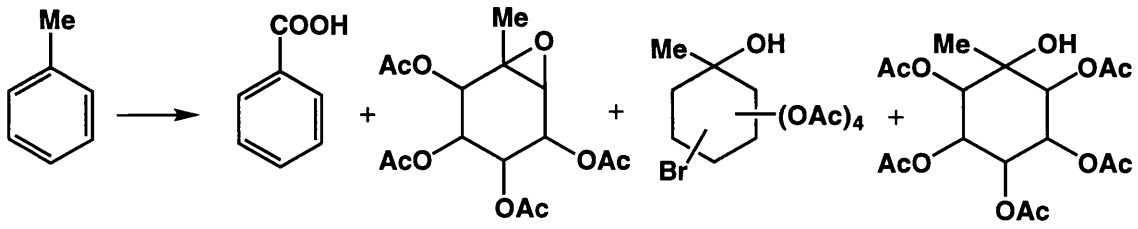
δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.8, 169.6, 169.5, 169.4, 74.8, 73.5 (C-1), 72.8, 71.0, 70.0, 50.3 (C-3), 22.7 (C-7), 20.9, 20.7, 20.6.

ν_{max} (CH_2Cl_2) 3446, 2923, 2851, 1753, 1373, 1223, 1042 cm^{-1}.

m/z (70 eV, NH_3) 444/442 (43%, $[M+NH_4]^+$), 345 (18%, $[M-Br]^+$).

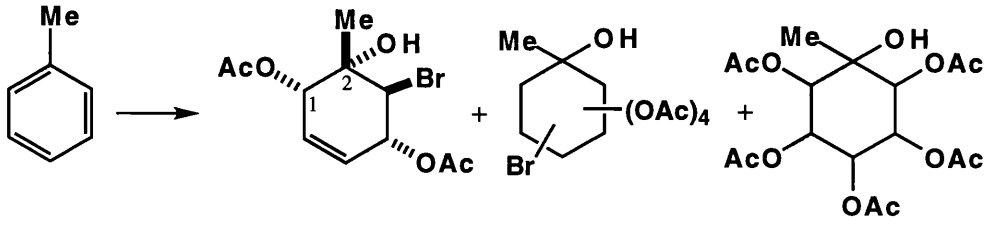
m/z (FAB, NH_3) $C_{15}H_{25}NO_9Br$ requires: 442.0713, found 442.0717.

6. Photoosmylation of toluene with sodium bromate at 45 °C: cyclitol products and benzoic acid.



Photoosmylation of toluene was carried out according to general procedure A. Sodium bromate (2.75 g, 18 mmol) was used instead of barium chlorate. The brown oil obtained (132 mg) contained benzoic acid (ca. 90%) as compared to an authentic sample by ^1H NMR. The remaining 10% consisted of peaks attributable to the anhydro inositols, deoxy-bromo inositols and inositols isolated in experiment 5.

7. Photoosmylation of toluene with sodium bromate at 15 °C: cyclitol products and (1α,2α,3β,4α)-2β-methyl-3-bromo-cyclohex-5-ene-1,4-di-*O*-acetate-2-ol **114**.



114

Photoosmylation of toluene (0.77 mL) was carried out according to general procedure A with the use of a water cooled reaction vessel E. Sodium bromate (2.75 g, 18 mmol) was used instead of barium chlorate and an acetic acid, acetic anhydride acetylation protocol was employed as already described. Column chromatography (1:1 to 1:0 ether:petrol) gave **114** (52 mg, 2.3%) as a yellow oil. The remainder of the fractions (623 mg) contained a large mixture of cyclitol products the separation of which was not attempted.

(1α,2α,3β,4α)-2β-Methyl-3-bromo-cyclohex-5-ene-1,4-di-*O*-acetate-2-ol. 114

δ^1H(400 MHz, r.t., $CDCl_3$) 5.98 (1H, ddd, J=2.0, 5.1, 10.0 Hz, H-6), 5.79 (1H, dd, J=2.5, 10.0 Hz, H-5), 5.50 (1H, ddd, J=2.0, 2.5, 9.0 Hz, H-4), 5.30 (1H, d, J=5.1 Hz, H-1), 4.37 (1H, d, J=9.0 Hz, H-3), 2.57 (1H, br s, OH), 2.14, 2.11 (2x3H, s, $OCOCH_3$), 1.36 (3H, s, H-7).

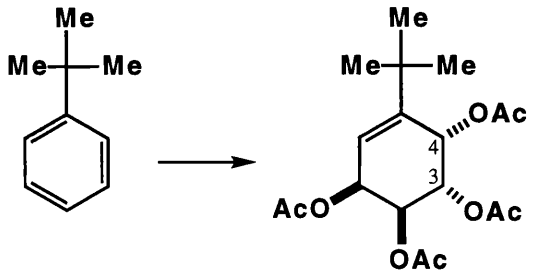
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.2, 170.0, 130.3, 126.6, 73.8, 71.9, 71.6 (C-2), 21.1 (C-7), 21.0, 20.9.

ν_{max} (CH_2Cl_2) 3474, 2985, 2937, 1732, 1433, 1372, 1232, 1024, 957, 869 cm^{-1}.

m/z (70 eV, EI) 326/324 (33%, $[M+NH_4]^+$), 291/289 (9%, $[M-OH]^+$), 249/247 (100%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na) $C_{11}H_{15}O_5BrNa$ requires: 329.0001, found: 329.0006.

8. Photoosmylation of *tert*-butylbenzene: (1β,2β,3α,4α)-5-*tert*-butyl-cyclohex-5-ene tetra-*O*-acetate **115**.



115

Photoosmylation of *tert*-butylbenzene (1.14 mL) was carried out according to the general procedure A. Column chromatography (1:1, ether:petrol) of the oil obtained gave **115** (38 mg, 1.4%) as a yellow oil that crystallised on standing.

(1β,2β,3α,4α)-5-*tert*-Butyl-cyclohex-5-ene tetra-*O*-acetate.

(5-*tert*-Butyl-conduritol E tetra-*O*-acetate) 115

δ^1H(400 MHz, r.t., $CDCl_3$) 5.89 (1H, d, J=3.6 Hz, H-4), 5.75 (1H, d, J=5.4 Hz, H-6), 5.72 (1H, dd, J=4.6, 5.1 Hz, H-1), 5.46 (1H, dd, J=4.3, 11.5 Hz, H-2), 5.27 (1H, dd, J=3.6, 11.5 Hz, H-3), 2.07, 20.7, 2.00, 1.98 (4x3H, s, $OCOCH_3$), 1.05 (9H, s, ^{t}Bu).

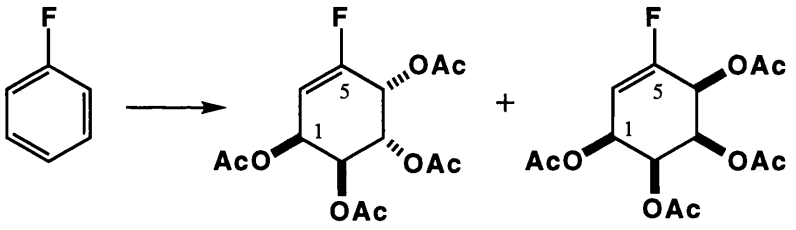
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.4, 170.4, 170.3, 170.1, 147.9 (C-5), 121.7 (C-6), 68.0, 66.2, 66.2, 65.7, 35.5, 29.1, 21.0, 20.9, 20.7, 20.7.

ν_{max} (CH_2Cl_2) 3063, 2969, 2875, 1738, 1435, 1372, 1258, 1109, 1072, 960 cm^{-1}.

m/z (70 eV, NH_3) 388 (100%, $[M+NH_4]^+$), 311 (39%, $[M-CH_3CO_2]^+$).

$C_{18}H_{26}O_8Na$ requires: 393.1525, found: 393.1521.

9. Photoosmylation of fluorobenzene: (1β,2β,3α,4α)-5-fluoro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **116** and (1β,2β,3β,4β)-5-fluoro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **117**.



116 **117**

Photoosmylation of fluorobenzene (0.68 mL) was carried out according to the general procedure A. 50 mg of osmium tetroxide was used for this reaction (in carbon tetrachloride, 0.5 mL). Column chromatography (6:4, ether:petrol) of the oil obtained gave **116** (12 mg, 0.5%) as a white solid and **117** (2.7 mg, 0.1%) as an oil. Prior to chromatography the diastereomers were shown to be present in a 4.4:1 ratio by ^{1}H NMR.

(1β,2β,3α,4α)-5-Fluoro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate.

(5-Fluoro conduritol E tetraacetate) 116

δ^1H(400 MHz, r.t., $CDCl_3$) 5.88 (1H, dd, J=4.4, 7.7 Hz, H-4), 5.73 (1H, dd, J=4.7, 10.1 Hz, H-1) 5.60 (1H, dd, J=6.0, 11.8 Hz, H-6), 5.51 (1H, dd, J=4.5, 11.0 Hz, H-3), 5.37 (1H, dd, J=4.0, 11.0 Hz, H-2), 2.11, 2.06, 2.00, 1.99 (4x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.1, 169.9, 169.8, 169.6, 157.5 (d, J=270.6 Hz, C-5), 105.5 (d, J=17.8 Hz, C-6), 65.7 (d, J=17.6 Hz, C-4), 65.6 (C-2/3), 65.3 (C-2/3), 64.9 (d, J=13.7 Hz, C-1), 20.8, 20.6, 20.5, 20.5.

δ^{19}F(400 MHz, r.t., $CDCl_3$) -107.3 (s).

ν_{max} (CH_2Cl_2) 2963, 1750, 1374, 1224, 1072, 1016, 933, 920, 885, 867 cm^{-1}.

m/z (70 eV, NH_3) 350 (100%, $[M+NH_4]^+$), 273 (6%, $[M-CH_3CO_2]^+$).

m.p. 141-143 °C (ethanol).

Elemental analysis; calculated: C 50.60, H 5.16; found: C 50.22, H 5.10.

(1β,2β,3β,4β)-5-Fluoro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate.

(5-Fluoro conduritol D tetraacetate) 117

δ^1H(400 MHz, r.t., $CDCl_3$) 5.81 (1H, br t, J~4 Hz, H-4), 5.64 (1H, m, H-1), 5.52 (1H, dd, J=3.7, 13.7 Hz, H-6), 5.41 (1H, m, H-2), 5.35 (1H, m, H-3), 2.13, 2.12, 2.09, 2.08 (4x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.8, 169.7, 169.5, 156.2 (d, J=267.6 Hz, C-5), 105.3 (d, J=18.1 Hz, C-6), 66.7 (d, J=9.2 Hz, C-1), 66.4 (C-2), 65.2 (d, J=11.7 Hz, C-3), 63.7 (d, J=25.0 Hz, C-4), 20.7, 20.6, 20.5, 20.4.

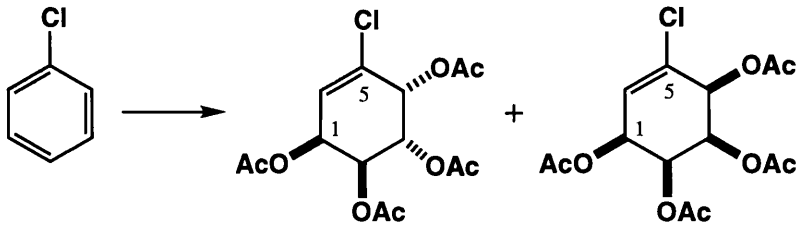
δ^{19}F(400 MHz, r.t., $CDCl_3$) -112.5 (s).

ν_{max} (CH_2Cl_2) 2962, 1749, 1220, 1065, 982, 932, 845, 735 cm^{-1}.

m/z (70 eV, NH_3) 350 (100%, $[M+NH_4]^+$), 273 (23%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na)$C_{14}H_{17}O_8FNa$ requires: 355.0805, found: 355.0801.

10. Photoosmylation of chlorobenzene: (1β,2β,3α,4α)-5-chloro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **118** and (1β,2β,3β,4β)-5-chloro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **119**.



118 **119**

Photoosmylation of chlorobenzene (0.74 mL) was carried out according to the general procedure A. Column chromatography (1:1 to 7:3, ether:petrol) of the brown oil obtained gave **118** (71 mg, 2.8%) as a white solid and **119** (14 mg, 0.6%) as an oil. Prior to chromatography the diastereomers were shown to be present in a 5.0:1 ratio by ^{1}H NMR.

(1β,2β,3α,4α)-5-Chloro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate.

(5-Chloro conduritol E tetraacetate) 118

δ^1H(400 MHz, r.t., $CDCl_3$) 6.07 (1H, d, J=5.5 Hz, H-6), 5.80 (1H, d, J=4.2 Hz, H-4), 5.67 (1H, dd, J=5.5, 4.2 Hz, H-1), 5.51 (1H, dd, J=10.7, 4.3 Hz, H-3), 5.38 (1H, dd, J=10.7, 4.1 Hz, H-2), 2.14, 2.09, 2.04, 2.02 (4x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.0, 169.9, 169.8, 169.6, 133.9 (C-5), 125.6 (C-6), 69.4, 66.2, 65.6, 65.3, 20.7, 20.6, 20.5, 20.5.

ν_{max} (CH_2Cl_2) 1750, 1372, 1247, 1223, 1077, 1053, 1016, 950 cm^{-1}.

m/z (70 eV, NH_3) 368/366 (100%, $[M+NH_4]^+$), 291/289 (15%, $[M-CH_3CO_2]^+$).

m.p. 109-110 °C (ethanol).

Elemental analysis; calculated : C 48.22, H 4.91, Cl 10.17.

found : C 48.29, H 4.85, Cl 10.43.

(1β,2β,3β,4β)-5-Chloro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate.

(5-Chloro conduritol D tetraacetate) 119

δ^1H(400 MHz, r.t., $CDCl_3$) 6.00 (1H, d, J=3.3 Hz, H-6), 5.69 (1H, dd, J=1.4, 5.0 Hz, H-4), 5.50 (1H, ddd, J=1.5, 3.4, 4.4 Hz, H-1), 5.42 (1H, dd, J=2.0, 4.4 Hz, H-2), 5.30 (1H, dd, J=2.0, 5.0 Hz, H-3), 2.11, 2.09, 2.05, 2.04 (4x3H, s, $OCOCH_3$).

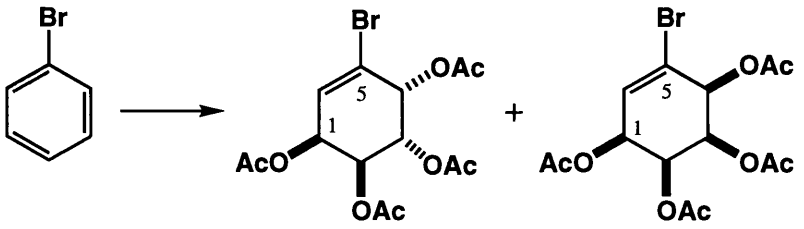
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.0, 169.8, 169.7, 169.6, 132.2 (C-5), 125.8 (C-6), 67.2, 66.8, 66.5, 66.1, 20.7, 20.7, 20.6, 20.5.

ν_{max} (CH_2Cl_2) 2925, 2853, 1753, 1650, 1433, 1373, 1253, 1219, 1047, 941 cm^{-1}.

m/z (70 eV, NH_3) 368/366 (77%, $[M+NH_4]^+$), 291/289 (10%, $[M-CH_3CO_2]^+$).

m/z (FAB, Na) $C_{14}H_{17}O_8ClNa$ requires: 371.0510, found: 371.0515.

11. Photoosmylation of bromobenzene: (1β,2β,3α,4α)-5-bromo-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **120** and (1β,2β,3β,4β)-5-bromo-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **121**.



120 **121**

Photoosmylation of bromobenzene (0.77 mL) was carried out according to the general procedure A. Column chromatography (1:1 to 7:3, ether:petrol) of the oil obtained gave **120** (63 mg, 2.2%) as a white solid and **121** (11 mg, 0.4%) as an oil. Prior to chromatography the diastereomers were shown to be present in a 5.5:1 ratio by ^{1}H NMR.

(1β,2β,3α,4α)-5-Bromo-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate.

(5-Bromo conduritol E tetraacetate) 120

δ^1H(400 MHz, r.t., $CDCl_3$) 6.28 (1H, d, J=5.3 Hz, H-6), 5.83 (1H, d, J=4.1 Hz, H-4) 5.60 (1H, br t, J=5.0 Hz, H-1), 5.50 (1H, dd, J=4.2, 10.6 Hz, H-3), 5.36 (1H, dd, J=3.9, 10.4 Hz, H-2), 2.13, 2.08, 2.02, 2.00 (4x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.9, 169.8, 169.7, 169.6, 129.8 (C-6), 123.8 (C-5), 70.7, 66.4, 66.2, 65.5, 20.7, 20.6, 20.5, 20.5.

ν_{max} (CH_2Cl_2) 3064, 2972, 2850, 1738, 1435, 1372, 1224, 1072, 947, 817 cm^{-1}.

m/z (70 eV, NH_3) 412/410 (100%, $[M+NH_4]^+$), 335/333 (10%, $[M-CH_3CO_2]^+$).

m/z (CI, NH_3) $C_{14}H_{21}NO_8Br$ requires: 410.0451, found: 410.0456.

(1β,2β,3β,4β)-5-Bromo-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate.

(5-Bromo conduritol D tetraacetate) 121

δ^1H(400 MHz, r.t., $CDCl_3$) 6.23 (1H, d, J=3.2 Hz, H-6), 5.73 (1H, br d, J=4.8 Hz, H-4), 5.49 (1H, m, J=3.2, 4.5 Hz, H-1), 5.44 (1H, dd, J=2.0, 4.4 Hz, H-2), 5.31 (1H, dd, J=2.0, 5.0 Hz, H-3), 2.12, 2.09, 2.05, 2.04 (4x3H, s, $OCOCH_3$).

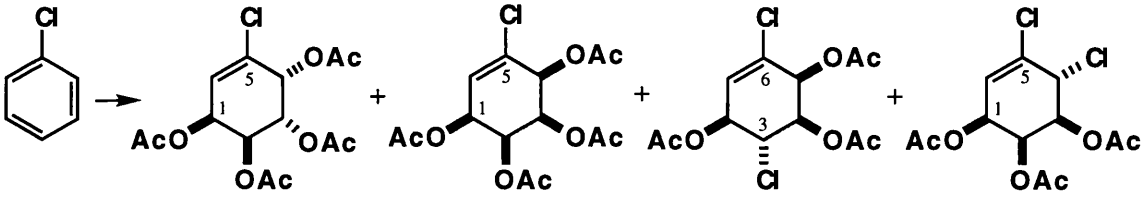
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.0, 169.8, 169.7, 169.6, 130.0 (C-6), 122.2 (C-5), 68.4, 67.3, 66.9, 66.1, 20.7, 20.7, 20.6, 20.6.

ν_{max} (CH_2Cl_2) 3060, 2924, 2849, 1752, 1371, 1224, 1047, 941, 915 cm^{-1}.

m/z (70 eV, NH_3) 412/410 (100%, $[M+NH_4]^+$), 335/333 (9%, $[M-CH_3CO_2]^+$), 313 (11%, $[M-Br]^+$).

m/z (CI, NH_3) $C_{14}H_{21}NO_8Br$ requires: 410.0451, found: 410.0456.

12. Photoosmylation of chlorobenzene using general procedure C: (1β,2β,3α,4α)-5-chloro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **118** and (1β,2β,3β,4β)-5-chloro-cyclohex-5-ene-1,2,3,4-tetra-*O*-acetate **119**, (1β,2β,3α,4β)-3,6-dichloro-cyclohex-5-ene-1,2,4-tri-*O*-acetate **122** and (1β,2β,3β,4α)-4,5-dichloro-cyclohex-5-ene-1,2,3-tri-*O*-acetate **123**.



118 **119** **122** **123**

Photoosmylation of chlorobenzene (15 mL) was carried out according to the general procedure C. Column chromatography (3:7 to 5:5, ether:petrol) of the brown oil obtained gave **122** (8 mg); **123** (10 mg); **118** (6 mg) and **119** (1 mg) as oils.

(1β,2β,3α,4β)-3,6-Dichloro-cyclohex-5-ene-1,2,4-tri-*O*-acetate 122

δ^1H(400 MHz, r.t., $CDCl_3$) 6.03 (1H, d, J=2.7 Hz, H-5), 5.76 (1H, d, J=4.0 Hz, H-1), 5.34 (1H, dd, J=2.7, 8.5 Hz, H-4), 5.21 (1H, dd, J=4.1, 11.7 Hz, H-2), 4.23 (1H, dd, J=8.5, 11.6 Hz, H-3), 2.17, 2.16, 2.08 (3x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.8, 169.7, 169.3, 130.8 (C-6), 128.4 (C-5), 73.0, 69.4, 69.3, 55.3 (C-3), 20.7, 20.6, 20.4.

ν_{max} (CH_2Cl_2) 2928, 2855, 1758, 1652, 1486, 1372, 1217, 1050, 970, 929, 864 cm^{-1}.

m/z (70 eV, NH_3) 346/344/342 (10.4%, 60.1%, 100%, $[M+NH_4]^+$).

m/z (FAB, Na) $C_{12}H_{14}O_6Cl_2Na$ requires: 347.0065, found: 347.0060.

(1β,2β,3β,4α)-4,5-Dichloro-cyclohex-5-ene-1,2,3-tri-*O*-acetate 123

δ^1H(400 MHz, r.t., $CDCl_3$) 5.97 (1H, d, J=3.0 Hz, H-6), 5.61 (1H, dd, J=3.0, 7.6 Hz, H-1), 5.52 (1H, dd, J=2.5, 7.5 Hz, H-2), 5.51 (1H, m, H-3), 4.40 (1H, d, J=3.2 Hz, H-4), 2.14, 2.10, 2.06 (3x3H, s, $OCOCH_3$).

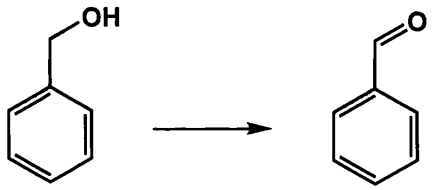
δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.3, 169.8, 169.5, 132.6 (C-5), 126.2 (C-6), 72.3, 68.7, 67.3, 56.9 (C-4), 20.9, 20.8.

ν_{max} (CH_2Cl_2) 2923, 2851, 1750, 1652, 1372, 1220, 1052, 978, 935, 905, 821 cm^{-1}.

m/z (70 eV, NH_3) 346/344/342 (7.1%, 40.9%, 63.4%, $[M+NH_4]^+$).

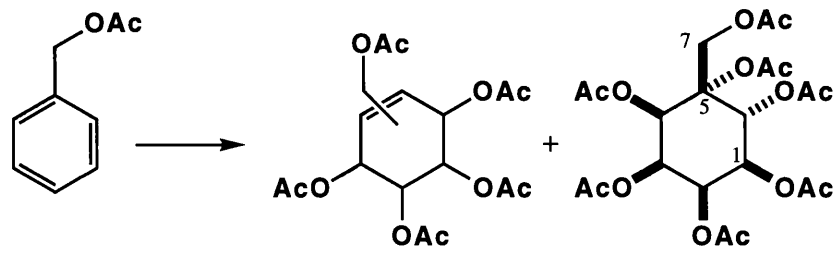
m/z (FAB, Na) $C_{12}H_{14}O_6Cl_2Na$ requires: 347.0065, found: 347.0060.

13. Photoosmylation of benzyl alcohol using general procedure A: benzaldehyde.



Photoosmylation of benzyl alcohol (0.75 mL) was carried out according to the general procedure A. Prior to the reductive quench with sodium metabisulphite the reaction mixture was extracted with ether (20 mL). The ethereal extract was dried over $MgSO_4$ and evaporated under reduced pressure at 0 °C (ice-water bath). The residue (343 mg) was shown to consist of a 5:1 mixture of benzyl alcohol : benzaldehyde by ^{1}H NMR. Inspection by ^{1}H NMR of the acetylated aqueous layer showed no cyclitol or aromatic type products and was not further investigated.

14. Photoosmylation of benzyl acetate using general procedure A: a mixture of hydroxymethyl conduritol pentaacetates **129** and 5-*C*-hydroxymethyl-*allo*-inositol hepta-*O*-acetate **128**.



129 **128**

Photoosmylation of benzyl alcohol (0.75 mL) was carried out according to the general procedure A. Column chromatography (4:1 to 1:0, ether:petrol) gave the mixture **129** (14 mg, 0.5 %) as an oil in a 4.2:2:1 mixture by ^{1}H NMR; and a mixture of inositols (78 mg) as an oil. Trituration of this oil with ethanol induced crystallisation of **128** (21 mg, 0.6%) as a clear colourless needles.

hydroxymethyl conduritol pentaacetates 129

δ^1H(400 MHz, r.t., $CDCl_3$) *inter alia* major isomer 4.85 (1H, d, J=11.9 Hz), 4.41 (1H, d, J=11.9 Hz). middle isomer 4.78 (1H, d, J=12.2 Hz), 4.69 (1H, d, J=12.2 Hz). minor isomer 4.80 (1H, d, J=12.2 Hz), 4.53 (1H, d, J=12.2 Hz).

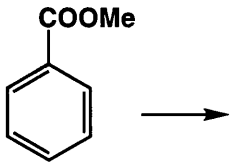
m/z (70 eV, NH_3) 404 (100%, $[M+NH_4]^+$), 327 (45%, $[M-CH_3CO_2]^+$).

1-*C*-hydroxymethyl-*allo*-inositol hepta-*O*-acetate 128

δ^1H(400 MHz, r.t., $CDCl_3$) 5.90 (1H, dd, J=1.2, 3.4 Hz, H-4), 5.70 (1H, d, J=10.7 Hz, H-6) 5.63 (1H, dt, J=1.3, 3.4 Hz, H-2), 5.32 (1H, dd, J=3.4, 10.6 Hz, H-1), 5.25 (1H, t, J=3.6 Hz, H-3), 4.79 (1H, d, J=12.3 Hz, H-7a), 4.53 (1H, d, J=12.3 Hz, H-7b), 2.18, 2.15, 2.13, 2.07, 2.01, 2.00, 1.99 (6x3H, s, $OCOCH_3$).

m/z (70 eV, NH_3) 522 (100%, $[M+NH_4]^+$), 445 (15%, $[M-CH_3CO_2]^+$).

15. Photoosmylation of methyl benzoate: lactones **130** and **131**.



Photoosmylation of methyl benzoate (0.91 mL) was carried out according to the general procedure A. Column chromatography (7:3 to 8:2 ether:petrol) of the yellow oil obtained gave **130** (33 mg, 1.1%) as an oil and **131** (36 mg, 1.2%) as an oil that crystallised on standing. Recrystallisation from methanol gave ^{1}H NMR pure **131**.

lactone 130

δ^1H(400 MHz, r.t., $CDCl_3$) 6.03 (1H, s), 5.56 (1H, d, J=2.1 Hz), 5.40 (1H, dm, J=2x<0.5, 5.3 Hz), 5.33 (1H, ddd, J=1.5, 2.1, 5.3 Hz), 4.82 (1H, br s).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 169.2, 169.1, 169.9, 168.8, 168.3, 167.2, 81.1, 80.3, 73.3, 70.3, 67.8, 66.3, 21.0, 20.7, 20.6, 20.5, 20.4.

ν_{max} (CH_2Cl_2) 2962, 1820, 1760, 1371, 1221, 1049, 920 cm^{-1}.

m/z (FAB) 417 (60%, $[M+H]^+$), 357 (22%, $[M-CH_3CO_2]^+$).

m/z (FAB, H^+) $C_{17}H_{21}O_{12}$ requires: 417.1033, found: 417.1038.

lactone 131

δ^1H(400 MHz, r.t., $CDCl_3$) 6.15 (1H, s), 5.82 (1H, d, J=7.8 Hz), 5.30 (1H, dd, J=0.8, 8.1 Hz), 4.95 (1H, dd, J=0.8, 1.5 Hz), 4.80 (1H, br s), 2.19, 2.17, 2.12, 2.11, 2.11 (5x3H, s, $OCOCH_3$).

$\delta^{13}C$(100 MHz, r.t., $CDCl_3$) 169.6, 169.2 (3xC), 168.5, 168.3, 162.8, 78.9, 71.9, 69.6, 65.8, 64.6, 21.1, 20.7, 20.6, 20.3, 20.2.

ν_{max} (CH_2Cl_2) 1801, 1759, 1372, 1221, 1134, 1080, 1055, 916 cm^{-1}.

m/z (FAB) 417 (99%, $[M+H]^+$), 357 (14%, $[M-CH_3CO_2]^+$).

m/z (FAB, H^+) $C_{17}H_{21}O_{12}$ requires: 417.1033, found: 417.1038.

m.p. 219-221° C (methanol).

16. Attempted photoosmylation of 1-phenyldodecane.

Photoosmylation of 1-phenyldodecane (2.1 mL) was carried out according to the general procedure A. The yellow oil obtained was shown to only contain the starting material by ^1H NMR.

17. Attempted photoosmylation of diethylphenylphosphate.

Photoosmylation of diethylphenylphosphate (1.679 g) was carried out according to the general procedure A. A brown gum was obtained that showed no resonances attributable to cyclitol products in the ^1H NMR spectrum and was discarded.

18. Attempted photoosmylation of anisole.

Photoosmylation of anisole (0.79 mL) was carried out according to the general procedure A. An oil was obtained that showed no resonances attributable to cyclitol products in the ^1H NMR spectrum.

19. Attempted photoosmylation of thiophenol.

Photoosmylation of anisole (0.75 mL) was carried out according to the general procedure A. Prior to the reductive quench with sodium metabisulphate the reaction mixture was extracted with dichloromethane (10 mL). The organic extract was dried over $MgSO_4$ and the evaporated under reduced pressure to give a black oil. Tlc analysis of this oil (1:9, EtOAc:petrol) showed the starting material (Rf. 0.64) and 2 fainter spots (Rf. 0.50 and 0.45). ^1H NMR analysis of the dried and acetylated aqueous phase showed no resonances attributable to cyclitol products.

20. Attempted photoosmylation of acetanilide in dichloromethane.

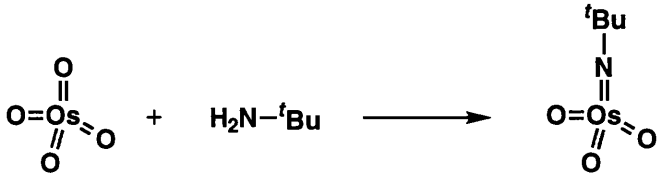
Photoosmylation of acetanilide (0.985 g) in dichloromethane (2 mL) was carried out according to the general procedure A. Prior to the reductive quench with sodium metabisulphate the reaction mixture was extracted with dichloromethane (15 mL). The organic extract was dried over $MgSO_4$ and the evaporated under reduced pressure to give the starting material (0.883 g, 89%) as white crystals. ^1H NMR analysis of the dried and acetylated aqueous phase showed no resonances attributable to cyclitol products.

21. Attempted photoosmylation of trimethylsilylbenzene.

Photoosmylation of trimethylsilylbenzene (1.23 mL) was carried out according to the general procedure A. ^1H NMR analysis of the dried and acetylated aqueous phase showed no resonances attributable to cyclitol products.

3.2.5 Experimental procedures for section 2.6

1. Preparation of trioxo(*tert*-butlyimido) osmium(VIII) **135.**



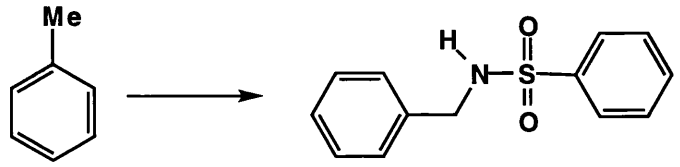
135

To osmium tetroxide (511 mg, 2.01 mmol) in pentane (5 mL, UV-VIS grade) was added *tert*-butylamine (0.278 mL, 2.01 mmol) upon which the solution turned orange. Agitation of the solution resulted in the precipitation of an orange solid. Removal of the pentane under reduced pressure afforded **135** (551 mg, 89%) as orange plates.

2. Attempted CT oxyamination of benzene.

To benzene (25 mL) was added **135** (250 mg, 0.8 mmol) and the resulting orange mixture stirred and irradiated for 10 hrs after which a black precipitate had developed. The reaction mixture was then poured into a solution of sodium metabisulphite (2g) in water (25 mL) and vigorously stirred for 2 h. The resulting precipitate was filtered and the filtrate extracted with EtOAc (2 x 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a residue that showed no resonances attributable to the expected cyclitol products in the ^1H NMR spectrum.

3. Attempted photooxyamination of toluene with chloramine-B: *N*-Benzyl-phenylsulphonamide **136**.



136

To a suspension of toluene (0.77 mL, 7.3 mmol) in a solution of Chloramine-B (5 g) in de-ionised water (50 mL) was added osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL) (reaction vessel type B). The mixture was irradiated in the usual way for 15 hrs after which the reaction mixture had taken on an opaque yellow-orange coloration. Sodium sulphite (2 g) was then added, and the solution stirred overnight. The mixture was then extracted with chloroform (3 x 100 mL), the organic extracts washed with NaOH solution (1%, 100 mL), brine (2 x 100 mL) and dried over $MgSO_4$. Evaporation of the chloroform under reduced pressure gave a red oil. Column chromatography of this oil (1:1, ether:petrol) gave **136** (41 mg, 2.3%) as a yellow oil.

_N_-Benzyl-phenylsulphonamide 136

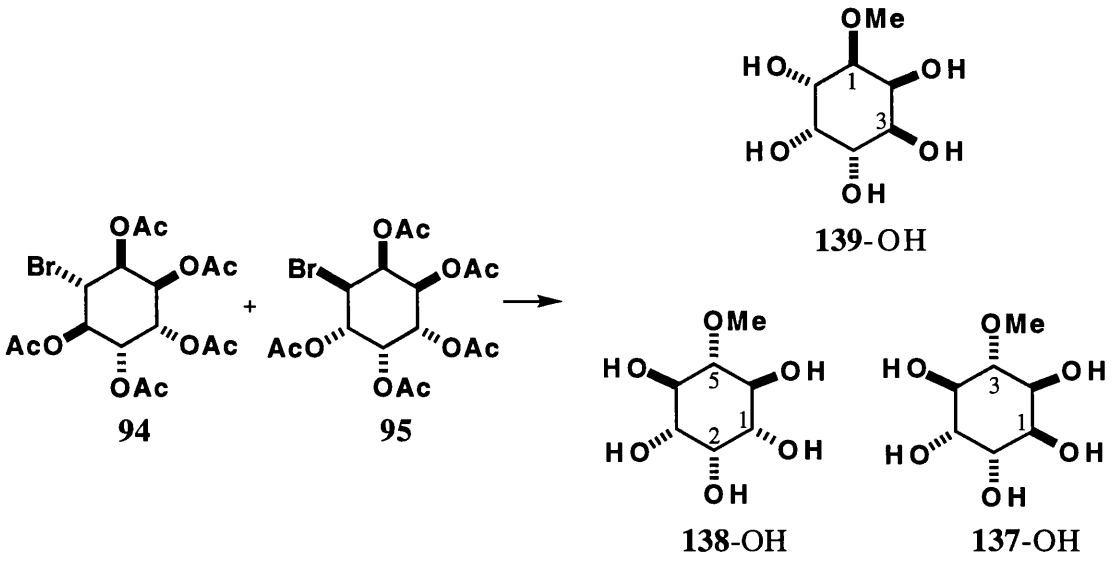
δ^1H(400 MHz, r.t., $CDCl_3$) 7.85 (2H, d, J=8.2, H-Ar), 7.55 (1H, m, H-Ar), 7.46 (2H, m, H-Ar), 7.24 (3H, m, H-Ar), 7.17 (2H, m, H-Ar), 4.97 (1H, t, J=5.9 Hz, NH), 4.11 (2H, d, J=6.2, CH_2).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 139.8, 136.1, 132.6, 129.1, 128.6, 127.8, 127.8, 127.0, 47.2.

m/z (70 eV, EI) 248 (1%, $[M+H]^+$), 182 (1%, $[M-HSO_2]^+$), 170 (2%, $[M-C_6H_5]^+$).

3.2.6 Experimental procedures for section 2.7

1. Preparation of pinitol **137**-OH, sequoyitol **138**-OH and 1-*O*-methyl-*neo*-inositol **139**-OH from 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94** and 1-deoxy-1-bromo-*neo*-inositol penta-*O*-acetate **95.**



A solution of **94** and **95** (360 mg, 0.8 mmol, **94**:**95** 3:2) in methanol (2 mL) and dichloromethane (2 mL) was added to a stirred solution of sodium methoxide (freshly prepared by adding sodium (0.1 g) to methanol (10 mL)) under nitrogen. After 5 min the solution darkened and a precipitate formed. Tlc analysis (8:2:1, EtOAc:EtOH:H_2O) after 30 min showed two spots (R_f. 0.54 and 0.40). After 2 h tlc analysis showed two spots (R_f. 0.40 and 0.30). The solution was then refluxed for 4.5 h after which tlc analysis showed that both spots (R_f. 0.40 and 0.30) had been consumed. The brown reaction mixture was allowed to cool to r.t., neutralised with acetic acid and evaporated to yield a mass of yellow salts. Column chromatography (3:7, MeOH:EtOAc) of the salts gave *pinitol* **137**-OH (44 mg, 29%); *sequoyitol* **138**-OH (39 mg, 26%) and *1*-O-*methyl*-neo-*inositol* **139**-OH (58 mg, 38%) as oils. The spectral properties (^1H and ^{13}C NMR) of *pinitol* **137**-OH were found to be the same as the reported values.[22,155] (see appendix A).

3-*O*-Methyl-*chiro*-inositol (Pinitol) 137-OH

δ^1H(400 MHz, r.t., D_2O) 3.98 (2H, m, H-1,6), 3.78 (1H, dd, J=2.9, 10.0 Hz, H-2), 3.73 (1H, dd, J=2.9, 10.0 Hz, H-5), 3.62 (1H, t, J=9.9 Hz, H-4), 3.57 (3H, s, H-7), 3.31 (1H, t, J=10.0 Hz, H-3).

δ^{13}C(100 MHz, r.t., D_2O) 85.6, 75.0, 74.5, 74.3, 73.4, 72.7, 62.6 (C-7).

m/z (70 eV, NH_3) 212 (100%, $[M+NH_4]^+$), 194 (1%, $[M]^+$).

m/z (70 eV, EI) 195 (1%, $[M+H]^+$), 194 (1%, $[M]^+$), 176 (1%, $[M-H_2O]^+$), 158 (1%, $[M-2H_2O]^+$), 144 (3%, $[M-CH_3OH-H_2O]^+$).

m/z (FAB, H^+) $C_7H_{15}O_6$ requires: 195.0869, found 195.0863.

5-*O*-Methyl-*myo*-inositol (Sequoyitol) 138-OH

δ^1H(400 MHz, r.t., D_2O) 4.05 (1H, t, J=2.8 Hz, H-2), 3.71 (2H, t, J=9.8 Hz, H-1,3), 3.61 (3H, s, H-7), 3.55 (2H, dd, J=2.9, 9.9 Hz, H-4,6), 3.08 (1H, t, J=9.6 Hz, H-5).

δ^{13}C(100 MHz, r.t., D_2O) 87.0, 74.8, 74.5 (2xC), 73.9 (2xC), 62.5 (C-7).

m/z (70 eV, NH_3) 212 (56%, $[M+NH_4]^+$), 194 (1%, $[M]^+$).

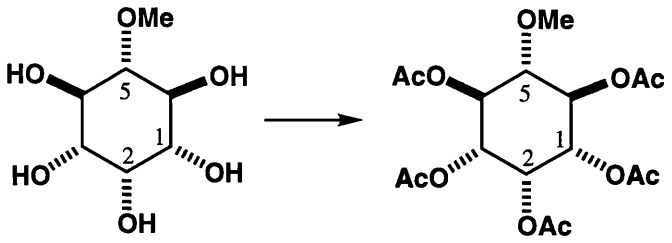
1-*O*-Methyl-*neo*-inositol 139-OH

δ^1H(400 MHz, r.t., D_2O) 4.39 (1H, t, J=2.7 Hz, H-2), 4.12 (1H, m, H-5), 3.88 (1H, dd, J=3.2, 10.3 Hz, H-6), 3.83 (2H, br t, J=2.4, 2.8 Hz, H-4,3), 3.51 (1H, dd, J=3.0, 10.3 Hz, H-1), 3.50 (3H, s, OCH_3).

δ^{13}C(100 MHz, r.t., D_2O) 82.0, 74.6, 74.0, 72.3, 72.2, 71.7, 70.1, 59.6 (C-7).

m/z (FAB) 176 (100%, $[M-H_2O]^+$).

2. Preparation of sequoyitol pentaacetate **138**.



138-OH **138**

To sequoyitol **138**-OH (30 mg, 0.15 mmol) was added triethylamine (2 mL), acetic anhydride (0.5 mL) and DMAP (cat). The reaction mixture was stirred overnight upon which water (5 mL) was added and stirred for a further 20 min. The reaction mixture was then extracted with ether (3 x 10 mL), the combined ethereal extracts were washed with brine (50 mL) and dried over $MgSO_4$. Evaporation of all volatiles under reduced pressure gave an off-white solid. Crystallisation from ethanol afforded *sequoyitol pentaacetate* **138** (18 mg, 30%) as clear colourless needles. The ^1H NMR spectrum of sequoyitol pentaacetate **138** was found to be the same as the reported spectrum.[149]

5-*O*-Methyl-*myo*-inositol penta-*O*-acetate (Sequoyitol pentaacetate). 138

δ^1H(400 MHz, r.t., $CDCl_3$) 5.53 (1H, t, J=2.9 Hz, H-2), 5.45 (2H, t, J=10.2, 10.0 Hz, H-4, 6), 4.99 (2H, dd, J=2.8, 10.5 Hz, H-1, 3), 3.44 (3H, s, OCH_3), 3.39 (1H, t, J=9.7 Hz, H-5), 2.18 (3H, s, $OCOCH_3$), 2.07 (6H, s, 2x$OCOCH_3$), 1.98 (6H, s, 2x$OCOCH_3$).

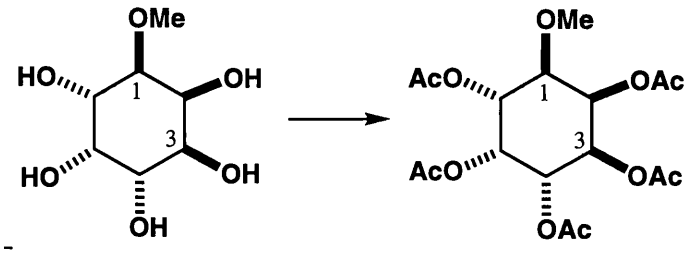
ν_{max} (CH_2Cl_2) 2942, 1747, 1437, 1369, 1230, 1169, 1144, 1092, 1044, 951 cm^{-1}.

m/z (70 eV, NH_3) 422 (100%, $[M+NH_4]^+$), 405 (1%, $[M+H]^+$), 373 (1%, $[M+CH_3O]^+$), 345 (20%, $[M-CH_3CO_2]^+$).

m.p. 201-202 °C (ethanol), (lit.[156]: 202 °C).

Elemental analysis; calculated: C 50.50, H 5.98; found: C 50.21, H 5.91.

3. Preparation of 1-*O*-methyl-*neo*-inositol penta-*O*-acetate **139.**



139-OH **139**

1-*O*-methyl-*neo*-inositol penta-*O*-acetate **139** was prepared from 1-*O*-methyl-*neo*-inositol **139**-OH (32 mg, 0.16 mmol) using the same procedure as for experiment 3. The oil obtained, upon evaporation of the organic volatiles under reduced pressure, was triturated with ethanol which induced crystallisation. Recrystallisation from ethanol afforded *1*-O-*methyl*-neo-*inositol penta*-O-*acetate* **139** (28 mg, 43%) as a white solid.

1-*O*-Methyl-*neo*-inositol penta-*O*-acetate 139

δ^1H(400 MHz, r.t., $CDCl_3$) 5.79 (1H, t, J=3.0 Hz, H-2), 5.61 (1H, t, J=3.0 Hz, H-5), 5.32 (1H, dd, J=3.0, 11.0 Hz, H-4), 5.23 (1H, dd, J=3.1, 10.6 Hz, H-6), 5.22 (1H, dd, 3.0, 10.9 Hz, H-3), 3.67 (1H, dd, J=3.0, 10.5 Hz, H-1), 3.37 (3H, s, OCH_3), 2.16, 2.16, 2.04, 2.02, 1.99 (3x3H, s, $OCOCH_3$).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 170.2, 170.2, 169.8, 169.7, 169.6, 75.6 (C-1), 68.9, 68.4, 68.2, 67.5, 66.1, 58.2 (C-7), 20.8, 20.7, 20.7, 20.6.

ν_{max} (CH_2Cl_2) 2930, 1749, 1436, 1372, 1228, 1114, 1062, 1044, 1022, 976 cm^{-1}.

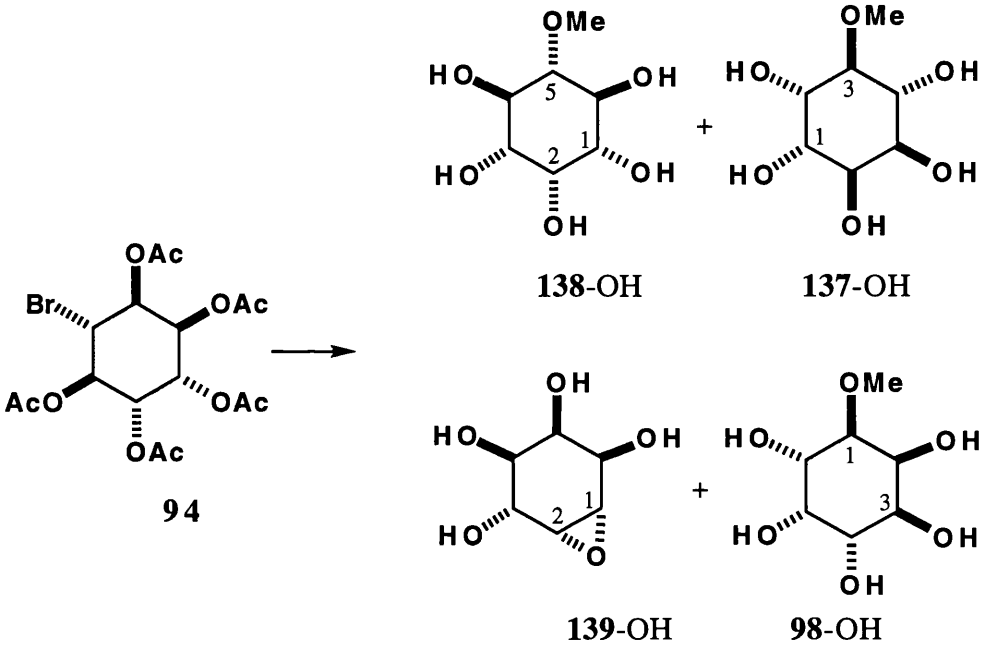
m/z (70 eV, NH_3) 422 (100%, $[M+NH_4]^+$), 405 (1%, $[M+H]^+$), 345 (9%, $[M-CH_3CO_2]^+$).

m.p.: 188.5-189 °C (ethanol).

Elemental analysis; calculated: C 50.50, H 5.98; found: C 49.66, H 5.83.

m/z (FAB, Na) $C_{17}H_{24}O_{11}Na$ requires: 427.1216, found: 427.1212.

4. Preparation of pinitol **137**-OH, sequoyitol **138**-OH, (1β,2β,3β,4α,5α,6α)-1,2-epoxy-cyclohexane-3,4,5,6-tetraol **98**-OH and 1-*O*-methyl-*neo*-inositol **139**-OH and **141** from 3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**.



+ **141**

To a stirred solution of **94** (468 mg, 1.03 mmol) in methanol (12 mL) and dichloromethane (2 mL) was added sodium (0.15 g) under nitrogen. Once the sodium had dissolved (5 min) the reaction mixture was lowered into an oil-bath preheated at 70 °C. The solution was then refluxed for 2 h after which tlc analysis indicated that the reaction had gone to completion (8:2:1, EtOAc:EtOH:H_2O gave base-line spot). The reaction was allowed to cool to r.t. and neutralised with HCl (2 M). Evaporation of all volatiles under reduced pressure gave a mass of white salts which upon column chromatography (3:7, MeOH:EtOAc) gave *(1β,2β,3β,4α,5α,6α)-1,2-Epoxy-cyclohexane-3,4,5,6-tetraol* **98**-OH (45 mg, 27%) as a colourless oil; **137**-OH (80 mg, 40%) as a gum; a mixture of **138**-OH, **139**-OH and **141** (34 mg, 17%) as an oil in a

8:1:1 ratio by ^{1}H NMR and a mixture of **139**-OH and **141** (8 mg, 4%) in a 2:3 ratio by ^{1}H NMR.

(1β,2β,3β,4α,5α,6α)-1,2-Epoxy-cyclohexane-3,4,5,6-tetraol.

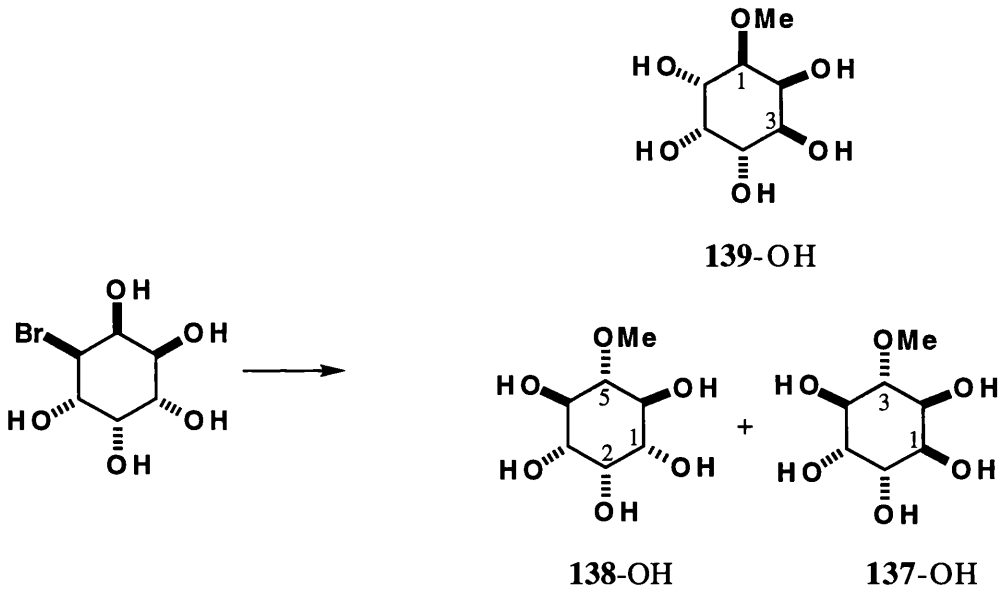
(1,2-Anhydro-*neo*-inositol) 98-OH

δ^1H(400 MHz, r.t., D_2O) 4.05 (1H, dd, J=2.5, 8.7 Hz, H-3), 3.86 (1H, d, J=3.9 Hz, H-5), 3.82 (1H, ddd, J=1.8, 2.0, 3.8 Hz, H-6), 3.41 (1H, dd, J=3.9, 2.5 Hz, H-2), 3.36 (1H, dd, J=1.7, 8.7 Hz, H-4), 3.17 (1H, dd, J=2.0, 3.9 Hz, H-1).

δ^{13}C(100 MHz, r.t., D_2O) 75.2, 72.3, 71.3, 69.8, 60.2 (C-1/2), 59.8 (C-1/2).

m/z (70 eV, NH_3) 180 (100%, $[M+NH_4]^+$), 160 (1%, $[M+H]^+$).

5. Preparation of pinitol **137**-OH, sequoyitol **138**-OH, 1-*O*-methyl-*neo*-inositol **139**-OH and **141** from 1-deoxy-1-bromo-*neo*-inositol **95**-OH.



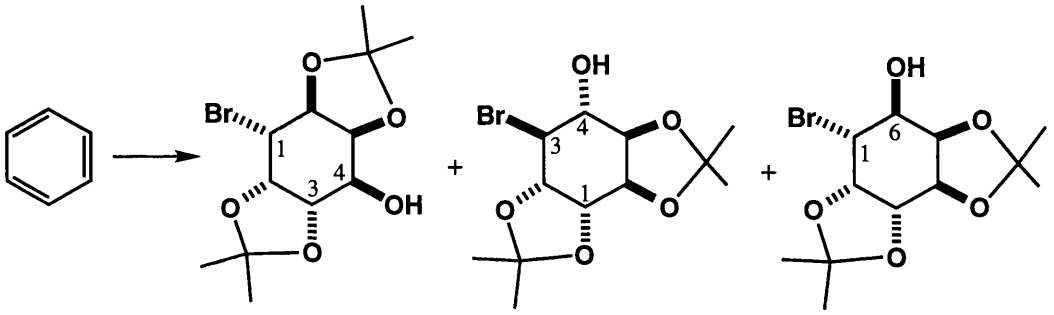
139-OH

138-OH **137**-OH

+ 141

To a suspension of **95**-OH (64 mg, 0.26 mmol) in methanol was added sodium (0.1 g) under nitrogen. The stirred reaction mixture was then lowered into an oil bath preheated to 70 °C and refluxed for 18 h. The reaction was then allowed to cool to r.t. and neutralised with HCl (2 M). Evaporation of all the volatiles under reduced pressure gave a mass of yellow salts. These salts were dissolved in D_2O and were shown to contain pinitol **137**-OH, sequoyitol **138**-OH, 1-*O*-methyl-*neo*-inositol **139**-OH and **141** in 3.3:2:1:1 ratio as determined by ^1H NMR. Filtration of these salts through a short pad of silica with ^{i}PrOH gave a semi solid residue (45 mg, 90%) upon evaporation of the ^{i}PrOH.

6. Photoosmylation of benzene with sodium bromate at 45 °C using acetone and iodine for cyclitol extraction: 1-deoxy-1-bromo-*neo*-inositol-2,3:5,6-di-*O*-isopropylidene-4-ol **146**, 3-deoxy-3-bromo-*chiro*-inositol-1,2:5,6-di-*O*-isopropylidene-4-ol **148** and 1-deoxy-1-bromo-*neo*-inositol-2,3:4,5-di-*O*-isopropylidene-6-ol **147**.



146 **148** **147**

To a florentine shaped flask fitted with a Teflon tap (reaction vessel C) was added sodium bromate (2.75 g, 18.2 mmol) and de-ionised water (50 mL). Upon solvation of the bromate salt, benzene was added (0.65 mL, 7.3 mmol) followed by a solution of osmium tetroxide (25 mg, 0.1 mmol) in carbon tetrachloride (0.25 mL). The tap was fastened and the reaction mixture stirred vigorously with a magnetic stirrer. Irradiation of the reaction mixture was carried out over 43 hrs without fan-assisted cooling $T_{irradiation}$=45 °C. After irradiation the reaction mixture was transferred to a thick 250 mL Büchi-type flask, cooled in an ice-water bath and treated portionwise with sodium metabisulphite (7 g, 37 mmol) over 15 min throughout which the reaction mixture turned orange, red and finally grey-black. The opaque slurry was then neutralised with NaOH (2 M) and evaporated (rotary evaporator, waterbath 40-45 °C). The dried residue was then powdered and treated with acetone (150 mL) and iodine (1.5 g) and stirred over night. The reaction was then quenched with an aqueous solution of sodium thiosulphate (10% w/v) until clear. The mixture was then concentrated under reduced pressure and extracted with dichloromethane (3 x 50 mL). The combined extracts were washed with brine and

dried over $MgSO_4$. Evaporation of all volatiles under reduced pressure gave an oil. Column chromatography (1:1 to 1:0, ether:petrol) of this oil gave **146** (32 mg, 1.4%); **147** (72 mg, 3.0%) and **148** (38 mg, 1.6%) as yellow oils.

1-Deoxy-1-bromo-*neo*-inositol-2,3:5,6-di-*O*-isopropylidene-4-ol 146

δ^1H(400 MHz, r.t., $CDCl_3$) 4.64 (1H, dd, J=2.2, 7.5 Hz, H-1), 4.60 (2H, m, H-2,6), 4.51 (1H, dd, J=3.0, 7.1 Hz, H-3/5), 4.41(1H, br dd, J=3.6, 7.1 Hz, H-3/5), 4.16 (1H, br dt, J=1.0, 2.8, 3.6 Hz, H-4), 2.54 (1H, d, J=1.1 Hz, OH), 1.54, 1.47, 1.39, 1.36 (4x3H, s, isopropylidene CH_3).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 109.2, 108.4, 76.9, 76.6, 75.4, 74.0, 67.0 (C-4), 49.8 (C-1), 26.3, 26.0, 23.6, 23.2.

ν_{max} (CH_2Cl_2) 3479, 2988, 2933, 1382, 1266, 1210, 1163, 1059, 975, 856 cm^{-1}.

m/z (70 eV, NH_3) 342/340 (100%, $[M+NH_4]^+$), 325/323 (95%, $[M+H]^+$), 309/307 (43%, $[M-CH_3]^+$).

m/z (FAB, Na) $C_{12}H_{19}O_5BrNa$ requires: 345.0314, found: 345.0310.

3-Deoxy-3-bromo-*chiro*-inositol-1,2:5,6-di-*O*-isopropylidene-4-ol 148

δ^1H(400 MHz, r.t., $CDCl_3$) 4.64 (1H, dd, J=2.7, 7.8 Hz, H-6), 4.60 (1H, dd, J=8.0, 9.7 Hz, H-2), 4.52 (1H, dd, J=3.2, 7.9 Hz, H-5), 4.32 (1H, t, J=8.4 Hz, H-3), 3.90 (1H, dd, J=2.7, 9.7 Hz, H-1), 3.66 (1H, br, when decoupling at 2.35 ppm: dd, J=3.4, 8.6 Hz, H-4), 2.35 (1H, br d, J= 6.0 Hz, OH), 1.53 (6H, s, 2x isopropylidene CH_3), 1.38, 1.37 (2x3H, s, isopropylidene CH_3).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 109.7, 109.1, 77.1 (2xC), 77.0, 75.9, 71.0 (C-4), 49.4 (C-3), 26.9, 25.7, 24.0, 23.3.

ν_{max} (CH_2Cl_2) 3868, 2955, 1380, 1220, 1121, 1043, 914, 832 cm^{-1}.

m/z (70 eV, NH_3) 342/340 (100%, $[M+NH_4]^+$), 325/323 (77%, $[M+H]^+$), 309/307 (63%, $[M-CH_3]^+$).

m/z (FAB, Na) $C_{12}H_{19}O_5BrNa$ requires: 345.0314, found: 345.0310.

1-Deoxy-1-bromo-*neo*-inositol-2,3:4,5-di-*O*-isopropylidene-6-ol 147

δ^1H(400 MHz, r.t., $CDCl_3$) 4.48 (1H, dd, J=1.7, 6.2 Hz, H-4), 4.42 (2H, m, H-2,3), 4.14 (1H, dd, J=6.2, 7.9 Hz, H-5), 3.78 (1H, dd, J=8.8, 11.9 Hz, H-1), 3.61 (1H, ddd, J=2.1, 7.9, 11.9 Hz, H-6), 2.75 (1H, d, J=2.1 Hz, OH), 1.49 (6H, s, 2x isopropylidene CH_3), 1.38, 1.37 (2x3H, s, isopropylidene CH_3).

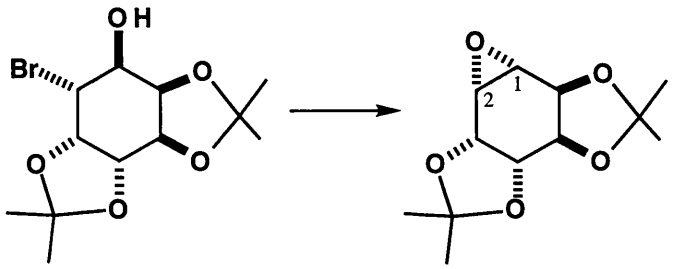
δ^{13}C(100 MHz, r.t., $CDCl_3$) 109.5, 109.3, 79.2, 78.1, 75.9, 74.9, 72.4 (C-6), 57.2 (C-1), 27.8 (2xC), 25.4, 25.3.

ν_{max} (CH_2Cl_2) 3446, 2987, 2936, 1383, 1244, 1220, 1162, 1066, 861 cm^{-1}.

m/z (70 eV, NH_3) 342/340 (100%, $[M+NH_4]^+$), 325/323 (99%, $[M+H]^+$), 309/307 (17%, $[M-CH_3]^+$).

m/z (FAB, Na) $C_{12}H_{19}O_5BrNa$ requires: 345.0314, found: 345.0310.

7. Preparation of (1β,2β,3β,4β,5α,6α)-1,2-Epoxy-3,4:5,6-di-*O*-isopropylidene-cyclohexane **142**.



147 **142**

To a solution of **147** (55 mg, 0.17 mmol) in methanol (4 mL) was added sodium carbonate (10 mg). The reaction mixture was stirred and heated to reflux. After 2h tlc analysis showed that all the starting material had reacted. The reaction mixture was allowed to cool to r.t. and silica was added to the reaction mixture. Evaporation of the solvent afforded the crude product preabsorbed onto silica which was filtered through a pad of silica to yield **142** (34 mg, 83%) as a white solid.

(1β,2β,3β,4β,5α,6α)-1,2-Epoxy-3,4:5,6-di-*O*-isopropylidene-cyclohexane (1,2-Anhydro-*allo*-inositol-3,4:5,6-di-*O*-isopropylidene) 142

δ^1H(400 MHz, r.t., $CDCl_3$) 4.55 (3H, m), 4.33 (1H, m), 3.33(2H, s, H-1, 2), 1.51, 1.41 (2x3H, isopropylidene CH_3), 1.36 (6H, s, 2x isopropylidene CH_3).

δ^{13}C(100 MHz, r.t., $CDCl_3$) 109.3, 108.9, 74.2, 72.1, 71.3, 69.7, 55.1 (C-1/2), 52.3 (C-1/2), 27.4, 26.4, 25.8, 24.9.

δ^1H(400 MHz, r.t., Acetone-d_6) 4.53 (1H, dd, J=2.5, 6.4 Hz, H-), 4.47 (2H, s, H-), 4.28 (1H, d, J=6.5 Hz, H-), 3.25 (2H, m, H-1, 2), 1.40, 1.35, 1.32, 1.29 (4x3H, s, isopropylidene CH_3).

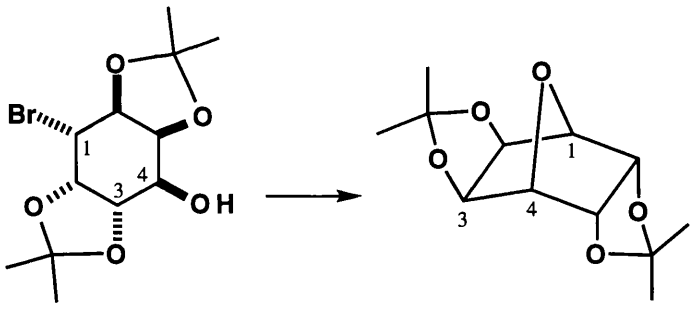
$\delta^{13}C$(100 MHz, r.t., Acetone-d_6) 109.3, 109.2, 75.2, 73.1, 72.1, 70.5, 55.5 (C-1/2), 52.7 (C-1/2), 27.6, 26.8, 26.0, 25.2.

ν_{max} (CH_2Cl_2) 2980, 1448, 1386, 1223, 1110, 1058, 974, 866 cm^{-1}.

m/z (70 eV, NH_3) 260 (40%, $[M+NH_4]^+$), 243 (100%, $[M+H]^+$), 227 (5%, $[M-CH_3]^+$).

m/z (EI, H^+) $C_{12}H_{19}O_5$ requires 243.1232, found 243.1237.

8. Preparation of (1β,2β,3β,4β,5α,6α)-1,4-Epoxy-2,3:5,6-di-*O*-isopropylidene-cyclohexane **149**.



146 **149**

To a solution of **146** (25 mg, 0.08 mmol) in methanol (2 mL) was added sodium carbonate (ca. 5 mg). The reaction mixture was stirred at r.t.. After 2h tlc analysis showed that no reaction had taken place and the reaction mixture was heated to reflux over night. Tlc analysis the showed that all the starting material had been consumed The reaction mixture was allowed to cool to r.t. and was filtered through a pad of cotton wool. Evaporation of the solvent afforded **149** (20 mg, 93%) as a white solid.

(1β,2β,3β,4β,5α,6α)-1,4-Epoxy-2,3:5,6-di-*O*-isopropylidene-cyclohexane. (1,4-Anhydro-*allo*-inositol-2,3:5,6-di-*O*-isopropylidene) 149

δ^1H(400 MHz, r.t., $CDCl_3$) 4.84 (2H, s, H-2, 3), 4.64 (2H, dd, J=2.2, 3.4 Hz, H-5, 6), 4.40 (2H, dd, J=2.2, 3.4, H-1,4), 1.49, 1.48, 1.33, 1.32 (4x3H, s, isopropylidene CH_3).

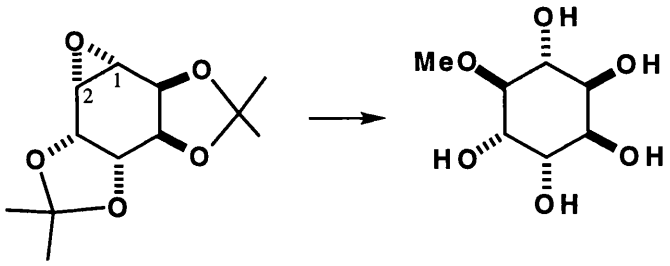
δ^{13}C(100 MHz, r.t., $CDCl_3$) 118.4, 110.6, 80.9 , 78.0, 77.9, 25.9, 25.8, 24.8, 24.4.

ν_{max} (CH_2Cl_2) 2971, 1458, 1380, 1273, 1122, 1072 cm^{-1}.

m/z (70 eV, NH_3) 260 (100%, $[M+NH_4]^+$), 243 (94%, $[M+H]^+$).

m/z (EI, H^+) $C_{12}H_{19}O_5$ requires 243.1232, found 243.1238.

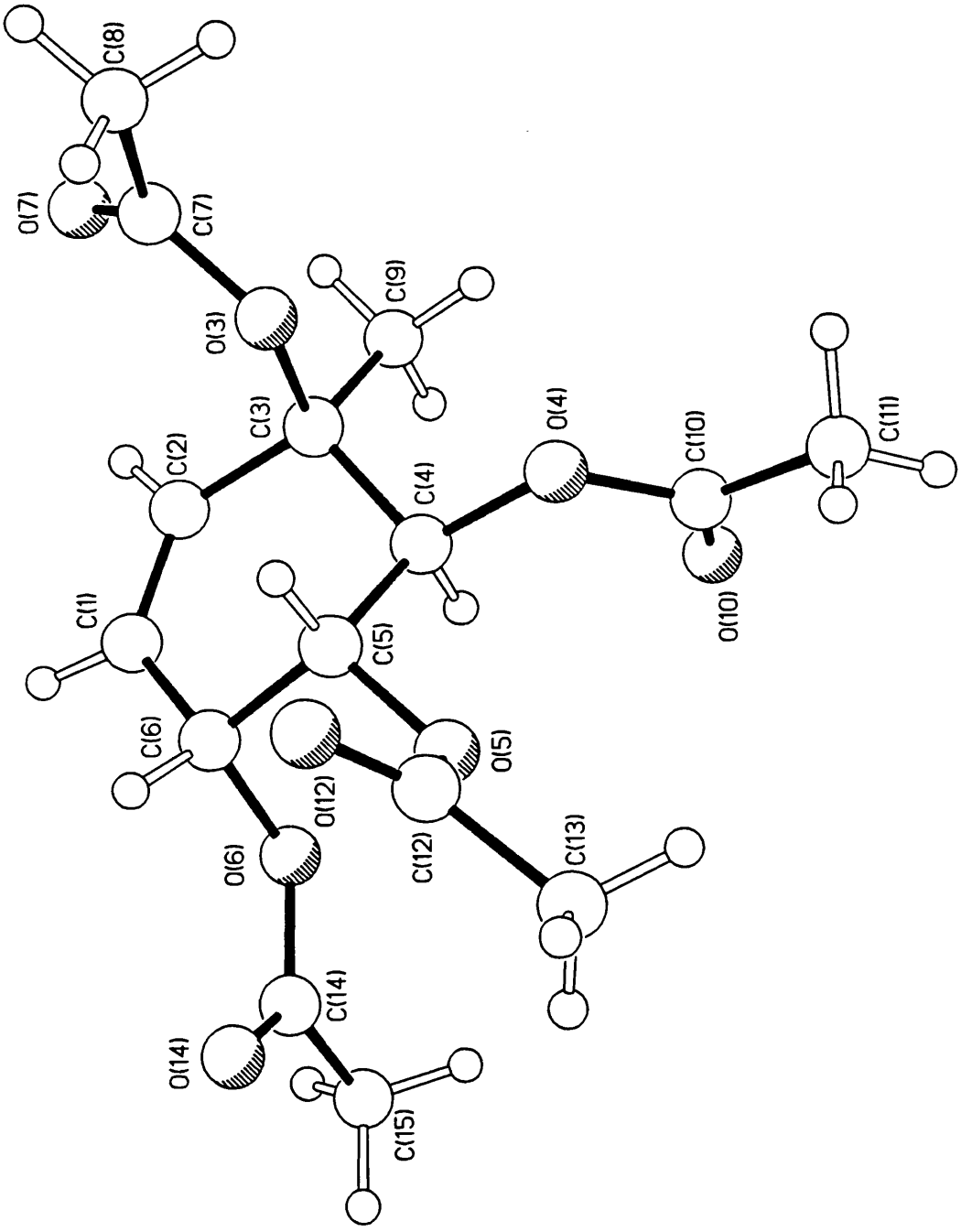
9. Preparation of pinitol **137**-OH.



142 **137**-OH

To flame dried Al_2O_3 (3 g) was added a solution of **142** (30 mg, 0.12 mmol) in methanol (5 mL) followed by a further 15 mL of methanol. The solution was vigorously stirred and refluxed under nitrogen for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure and analysed by ^{1}H NMR. The residue was the taken up in THF (20 mL) and water (20 mL) and c. HCl (3 drops) and stirred at 60 °C for 2 h. The reaction mixture was then allowed to cool to r.t. and the solvents evaporated. The remaining residue was then chromatographed (3:7, MeOH:EtOAc) to give **137**-OH (14 mg, 60%) as a gummy residue.

Appendix A: X-ray data



(1β,2β,3α,4α)-1α-methyl-cyclohex-5-ene tetra-*O*-acetate **73**

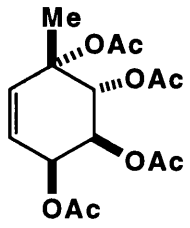


Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
C(1)	1665(3)	6236(3)	2983(3)	53(1)
C(2)	2252(3)	6534(3)	2098(3)	52(1)
C(3)	2950(3)	5469(3)	1443(2)	48(1)
O(3)	4823(2)	5837(2)	2071(2)	51(1)
C(4)	2238(3)	3871(3)	1583(2)	46(1)
O(4)	3010(2)	2808(2)	1123(2)	54(1)
C(5)	2582(3)	3883(3)	2941(2)	45(1)
O(5)	2077(2)	2337(2)	3043(2)	54(1)
C(6)	1569(3)	4798(3)	3420(2)	47(1)
O(6)	-251(2)	3934(2)	2901(2)	51(1)
C(7)	5827(4)	7267(4)	2298(3)	60(1)
O(7)	5326(3)	8332(3)	2051(3)	85(1)
C(8)	7667(4)	7359(5)	2902(3)	79(2)
C(9)	2564(4)	5522(4)	103(3)	65(1)
C(10)	1979(4)	1640(3)	145(3)	56(1)
O(10)	560(3)	1601(3)	-480(2)	77(1)
C(11)	2825(5)	459(4)	-53(4)	78(2)
C(12)	3078(4)	1968(4)	4013(3)	60(1)
O(12)	4313(4)	2861(3)	4786(2)	99(1)
C(13)	2422(6)	316(4)	3964(4)	95(2)
C(14)	-946(4)	3195(3)	3610(3)	58(1)
O(14)	-127(3)	3133(3)	4621(2)	88(1)
C(15)	-2819(4)	2477(4)	2978(4)	79(2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.324 (5)	C(1)-C(6)	1.485 (4)
C(2)-C(3)	1.508 (5)	C(3)-O(3)	1.475 (3)
C(3)-C(4)	1.511 (4)	C(3)-C(9)	1.511 (4)
O(3)-C(7)	1.331 (4)	C(4)-O(4)	1.442 (4)
C(4)-C(5)	1.524 (4)	O(4)-C(10)	1.346 (3)
C(5)-O(5)	1.424 (3)	C(5)-C(6)	1.521 (5)
O(5)-C(12)	1.338 (4)	C(6)-O(6)	1.458 (3)
O(6)-C(14)	1.340 (4)	C(7)-O(7)	1.202 (5)
C(7)-C(8)	1.494 (5)	C(10)-O(10)	1.199 (4)
C(10)-C(11)	1.479 (6)	C(12)-O(12)	1.180 (3)
C(12)-C(13)	1.481 (5)	C(14)-O(14)	1.192 (4)
C(14)-C(15)	1.478 (4)		

Table 3. Bond angles (°)

C(2)-C(1)-C(6)	124.1(3)	C(1)-C(2)-C(3)	123.8(3)
C(2)-C(3)-O(3)	110.8(2)	C(2)-C(3)-C(4)	108.1(3)
O(3)-C(3)-C(4)	104.1(2)	C(2)-C(3)-C(9)	112.5(3)
O(3)-C(3)-C(9)	109.0(3)	C(4)-C(3)-C(9)	112.1(2)
C(3)-O(3)-C(7)	119.6(2)	C(3)-C(4)-O(4)	111.9(2)
C(3)-C(4)-C(5)	110.3(2)	O(4)-C(4)-C(5)	107.5(2)
C(4)-O(4)-C(10)	117.4(2)	C(4)-C(5)-O(5)	108.3(2)
C(4)-C(5)-C(6)	109.6(2)	O(5)-C(5)-C(6)	110.6(2)
C(5)-O(5)-C(12)	117.1(2)	C(1)-C(6)-C(5)	111.4(3)
C(1)-C(6)-O(6)	104.6(2)	C(5)-C(6)-O(6)	109.7(2)
C(6)-O(6)-C(14)	118.6(2)	O(3)-C(7)-O(7)	124.9(3)
O(3)-C(7)-C(8)	110.3(3)	O(7)-C(7)-C(8)	124.8(3)
O(4)-C(10)-O(10)	122.9(3)	O(4)-C(10)-C(11)	111.6(3)
O(10)-C(10)-C(11)	125.4(3)	O(5)-C(12)-O(12)	123.3(3)
O(5)-C(12)-C(13)	110.7(2)	O(12)-C(12)-C(13)	126.0(3)
O(6)-C(14)-O(14)	123.2(3)	O(6)-C(14)-C(15)	111.6(3)
O(14)-C(14)-C(15)	125.2(4)		

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	47(2)	46(2)	67(2)	15(1)	26(1)	9(1)
C(2)	45(2)	48(2)	65(2)	15(1)	20(1)	17(1)
C(3)	36(1)	57(2)	49(2)	12(1)	14(1)	14(1)
O(3)	40(1)	59(1)	54(1)	13(1)	16(1)	17(1)
C(4)	39(1)	51(2)	47(1)	15(1)	16(1)	6(1)
O(4)	47(1)	56(1)	59(1)	18(1)	21(1)	2(1)
C(5)	41(1)	40(1)	48(1)	7(1)	13(1)	10(1)
O(5)	51(1)	43(1)	60(1)	7(1)	15(1)	12(1)
C(6)	41(1)	49(2)	45(1)	6(1)	15(1)	5(1)
O(6)	42(1)	60(1)	52(1)	11(1)	22(1)	14(1)
C(7)	51(2)	63(2)	62(2)	4(2)	26(1)	17(1)
O(7)	75(2)	63(2)	118(2)	10(1)	38(1)	35(1)
C(8)	47(2)	97(3)	78(2)	2(2)	18(2)	18(2)
C(9)	63(2)	80(2)	51(2)	20(2)	17(1)	21(1)
C(10)	67(2)	49(2)	55(2)	10(1)	32(2)	9(1)
O(10)	73(2)	64(1)	68(1)	16(1)	4(1)	-2(1)
C(11)	93(3)	63(2)	90(2)	27(2)	51(2)	13(2)
C(12)	68(2)	53(2)	62(2)	20(2)	25(2)	21(1)
O(12)	91(2)	77(2)	84(2)	2(1)	-16(2)	33(1)
C(13)	120(3)	59(2)	105(3)	24(2)	35(3)	32(2)
C(14)	60(2)	58(2)	63(2)	14(1)	32(2)	18(1)
O(14)	77(2)	119(2)	73(2)	18(1)	34(1)	44(1)
C(15)	59(2)	84(2)	94(3)	7(2)	38(2)	18(2)

The anisotropic displacement factor exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1A)	1271	6993	3364	63
H(2A)	2241	7486	1863	62
H(4A)	1020	3505	1140	54
H(5A)	3788	4343	3404	53
H(6A)	1971	5020	4306	56
H(8A)	8382	8394	3065	94
H(8B)	7824	7046	3666	94
H(8C)	7977	6690	2364	94
H(9A)	3035	6555	59	77
H(9B)	3083	4862	-255	77
H(9C)	1346	5184	-343	77
H(11A)	2061	-362	-751	92
H(11B)	3841	919	-206	92
H(11C)	3132	61	671	92
H(13A)	3155	65	4661	112
H(13B)	1282	97	3981	112
H(13C)	2393	-284	3214	112
H(15A)	-3287	1947	3498	94
H(15B)	-3339	3269	2800	94
H(15C)	-3048	1765	2219	94

3-deoxy-3-bromo-*chiro*-inositol penta-*O*-acetate **94**

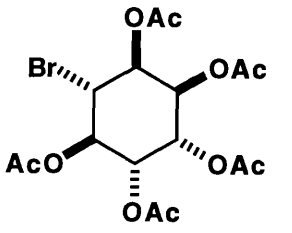


Table 1. Atomic coordinates ($x10^4$ Å) and equivalent isotropic displacement parameters ($Å^2x10^3$) for $C_{16}H_{21}BrO_{10}$.

	x	y	z	U(eq)
Br(1)	145(1)	1607(1)	4627(1)	67(1)
O(1)	1399(9)	370(4)	3773(4)	47(3)
O(2)	-19(9)	-760(4)	3356(4)	48(3)
O(3)	-2471(9)	-381(5)	3837(4)	53(3)
O(4)	-1993(8)	1014(4)	2655(4)	49(3)
O(5)	-2304(9)	1810(4)	3811(4)	53(4)
O(6)	1705(10)	-273(6)	4702(5)	82(5)
O(7)	-249(13)	-944(6)	2255(6)	98(5)
O(8)	-2553(14)	-1419(6)	3325(8)	99(6)
O(9)	-3826(12)	1576(5)	2508(5)	71(4)
O(10)	-4114(12)	1583(6)	4311(6)	94(5)
C(1)	25(12)	345(6)	3867(5)	41(4)
C(2)	-482(12)	-59(7)	3277(6)	45(5)
C(3)	-1936(13)	-56(6)	3247(7)	49(5)
C(4)	-2423(14)	690(7)	3254(6)	45(4)
C(5)	-1927(13)	1087(7)	3850(7)	50(5)
C(6)	-478(12)	1096(6)	3864(6)	41(5)
C(11)	2113(13)	9(7)	4208(8)	49(5)
C(12)	34(15)	-1157(7)	2791(8)	61(5)
C(13)	-2734(15)	-1070(8)	3805(10)	64(7)
C(14)	-2772(16)	1473(7)	2336(7)	51(6)
C(15)	-3418(19)	1988(10)	4071(8)	76(8)
C(21)	3496(15)	19(9)	4008(8)	78(7)
C(22)	468(16)	-1874(7)	2940(8)	75(6)
C(23)	-3308(16)	-1310(9)	4448(9)	91(8)
C(24)	-2111(15)	1805(7)	1766(7)	64(6)
C(25)	-3690(21)	2754(9)	3998(9)	115(9)

Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2. Bond lengths (Å) for $C_{16}H_{21}BrO_{10}$.

Br(1)-C(6)	1.931 (12)	O(1)-C(1)	1.459 (16)
O(1)-C(11)	1.343 (17)	O(2)-C(2)	1.436 (15)
O(2)-C(12)	1.367 (17)	O(3)-C(3)	1.451 (16)
O(3)-C(13)	1.350 (18)	O(4)-C(4)	1.426 (14)
O(4)-C(14)	1.361 (17)	O(5)-C(5)	1.441 (16)
O(5)-C(15)	1.327 (22)	O(6)-C(11)	1.207 (18)
O(7)-C(12)	1.187 (19)	O(8)-C(13)	1.188 (23)
O(9)-C(14)	1.179 (21)	O(10)-C(15)	1.170 (23)
C(1)-C(2)	1.511 (17)	C(1)-C(6)	1.533 (16)
C(2)-C(3)	1.531 (18)	C(3)-C(4)	1.518 (18)
C(4)-C(5)	1.509 (18)	C(5)-C(6)	1.525 (19)
C(11)-C(21)	1.510 (21)	C(12)-C(22)	1.476 (20)
C(13)-C(23)	1.497 (26)	C(14)-C(24)	1.481 (21)
C(15)-C(25)	1.503 (25)		

Table 3. Bond angles (°) for $C_{16}H_{21}BrO_{10}$.

C(1)-O(1)-C(11)	116.9(9)	C(2)-O(2)-C(12)	116.2(10)
C(3)-O(3)-C(13)	117.3(11)	C(4)-O(4)-C(14)	119.1(11)
C(5)-O(5)-C(15)	117.9(12)	O(1)-C(1)-C(2)	105.4(9)
O(1)-C(1)-C(6)	108.1(9)	C(2)-C(1)-C(6)	110.8(10)
O(2)-C(2)-C(1)	105.8(10)	O(2)-C(2)-C(3)	110.3(10)
C(1)-C(2)-C(3)	112.4(11)	O(3)-C(3)-C(2)	110.7(10)
O(3)-C(3)-C(4)	105.3(10)	C(2)-C(3)-C(4)	109.9(11)
O(4)-C(4)-C(3)	107.1(10)	O(4)-C(4)-C(5)	109.9(11)
C(3)-C(4)-C(5)	111.4(11)	O(5)-C(5)-C(4)	110.2(11)
O(5)-C(5)-C(6)	105.3(10)	C(4)-C(5)-C(6)	111.4(11)
Br(1)-C(6)-C(1)	110.8(8)	Br(1)-C(6)-C(5)	111.1(8)
C(1)-C(6)-C(5)	109.5(10)	O(1)-C(11)-O(6)	124.4(13)
O(1)-C(11)-C(21)	111.1(12)	O(6)-C(11)-C(21)	124.5(13)
O(2)-C(12)-O(7)	123.3(13)	O(2)-C(12)-C(22)	111.2(12)
O(7)-C(12)-C(22)	125.5(14)	O(3)-C(13)-O(8)	123.8(17)
O(3)-C(13)-C(23)	110.0(14)	O(8)-C(13)-C(23)	126.1(15)
O(4)-C(14)-O(9)	122.4(13)	O(4)-C(14)-C(24)	110.9(13)
O(9)-C(14)-C(24)	126.7(14)	O(5)-C(15)-O(10)	123.0(17)
O(5)-C(15)-C(25)	112.4(16)	O(10)-C(15)-C(25)	124.6(18)

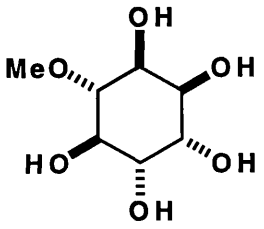
Table 4. Anisotropic displacement parameters ($Å^2x10^3$) for $C_{16}H_{21}BrO_{10}$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br(1)	68(1)	67(1)	65(1)	-24(1)	-11(1)	-1(1)
O(1)	49(7)	48(5)	45(5)	7(5)	2(5)	12(5)
O(2)	56(6)	42(5)	46(5)	-4(4)	-5(5)	13(5)
O(3)	60(6)	38(5)	61(6)	9(5)	-6(5)	-8(5)
O(4)	49(6)	59(6)	40(6)	4(5)	-4(4)	11(5)
O(5)	63(7)	46(6)	51(5)	-9(4)	9(5)	17(5)
O(6)	59(7)	131(10)	56(6)	30(7)	-11(6)	8(7)
O(7)	148(12)	81(8)	64(7)	-14(6)	-30(8)	47(8)
O(8)	98(10)	62(8)	137(11)	-15(8)	-22(9)	-6(7)
O(9)	63(7)	78(7)	71(6)	3(6)	-16(6)	21(7)
O(10)	65(9)	97(9)	121(10)	13(8)	31(7)	16(7)
C(1)	35(9)	46(7)	42(7)	12(6)	4(7)	-1(7)
C(2)	44(11)	43(8)	49(8)	-7(7)	-3(6)	8(6)
C(3)	57(11)	31(7)	58(9)	-4(8)	-23(7)	6(7)
C(4)	43(8)	56(8)	36(7)	-3(6)	1(7)	-13(7)
C(5)	42(10)	56(10)	53(9)	-1(8)	-1(7)	4(7)
C(6)	48(10)	41(7)	34(7)	-16(6)	-16(6)	-13(6)
C(11)	56(11)	43(8)	49(9)	-6(8)	2(8)	10(8)
C(12)	62(10)	57(8)	62(10)	-5(8)	-2(9)	25(9)
C(13)	57(11)	45(10)	91(13)	8(10)	-10(10)	-13(8)
C(14)	55(12)	44(9)	54(10)	-7(7)	-15(8)	2(8)
C(15)	71(15)	78(13)	78(12)	-1(9)	34(10)	19(11)
C(21)	77(13)	82(12)	76(11)	9(10)	1(10)	10(10)
C(22)	101(14)	48(8)	78(11)	-9(8)	-18(9)	32(9)
C(23)	58(12)	79(12)	136(18)	31(12)	-13(11)	-29(9)
C(24)	78(12)	54(9)	59(9)	-7(8)	-21(9)	3(8)
C(25)	131(18)	95(14)	118(16)	-16(12)	22(14)	75(13)

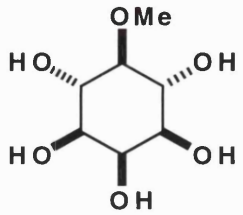
Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for $C_{16}H_{21}BrO_{10}$.

	x	y	z	U
H(1A)	-205	109	4272	80
H(2A)	-121	142	2881	80
H(3A)	-2233	-297	2857	80
H(4A)	-3335	694	3259	80
H(5A)	-2242	885	4256	80
H(6A)	-180	1315	3463	80
H(21A)	3996	-242	4322	80
H(21B)	3570	-190	3575	80
H(21C)	3797	492	3992	80
H(22A)	489	-2136	2533	80
H(22B)	1302	-1864	3134	80
H(22C)	-114	-2090	3246	80
H(23A)	-3513	-1798	4423	80
H(23B)	-2688	-1237	4792	80
H(23C)	-4062	-1048	4550	80
H(24A)	-2685	2120	1547	80
H(24B)	-1392	2060	1931	80
H(24C)	-1828	1457	1454	80
H(25A)	-4489	2864	4203	80
H(25B)	-3027	3021	4206	80
H(25C)	-3727	2866	3532	80

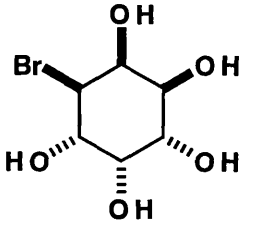
Pinitol **137**-OH

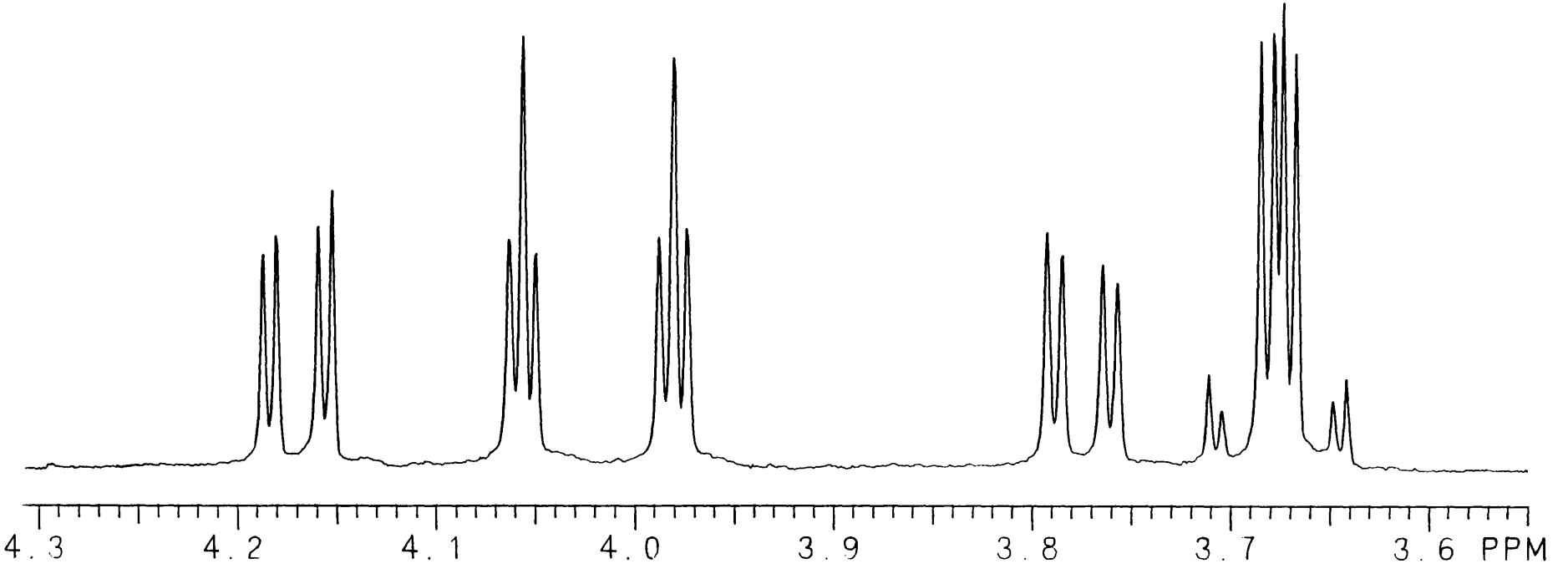


Sequoyitol **138**-OH

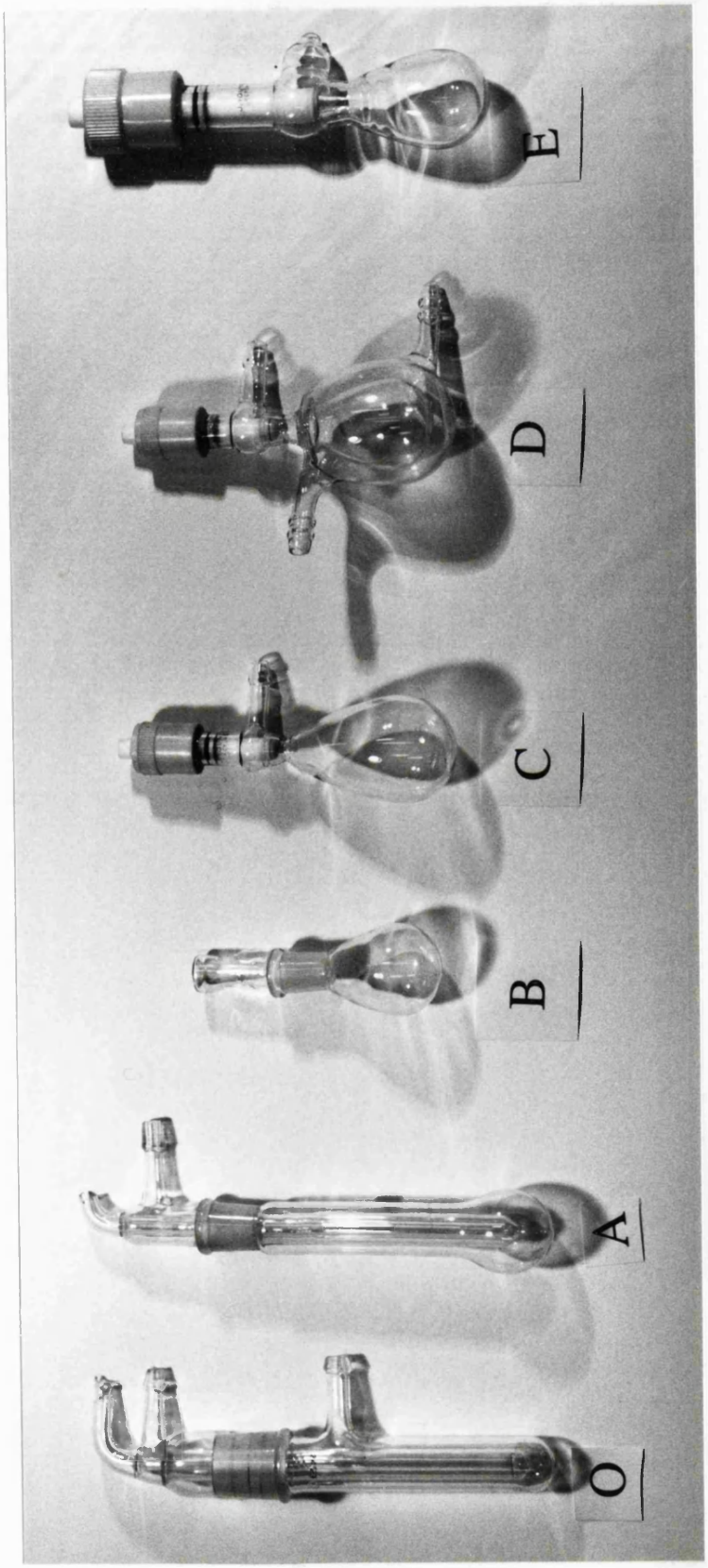


1-deoxy-1-bromo-*neo*-inositol **95**-OH





Appendix C: Photoosmylation glassware



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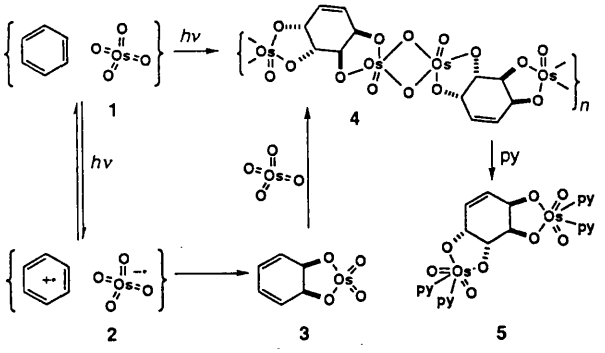
Catalytic Photoinduced Charge-Transfer Osmylation: A Novel Pathway from Arenes to Cyclitol Derivatives**

William B. Motherwell* and Alvin S. Williams

The ability of the enzymatic system present in strains of *Pseudomonas putida* to achieve stereospecific vicinal *cis* dihydroxylation[1] of benzene has spawned recent intense interest among synthetic organic chemists. The resultant *cis* diene diol and functionalized chiral derivatives have been widely used as starting materials for the syntheses of a diverse array of biologically important molecules including conduritols, inositols, prostaglandins, and carbohydrates.[2-4] It was therefore of interest to devise a simple *chemical* method for the production of these useful building blocks, particularly since the commonly encountered reagents for in vitro oxidation of arenes, such as ozone and ruthenium tetraoxide, also lead to the concomitant cleavage of the carbocyclic ring. We now present the results of a preliminary study in which we have achieved the first direct metal-catalyzed, one-pot conversion of benzene and some simple arenes to conduritol and inositol derivatives.

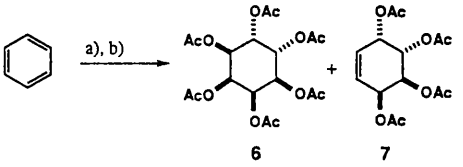
The basis for our work rests on an elegant study by Kochi and Wallis,[5] who demonstrated that actinic (UV) irradiation of the Electron Donor–Acceptor (EDA) complex[6] (**1**) formed on mixing benzene and osmium tetraoxide led, in the presence of an excess of the OsO_4 and at a frequency equal or greater than that of the absorption maxima, to a polymeric 2:1 adduct (**4** Scheme 1), which could be isolated as a monomer (**5**) by the addition of pyridine. The proposed mechanism involves photochemically induced charge transfer from the complex (**1**) to form an ion pair (**2**), which can collapse to the osmate ester of benzene diol (**3**) followed by a second thermal *anti* osmylation.



Scheme 1.

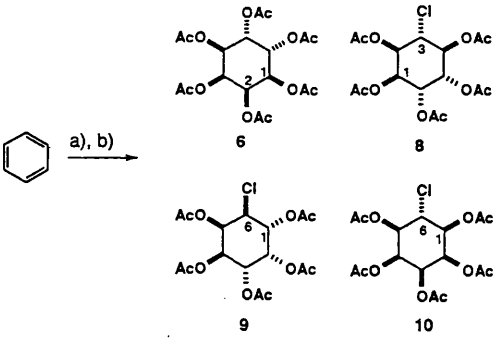
Although yields of the isolated adducts such as **5** were low even in the stoichiometric reaction, we envisaged that such a process could be made catalytic in osmium through careful selection of a suitable solvent system and oxygen atom transfer reagent. In this respect, since the heat of formation of the EDA complex between benzene and osmium tetraoxide has been estimated to be of the order of 0.5 kcal mol^{-1},[6] it was of paramount importance to avoid the use or generation of any molecule whose donor ability would give more stable OsO_4 complexes. Thus a series of simple control experiments served to indicate that *N*-methylmorpholine, pyridine, acetone, and *tert*-butanol were all fatal competitive inhibitors of the EDA complex. The use of aqueous solutions of barium chlorate[7] in a biphasic system with the arene were shown to provide suitable conditions for a catalytic photoosmylation.

In a typical early experiment, irradiation of benzene (0.65 mL) in the presence of aqueous barium chlorate (0.22 M, 75 mL) and osmium tetraoxide (25 mg; 1.3 mol%) led, after reductive workup with sodium disulfite and acetylation, to the *meso* derivative *allo*-inositol hexaacetate (**6**) in 31% yield[8] (Scheme 2). Conduritol E tetraacetate (**7**),[9] which is derived from the major but less reactive *anti*-isomer at the tetrol stage,[10] was also formed in 5% yield. This corresponds to a catalytic turnover for osmium tetraoxide of 76.



Scheme 2. a) OsO_4 (cat.), *hv*, $Ba(ClO_3)_2$ (0.22 M); b) Ac_2O, Et_3N, DMAP; **6**:**7** (6.2:1) 36%.

At a later stage, during studies using a higher chlorate concentration (1.10 M) and a reduced water:arene ratio (1:1.5) (see Experimental Procedure), we were intrigued to note that the formation of deoxychloroinositols is possible (Scheme 3). In this manner, photoosmylation of benzene (15 mL) followed by acetylation provided not only the anticipated *allo*-inositol hexaacetate on a gram scale (1.120 g) but also the deoxychloro-*chiro*- (**8**), *-neo*- (**9**) and *-epi*-inositols (**10**) (0.616 g, 2:2:1 respectively) corresponding to a catalytic turnover of 108 for osmium tetraoxide.



Scheme 3. a) OsO_4 (cat.), *hv*, $Ba(ClO_3)_2$ (1.10 M); b) Ac_2O, Et_3N, DMAP; **8**:**9**:**10** (2:2:1).

Since the formation of derivatives **8**, **9**, and **10** was indicative of competitive *trans* addition of hypochlorous acid at an early intermediate stage, it was of interest to examine the behavior of the inherently even more reactive bromate anion as the oxygen transfer reagent. Even under the original "standard" conditions that led only to vicinal dihydroxylation products with the chlorate anion, brominated derivatives were formed (Scheme 4), and even predominated over *allo*-inositol hexaacetate (**6**; 7.7%). The structure of the major diastereoisomer, isolated in 15.7% yield, was based on its ^1H and ^{13}C NMR

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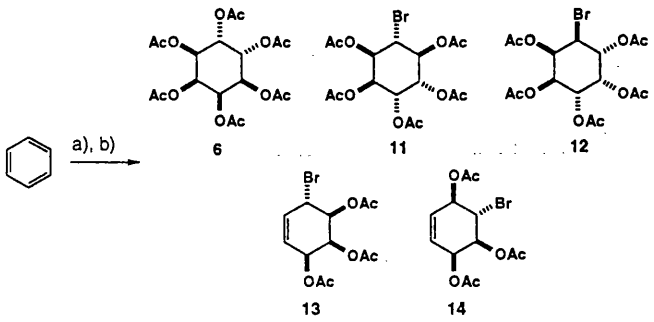
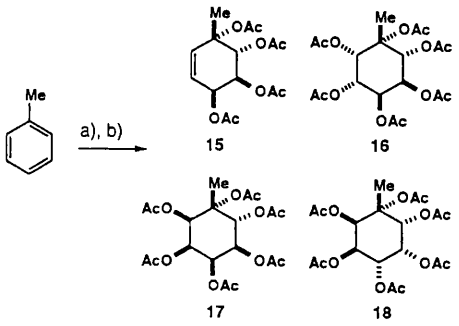


Scheme 4. a) OsO_4 (cat.), *hv*, $NaBrO_3$ (0.22 M); b) Ac_2O, AcOH; **6** 7.7%, **11**:**12** (5.1:1) 18.8%, **13**:**14** (1:5) 2.3%.

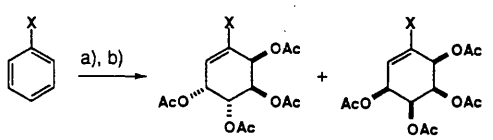
spectra and confirmed by X-ray analysis[11] to be the deoxybromo-*chiro*-inositol (**11**). Minor amounts of the deoxybromo-*neo*-inositol (**12**) (3.1%) and the bromoconduritols C (**13**) and F (**14**) (2.3% yield; **13**:**14** = 1:5) were also isolated.

A preliminary screening of some simple monosubstituted arenes gave the following results: Oxidation of the stereochemically more complex toluene (Scheme 5) was achieved in 13% overall yield (catalytic turnover 29) to the single C-methyl conduritol isomer E (**15**) and an isomeric mixture (ratio 2:1:1) of C-methyl-*allo*-inositols **16**, **17**, and **18** in a conduritol:inositol ratio of 1:5. Inspection of the relative configuration of **15** (X-ray analysis)[11] reveals it to be the precursor of the major portion of the inositol derivatives **16** and **17**, and also suggests that the initial photoosmylation step occurs at either the 1,2 or 3,4 positions. Interestingly, in contrast with the Etard oxidation,[12] which also involves metal-mediated electron transfer, only trace amounts of benzaldehyde were formed.



Scheme 5. a) OsO_4 (cat.), *hv*, $Ba(ClO_3)_2$ (0.22 M); b) Ac_2O, Et_3N, DMAP; **15** 2.2%, **16**:**17**:**18** (2:1:1) 10.8%.

As expected on the basis of their higher ionization potentials, the "catalytic" turnover of the oxidation of halogenated arenes under our initial conditions is very slow indeed (Scheme 6; combined yields: **19** 0.6%, **20** 3.4%, **21** 2.6%). Nevertheless, it is significant to note that no inositol derivatives were detected, presumably since the remaining double bond—a vinylic halide—is resistant to further osmylation on electronic grounds. In these experiments the preference for the formation of the *anti*-tetrols is much higher[13] than in the OsO_4-catalyzed vicinal dihydroxylation of the 2,3-diol produced by oxidation of bromobenzene with *Pseudomonas putida*, where the ratio of **21a**:**21b** is 1.1:1.0.[3c]



19 : X=F	**19a**	4.4 : 1	**19b**
20 : X=Cl	**20a**	5.0 : 1	**20b**
21 : X=Br	**21a**	5.5 : 1	**21b**

Scheme 6. a) OsO_4 (cat.), *hv*, $Ba(ClO_3)_2$ (0.22 M); b) Ac_2O, Et_3N, DMAP; **19** 0.6%, **20** 3.4%, **21** 2.6%.

In view of the many kinetically discrete photochemical and thermal steps involving formation and oxidative hydrolysis of different regio- and stereoisomeric osmate esters during a single reaction sequence, it is not surprising that the nature and relative ratios of the products isolated are influenced by temperature, relative concentrations of reactants and reagents, and the duration of the radiation and its intensity. Although we have not yet carried out systematic optimization studies for each system, the present work indicates for the first time that the controlled catalytic vicinal dihydroxylation of benzene and simple arenes can lead to a variety of usefully functionalized inositol and conduritol derivatives without cleavage of the carbocyclic ring.

Experimental Procedure

6, **8**, **9**, **10**: To deionized water (10 mL) in a 25 mL Pyrex florentine flask fitted with a Teflon tap was added $Ba(ClO_3)_2$ (3.53 g), benzene (15 mL), and OsO_4 (25 mg, 0.1 mmol) in CCl_4 (0.25 mL). The biphasic system was stirred vigorously and irradiated with a 400 W medium-pressure Hg bulb for 43 h. The solution was then cooled to 0 °C and reduced with $Na_2S_2O_5$ (15 g), stirred for a further 2 h, and evaporated to dryness under reduced pressure. The dried salts were then powdered, treated with Et_3N (70 mL), Ac_2O (20 mL), and 4-dimethylaminopyridine (DMAP, catalytic amount), and heated (70 °C) for 3 h. The reaction mixture was cooled (0 °C), water was added (100 mL), and the mixture was filtered through a pad of Celite and extracted with ether (3 × 100 mL). The extract was washed with brine (100 mL), dried over $MgSO_4$, and concentrated at reduced pressure to give a yellow oil, which crystallized on standing. Column chromatography (SiO_2, 70% ether in petroleum spirits) gave, in order of elution, **8** and **9** as a 1:1 mixture (0.495 g, 1.21 mmol), **10** (0.121 g, 0.30 mmol), and **6** (1.120 g, 2.59 mmol). Compound **8** was separated from **9** by HPLC (SiO_2, 25% EtOAc in hexane).

6: ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C, $CHCl_3$): δ = 2.05 (bs, 18H; 6 × CH_3), 5.30 (m, 2H; H-3, 6), 5.44 (m, 4H, H-1, 2, 4, 5); ^{13}C NMR (100 MHz): δ = 20.5–20.6 (6 × CH_3), 67.4–67.7 (6 × CH), 169.2, 169.3, 169.5 (6 × OCOMe); MS (70 eV, NH_3): *m/z*(%): 450 $[M + NH_4]^+$. Correct elemental analysis; m. p. 140–141 °C (methanol; ref. [10]: 138–139 °C).

8: ^{1}H NMR (400 MHz, $CDCl_3$, RT, $CHCl_3$): δ = 2.00, 2.07, 2.11, 2.17, 2.20 (5 × s, 15H, 5 × CH_3), 4.15 (t, ^3J(H,H) = 10.9, 10.9 Hz, 1H, H-3), 5.21 (dd, ^3J(H,H) = 10.3, 2.8 Hz, 1H, H-5), 5.31 (dd, ^3J(H,H) = 11.0, 2.7 Hz, 1H, H-2), 5.36 (m, ^3J(H,H) = 2.9, 5.6 Hz, 2H, H-1, 6), 5.49 (dd, ^3J(H,H) = 10.3, 10.3 Hz, 1H, H-4); ^{13}C NMR (100 MHz): δ = 20.4, 20.5, 20.5, 20.6, 20.7 (5 × CH_3), 57.4 (CH, C-3), 67.1, 67.5, 69.3, 70.5, 70.8 (5 × CH), 168.7, 169.0, 169.3, 169.3, 169.7 (5 × OCOMe); MS (70 eV, NH_3): *m/z*(%): 428 (34.8), 426 (100) $[M + NH_4]^+$. Correct elemental analysis; m. p. 146–147 °C (ethanol; ref. [14]: 144 °C).

9: ^{1}H NMR (400 MHz, $CDCl_3$, RT, $CHCl_3$): δ = 2.00 (s, 6H, 2 × CH_3), 2.07, 2.16, 2.20 (3 × s, 9H, 3 × CH_3), 4.34 (dd, ^3J(H,H) = 11.1, 3.0 Hz, 1H, H-6), 5.23 (dd, ^3J(H,H) = 11.0, 3.0 Hz, 1H, H-4), 5.32 (dd, ^3J(H,H) = 11.2, 2.8 Hz, 1H, H-1), 5.34 (dd, ^3J(H,H) = 11.2, 3.0 Hz, 1H, H-3), 5.65 (dd, ^3J(H,H) = 3.0, 3.0 Hz, 1H, H-2), 5.72 ((dd, ^3J(H,H) = 3.0, 2.9 Hz, 1H, H-5); ^{13}C NMR (100 MHz): δ = 20.4, 20.5, 20.6 (5 × CH_3), 54.7 (CH, C-6), 67.0, 68.4, 68.6, 69.4, 69.5 (5 × CH), 169.3, 169.4, 169.6, 169.7, 169.9 (5 × OCOMe); MS (70 eV, NH_3): *m/z*(%): 428 (34.7), 426 (100) $[M + NH_4]^+$. Correct elemental analysis; m. p. 137–139 °C (ethanol).

10: ^{1}H NMR (400 MHz, $CDCl_3$, RT, $CHCl_3$): δ = 2.08 (s, 6H, 2 × CH_3), 2.10 (s, 6H, 2 × CH_3), 2.12 (s, 3H, CH_3), 4.36 (dd, ^3J(H,H) = 11.1, 3.0 Hz, 1H, H-6), 5.37 (m, 5H, H-1, 2, 3, 4, 5). ^{13}C NMR (100 MHz, 55 °C): δ = 20.4 (4 × CH_3), 20.6 (CH_3), 54.0 (CH, C-6), 67.7 (CH, C-3), 68.3 (2 × CH, C-1, 5), 71.1 (2 × CH, C-2, 4), 169.0–169.2 (5 × OCOMe); MS (70 eV, NH_3): *m/z*(%): 428 (33.1), 426 (92.4) $[M + NH_4]^+$. Correct elemental analysis; m. p. 170–171 °C (ethanol; ref. [15]: 185 °C from 2-propanol).

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Corrigenda