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SYNTHESIS OF FUNCTIONALISED CYCLOHEXANES FROM CARBOHYDRATES

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ABBREVIATIONS

The following abbreviations were used in the text:

aqu.	aqueous
dil.	dilute
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DMF	*N*,*N*-dimethylformamide
LAH	lithium aluminium hydride
NBS	*N*-bromosuccinimide
PBA	perbenzoic acid
PG	prostaglandin
PY	pyridine
THP	tetrahydropyran
t.l.c.	thin layer chromatography
TMS	tetramethyl silane

ABSTRACT

β-D-glucopyranose pentaacetate was photobrominated to give the 5-bromide from which 6-deoxy-β-D-*xylo*-hex-5-enopyranose tetraacetate was obtained by reductive elimination. This reaction sequence represents an efficient new route to the 5-ene.

A detailed investigation into the photobromination of β-D-glucopyranose pentaacetate with bromine and with NBS led to the isolation of several by-products containing bromine substituents at C-1 and/or C-5; their reactions with zinc-acetic acid were studied, and the conformations in solution of four alkenes derived from the 5-bromo compound were determined.

2,3,4-Triacylated 2,3,4,5-tetrahydroxycyclohexanones were obtained by mercury(II) catalysed rearrangement of 6-deoxyhex-5-enopyranose esters. The mechanism of this rearrangement, and some reactions of the products were examined.

The use of these new carbocyclic compounds in the synthesis of branched-chain cyclitol derivatives was explored. By means of diazomethane or, alternatively, hydrogen cyanide, substituted cyclohexanes with one-carbon branches and tertiary hydroxyl groups at the site of chain-branching were prepared. Attempts to eliminate water from these tertiary alcohols to give substituted cyclohexene-carbonitriles or -carbaldehydes were unsuccessful.

CHAPTER ONE

INTRODUCTION

This thesis describes the preparation from D-glucose of optically pure functionalised cyclohexane derivatives related to natural products with antibiotic activity.

The introductory chapter starts with a brief discussion of the use of carbohydrates as starting materials for the synthesis of enantiomerically pure non-carbohydrate products; this is followed by a short survey of known cyclitols and their synthesis, with emphasis on the preparation of six-membered compounds from carbohydrate precursors.

SYNTHESIS OF ENANTIOMERICALLY PURE NATURAL PRODUCTS FROM CARBOHYDRATES

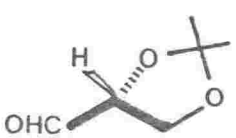
Among the major problems in the synthesis of natural products are the control of absolute stereochemistry and the stereo- and regio-specific introduction of functionality at predetermined sites.[1] The vast majority of natural products are optically active substances, but almost all the great syntheses start from simple achiral molecules and necessarily give racemic mixtures which require resolution. Traditionally resolution is performed at the end of a synthesis with the help of an optically pure, chemical resolving agent, or, infrequently, by an enzymatic transformation.[2]

Alternatively, the desired absolute configuration can be introduced by asymmetric synthesis, *i.e.* by conversion of an achiral compound to predominantly one of the two possible stereoisomeric chiral products. This is achieved most efficiently by use of microbiological enzyme systems. Many enzymatic reductions of ketones for instance, lead to secondary alcohols with the (S)-configuration in high enantiomeric excess.[2,3] There are also a wide variety of purely chemical reagents and methods available for asymmetric synthesis.[4] These, like enzymes, are employed as auxiliaries and do not become part of the final product. Excellent enantioselectivity has been attained in isolated cases, notably in work with chiral hydrogenation catalysts,[4] but in general optical yields are inadequate for preparative

purposes, which represents a significant limitation of this method.

Yet another, more direct way to produce enantiomerically pure compounds is to synthesise them from enantiomerically pure building blocks. This allows, as does a highly efficient asymmetric synthesis, the preparation of optically active products without loss of material with alternative absolute configuration, as is the case with a resolution dependent synthesis. In contrast to asymmetric synthesis, however, this approach leads to incorporation of the chiral reactant into the product. The synthesis of Vitamin B_{12}[5] and of several steroidal sapogenins[6] are examples of early syntheses in which optically pure reactants were used - although only at a late stage in the synthetic processes and after resolution of racemic intermediates. For efficiency, the required absolute stereochemistry should be established as early as possible, and the use of an appropriate chiral starting material is, therefore, of particular attraction.

Nature offers a multitude of enantiomerically pure compounds, such as amino acids, hydroxy acids, terpenes, and carbohydrates, which can serve as starting materials. In the simplest cases, a starting compound with only one asymmetric centre is built into a product without generation of further chirality. Resolved amino acids and hydroxy acids have been used this way, for example, to prepare a number of insect pheromones each containing one oxygenated chiral carbon atom,[7-9] and 2,3-O-isopropylidene-D-glyceraldehyde (1), which is conveniently prepared from D-mannitol,[10] was the precursor for



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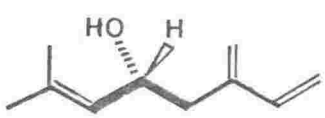

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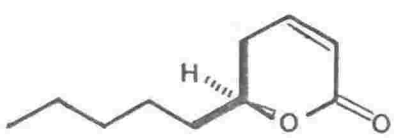
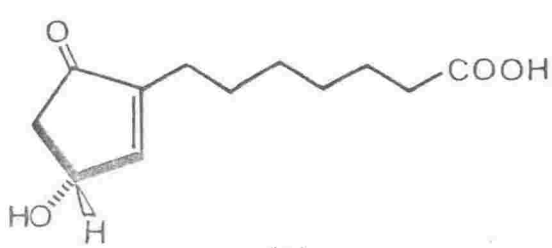


(3)

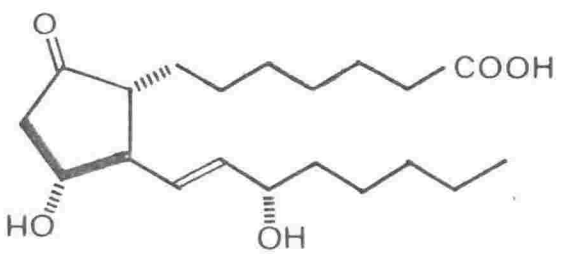
The bold lines indicate the carbon chains incorporated from the carbohydrate precursor



(4)

such diverse compounds as the pheromones (R)-(-)-ipsdienol (2)[11] and (S)-(+)-massoilactone (3),[12] and the prostaglandin intermediate (4).[13]

Once chirality is established in a molecule, creation of further asymmetric centres will, under the influence of the asymmetric centre or centres already present, give diastereoisomers in unequal proportions (asymmetric induction). This fact, of which use is made in numerous syntheses of racemic products, can of course be exploited in the same way in work with enantiomerically pure compounds. In the synthesis of prostaglandin E_1 (5) from intermediate (4), for example, the single chiral centre of the precursor serves to control the stereochemistry during the generation of the rest of

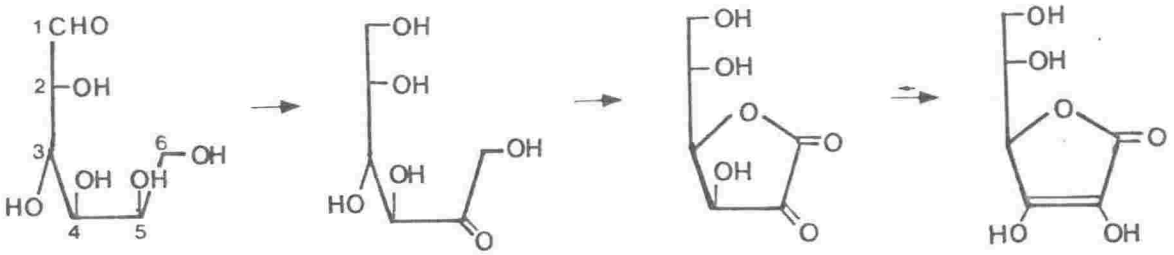


(5)

the PGE_1 molecule.[13] Other classical examples of syntheses of products with several asymmetric carbon atoms from optically pure single centre starting materials are the preparation of cephalosporin C from (S)-(+)-cysteine,[14] and of patchouli alcohol from (+)-camphor.[15]

Regrettably asymmetric induction under the influence of a single chiral centre is often not as effective as would be desirable. For the synthesis of complex, enantiomerically pure natural products, therefore, multicentre chiral precursors like pentoses and hexoses and their derivatives are of great interest,[1,16] because, in addition to being optically pure, carbohydrates, especially in cyclic form, provide excellent chiral frameworks consisting of several centres of well defined configuration and functionality. Due to a great wealth of experience, amassed since the pioneering work of Emil Fischer, both the stereochemistry and the functionality of carbohydrates can be modified in controlled manner. The presence of several sites of asymmetry close together and the conformational bias displayed by most sugar derivatives ensures a high degree of regio- and stereo-selectivity in many reactions.

The idea of using carbohydrates as convenient chiral precursors is not new. Almost 50 years ago D-glucose (6) was chosen as the starting material for the preparation of ascorbic acid (vitamin C)[17] (8), a compound with the L-configuration. For the industrial synthesis of the vitamin based

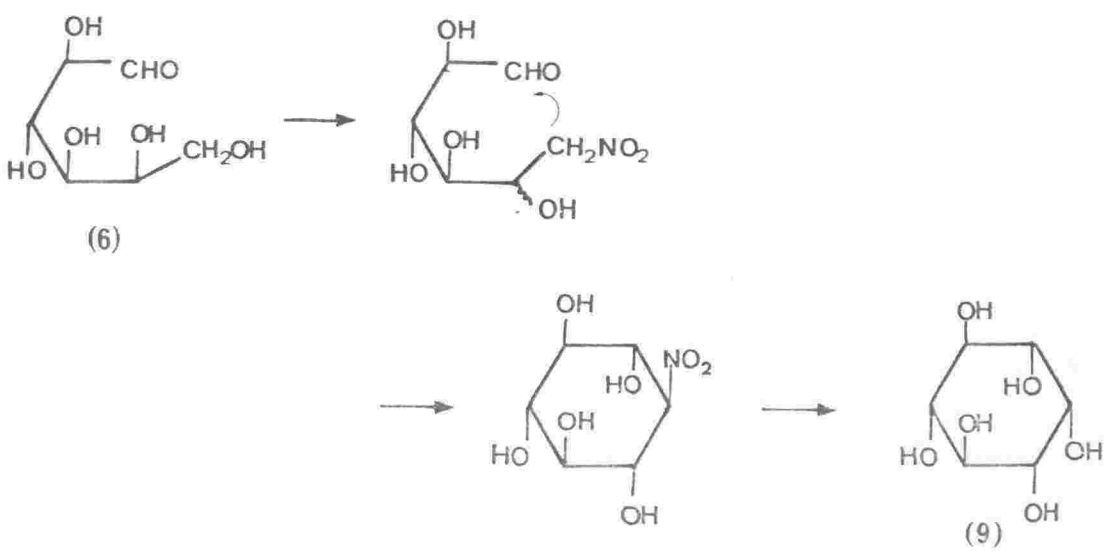


(6) (7) (8)

Scheme 1

on this method it was important that a cheap, readily available D-sugar could be used to manufacture the L-product. In Reichstein's synthesis[17] (Scheme 1) D-glucose (6) was first converted to L-sorbose (7) by catalytic reduction of the aldehydo group and regiospecific bacteriological oxidation at C-5. This was followed by oxidation at the site of the original C-6 to give an α-ketoacid which could be lactonised. The resulting α-ketolactone then enolised to the stable tautomer (8).

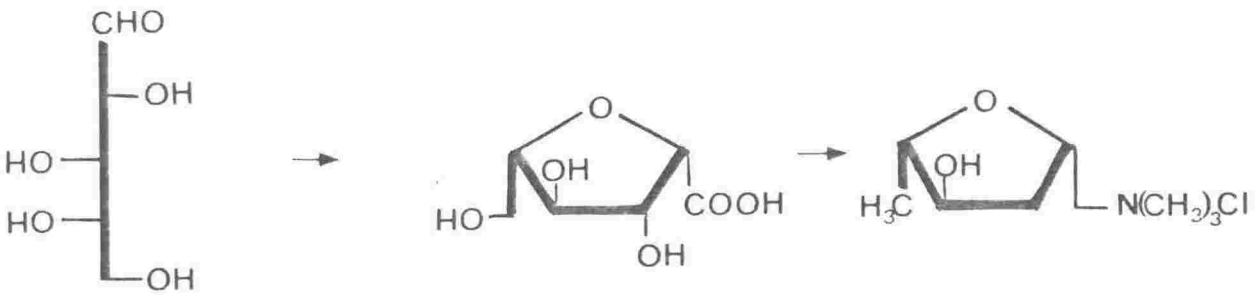
In 1948 Grossheintz and Fischer[18] prepared myo-inositol (9) from D-glucose (6), as outlined in Scheme 2, in order to confirm the hypothesis that the



(6) (9)

Scheme 2

biosynthesis of inositols involves the cyclisation of this sugar (see also Scheme 22, p.23). This was later found to be an ideal method for preparing the ^{14}C-labelled inositol.[19,20] An early synthesis of streptamine (p. 11) is based on the same reaction.[21] Somewhat later, in 1957, a synthesis of L-(+)-muscarine (12) from 2,5-anhydro-L-gluconic acid (11), which in turn was derived from L-arabinose (10), was undertaken mainly to prove the L-configuration of the natural muscarine[22] (Scheme 3).



(10) (11) (12)

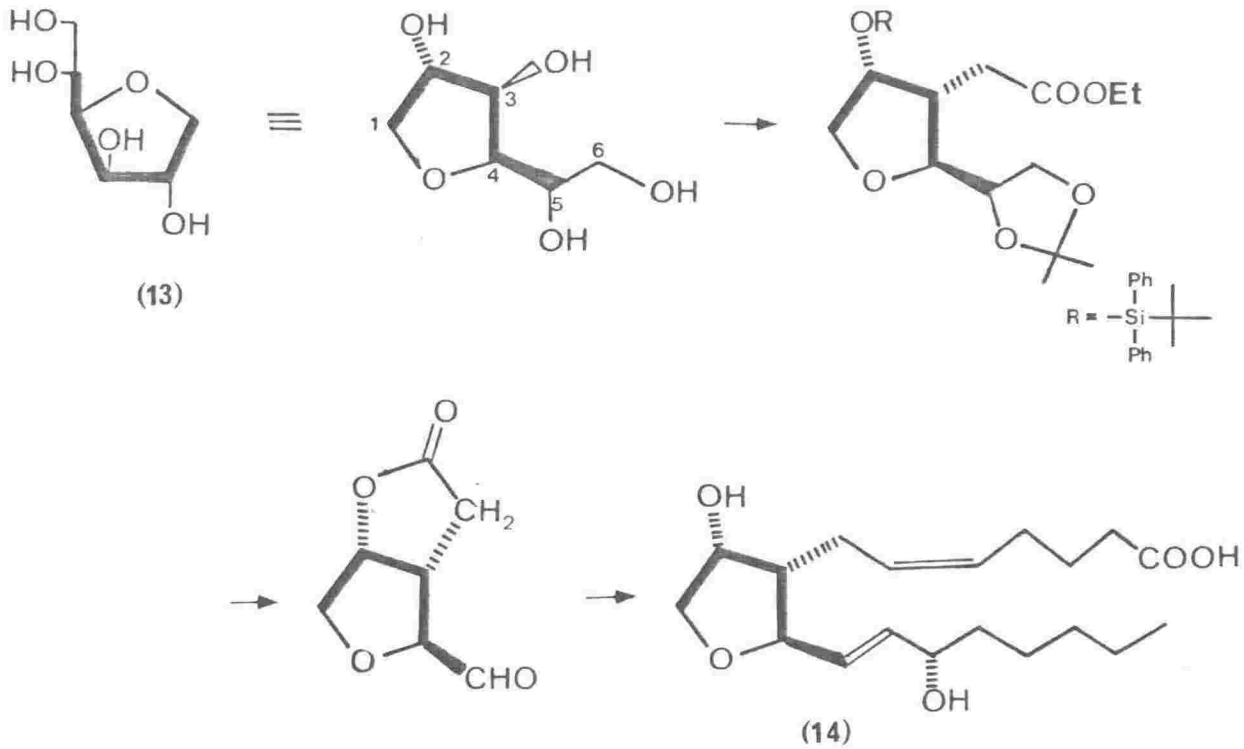
Scheme 3

Within the past decade, the use of carbohydrates as chiral synthons has become much more widespread. This is, at least partly, due to the availability of new and improved techniques. Chromatography, for example, greatly facilitates the isolation of carbohydrate derivatives, which have long had a reputation of being sensitive and difficult to purify, and ^{1}H n.m.r. spectroscopy, in particular, is invaluable for the characterisation of new synthetic compounds. Methods of preparation usually limit the probable configurations of new carbohydrate products, and configurational analysis is often possible by examination of their ^{1}H n.m.r. spectra.

Syntheses of natural products from carbohydrates can be considered in two groups: (i) syntheses in which the sugar portion is still apparent in the product (cyclic or acyclic transfer[16]); clearly, the older syntheses shown above belong to this class; and (ii) syntheses in which the products bear imperceptible resemblance to their sugar precursors (transcription[16]).

Several biologically active substances containing tetrahydropyranoid or tetrahydrofuranoid rings have been synthesised from carbohydrates, and in the structural formulae of these compounds the sugar portions are still readily discernible. In these syntheses the synthetic process involves a transfer of a substantial part of the sugar derivative, namely the pyranoid

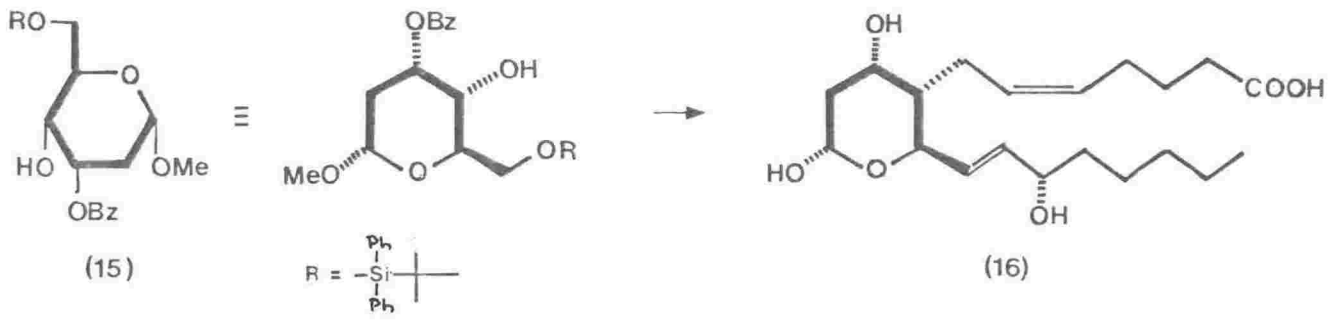
or furanoid ring, into the product (cyclic transfer[16]). The synthesis of 11-oxa-prostaglandin $F_{2\alpha}$ (14) from 1,4-anhydro-D-glucitol (13)[1] (Scheme 4) is an example of such a synthesis, requiring three basic operations: (i) protection of the hydroxyl group at C-2, which has the wanted



Scheme 4

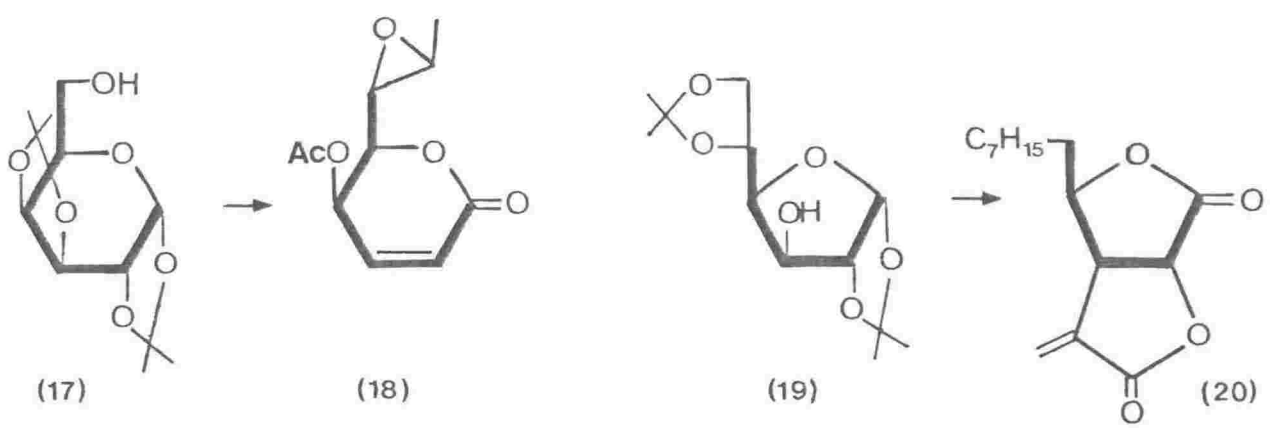
stereochemistry, with the bulky t-butyldiphenylsilyl group; (ii) introduction of an acetic acid side chain at C-3 by use of a Wittig-Horner reaction, followed by stereocontrolled catalytic hydrogenation, the stereocontrol being due, to a great extent, to the bulk of the protecting group at C-2; (iii) periodate cleavage of the C-5-C-6 bond to form an aldehydo group which serves as the origin of the ω side chain. Elaboration of both side chains was readily carried out using standard methods.[23]

A very similar reaction sequence was employed to synthesise thromboxane B_2 (16) from a suitably protected methyl 2-deoxy-α-D-ribo-hexopyranoside derivative (15)[24] (Scheme 5).



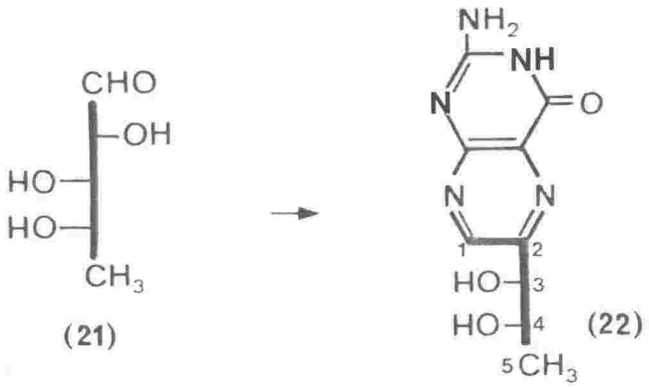
Scheme 5

Other examples of cyclic transfer are the preparation of the antibiotic asperlin (18) from di-O-isopropylidene-D-galactose (17)[25] and of avenaciolide (20) and related fungal metabolites from di-O-isopropylidene-D-glucose (19)[26,27] (Scheme 6).



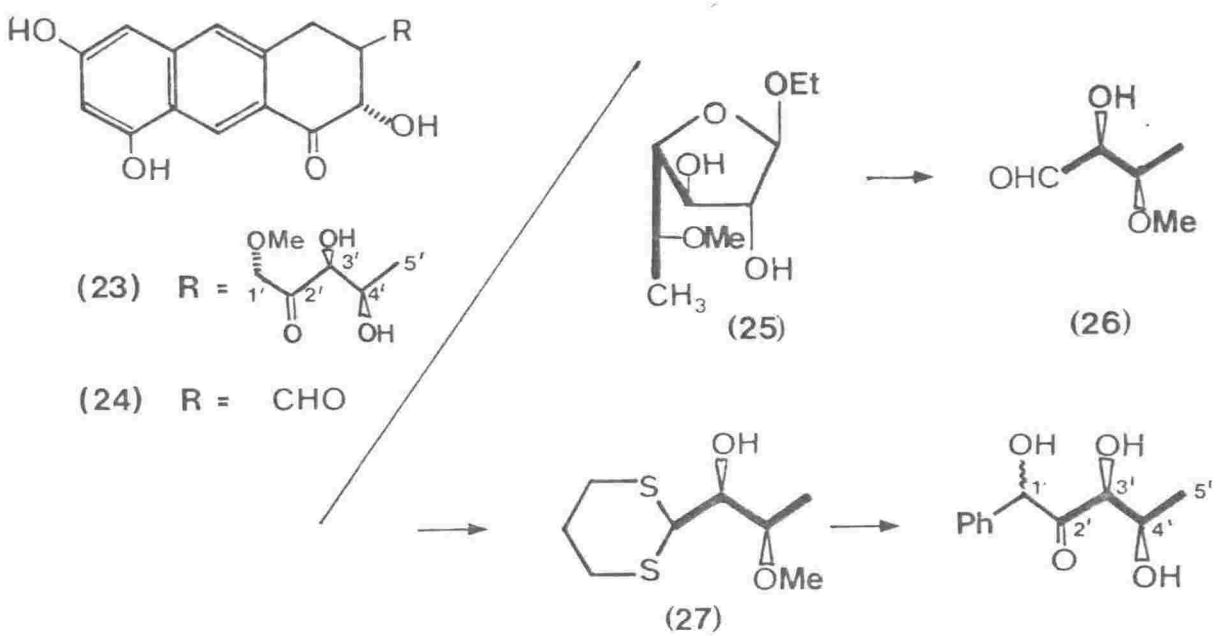
Scheme 6

A number of non-carbohydrate natural products have polyhydroxyalkyl side chains, and these are obvious target structures for synthesis from sugars. Here an acyclic fragment of known absolute configuration, contained in a sugar, is transferred into, or attached to, the framework of the product (acyclic transfer[16]). The side chain of L-erythro-biopterin (22), for example, was derived from 5-deoxy-L-arabinose (21)[28] (Scheme 7). Carbon atoms 3-5 were used to form the side chain, while carbon atoms 1 and 2 became part of the bicyclic ring system. A different strategy was planned in an approach to



Scheme 7

the synthesis of chromomycinone (23),[29] the aglycon of the antitumor agent chromomycin[30] (Scheme 8). Here the side chain was constructed separately for attachment to the preformed tetrahydroanthracene carbaldehyde (24). The carbohydrate derivative needed was 4-deoxy-3-O-methyl-D-threose (26) which was

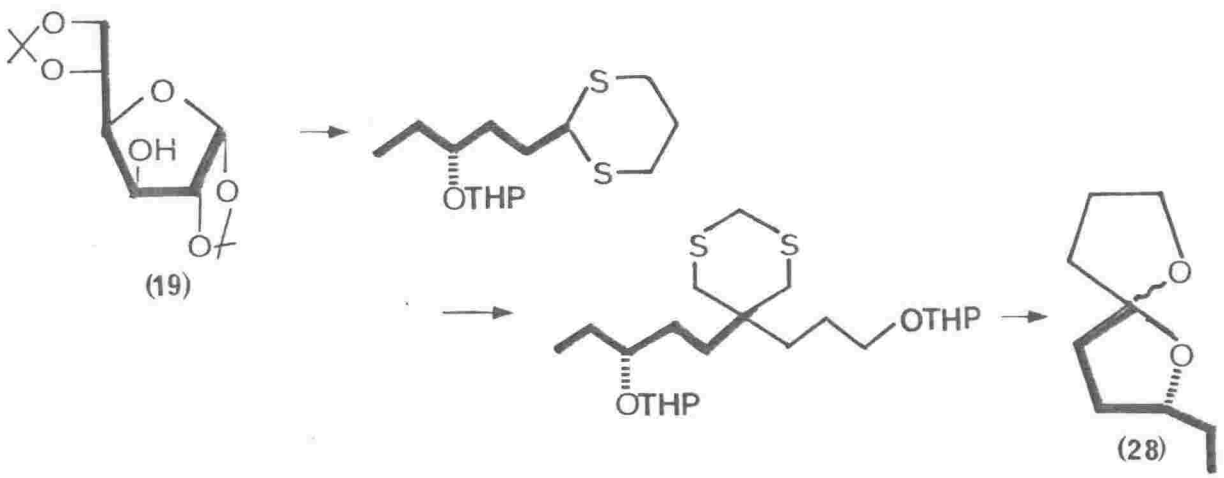


Scheme 8

obtained from an appropriately protected 6-deoxy-D-galactose derivative (25) by periodate cleavage. Attachment by use of the dithiane (27) has so far

been tried only with benzaldehyde as a simple model aldehyde, and a way to methylate the 1'-hydroxyl specifically has yet to be devised.

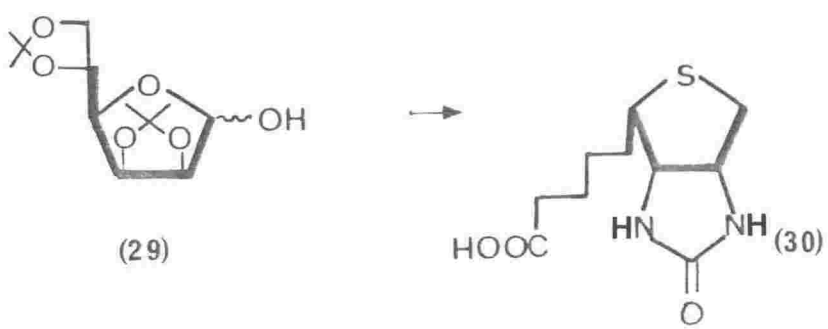
Often it is more difficult to discern in the product the original carbohydrate fragment, because it has been modified or degraded beyond recognition (transcription[16]). For example, in the preparation of the spiroketal pheromone chalcogran (28) from di-O-isopropylidene glucose(19)[31] (Scheme 9), the entire six-carbon chain of the starting material was transferred into the product, but only one chiral centre remained. The hydroxyl functions at carbon atoms 2, 3, 5 and 6 were removed by converting



Scheme 9

them successively to dithiocarbonate derivatives which could then be reduced with tributyltin hydride.

To convert di-O-isopropylidene -D-mannofuranose (29) to (+)-biotin (30)[32] (Scheme 10) all the oxygen functions of the starting material had to be reduced or replaced by either a carbon-, nitrogen- or sulphur-substituent. The choice

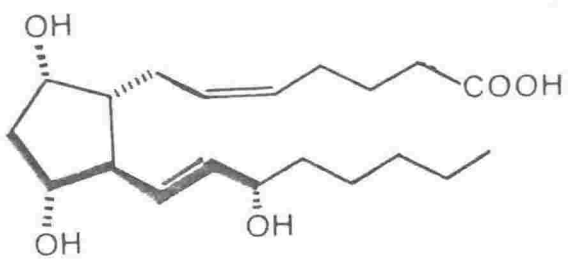


Scheme 10

of a mannose derivative ensured that, by introducing the heterofunctions at C-2, C-3 and C-4 with inversion of configuration, the desired stereochemistry was obtained.

A novel method for the preparation of functionalised cycloalkanes from carbohydrates, in which the sugar moiety is destroyed as an entity after having served its stereochemical purpose, is described on p.27. Other preparations of cyclitol derivatives from carbohydrates will also be dealt with later (p. 19).

The most elegant and imaginative examples of the use of carbohydrates as chiral synthons are no doubt Stork's synthesis of prostaglandin $F_{2\alpha}$ (31)[33] from D-glycero-D-gulo-heptonolactone, and Nicolaou's[34] and Hanessian's[35] approaches to the synthesis of macrolide antibiotics. The aglycon (32) of carbomycin B has been prepared from D-glucose and (R)-β-hydroxybutyric acid,[34] while the yet incomplete synthesis of erythronolide A (33)[35] starts from two molecules of D-glucose.



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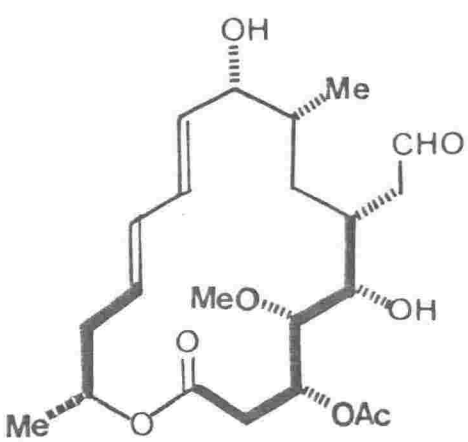

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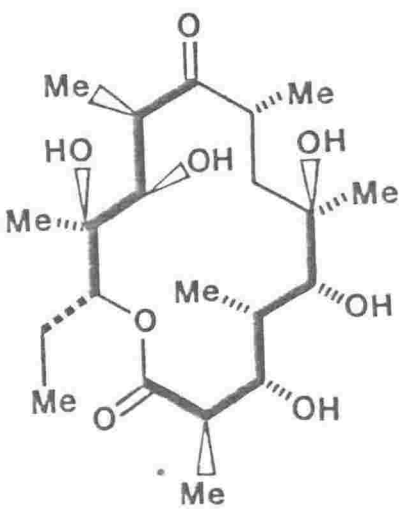

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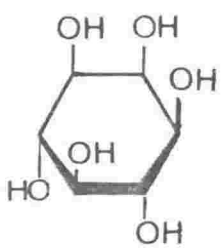
CYCLITOLS

Cyclitols are polyhydroxy carbocyclic compounds closely related to the carbohydrates.[36-38] Primarily these constitute the polyhydroxycylo-hexanes and -hexenes and their derivatives. Cyclitols having rings other than six-membered are known however (see pp. 15, 18, 24, 26, 27).

The hexahydroxycyclohexanes, or inositols, are found in animal and plant tissue both uncombined and in the form of various derivatives, such as mono- and di-methyl ethers, phosphoric acid esters or as inositol-containing phospholipids. Of the nine possible isomers, myo-inositol (9) is by far the most abundant and most extensively investigated. It appears to be present, free or combined, in nearly all living cells. Myo-inositol is the parent substance of many naturally occurring cyclitol derivatives and the raw material for the chemical synthesis of other cyclitols, and it was realised very early that it is configurationally related to D-glucose (6),[39] the most abundant sugar (see Schemes 2 and 18).



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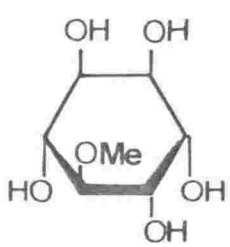

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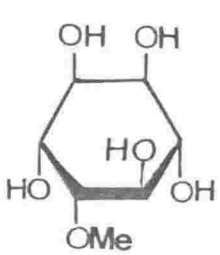

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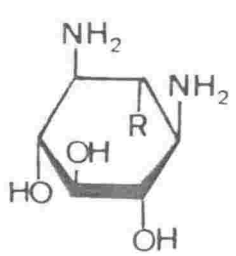


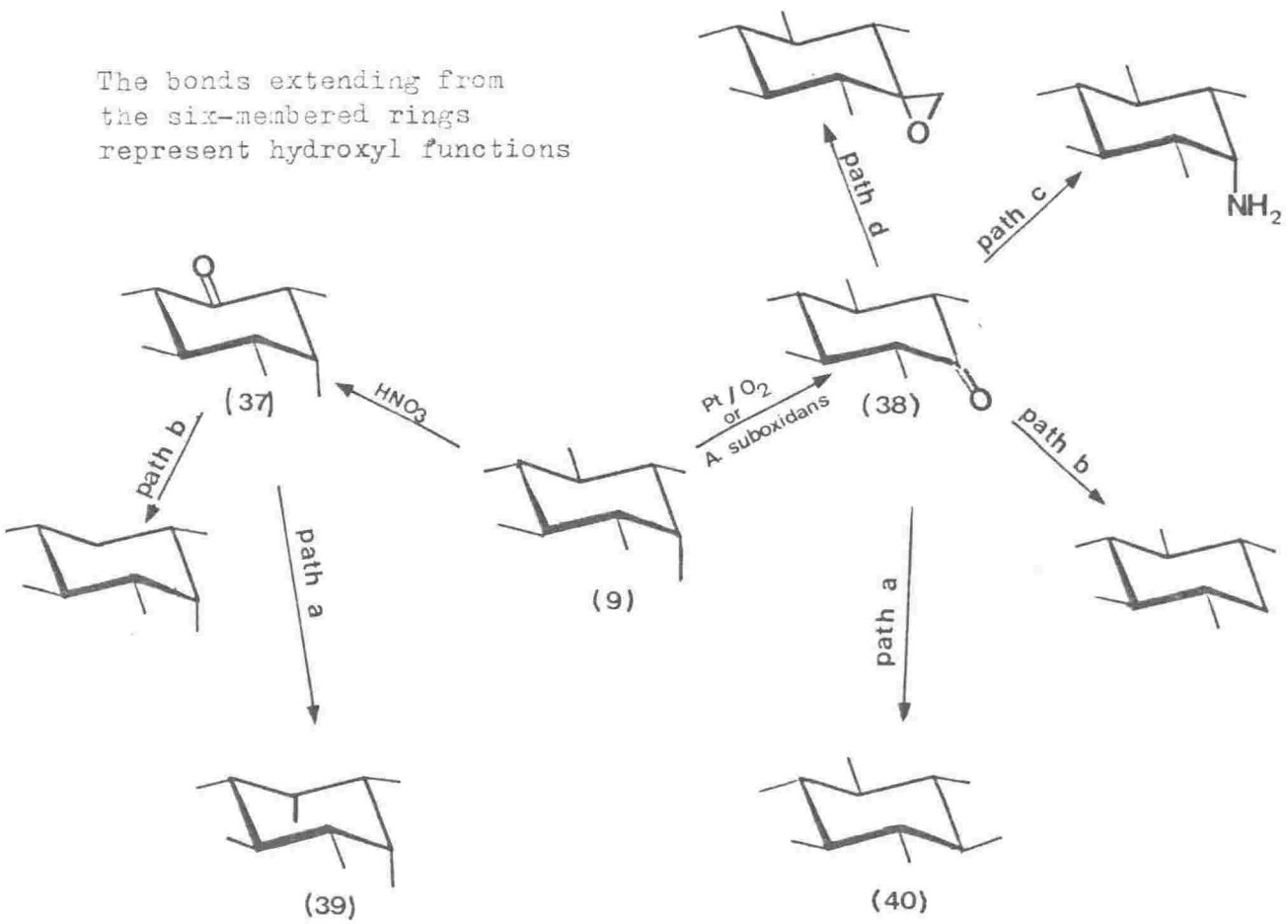
(36)

Other cyclitols found in nature are important as starting materials for the preparation of related compounds. Since all inositols except the two enantiomeric chiro-isomers are symmetrical, the naturally occurring chiro-derivatives D-(+)-pinitol (34) and L-(-)-quebrachitol (35) are especially useful, because, from them, optically active products are obtainable without recourse to resolution.[40,41]

Cyclitols bearing amino groups or substituted amino groups, usually referred to as inosamines, are components of many antibiotics. The best known are streptamine (36, R = OH) and deoxystreptamine (36, R = H), hydrolysis products from streptomycins and other antibiotics.[42] The search for improved antibiotics containing natural as well as purely synthetic inosamines has

greatly stimulated research in the cyclitol field, but the available synthetic methods all suffer from a lack of readily accessible starting materials.[38]

Cyclic monoketone derivatives, or inososes, are important intermediates in cyclitol synthesis and biosynthesis. The biosyntheses of myo-inositol (9)[43] and of shikimic acid (p.13)[44,45] from D-glucose (6), for example, proceed via inososes (see Schemes 18 and 19, p.20). In keeping with this, small quantities of inososes have been found in animal tissues[46] and in bacterial culture filtrates.[44] Scheme 13 shows a number of useful reactions involving myo-inosose-2 [2,4,6/3,5-pentahydroxycyclohexanone] (38)[47,48] and epi-inosose-2 [DL-2,3,4,6/5-pentahydroxycyclohexanone] (37),[49] which are both obtained from myo-inositol (9), the former by bacterial (acetobacter suboxidans) or catalytic (O_2/Pt) oxidation, the latter by nitric acid

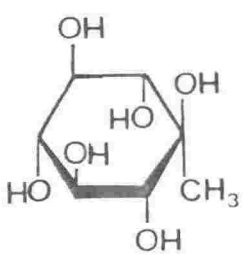


Reagents: Path a: Ac_2O/ py – $NaBH_4$ – OH^-; path b: H_2/Pt, H^+; path c: NH_2OH – Na(Hg) /HOAc; path d: CH_2N_2.

Scheme 13

treatment. In all three types of oxidation one hydroxyl group is oxidised specifically. The carbonyl group of an inosose can, as a rule, be reduced to give either an equatorial or an axial hydroxyl group preferentially. Thus, oxidation-reduction cycles can sometimes be used to invert the configuration at one particular carbon atom (*e.g.* scyllo-inositol (40)[50] or epi-inositol (39)[50] from myo-inositol (9), path a); catalytic hydrogenation in dilute mineral acid reduces the carbonyl group to a methylene group[51] (path b); oxime derivatives of inososes can be reduced to inosamines[38,52,53] (path c); and reaction of inososes with carbon nucleophiles (*e.g.* diazomethane,[54-56] path d) leads to branched-chain cyclitols.

Several cyclitol derivatives bearing side chains occur in nature; mytilitol (41) and (-)-laminitol (42), for example, are C-methylinositols found in algae, and L-(-)-quinic acid (43) and L-(-)-shikimic acid (44), which are both biochemically derived from D-glucose (see p. 20, Scheme 19), have long been known as plant constituents. (-)-Shikimic acid is an



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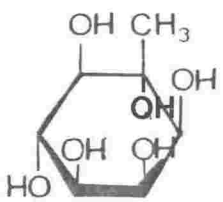

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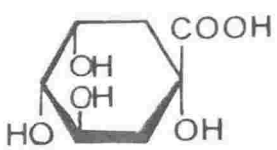

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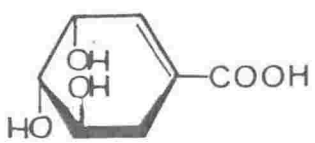
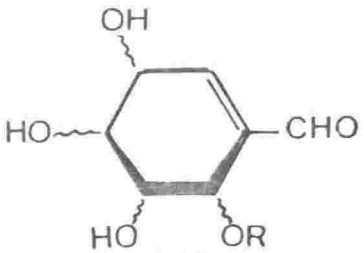


(44)

intermediate in the biosynthesis of aromatic compounds and (-)-quinic acid is a side product of this process.[44,45] (-)-Quinic acid, being enantiomerically pure and readily available, is a convenient starting material for the synthesis of optically active compounds, and it has, for example, been used in synthetic approaches to the anticancer agents daunomycin[57] and maytansine,[58] and to cyclopentanoid natural products.[59]

A complex mixture of carbocyclic carbaldehyde derivatives was obtained by Argoudelis et al.[60] from a streptomyces species under certain fermentation conditions. Four components were separated and designated rancinamycins I, II, III, and IV. All showed broad spectrum antibiotic activity in vitro. Rancinamycin IV (46) was found to be 3,4-dihydroxybenzaldehyde, while rancinamycins I-III are 3,4,5,6-tetrahydroxycyclohexene carbaldehydes of structure (45) with R = butanoyl, pentanoyl, and hydrogen. Although



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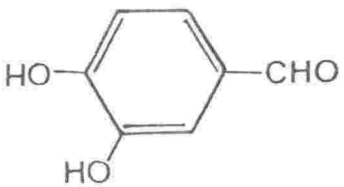

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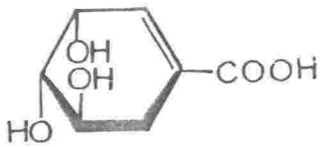
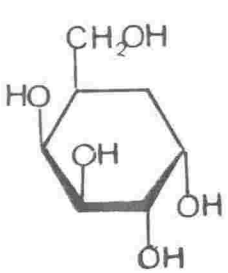


(44)

crystalline and behaving as single entities in paper and thin layer chromatography, rancinamycins I-III were found by gas chromatographic-mass spectroscopic analysis each to consist of 4 or 5 isomeric compounds. These are thought to differ in the isomeric structure of the acyl group R and/or in their stereochemistry. No stereochemical assignments were made, but a hypothesis was put forward, that rancinamycins might have a biogenetic origin similar to that of shikimic acid (44).[60]

Pseudo-sugars are an almost entirely synthetic group of compounds, only pseudo-α-D-galactopyranose (47) having been reported to occur in nature.[61] They are formally derived from pyranoses (or furanoses) by replacement of the ring oxygen atom with a methylene group. In their geometry and, in particular, in the arrangement of their hydroxyl groups such carbocyclic analogues are very similar to the corresponding natural sugars and it is very likely that they would be acceptable substrates for appropriate carbohydrate enzymes. On the other hand, they lack an acetal or hemiacetal group which makes carbohydrates susceptible to enzymatic fission, and pseudo-sugars may



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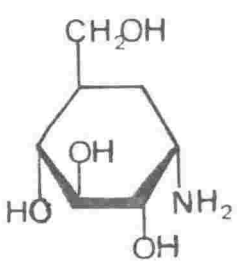

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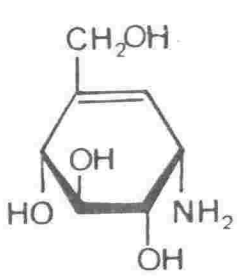

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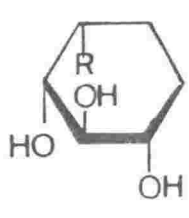
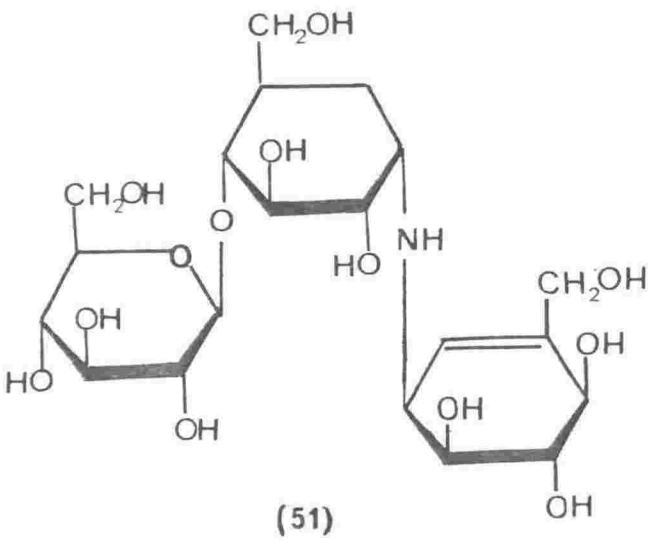


(50)

therefore have the potential either to mimic or to antagonise the functions of natural sugars in biological systems.

Quite a number of pseudo-hexopyranoses have been synthesised,[56,61-63] as well as pseudo-ribofuranose which has been incorporated into several pseudo-nucleotides.[64] In most cases the products were obtained not only as DL-mixtures, but also as mixtures of stereoisomers, which had to be separated by chromatography.

Closely related to pseudo-sugars are several branched-chain cyclitols and aminocyclitols obtained by degradation of the validamycin antibiotics, whose main component, validamycin A, has structure (51).[65,66] Microbial hydrolysis



(51)

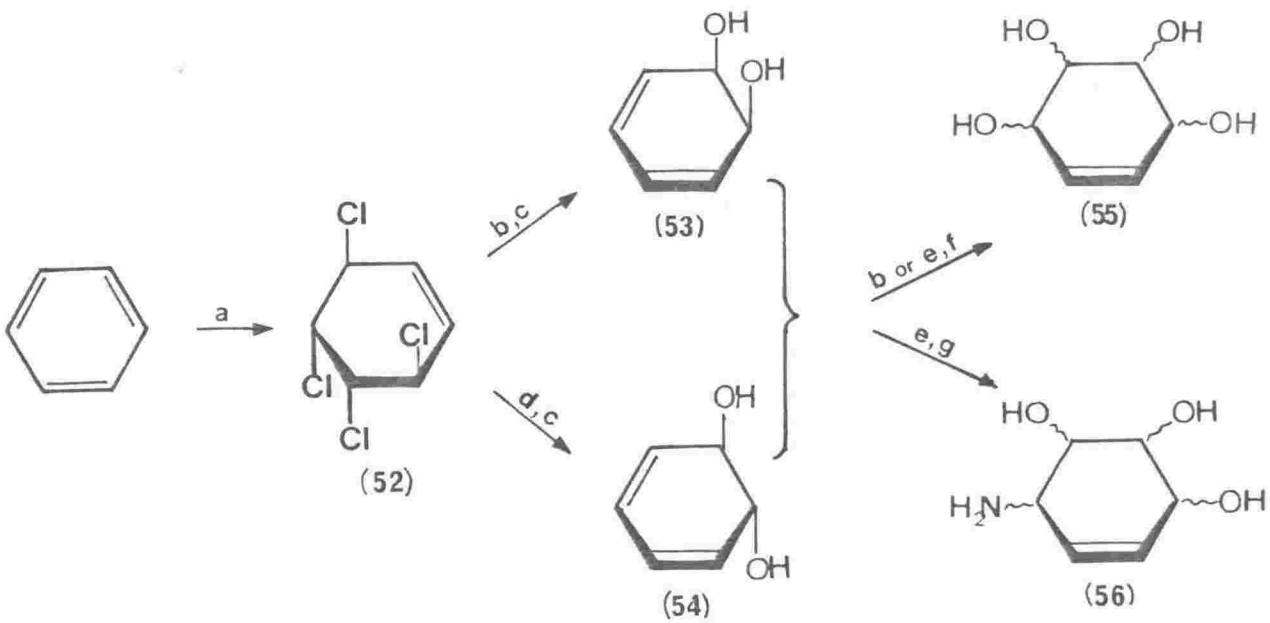
of validamycin A produces D-glucose (6), validamine (48) and valienamine (49), while hydrogenolysis affords β-D-glucopyranosylvalidamine, validatol (50, R = CH_2OH) and deoxyvalidatol (50, R = CH_3).[67] Several syntheses of these and similar degradation products have been reported[40,63,66-71] (see p.19) As in the case of pseudo-sugars, these syntheses, with one exception,[40] started from achiral molecules and gave racemic mixtures as well as mixtures of stereoisomers.

SYNTHESIS OF CYCLITOLS

Apart from chemical and biochemical modification of readily available natural members of the series there are three main methods for cyclitol synthesis: by hydroxylation of benzene ("benzeneglycol" synthesis), by application of the Diels-Alder reaction, and by rearrangement of carbohydrates.

A. The "Benzeneglycol" Synthesis

The "benzeneglycol" synthesis, illustrated in Scheme 14, starts from 3,6/4,5-tetrachlorocyclohexene (52) which is available as one of several products and in rather low yield by iodine inhibited chlorination of benzene. Hydroxylation of the double bond of this compound, followed by dechlorination



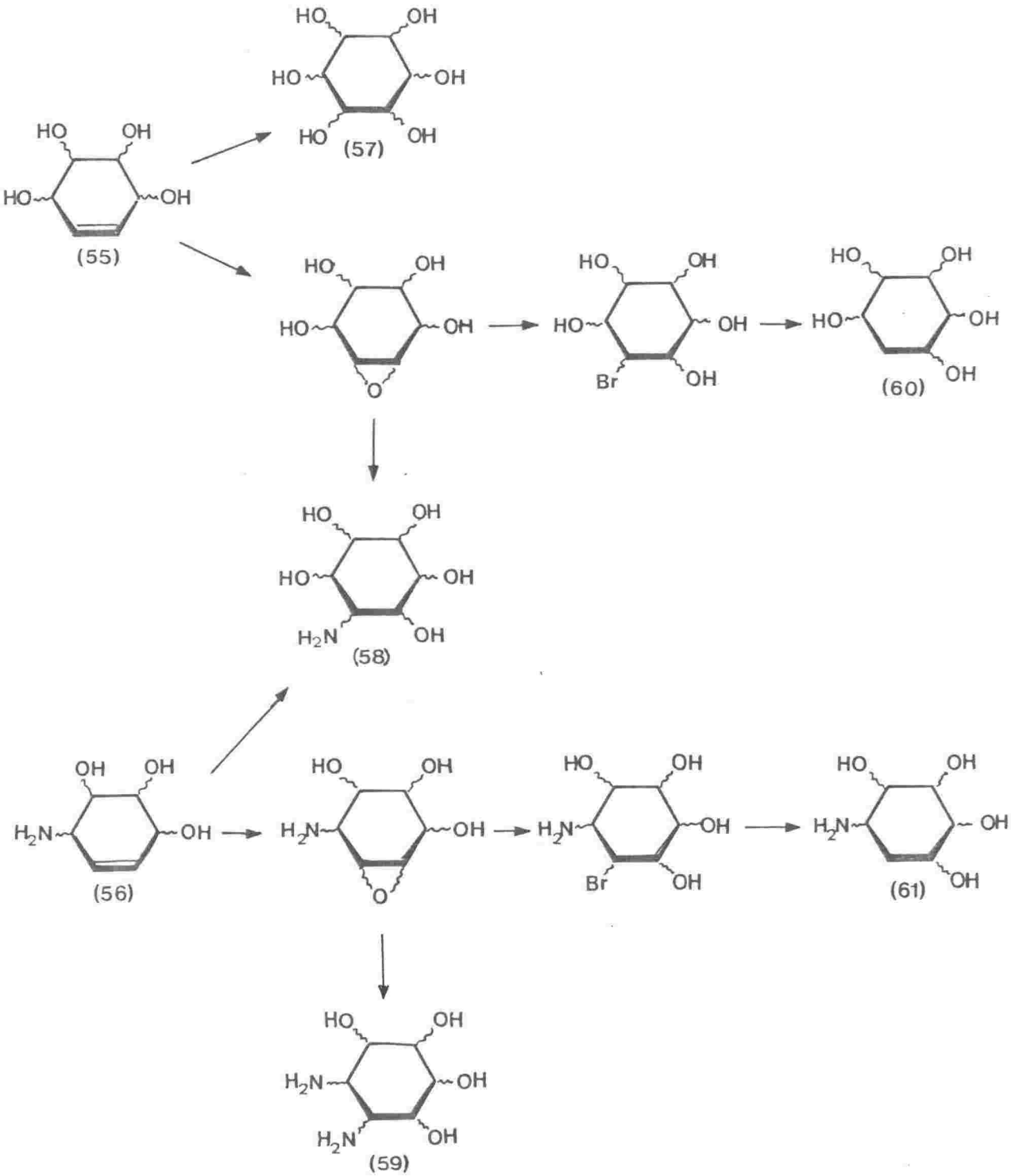
Reagents: a) Cl_2, I_2, hν ; b) $KMnO_4$; c) Zn ; d) CrO_3 ; e) PBA ; f) H^+ ; g) NH_3/MeOH

Scheme 14

with zinc gives, depending on the oxidising agent used, either (Z)- or (E)-1,3-cyclohexadiene-5,6-diol (53, 54),[72,73] referred to as "benzeneglyc ls". These dienes can be monohydroxylated to give 5-cyclohexene-1,2,3,4-tetrols (conduritols) (55),[74] or oxidised to the corresponding oxiranes which on oxirane ring opening with methanolic ammonia afford 4-amino-5-cyclohexene-1,2,3-triols (conduramines) (56),[75] specific isomers being preferentially obtained by suitable choice of starting material and reaction conditions.

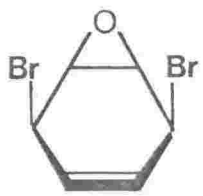
In Scheme 15 some further transformations of conduritols (55) and conduramines (56) are outlined. Hydroxylation of the remaining double bond gives inositols (57)[76] or inosamines (58),[75] while epoxidation followed by opening of the oxirane ring with various reagents leads to inosamines (58),[77] inosadiamines (59),[78] deoxyinositols (60),[79] deoxyinosamines (61),[80]

etc.. Again, different isomers can be produced preferentially depending on starting compounds and reaction conditions.

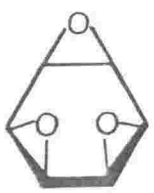


Scheme 15

In place of the tetrachlorocyclohexene (52) the dibromoepoxide (62), an intermediate in the synthesis of cis-trioxatris-σ-homobenzene (63) and available from benzene in three steps and high overall yield, has been employed as the starting material for the preparation of inositols and inosamines by similar routes.[81] Compound (63) itself has served as the precursor in an efficient synthesis of streptamine (36, R = OH).[81]



(62)

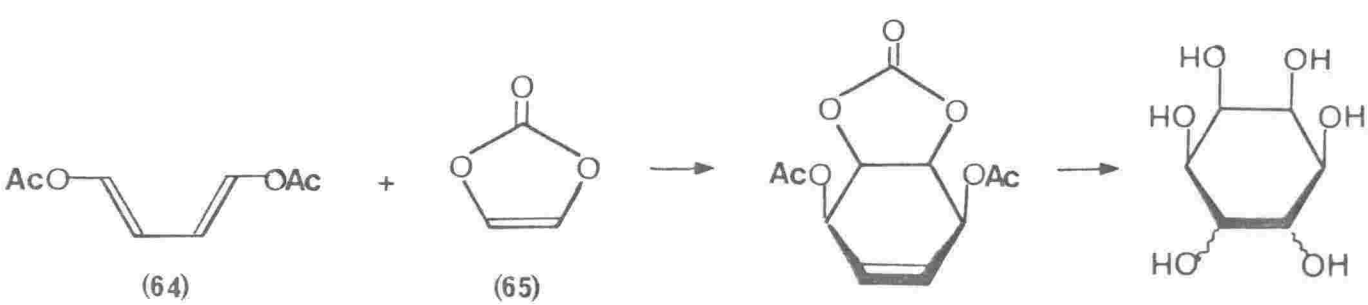


(63)

By procedures analogous to those just described many cyclopentanepolyols and aminocyclopentanepolyols have been prepared from cyclopentenediols.[82] As can be seen, the "benzeneglycol" synthesis is very versatile and has given rise to a large number of cyclitol derivatives, but its usefulness for preparative purposes is severely limited by the frequently inadequate stereoselectivity and by the fact that the products obtained are racemic.

B. Application of the Diels-Alder reaction

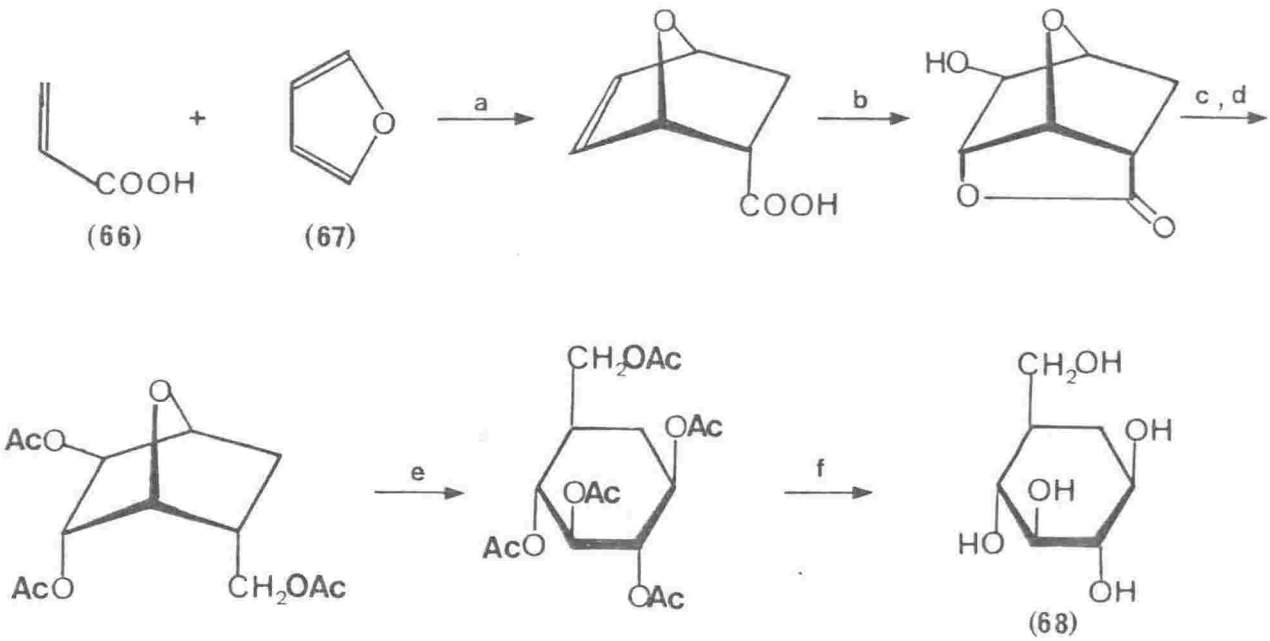
Construction of the cyclitol ring by use of the Diels-Alder reaction has been successfully accomplished in several instances. Carried out, for



(64) (65)

Scheme 16

example, with 1,4-trans-trans-diacetoxycyclobutadiene (64) as the diene and furan or vinylene carbonate (65) as the dienophile[83,84] cyclohexenyl products with four substituted hydroxyl groups were obtained (Scheme 16), and two further hydroxyl groups could be introduced by stereospecific hydroxylation of the remaining double bond.[84,85] DL-shikimic acid (44),[86-88] DL-quinic acid (43),[89] DL-validamine (48)[63,66,68] and related compounds,[40,69-71] and DL-pseudo-sugars[61-63] have been prepared by this method, and the synthesis of β-DL-pseudo-glucose (68) from acrylic acid (66) and furan (67) is shown in Scheme 17.[63]



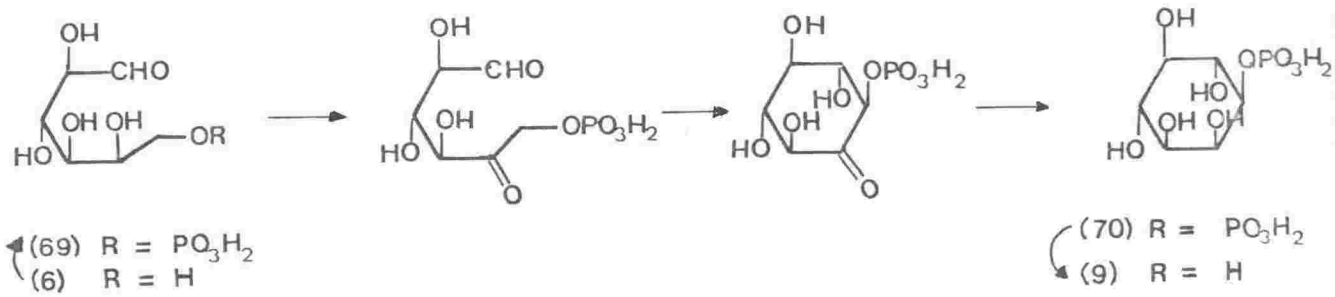
Reagents: a) RT, 72 d ; b) H_2O_2, H^+ ; c) LAH ; d) Ac_2O/py ; e) H_2SO_4/HOAc ; f) MeONa/MeOH

Scheme 17

C. Rearrangement of Carbohydrates

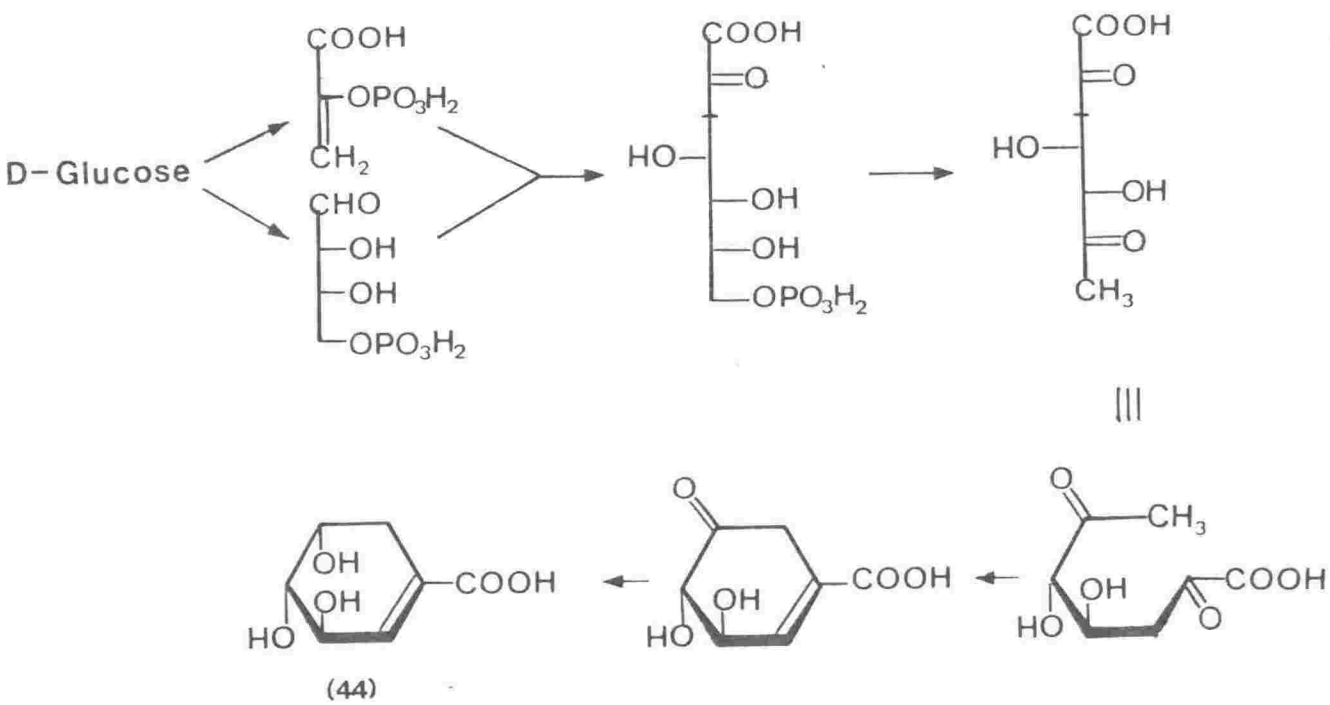
While the two synthetic methods described above have the disadvantage of leading to racemic products, optically pure cyclitols are available by synthesis from carbohydrates to which they are closely related. It was suggested more than 90 years ago by Maquenne[39] that the biosynthesis of myo-inositol (9) involves the cyclisation of D-glucose (6), C-1 bonding to C-6, and this hypothesis has since been confirmed by a large number of

experiments with biological systems, using labelled D-glucose. The biosynthetic cyclisation proceeds, as shown in Scheme 18, via D-glucose



Scheme 18

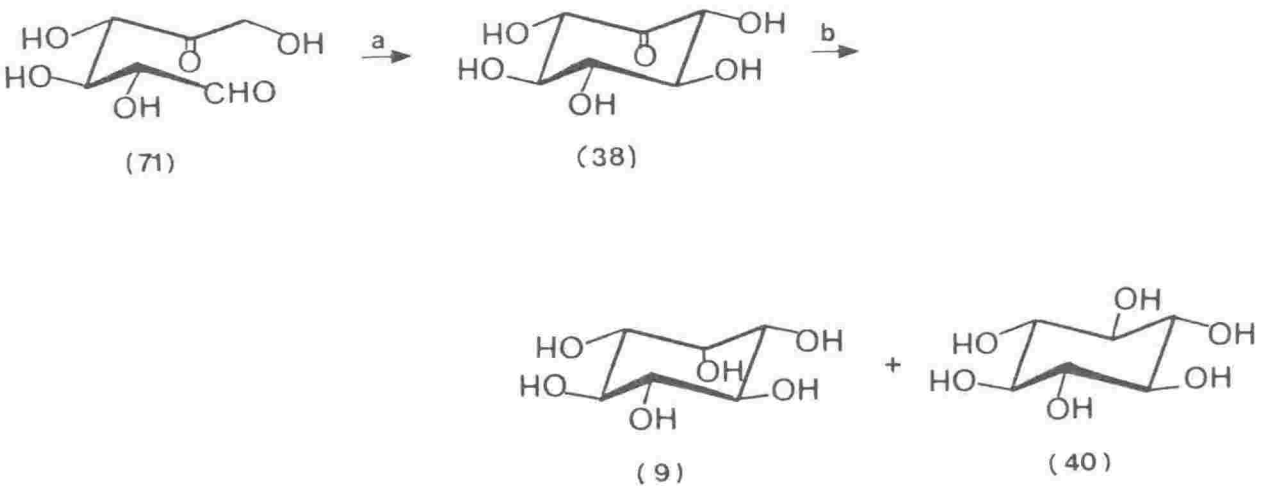
6-phosphate (69) and L-myo-inositol 1-phosphate (70) and includes an oxidation and a reduction step, C-6 being activated by the keto function at C-5.[43]



Scheme 19

Likewise, the biosynthesis of (-)-shikimic acid (44) starts from D-glucose (6) and includes an oxidation-cyclisation-reduction sequence (Scheme 19),[44,45] but in this case the carbon skeleton of glucose is rearranged prior to ring closure. In both biosyntheses the cyclising species is a 1,5-dicarbonyl compound and the cyclisation reaction is an enzyme catalysed intramolecular aldol condensation.

The majority of chemical syntheses of cyclitols from carbohydrates use intramolecular aldol reactions, *i.e.* ring formation by nucleophilic attack at the aldehydic carbonyl carbon atom by a carbanion at C-6, and three ways to generate the required carbanionic centre have been devised. The simplest method, used by Kiely *et al.*[90-92] involves hexos-5-ulose derivatives which form carbanions at C-6 in basic media. *E.g.* treatment of D-xylo-hexos-5-ulose (71)[90] (Scheme 20) with dilute alkali gave an inosose, which was not



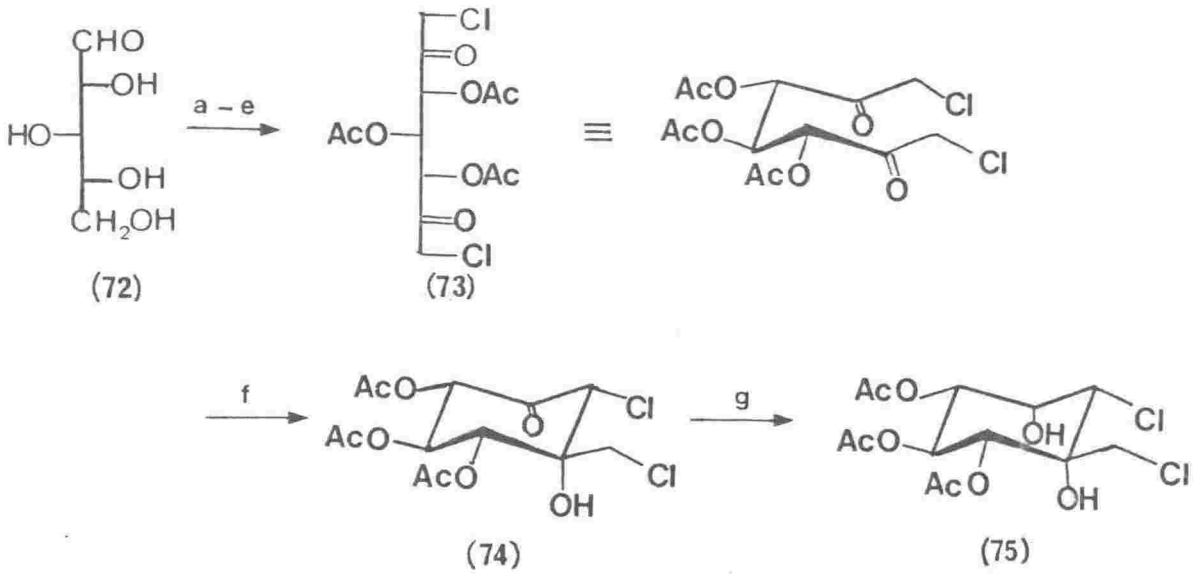
(71) (38) (9) (40)

Reagents : a) NaOH dil.; b) $NaBH_4$

Scheme 20

isolated but may be assumed to have been the all-equatorial myo-inosose-2 (38), since ring closure took place under equilibrating conditions and since its reduction with sodium borohydride gave a mixture of myo- and scyllo-inositols (9, 40). The same reaction, carried out with the 6-phosphate ester of hexosulose (71) to give, as one of the products, L-myo-inositol 6-phospate (70)[91] represents a very close analogy to the biosynthetic process (c.f. Scheme 18).

Similarly, base catalysed cyclisation of 1,5-dicarbonyl carbohydrate derivatives has been applied to the synthesis of branched chain cyclitols. Treatment of 1,7-dichloro-hepto-2,6-diulose (73)[92] (Scheme 21), obtained



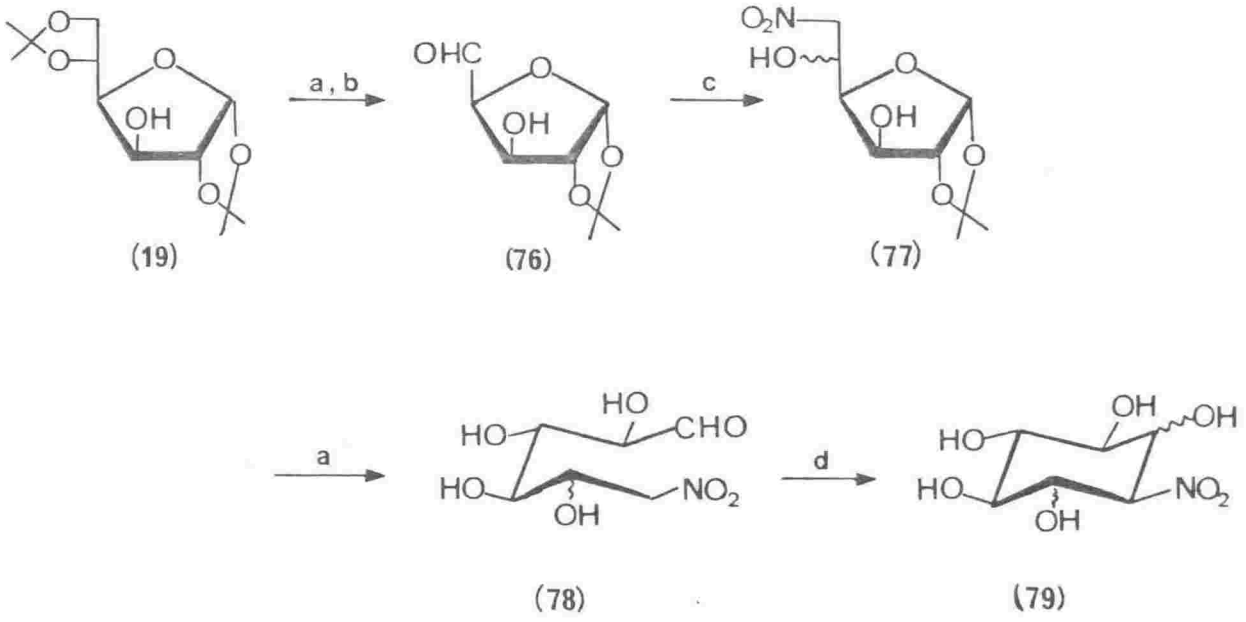
(72) (73) (74) (75)

Reagents : a) HNO_3 ; b) Ac_2O , H_2SO_4 ; c) $SOCl_2$; d) CH_2N_2 ; e) HCl_g ; f) NaOAc ; g) $NaBH_4$

Scheme 21

from D-xylose (72) in 5 steps, with aqueous sodium acetate gave again the least sterically constrained inosose derivative (74), whose reduction with sodium borohydride proceeded with high stereoselectivity, due to steric interference by the axial hydroxyl group in the β-position, to give the epi-product (75) almost exclusively.

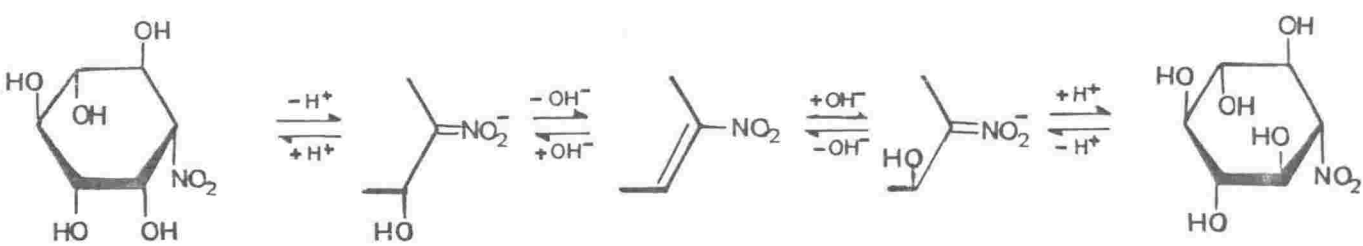
The method used most often to prepare cyclitols from sugars is the intramolecular condensation of 6-deoxy-6-nitro derivatives (nitroinositol synthesis) first introduced by Grossheintz and Fischer[18] and studied in detail by Lichtenthaler[93] and by Baer *et al.*[94-96] In this approach the carbanion at C-6 is generated in consequence of the presence of the activating nitro group at this site, and Scheme 22 shows the transformations of di-O-isopropylidene-D-glucose (19) to a mixture of isomeric nitroinositols (79).[93] The base catalysed condensation of aldehyde (76) with nitromethane was not stereospecific. However, separation of the mixture of D-gluco- and L-ido-



Reagents : a) HOAc ; b) HIO_4 ; c) $MeNO_2$, OH^- ; d) NaOH dil.

Scheme 22

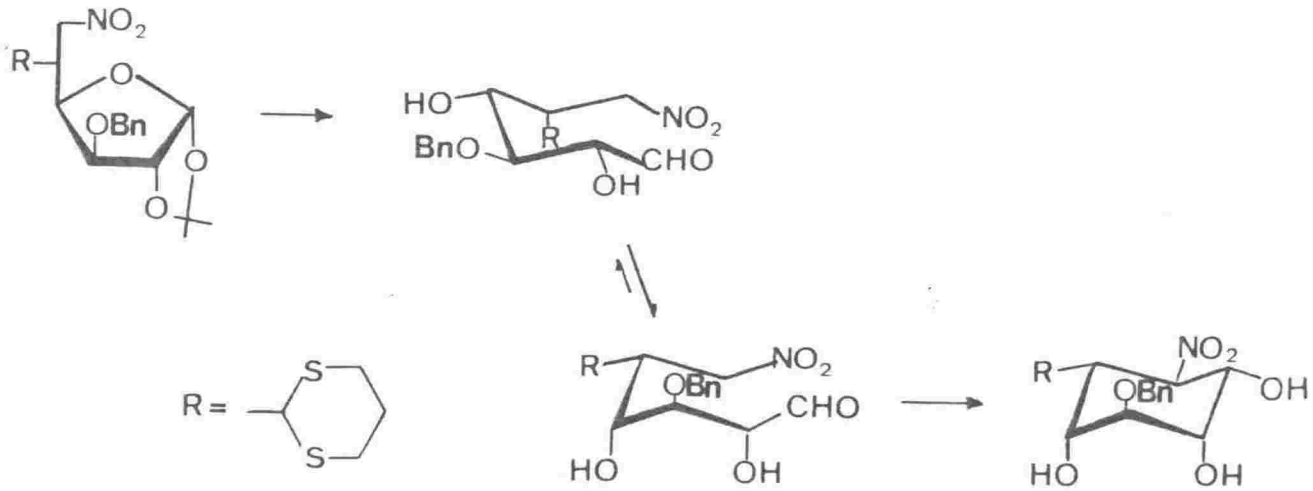
6-deoxy-6-nitro derivatives (77, *ca.* 1:1) was not necessary, as under the cyclisation conditions epimerisation at C-5 was expected (see Scheme 23). Hydrolysis of the nitro sugars (77) and base treatment of the hydrolysis products (78), which were not isolated, then gave a mixture of nitroinositols



Scheme 23

(79) in which the all-equatorial nitro-scyllo-inositol was predominant. The percentages reported by different authors[93,94] for the isomeric composition of the "equilibrated" product mixture (79) vary considerably, and the distribution of stereoisomers seems to be governed by a complex interplay of kinetic and thermodynamic factors. Epimerisation of the cyclisation products in slightly alkaline media, at any rate, takes place through intermediate nitronate ions and nitroalkenes and involves reversible elimination of hydroxyl ions[93,94,96] (Scheme 23).

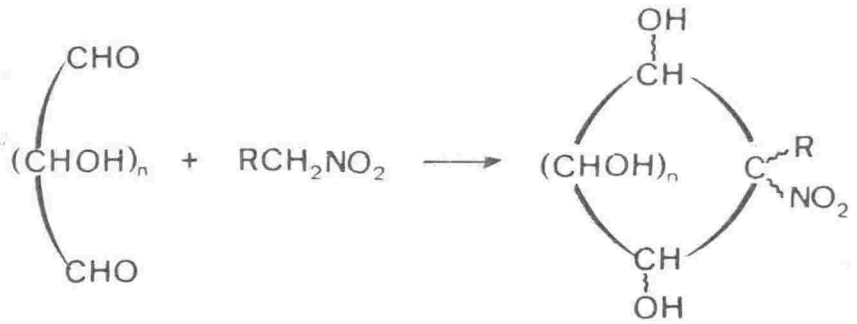
Funabashi and Yoshimura[97] were able to increase the stereoselectivity of the nitroinositol synthesis considerably by introducing bulky substituents at C-3 and C-5 of the starting material (Scheme 24). Both the nitro and the



Scheme 24

dithianyl group have a strong tendency to occupy equatorial orientations throughout the ring closure, and the newly formed hydroxyl group at C-1 (carbohydrate numbering) also becomes equatorial, avoiding 1,3-diaxial interaction with the benzyloxy substituent at C-3.

In a variation of the method just described, and outlined schematically in Scheme 25, a nitroalkane can be condensed under mildly basic conditions with a polyhydroxydialdehyde, resulting in a twofold addition that joins both aldehydic carbon atoms with the same nitroalkane molecule[41,98,99] and affording similar mixtures of isomeric nitroinositols as are obtained in the intramolecular condensation of 6-nitro sugars. Five-, six- and seven-membered ring cyclitol derivatives have been prepared in this way from 1,4-, 1,5-, and 1,6-dialdehydes, respectively, which are all readily available from inositols (*e.g.* by periodate cleavage of partially protected quebrachitol[41])

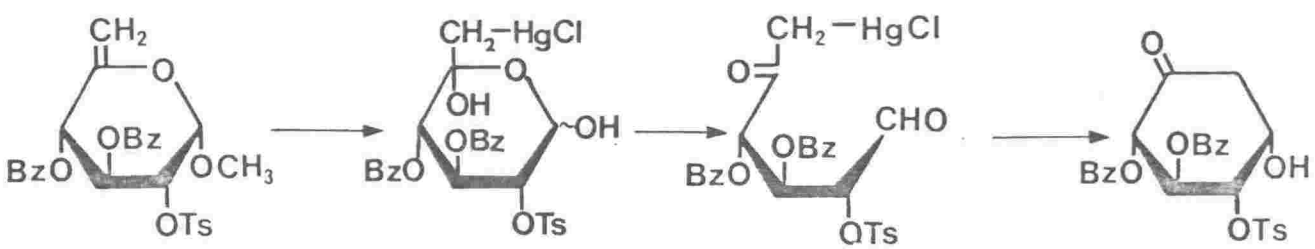


Scheme 25

or sugars (*e.g.* by periodate cleavage of 1,2-O-isopropylidene-D-glucofuranose followed by hydrolysis[98]).

The nitro group of nitroinositols can be converted to a hydroxyl group[19,20,98] or reduced to an amino group,[21,98,100] both transformations proceeding smoothly, making the nitroinositol synthesis a valuable method for the preparation of optically pure inositols and inosamines, and especially of ^{14}C-labelled derivatives.[19,20,98]

A third way to effect carbocyclic ring formation by intramolecular aldol condensation involves the mercury(II) catalysed rearrangement of a hex-5-enose, discovered by Ferrier,[101] which resembles the base catalysed ring closure of 1,5-dicarbonyl compounds, but proceeds in mildly acidic media. Treatment of enol ether (80) (Scheme 26) with aqueous mercury(II) chloride gave, after loss of water, the unstable 6-chloromercury-5-ulose (81), which cyclised under the

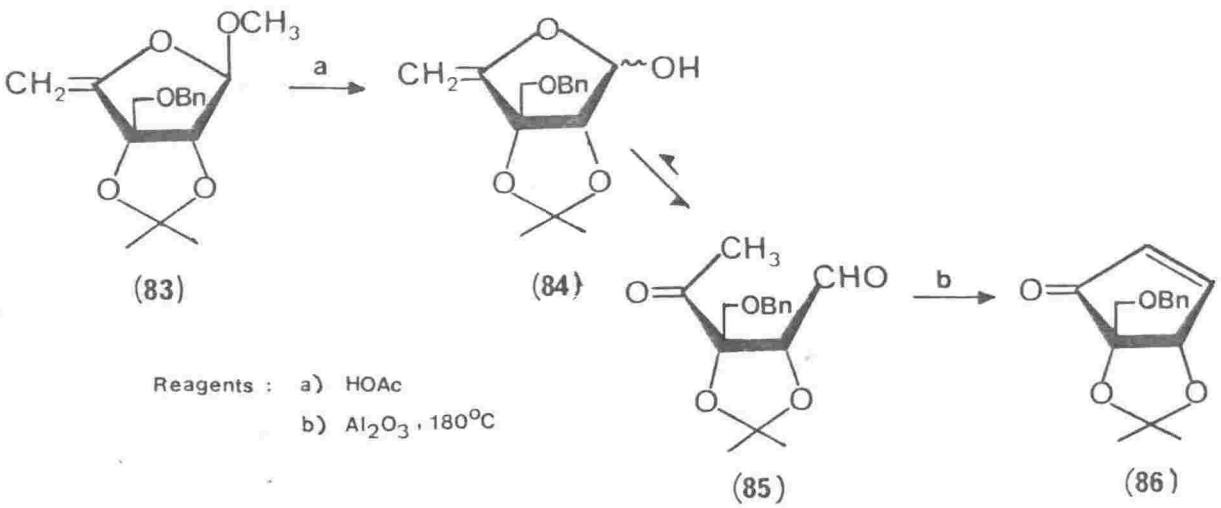


(80) (81) (82)

Scheme 26

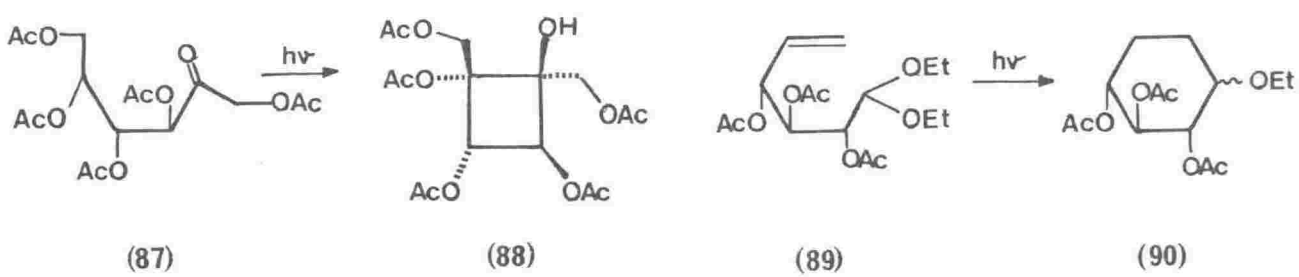
reaction conditions with good stereoselectivity to the deoxyinososе (82).

Closely related to this rearrangement of a hex-5-enopyranoside to a substituted cyclohexanone derivative is the transformation of pent-4-enofuranoside (83) to a functionalised cyclopentenone (86)[102] (Scheme 27) brought about by hydrolysis of enol ether (83) and heating of pent-4-ulose (85), the tautomeric form of the hydrolysis product (84), over alumina.



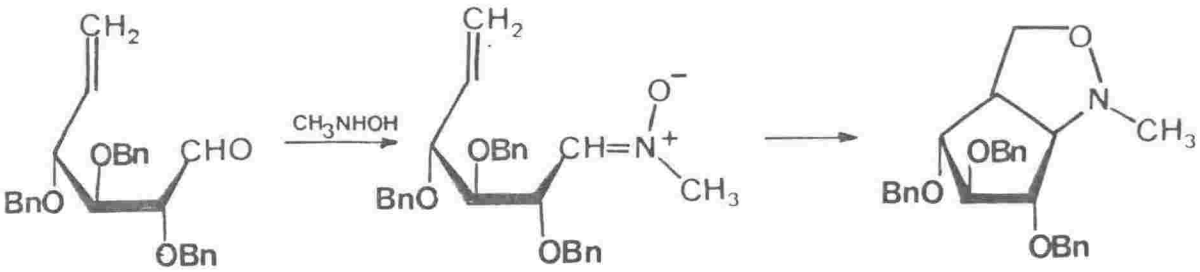
Scheme 27

There are several cases of carbocyclic ring formation from carbohydrates which do not involve intramolecular aldol condensations. As they lead mainly to rings other than six-membered, they will be mentioned here only briefly. In Stork's[33] synthesis of prostaglandin $F_{2\alpha}$ [(31), p.10] from D-glycero-D-gulo-heptonolactone, for example, a cyclopentane ring was formed from a carbohydrate-derived intermediate by intramolecular alkylation. Photochemical procedures have led to the preparation of a functionalised cyclobutane (88) from D-fructose pentaacetate (87)[103] and to a dideoxyinositol derivative (90) from a hexenose diethyl acetal (89)[104] (Scheme 28).



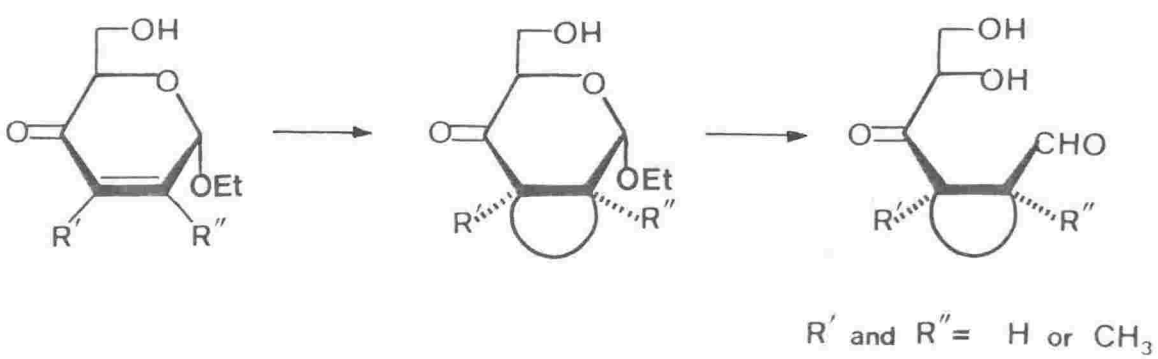
Scheme 28

In a more generally useful method for the preparation of functionalised cyclopentanes, developed by Bernet and Vasella,[105] a nitrone-olefin cycloaddition is applied to carbohydrate enals (Scheme 29). Cycloaddition



Scheme 29

reactions have also been used by Fraser-Reid[16] to prepare cycloalkane derivatives of various ring sizes from sugar enones, by an approach which is however fundamentally different and is outlined, in general form, in Scheme 30. After annulation and, if applicable, modification of the new



Scheme 30

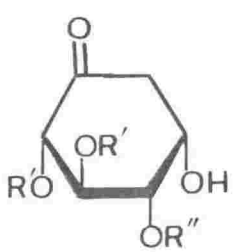
ring, the sugar moiety is hydrolysed, leaving two cis-related side chains amenable to diverse transformations.

CHAPTER TWO

6-DEOXYHEX-5-ENOPYRANOSE DERIVATIVES AND RELATED UNSATURATED COMPOUNDS

As mentioned in the introduction (page 12), inososes are versatile synthetic intermediates. The recently discovered mercury(II) catalysed rearrangement of a 6-deoxyhex-5-enopyranoside[101] (Scheme 26) promised to be a very efficient new route to deoxyinososes, and it became the aim of the present work to prepare branched chain cyclitol derivatives from the known tosylate (82) or from analogous inosose derivatives.

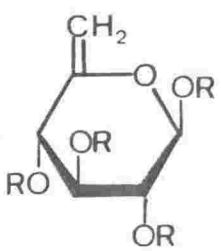
One undesirable property of the tosylated deoxyinosose (82) was its low solubility in most solvents. To overcome this problem, as well as to establish the general applicability of the mercury(II) catalysed rearrangement, it was decided to prepare the triacylated analogues (91) and (92) which should be obtainable, for example, from the unsaturated peresters (93) and (94) and pyranosides (95) and (96). The initial objective was



(82) R′ = Bz , R″ = Ts

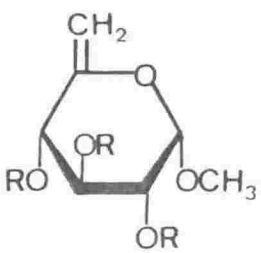
(91) R′ = R″ = Bz

(92) R′ = R″ = Ac



(93) R = Bz

(94) R = Ac



(95) R = Bz

(96) R = Ac

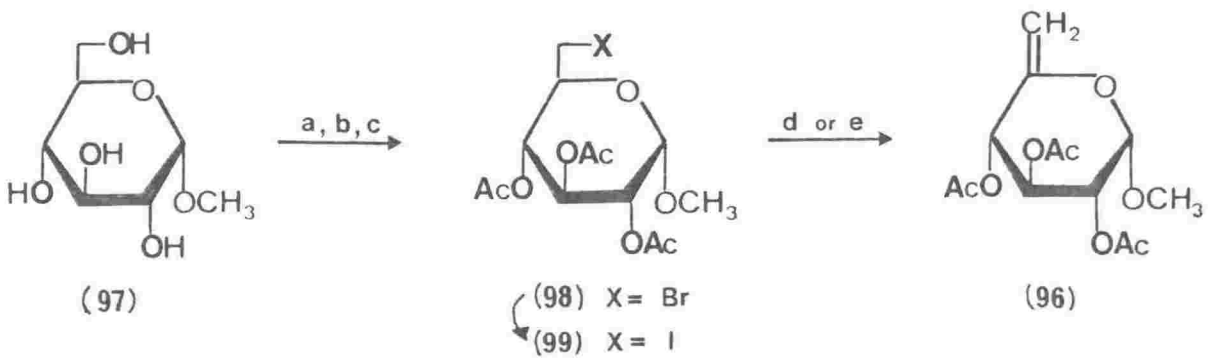
therefore the preparation of sizeable quantities of these 6-deoxyhex-5-enopyranose derivatives. In the first part of this chapter, the synthesis of such alkenes is described, while the second part deals with the structures and conformational equilibria of several new, unsaturated compounds obtained in the course of this preparative work.

PREPARATION OF SOME 6-DEOXYHEX-5-ENOPYRANOSE DERIVATIVES

The best known method for the synthesis of 5,6-unsaturated hexopyranose derivatives uses dehydrohalogenation of the corresponding primary halides, and traditionally employs silver fluoride in dry pyridine.[106,107] More recently, 6-deoxyhex-5-enopyranosides have been prepared by application of the Chugaev reaction to 6-O-[(alkylthio)thiocarbonyl]-hexopyranosides,[108] and the newest route, developed by Tyler,[109] involves elimination of the elements of acyl hypobromite from peracylated 5-bromo-hexopyranoses. Each of these methods was assessed with a view to finding an efficient way of preparing the required unsaturated sugars using, if possible, inexpensive and readily available reagents.

A. Dehydrohalogenation of 6-Halides

Synthesis of methyl tri-O-acetyl-6-deoxy-α-D-xylo-hex-5-enopyranoside (96) by dehydrobromination of the 6-bromide (98), obtained from methyl α-D-glucopyranoside (97) by selective bromination at C-6 with NBS and triphenyl phosphine in DMF and acetylation of the crude product,[110] was attempted with silver fluoride in pyridine at room temperature, as described by Helferich and Himmen,[106] and at 50°C, following a modification of the same method by Ikeda et al.[111] (Scheme 31). At best, 1:1 mixtures of alkene (96) and starting material (98) were produced (^{1}H n.m.r. evidence) even with a large



(97) (98) X = Br (99) X = I (96)

Reagents : a) NBS, PPh_3/DMF ; b) Ac_2O/py ; c) NaI/acetone ; d) AgF/py ; e) DBU/DMF

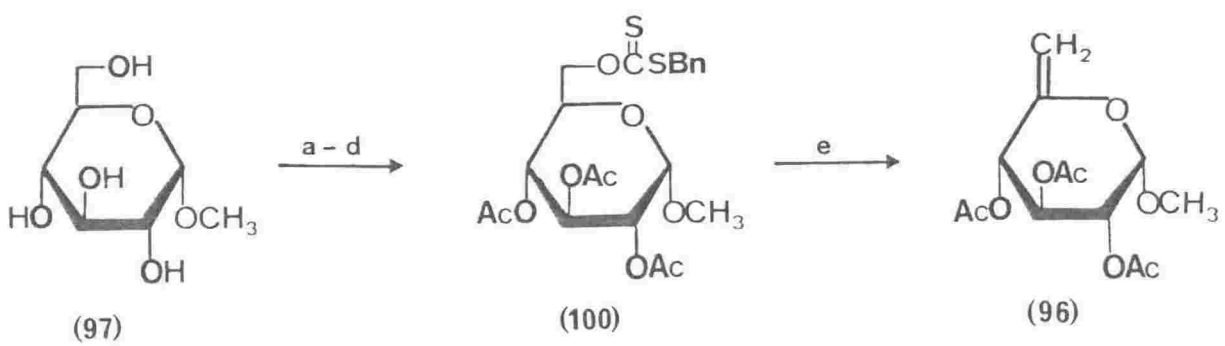
Scheme 31

excess of silver fluoride and long reaction times.

To increase reactivity, the 6-bromide (98) was therefore converted to the 6-iodide (99) by heating with sodium iodide in acetone, and successful dehydroiodination with silver fluoride[107] then gave the known, crystalline alkene (96) in 42% overall yield from the methyl pyranoside (97). Elimination of hydroiodic acid could also be effected with DBU, reaction with this base in DMF at room temperature affording the 5-ene (96) in 40% yield from the starting glucoside (97). This represents a satisfactory route to the unsaturated glycoside (96) which was later successfully converted to the deoxyinososе derivative (92) (see Chapter 4). In the end, however, preference was given to the pathway via the alternative acetylated alkene (94) as it became available in somewhat higher yield and by a shorter reaction sequence, as described below (Section C, p.31).

B. Chugaev Elimination from 6-Dithiocarbonates

Descotes et al.[108] reported the synthesis of 6-deoxyhex-5-enopyranoside (96) and several other 5,6-unsaturated hexopyranosides by pyrolysis of substituted hexos-6-dithiocarbonates (Scheme 32). Following the procedure given by these authors, the acetylated S-benzyl derivative (100) was prepared from methyl-α-D-glucopyranoside (97), although in much lower yield than that recorded.[108] As the main by-product, methyl tetra-O-acetyl-α-D-glucopyranoside was isolated, suggesting incomplete reaction with carbon disulphide.



(97) (100) (96)

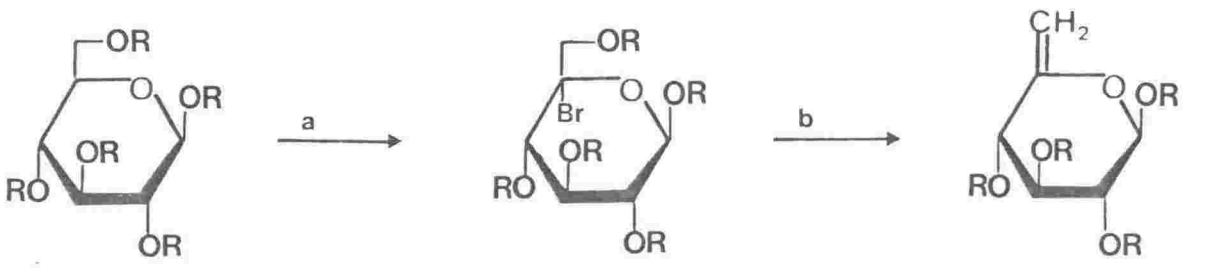
Reagents : a) NaOH ; b) CS_2 ; c) BnBr ; d) Ac_2O/py ; e) heat

Scheme 32

A number of pyrolysis experiments (Table 9, see Experimental) failed however to afford preparatively useful amounts of alkene (96). Stability of some dithiocarbonates under the conditions of Chugaev elimination has been mentioned by several authors;[112-114] Willard and Pacsu,[112] in particular, recovered only unchanged starting material after heating the same S-benzyl compound (100) for 1 h at 250°. Such behaviour was attributed[113,114] to a lack in highly purified dithiocarbonates of peroxides or similar impurities necessary for successful thermal decomposition to alkenes. In view of the good results achieved by the dehydrohalogenation method (see above) as well as by the photobromination-reduction pathway discussed in the following section, attempts to prepare alkenes by pyrolysis of dithiocarbonates were discontinued.

C. Reductive Elimination from 5-Bromides

The procedure developed by Tyler[109] for radical bromination (photobromination) of penta-O-benzoyl-β-D-glucopyranose (101), followed by elimination of benzoyl hypobromite from the resultant 5-bromide (103) (Scheme 33), was conveniently adapted to a 10-30 g scale to give 6-deoxyhex-5-enopyranose (93) in 50% yield from the pentabenzoate (101). An analogous reaction sequence was then, with minor changes, applied to the preparation of the acetylated alkene (94) from penta-O-acetyl-β-D-glucopyranose (102).



(101) R = Bz
(102) R = Ac

(103) R = Bz
(104) R = Ac

(93) R = Bz
(94) R = Ac

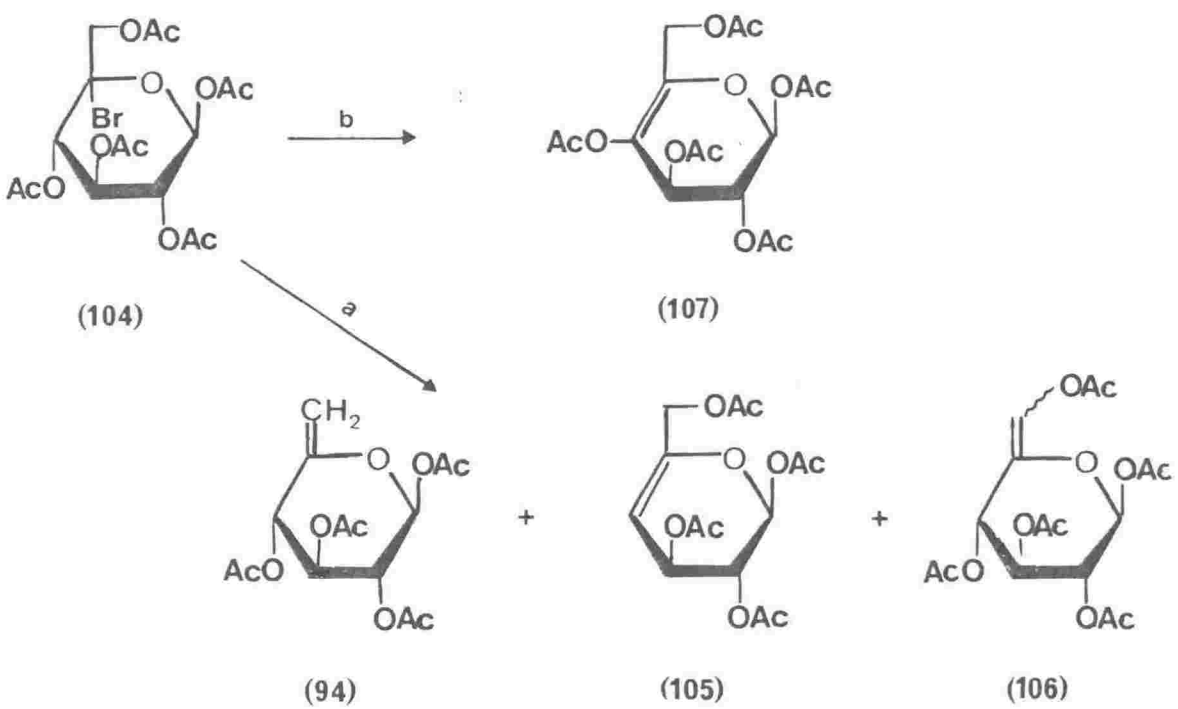
Reagents : a) Br_2/CCl_4, hν ; b) Zn/HOAc

Scheme 33

As will be reported in Chapter 3, where a detailed investigation into the photobromination of glucose pentaacetate (102) is described, the 5-bromide (104) was, under optimal conditions, obtained in 80% yield. When treated with zinc-acetic acid, a reagent often used to remove the elements of acyl hypobromite from 1,2-bromoesters,[115] it afforded the alkene (94) in *ca.* 50% yield from the ester (102).

UNSATURATED COMPOUNDS FROM PENTA-O-ACETYL-5-BROMO-β-D-GLUCOPYRANOSE (104)

The above elimination reaction, by which the 6-deoxy-hex-5-ene (94) was prepared gave, in addition, two by-products (Scheme 34) the endocyclic tetra-O-acetyl-α-L-*threo*-hex-4-enopyranose (105), and penta-O-acetyl-β-D-*xylo*-hex-5-enopyranose (106), a product of simple dehydrobromination. The three alkenes were isolated in 80% total yield in a ratio of 12:3:1, the known[107] main product (94) by direct crystallisation, the two minor compounds (105) and (106) by column chromatography. Elimination of hydrobromic acid from

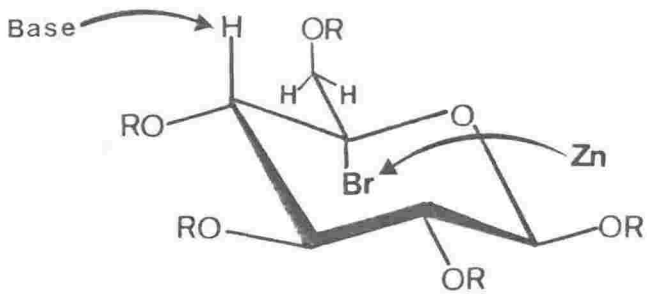


Reagents : a) Zn/HOAc ; b) DBU/ DMF.

Scheme 34

the bromide (104) by use of DBU, on the other hand, gave crystalline penta-O-acetyl-α-L-threo-hex-4-enopyranose (107), as the only isolable product, in 65% yield; there was no evidence (t.l.c., ^{1}H n.m.r.) of the exocyclic isomer (106).

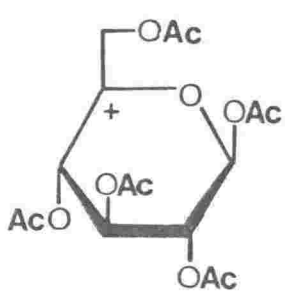
As suggested by Tyler,[109] who studied the analogous elimination reactions of the benzoylated bromide (103), the predominant formation of an exocyclic alkene in the zinc-acetic acid induced reductive elimination, and of an endocyclic product in the base promoted dehydrobromination, can best be



R = Bz or Ac

(108)

explained as preferential anti-elimination of acyl hypobromite or hydrogen bromide, respectively, by concerted E_2 mechanisms from the most stable conformer and rotamer (C-5—C-6 bond) (108). Formation of the exocyclic dehydrobromination product (106), in small amounts, under the conditions of reductive elimination requires, however, a different explanation. Possibly this compound was produced by an E_1 process involving the carbonium ion (109).



(109)

Structures and conformations of the four unsaturated compounds (94), (105), (106), and (107) could readily be assigned from their ^{1}H n.m.r. spectra (Table 1), which, as expected, all lacked resonances for H-5. Chemical

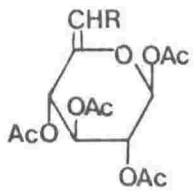
TABLE 1

^{1}H n.m.r. Spectral Data of Elimination Products from 5-Bromide (104)

Compound	Chemical shifts (δ) in p.p.m. downfield from TMS[a]							Coupling constants in Hz		
	H-1	H-2	H-3	H-4	H-6	H-6'	OAc	$J_{1,2}$	$J_{2,3}$	Others
94[b]	5.98 d	← 4.95-5.2 →		5.60 m	4.56 t	4.83 t	2.07, 2.09, 2.13, 2.15	5		1.7 ($J_{4,6} = J_{4,6'} = J_{6,6'}$)
106[c]	6.01 d	← 4.8 -5.2 →		5.40 m	6.84 s	—	2.00(X4) 2.10	5		
105[b]	6.23 d	← 5.0 -5.25 →			← 4.52 m →		2.08, 2.09, 2.11, 2.12	3		
107[b]	6.23 dd	5.15 t	5.48 m	—	← 4.60 m →		2.06, 2.09, 2.14(X3)	3	3	1 ($J_{1,3}$)

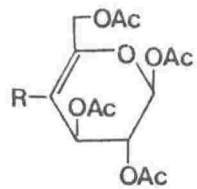
[a]Observed multiplicities: s, singlet; d, doublet; dd, pair of doublets; t, triplet; m, multiplet

[b]Measured at 80 MHz in $CDCl_3$. [c]Measured at 60 MHz in $CDCl_3$.



(94) R = H

(106) R = OAc



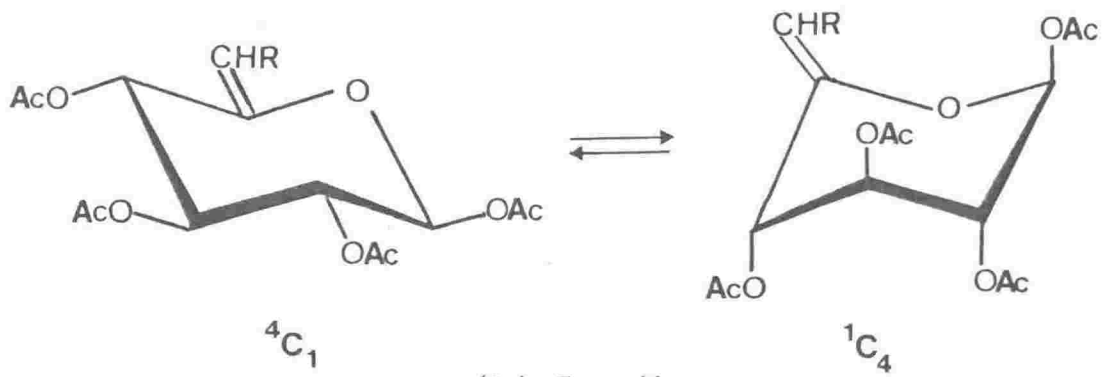
(105) R = H

(107) R = OAc

shifts for the ring protons of the two exocyclic alkenes (94) and (106) were very similar, but H-6 and H-6' of compound (94) resonated as two narrow triplets ($J_{4,6} = J_{4,6'} = J_{6,6'} = 1.7$ Hz) at δ 4.56 and δ 4.83 respectively, while H-6 of derivative (106) appeared as a singlet at low field (δ 6.84). The geometry of the double bond of the latter derivative is not known. The spectrum of the endocyclic pentaacetate (107), apart from the absence of a signal for H-4, differed from that of the tetraacetate (105) mainly in the chemical shift of the allylic proton (H-3) which was deshielded by *ca.* 0.3 p.p.m. Similar deshielding (by 0.25 p.p.m.) is observed for H-3 in tetra-O-acetyl-2-hydroxy-D-glucal[116] in relation to the same proton in tri-O-acetyl-D-glucal.[117]

Valuable information as to the conformational equilibria of these unsaturated sugars was gained from an inspection of the coupling constants in their ^{1}H n.m.r. spectra. The conformational analysis of pyranoid compounds by ^{1}H n.m.r. spectroscopy[118,119] is based on the assumption that they exist in solution at room temperature as rapidly interconverting chair or half-chair conformers, and that their ^{1}H n.m.r. spectra represent the result of time-averaging. Since spin-spin coupling between vicinal protons depends on the dihedral angle between the C-H bonds,[120] time-averaged coupling constants, especially of trans-disposed, vicinal protons in six-membered rings, provide a good measure of the conformational equilibrium. Values for J_{vic} between antiparallel protons are usually 8-11 Hz and those between gauche-disposed protons 1-3 Hz. As coupling between the anomeric proton and H-2 in pyranoid rings is weakened by the presence of the electronegative ring oxygen atom, relatively low $J_{1,2}$ values of 8 Hz and 1 Hz, respectively, are found for the diaxial and diequatorial disposition of these protons.[119]

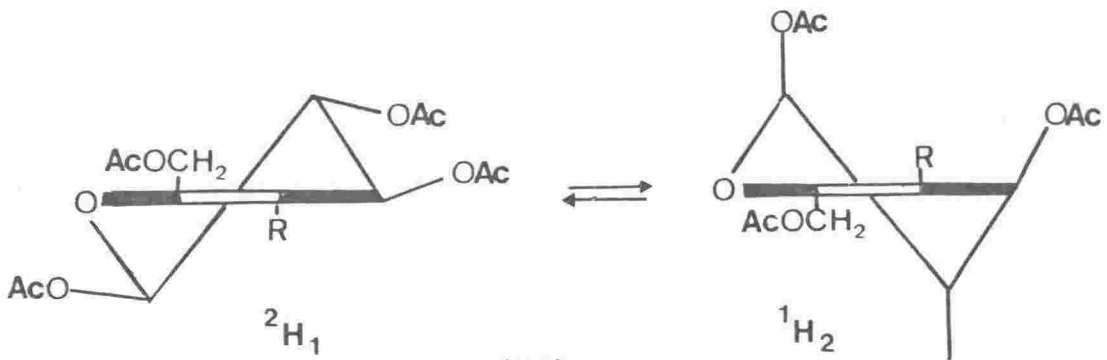
The only vicinal coupling constants that could be determined for the exocyclic alkenes (94) and (106) were $J_{1,2}$ values of *ca.* 5 Hz, which indicate



(94) R = H

(106) R = OAc

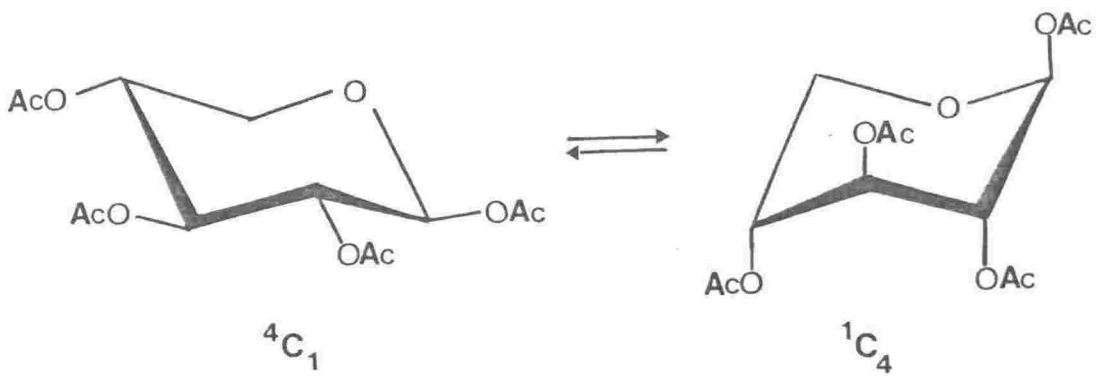
that the $^{1}C_{4}$ [121] chair form contributes substantially (roughly 50%) to the conformational equilibria of these two compounds. The endocyclic alkenes (105) and (107) had even smaller $J_{1,2}$ values (3 Hz). In the spectrum of compound (105) the resonances for all protons except H-1 were unresolved, but for derivative (107) $J_{2,3}$ (3 Hz) and $J_{1,3}$ (1 Hz) could be measured, and all these data indicate that both 4-enes adopt the $^{1}H_{2}$ [121] conformation almost exclusively.



(105) R = H
(107) R = OAc

The conformational equilibria of peracylated pyranose derivatives in solution are governed by several factors,[118] the most important ones being syn-diaxial interactions, the anomeric effect[122] - *i.e.* the preference of an electronegative substituent at the anomeric centre for axial orientation - and, in unsaturated compounds, allylic strain[123,124] (see below). In saturated aldohexopyranoses the dominant influence is the tendency of the bulky substituent at C-5 to be equatorially disposed.[118,125] β-D-Glucose pentaacetate, for example, is found almost exclusively in the $^{4}C_{1}$ form ($J_{1,2}$ 8 Hz[126]), but its C-5 epimer α-L-idose pentaacetate assumes the $^{1}C_{4}$ conformation ($J_{1,2}$ 2.1 Hz[127]) with all substituents except the acetoxymethyl group axial.

In the absence of this determinant, *i.e.* when C-5 is unsubstituted as in the aldopentoses,[118] or trigonal as in 4,5- and 5,6-unsaturated compounds,[128] the anomeric effect becomes more important and, with the alkenes, allylic strain also contributes; thus, tetra-O-acetyl-β-D-xylopyranose (110), which is related to alkenes (94) and (106) by loss of C-6, exists in solution to *ca.* 30% in the all-axial $^{1}C_{4}$ chair form ($J_{1,2}$ 6.6 Hz).[118] Introduction of an exo-cyclic methylene group should not disturb the conformation of the six-membered ring,[129] but it causes allylic ($A^{(1,3)}$) strain between the vinylic C-6 group and an equatorial acetoxy group at C-4 in the $^{4}C_{1}$ conformation,



(110)

making this conformer less stable for alkenes (94) and (106) than for the pentopyranose derivative (110). Therefore, in the all-axial $^1C_4$ form the 5-enes (94) and (106) are subject to favourable anomeric effect as well as minimal $A^{(1,3)}$ strain; on the other hand, absence of <u>syn</u>-diaxial interactions makes the alternative $^4C_1$ conformation equally stable, the result being a roughly 1:1 equilibrium mixture.

Introduction of an endocyclic double bond into a six-membered ring causes partial flattening of the ring to give compounds with half-chair shapes. Here, in addition to the anomeric effect, the allylic effect[124] ($A^{(1,2)}$ strain[123]) - *i.e.* the preference of an allylic substituent to assume <u>quasi</u>-axial orientation - becomes operative. For alkenes (105) and (107) the $^1H_2$ conformation incorporates both favourable anomeric and allylic effects and these offset <u>syn</u>-diaxial interactions which play a reduced role in unsaturated six-membered rings, since they are considerably modified by the <u>quasi</u>-axial disposition of the allylic substituents.[123] Thus, for both 4-enes the conformational equilibrium lies entirely on the side of the all-axial $^1H_2$ form. Conformational analysis of several related 4,5-unsaturated pyranuronic acid derivatives has shown[109,128] that in these compounds the equilibrium position is largely determined by the anomeric effect.

CHAPTER THREE

THE PHOTOBROMINATION OF β-D-GLUCOPYRANOSE PENTAACETATE

In Chapter 2 (p.31) a convenient synthesis of 6-deoxyhex-5-enopyranose derivatives (93) and (94) was described, by a method which involves photobromination of the corresponding peresters (101) and (102) (*cf.* Scheme 33). It was recently discovered in this laboratory, that a bromine atom can be introduced at C-5 of certain pyranose compounds by photobromination, *i.e.* by heating them with a brominating agent in carbon tetrachloride under bright artificial light.[109,130,131] The photobromination of β-D-glucose pentabenzoate (101) with either NBS or bromine to give crystalline 5-bromide (103) in 43% and 77%, respectively, by direct crystallisation, has been reported by Tyler,[109] who also examined, perfunctorily, the photobromination of β-D-glucose pentaacetate (102) with bromine. No attempt was made by this author to isolate a brominated compound, but the crude reaction product gave a ^{1}H n.m.r. spectrum indicating that bromide (104) was indeed its main component, a conclusion which was substantiated by the fact that on zinc-acetic acid treatment the expected 5-ene (94) was obtained, although in rather low yield [33% from pentaacetate (102)[109]].

In a series of experiments (Table 2) Tyler's results were confirmed, and, in addition, it was found that, while on a small scale (0.2 g starting material), the bromination of peracetate (102) with bromine was fast and specific (t.l.c. evidence), the process became progressively less efficient when performed with 2 g, 5 g, and 10 g of starting material. The time for complete reaction increased from 45 min. to 4 h, and increasing amounts of at least two by-products were detected by t.l.c. At the same time, the yield of crystalline alkene (94) from zinc-acetic acid reduction of the crude bromination product decreased markedly.

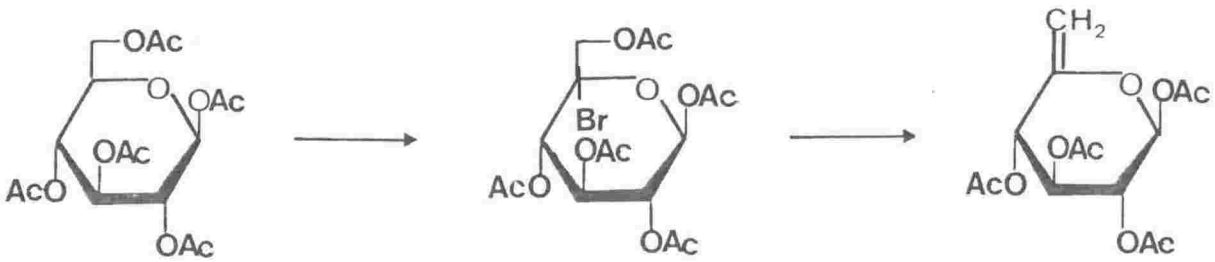
Photobromination of the ester (102) with NBS, on the other hand, and subsequent reductive elimination, was found to afford the 5-ene (94) in *ca.* 60% yield from pentaacetate (102) regardless of the weight of starting material used. This was rather surprising, as the reactions with NBS were much slower than those with bromine and substantial quantities of a by-product were formed, during the long irradiation time (16 h) necessary for complete conversion in the experiment with 5 g pentaacetate (102).

TABLE 2

Preparation of alkene (94) from glucose pentaacetate (102) via the 5-bromide (104)[a]

Brominating agent	Weight of pentaacetate (102)	Bromination time	Yield of alkene (94) crystalline[b]	Total[c]
	(g)	(h)	%	%
Br_2	0.2	0.7	52	-
Br_2	2.0	1.5	37	49
Br_2	5.0	3.0	9.5	14
Br_2	6.0	3.5	3.6	-
Br_2	10.0	4.0	0	6.5
Br_2[d]	10.0	4.0	38	47
NBS	0.2	2.0	48	-
NBS	5.0	16	47	59

[a]By photobromination in carbon tetrachloride solution (*ca.* 1.5%) and subsequent treatment of the crude reaction product with zinc-acetic acid. [b]By direct crystallisation. [c]By direct crystallisation followed by column chromatography of the mother liquors. [d]Photobromination in the presence of dry potassium carbonate.



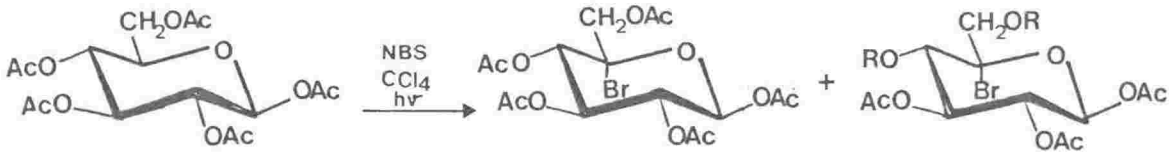
(102) (104) (94)

Since, for the preparation of alkene (94) in relatively large amounts, it was crucial that the bromination could be conducted on at least a 5-10 g scale, and preferably with bromine, which is both cheaper and easier to use than NBS, it was decided to study in more detail the processes undergone by β-D-glucose pentaacetate (102) when heated separately in carbon tetrachloride solution with bromine and NBS under bright, artificial light, in the hope of finding a way to modify the procedure and make it more attractive for synthetic purposes.

PHOTOBROMINATION WITH NBS

Photobromination with NBS on a small scale [0.2 g pentaacetate (102)] caused, within 2 h, conversion of the starting material into the 5-bromide (104), which was obtained in 50% yield by direct crystallisation and in 80% yield after column chromatography. In the ^{1}H n.m.r. spectrum of this compound (Table 3, p.44) the most notable feature was the absence of a signal for H-5; H-6 and H-6' resonated as an AB pair of doublets ($J_{6,6'}$ = 12.5 Hz), and H-4 as a doublet, indicating replacement of H-5. $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ values of 9 Hz, similar to those reported for the starting material (102),[126] showed that the conformation and anomeric configuration had not changed, while deshielding of H-1 and H-3 by *ca.* 0.4 p.p.m. was consistent with their having syn-diaxial relationships with the bromine atom at C-5. In accordance with Hudson's Isorotation Rules,[132] and as was found in previous photobrominations[130,131] introduction of an axial bromine at C-5, *i.e.* formation of a new anomeric centre with the (S)-configuration, makes product (104) appreciably more levorotatory ($[\alpha]_D$ -91°) than its precursor (102) ($[\alpha]_D$ +4°[133]).

Photobromination with NBS on a larger scale [5.0 g pentaacetate (102)] was much slower (16 h) and gave, in addition to bromide (104), which was isolated by column chromatography in 65% yield, a chromatographically much more mobile by-product (14% isolated) (Scheme 35). Although uniform by t.l.c., this was shown by ^{1}H n.m.r. spectroscopy to consist of several components, sharp singlets at δ 3.82 and 3.96, and at δ 5.80 and 5.90 suggesting the presence of two monobrominated[130,134] and two dibrominated[134] acetoxy groups. Bromine analysis indicated a content of approximately five bromine atoms per molecule, only one being ionisable, and the material is therefore believed to have been a mixture (111) of mono-, di-, and possibly tri-bromoacetyl analogues of derivative (104). Bromination of

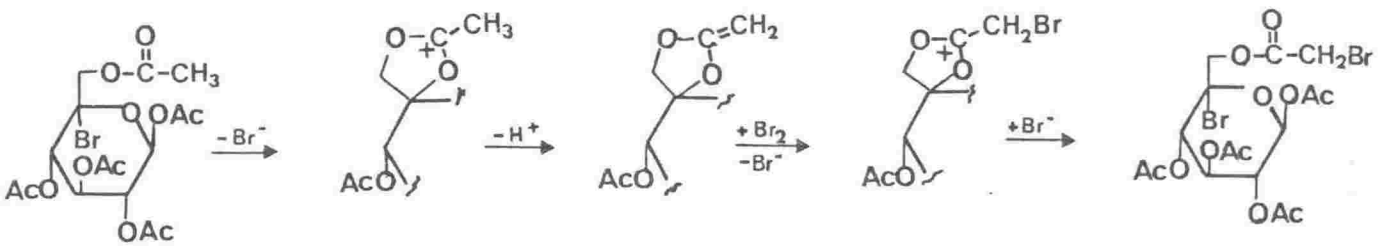


(102) (104) (111)

R = $-\overset{O}{\overset{\|}{C}}-CH_2Br$ or $-\overset{O}{\overset{\|}{C}}-CHBr_2$ or $-\overset{O}{\overset{\|}{C}}-CBr_3$

Scheme 35

acetyl groups has been encountered before, in photobrominations with NBS[130] and with bromine,[109] and proceeds most likely by an ionic mechanism[109] outlined in Scheme 36. Loss of bromide ion from C-5 of the bromide (104), with participation of the acetoxy group at C-6, leads, by way of acetoxonium ion

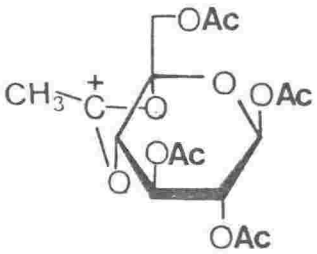


(104) (112) (113) (114)

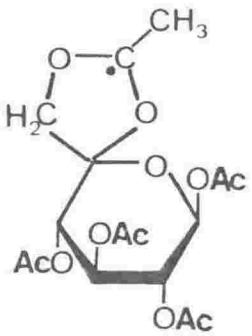
Scheme 36

(112), to the unsaturated species (113) which can be brominated to give a bromoacetate (114). The acetoxy group at C-4 can be brominated in a similar way via acetoxonium ion (115). Alternatively, an analogous homolytic process can be envisaged involving the radical species (116) and (117) as intermediates, giving rise to the same polybrominated products.

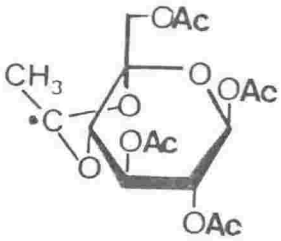
Treatment of the 5-bromide (104) and the mixed polybrominated products (111) separately with zinc-acetic acid gave almost identical mixtures of alkenes (94), (105), and (106) (12:3:1, 80% total, *cf.* Chapter 2, Scheme 34),



(115)



(116)



(117)

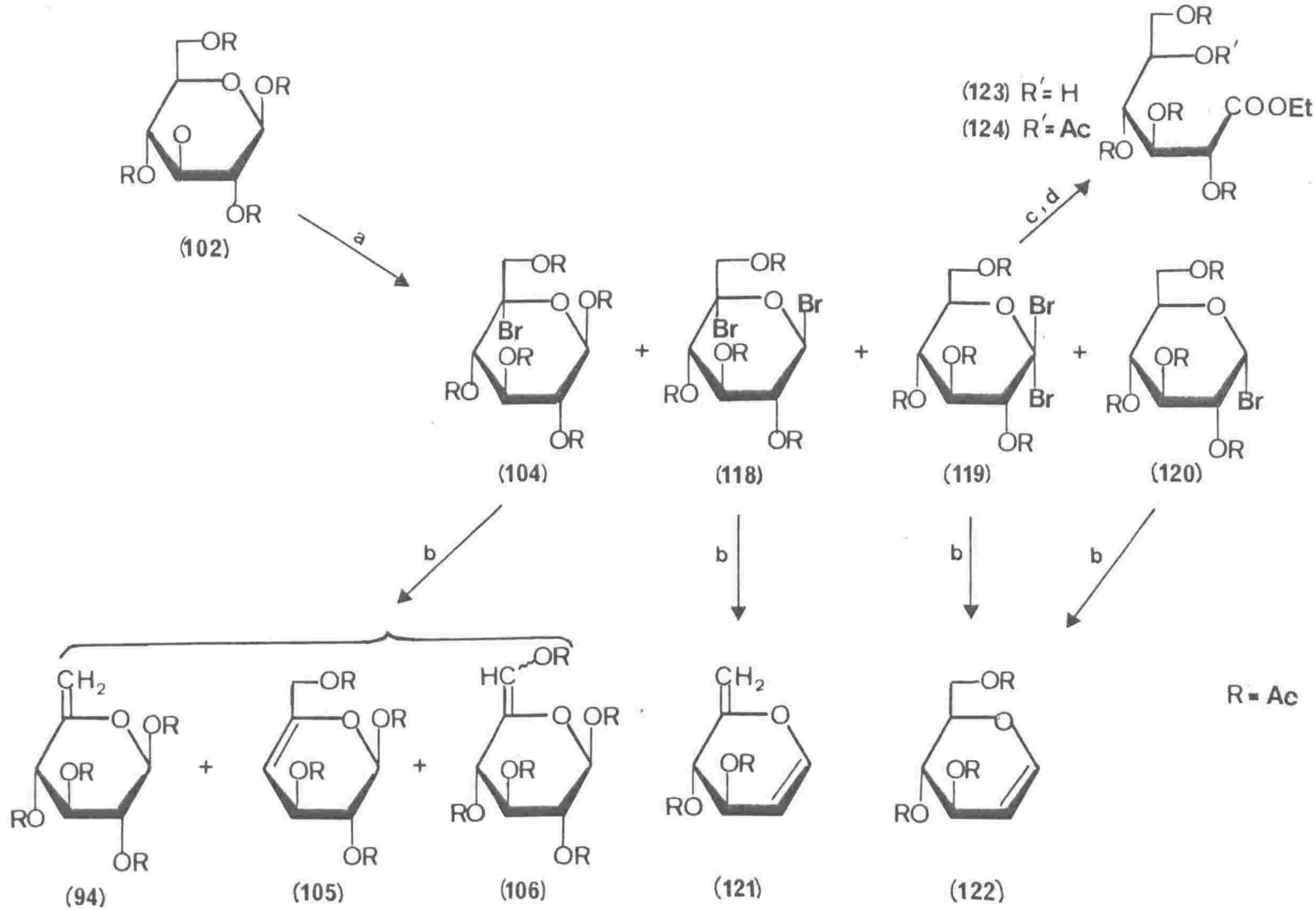
which means that these reaction conditions promote not only reductive elimination but also reductive substitution of bromine[135] within the ester groups.

PHOTOBROMINATION WITH BROMINE

Photobromination of β-D-glucose pentaacetate (102) with bromine in refluxing carbon tetrachloride on a 0.2 g scale was complete within 45 min. to afford the 5-bromide (104) in 80% yield (by column chromatography). However, when carried out with 10 g starting material, the reaction took 4 h and the crude product gave rise, on t.l.c. plates, to three spots of about equal intensity, the slowest one corresponding in its R_F value to the 5-bromide (104). Resolution by column chromatography gave, in fact, pure samples of four compounds, identified as the initial bromide (104) (20%), tetra-O-acetyl-5-bromo-β-D-glucopyranosyl bromide (118) (13%), tetra-O-acetyl-1-bromo-D-glucopyranosyl bromide (119) (18%), and tetra-O-acetyl-α-D-glucopyranosyl bromide (120) (3%) (Scheme 37), as well as a substantial quantity (*ca.* 20%) of still unresolved material containing mainly 1,1-dibromide (119) and acetobromoglucose (120) which had almost identical chromatographic mobilities.

The structural assignment of these compounds was based on bromine analysis, ^{1}H n.m.r. spectroscopy (Table 3) and conversion to known compounds as outlined in Scheme 37. The ^{1}H n.m.r. spectrum of the 1,5-dibromide (118) was very similar to that of the 5-bromide (104): lack of a resonance for H-5, an AB pair of doublets for H-6 and H-6', and a value of 8 Hz for $J_{1,2}$ indicated

Scheme 37



Reagents : a) Br_2/CCl_4, hν; b) Zn/HOAc ; c) $AgNO_3$/ EtOH ; d) Ac_2O/py

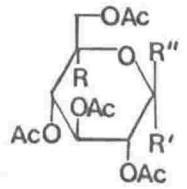
TABLE 3

^{1}H n.m.r. Spectral Data of Bromination Products of Glucose Pentaacetate (102)[a]

Compound	Chemical shift (δ) in p.p.m. downfield from TMS[b]								Coupling constants in Hz			
	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	OAc	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{6,6'}$
102[c]	5.70 d	← 4.9-5.6 →			3.87 m	← 4.05-4.2 →			8			
104[d]	6.17 d	5.18 dd	5.55 t	5.14 d	-	4.56 d	4.23 d	1.98, 2.04, 2.07, 2.09, 2.11	9	9	9	12.5
118[d]	5.86 d	← 5.05-5.55 →			-	4.64 d	4.34 d	1.98, 2.05, 2.08, 2.11	8			12.5
119[d]	-	← 5.1-5.4 →			← 4.0 - 4.4 →			1.95, 2.00, 2.10, 2.15				
120[e]	6.62 d	4.82 d	5.59 t	5.14 t	4.28 m	← 4.05-4.4 →			4	10	9.5	

[a]Some spectral parameters of pentaacetate (102) are included. [b]Observed multiplicities: d, doublet; dd, pair of doublets; t, triplet; m, multiplet. [c]See ref. 126. [d]Measured at 60 Hz in $CDCl_3$.

[e]See ref. 138.

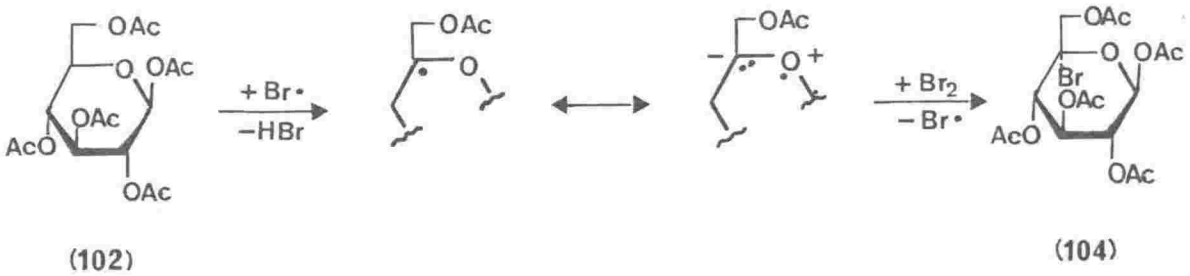


	R	R'	R''
102	H	H	OAc
104	Br	H	OAc
118	Br	H	Br
119	H	Br	Br
120	H	Br	H

substitution at C-5 by an axial bromine atom and retention of the $^4C_1$ conformation and β-configuration. H-1 and H-3 were, as in the spectrum of the monobromide (104), deshielded with respect to these protons in the spectrum of the starting material (102).[126] Replacement of the equatorial acetoxy group at C-1 by bromine had, however, caused these downfield shifts to be less pronounced [*ca.* 0.2 p.p.m., *cf.* 0.4 p.p.m. for bromide (104)], and, in consequence, the resonances for H-2, H-3, and H-4 of dibromide (118) were not well resolved. This is consistent with the observation[136] that the anomeric proton of tetra-O-acetyl-β-D-glucopyranosyl bromide resonates at higher field (by 0.2 p.p.m.) than that of β-D-glucose pentaacetate (102). Zinc acetic acid treatment of dibromide (118) gave, in good yield, the known diene (121).[137]

The absence of a signal for H-1 in the ^{1}H n.m.r. spectrum of the dibromide (119) indicated that C-1 of this compound was doubly substituted by bromine. In keeping with the presence of an axial bromine substituent at this site, H-3 and H-5 were deshielded relative to their positions in the spectrum of the precursor (102).[126] This deshielding was, however, weaker (*ca.* 0.2 p.p.m.) than that experienced by H-3 and H-5 of tetra-O-acetyl-α-D-glucopyranosyl bromide (120) (*ca.* 0.4 p.p.m.[138]), which is consistent with the observations reported above for other compounds with an equatorial bromine at C-1. Reduction of the 1,1-dibromide (119) with zinc-acetic acid gave tri-O-acetyl-D-glucal almost quantitatively, confirming again the ability of this reagent to effect both reductive elimination and debromination.[135] Further proof of the geminal dibromide structure was obtained from the fact that, on alcoholysis with moist ethanolic silver nitrate, a product was obtained, whose optical rotation and ^{1}H n.m.r. spectrum were consistent with those of ethyl 2,3,4,6-tetra-O-acetyl-D-gluconate (123).[139] On acetylation this gave the known pentaacetate (124).[140]

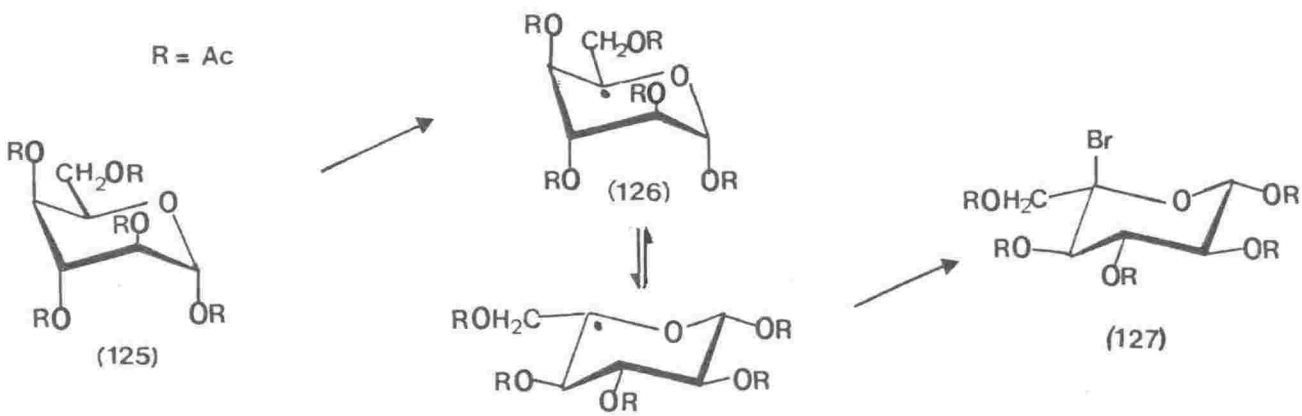
Mechanistically, it seems quite certain that the main bromide (104) was formed by radical substitution, as outlined in Scheme 38 [no bromination took place on heating a solution of pentaacetate (102) with bromine in the dark]. The reaction is thought to proceed by abstraction of a hydrogen atom from C-5 of the ester (102) by atomic bromine to form a tertiary radical which is stabilised by electron transfer from the adjacent ring oxygen atom.[141] Bromination from the axial direction then leads to bromide (104) with retention of configuration, as was the case with other D-glucopyranose derivatives.[109,130,131]



(102) (104)

Scheme 38

Strong evidence in favour of this mechanism was provided by the findings that penta-O-acetyl-α-D-idopyranose (125), the enantiomer of the C-5 epimer of the β-D-glucose ester (102), undergoes photobromination at C-5 with configurational inversion (Scheme 39). When small samples (0.2 g) of the pentaacetates (102) and (125) were treated separately with NBS in carbon tetrachloride under bright light, the two unfractionated products obtained were identical by t.l.c., i.r., and ^{1}H n.m.r. spectroscopy, and consisted mostly of penta-O-acetyl-5-bromo-β-glucopyranose. But, whereas the specific rotation of the crude 5-bromide derived from the β-D-gluco-starting material



Scheme 39

(102) was -66° - that of the pure 5-bromide (104) being -90° - the product obtained from the α-D-idose ester (125) had a specific rotation of +70° and was therefore mainly the 5-bromo-β-L-glucopyranose derivative (127). This

implies that abstraction of the axial hydrogen atom from C-5 of pentacetate (125), which exists in solution in the $^4C_1$ conformation,[127] leads to a conformationally unstable, all-axial radical (126) which ring-inverts prior to its bromination from the axial direction to give the L-gluco-bromide (127), *i.e.* the enantiomer of bromide (104).

The three by-products (118)-(120), on the other hand, arose, in all probability, from the ionic action of hydrogen bromide - formed concurrently during the radical reaction - with unused starting material (102) and with the initial product (104). Tetra-O-acetyl-α-D-glucopyranosyl bromide (120) is usually prepared by treating glucose pentaacetate with a solution of hydrobromic acid in glacial acetic acid,[142] the stable α-isomer being produced under the acidic conditions, which permit equilibration. When, in a control experiment, glucose pentaacetate (102) was heated in refluxing carbon tetrachloride saturated with hydrogen bromide, only very slow reaction took place, but, on addition of a small amount of bromine, glucosyl bromide (120) was formed rapidly and quantitatively. Similarly, reaction of hydrogen bromide with product (104) could have led to the 1,5-dibromide (118), again the more stable anomer being isolated, in this case the β-form in which destabilising 1,5-syn-axial-axial interaction between the two bromine atoms is avoided.

The 1,1-dibromide (119) could have been formed by radical bromination of glucosyl bromide (120), which was, however, found not to react under comparable photobromination conditions. Conceivably its less stable β-anomer, present as a short-lived intermediate, could have been a precursor, or, alternatively, radical bromination of the starting material at C-1 and nucleophilic displacement of the acetoxy group at this site by bromide ion could have produced a gem-dibromide.

Substantial support for the role of hydrogen bromide in promoting side-reactions was provided by the finding that in the presence of solid potassium carbonate, but with otherwise unaltered photobromination conditions [10 g pentaacetate (102)], the main bromide (104) was formed in much higher proportions (see Table 2). Direct eliminative reduction of the crude bromination product gave the two alkenes (94) and (105) derived from the 5-bromide (104) in 47% and 16% yield from pentaacetate (102), respectively (column chromatographic isolation), and only small amounts (8% together) of the unsaturated compounds (121) and (122) resulting from the bromination by-products.

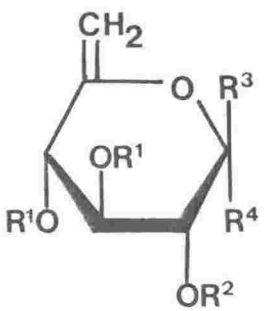
This study has thus revealed an important cause of loss of specificity during the photobromination of glucose pentaacetate (102) with bromine, and

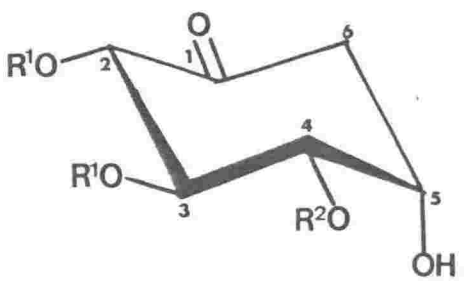
has thereby led to a slight modification of the procedure which now represents a reasonably efficient route to bromide (104) and, subsequently, to alkene (94).

CHAPTER FOUR

PREPARATION AND REACTIONS OF TRI-O-ACYL-TETRAHYDROXYCYCLOHEXANONES

In 1979 Ferrier[101] reported that the 6-deoxyhex-5-enopyranoside (80) on heating in aqueous acetone with mercury(II) chloride, was converted into the substituted cyclohexanone derivative (82) (*cf.* Scheme 26, p.25), the product crystallising directly in ca. 80% yield from the reaction solution on cooling. The application of this rearrangement reaction to the preparation of the triacylated deoxyinososes (91) and (92) from the unsaturated sugars (93),





	R¹	R²	R³	R⁴
80	Bz	Ts	H	OMe
93	Bz	Bz	OBz	H
94	Ac	Ac	OAc	H
96	Ac	Ac	H	OMe

	R¹	R²
82	Bz	Ts
91	Bz	Bz
92	Ac	Ac

and (94) or (96), respectively, is described in the first part of the present chapter, which also includes a brief investigation into the mechanism of the reaction. This is followed by a discussion of attempts to protect the free hydroxyl group at C-5 (cyclitol numbering[143]) of the new carbocyclic compounds (91) and (92), since for their use in the planned synthesis of branched chain cyclitols fully protected derivatives were required.

THE MERCURY(II) CATALYSED REARRANGEMENT OF 6-DEOXYHEX-5-ENOPYRANOSE DERIVATIVES

A. Preparation of the Tri-O-benzoyl- and Tri-O-acetyl-tetrahydroxycyclohexanones (91) and (92).

When the perbenzoylated alkene (93) was heated under reflux in aqueous acetone in the presence of mercury(II) chloride for 3 h, reaction took place to give mainly one product which was chromatographically less mobile than the starting material and gave rise to a bright red spot on t.l.c. plates developed with sulphuric acid-anisaldehyde spray. (In contrast, the compounds encountered so far had all given t.l.c. spots of a dull, brownish colour). This product, unlike the tosylated deoxyinososе (82) in the original example,[101] did not crystallise from the reaction solution, and extractive processing gave a syrup which resisted all attempts at crystallisation, but after column chromatographic purification the crystalline deoxyinososе tribenzoate (91) was obtained in 55% yield.

^{1}H N.m.r. spectroscopy (Table 4, p.52) showed compound (91) to contain one unprotected and three benzoylated hydroxyl groups. H-2, H-3 and H-4 ... (cyclitol numbering[143]) resonated as a doublet, a triplet, and a doublet of doublets at δ 5.83, 6.42, and 5.77, respectively, with $J_{2,3} = J_{3,4} = 10$ Hz indicating that all were axial on a six-membered ring. H-5 appeared *ca.* 1.5 p.p.m. upfield, as a broad singlet ($W_{1/2} = 8$ Hz) and was, as shown by a $J_{4,5}$ value of 2.5 Hz, equatorial. In the spectrum measured in $CDCl_3$ the two methylene protons, H-6 and H-6', were unresolved, but in $(CD_3)_2CO$ they gave rise to two pairs of doublets, at δ 3.38 and 2.79, with geminal coupling of 14 Hz and secondary splittings of 3 and 4 Hz, respectively, confirming the equatorial orientation of H-5. ^{13}C N.m.r. data were consistent with the assigned structure and a signal at δ 197, in particular, confirmed the presence of a keto group.

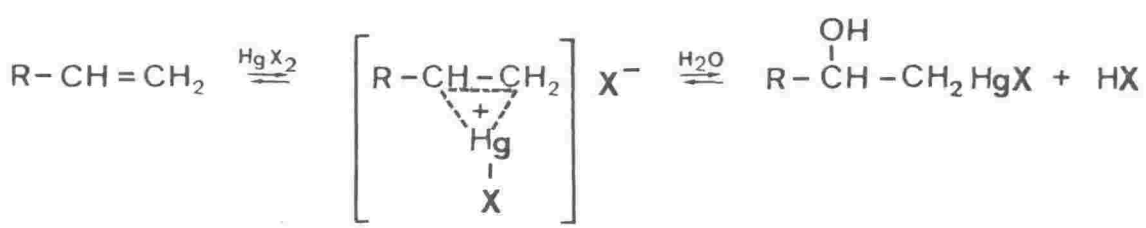
The acetylated 6-deoxyhex-5-enes (94) and (96), on being subjected separately to the above reaction conditions [mercury(II) chloride in refluxing aqueous acetone] for 1.5 h, gave, after column chromatography, the crystalline cyclohexanone derivative (92) in *ca.* 60% yield (from either starting material). The ^{1}H n.m.r. spectrum of this product (Table 4, p.52) was very similar to that of its benzoylated analogue (91), apart from the upfield shifts expected for all ring protons on replacement of the benzoyl- by acetyl-groups (*ca.* 0.6 p.p.m. for H-2, H-3, and H-4). The ring proton splitting pattern, identical to that of compound (91), indicated again the presence of a

cyclohexyl system with H-2, H-3, and H-4 axially and H-5 equatorially disposed.

In view of the ease and efficiency with which the original, tosylated rearrangement product (82) has been obtained,[101] the moderate yields and the necessity for chromatography in the isolation of the triesters (91) and (92) was rather disappointing. A considerable improvement was achieved, consequent upon the observations reported in the next section, by use of mercury(II) acetate in place of mercury(II) chloride. The crystalline tribenzoate (91) thus became available directly, from a concentrated chloroform extract, in>90% yield. The preparation of the acetylated derivative (92) was, however, still somewhat unsatisfactory, in spite of the slightly higher yield obtained (75%), as the unpurified product was prone to decompose, making expeditious isolation by column chromatography necessary for this compound.

B. The Mechanism of the Mercury(II) Catalysed Rearrangement

In aqueous media, alkenes are known to react with mercury(II) salts according to Scheme 40 to form (β-hydroxyalkyl)-mercury derivatives.[144-146] The addition to the double bond proceeds in the expected sense, probably via a mercurinium ion (128), and is fully reversible, *i.e.* the alkene is



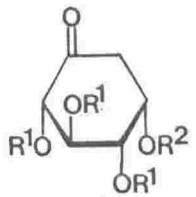
(128)

Scheme 40

regenerated from the mercurial by dilute mineral acid. Halogen acids, in particular, seem to promote the reversal of the hydroxymercuration, the proton coordinating with the hydroxyl group and the halide ion with the mercury atom. The rate of addition depends strongly on the nature of the mercury salt used. Thus, hydroxymercuration with the highly covalent mercury(II) chloride (for

TABLE 4

^{1}H n.m.r. Spectral Data for 2-Deoxyinososе Derivatives



Compound	R^1	R^2	Chemical shifts (δ) in p.p.m. downfield from TMS[a] H-2	H-3	H-4	H-5	H-6	H-6'	Others	Coupling constants in Hz $J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
91[b]	Bz	H	5.83 d	6.42 t	5.77 dd	4.60 br s	2.88 m		7.1-8.1 (3 x OBz; 2.9 (OH)	10	10	2.5			
91[c]	Bz	H	6.09 d	6.45 t	5.98 dd	4.75 br s	3.38 dd	2.79 dd	7.1-8.1 (3 x OBz); 5.2 (OH)	9	9	2.5	3	4	14
92[b]	Ac	H	5.34 d	5.73 t	5.25 dd	4.40 br s	2.75 m		2.05, 2.11, 2.15 (3 x OAc); 3.2 (OH)	10	10	2			
92[d]	Ac	H	5.49 d	5.75 t	5.39 dd	4.42 br s	3.08 dd	2.58 dd	2.01, 2.02, 2.06 (3 x OAc); 4.8 (OH)	10	10	2	3	4	15
140[b]	Bz	Ac	5.34 t	5.7-5.95			2.99 m		7.1-8.1 (3 x OBz); 2.13 (OAc)	10	10				
141[b]	Bz	THP	5.87 d	6.44 t 6.32 t	5.77 dd	∿4.60 m	2.85 m		7.1-8.1 (3 x OBz)[e]	10	10	2			

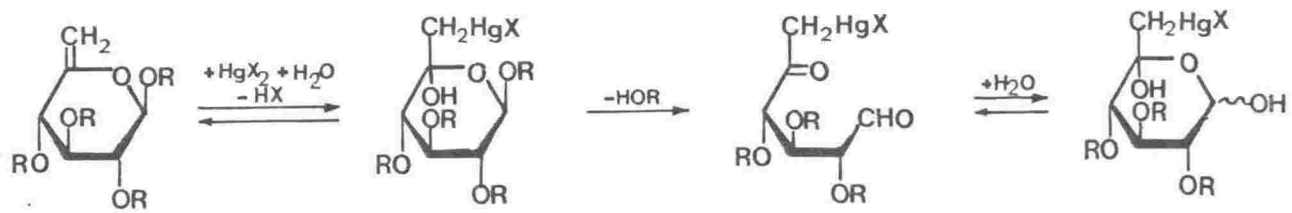
[a]Observed multiplicities: d, doublet; dd, pair of doublets; s, singlet; br s, broad singlet; t, triplet; m, multiplet.

[b]Measured at 80 MHz in $CDCl_3$; [c]Measured at 60 MHz in $(CD_3)_2CO$; [d]Measured at 80 MHz in $(CD_3)_2CO$;

[e]The expected signals for the THP group were also observed.

the equilibrium $HgCl_2 \rightleftharpoons HgCl^+ + Cl^-$, log $\underline{K}$ is $\underline{ca}$. -6.55[147]) is relatively slow and, unless the hydrochloric acid formed concurrently is neutralised, a considerable excess of the chloride must normally be employed if the reaction is to be made to go to completion. With mercury(II)acetate, on the other hand, which in aqueous solution is fully ionised,[146] addition occurs quickly and, since the acetic acid liberated is not strong enough to effect elimination from the hydroxymercurial, only the stoichiometric quantity of reagent is required, even without neutralisation.

In the case of the unsaturated pyranose derivative (93) - a vinyl ether - mercury would be expected to bond to C-6, with formation of a hemiacetal centre at C-5 (Scheme 41). The adduct could then ring-open, as shown, and lose the



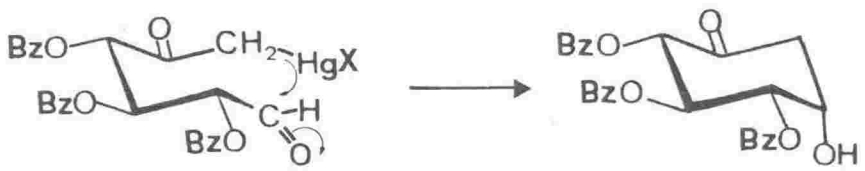
(93) (129) (130)

X = Cl or AcO
R = Bz

Scheme 41

ester group from the anomeric centre. In aqueous media the resulting mercurial may be assumed to exist predominantly in the hydrated, cyclic form (130)[109] in equilibrium with a small amount of the acyclic ketoaldehyde (129). C-6 of structure (129) would possess strong carbanionic character, ionisation at this site being facilitated by (i) the polarisation of the carbon-metal bond and (ii) stabilisation of the anion by the carbonyl group. Ring closure by intramolecular aldol condensation should therefore occur readily (Scheme 42).

When the reaction between alkene (93) and mercury(II) chloride in aqueous acetone was conducted at room temperature it could be seen, by polarimetry and by t.l.c., to proceed in two stages. First, the optical rotation of the reaction solution increased quite rapidly and, on t.l.c. plates, a bright yellow spot - visible without spraying - appeared near the baseline, suggesting formation of a mercury containing intermediate. After 6 h, all the alkene had reacted, and there followed a slow but steady decrease



(129) (91)

Scheme 42

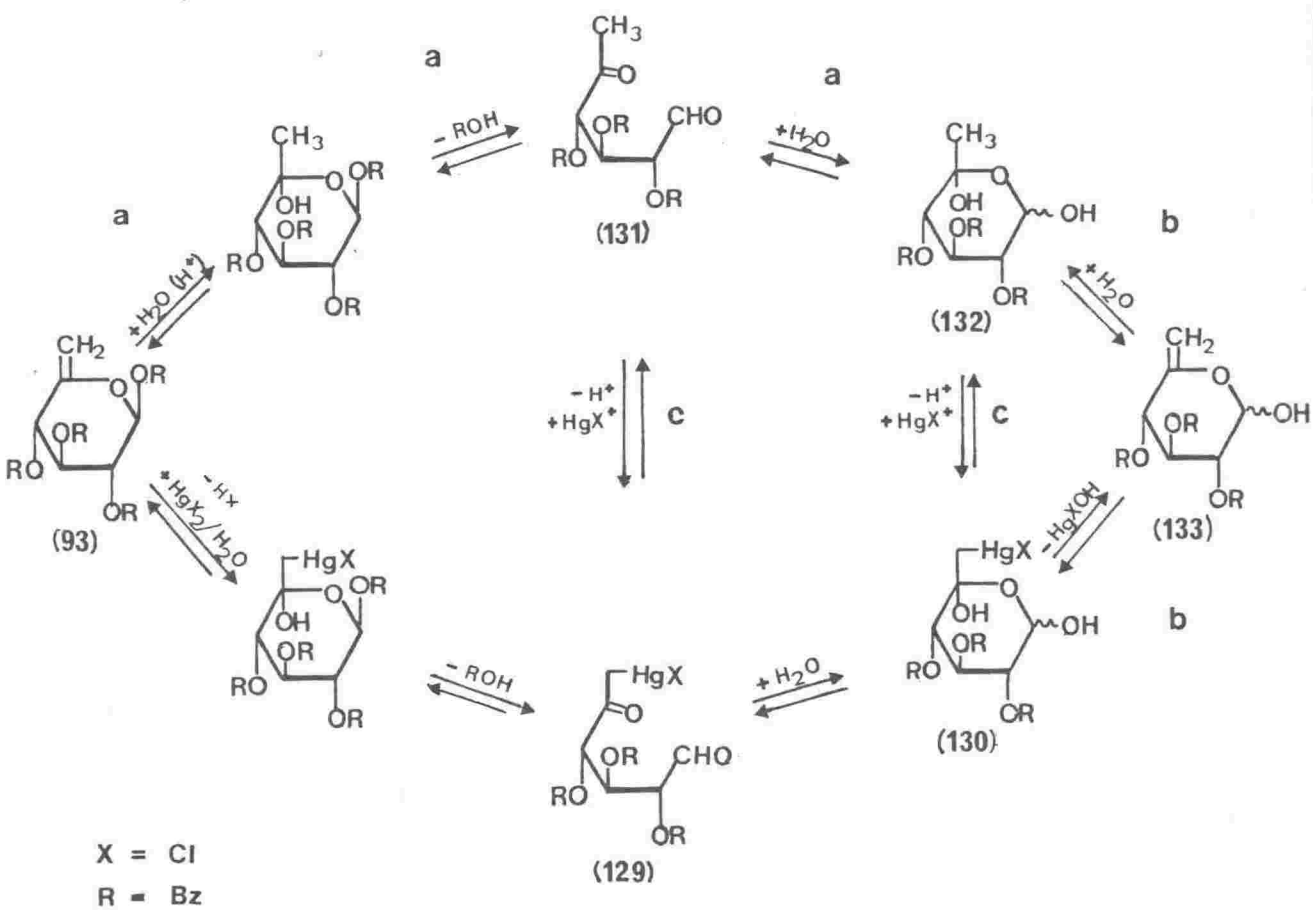
in optical rotation. Simultaneously, the compound giving rise to the yellow spot on chromatograms was replaced by two slightly more mobile ones, the faster of which corresponded to the carbocyclic product (91).

For isolation of the mercuriated intermediate, the room temperature reaction was discontinued as soon as the optical rotation had reached its maximal value (6 h), and the organic product was, after removal of the acetone, extracted into benzene. After exhaustive drying, a glass was obtained whose chlorine and mercury content, and ^{1}H n.m.r. spectrum were consistent with its being the 1,5-dicarbonyl compound (129). The presence of a formyl resonance (sharp singlet at δ 9.58), and small coupling constants ($J_{2,3} = J_{3,4} = 4$ Hz) were good evidence of an acyclic structure. Similar J values have been reported for a number of acyclic 5-uloses and 5-ulonic esters with the xylo-configuration.[109,148] With respect to the ^{1}H n.m.r. spectrum of tetra-O-benzoyl-D-xylo-hexos-5-ulose[109] H-6 and H-6', being geminal to mercury, were strongly (1.5 p.p.m.), and H-2, H-3 and H-4 weakly (0.3 p.p.m.) shielded.

The mercurial (129) on treatment in dry benzene with hydrogen sulphide cyclised to the deoxyinososе derivative (91) (Scheme 42) which was isolated as a foam in 75% yield (from the mercurial) after preparative t.l.c.. Ring-closure also took place spontaneously though slowly, when the room temperature reaction between the alkene (93) and mercury(II) chloride was allowed to proceed for longer than 6 h, complete conversion being attained after 8 days. Under these conditions, however, the cyclisation was accompanied by the formation of a by-product which, by ^{1}H n.m.r. analysis, constituted *ca.* 40% of the unfractionated reaction products. This compound was isolated by

preparative t.l.c. followed by exhaustive drying and, although not fully characterised, is believed to have been the hexos-5-ulose (131) on the basis of its ^{1}H n.m.r. spectrum which consisted of a formyl resonance at δ 9.63, a triplet and two doublets near δ 6.0 for H-3, and H-2 and H-4, respectively, small splittings (4.5 Hz) indicating an acyclic structure, and a sharp three-proton singlet at δ 2.26 typical for a methyl ketone.

The ketoaldehyde (131), which in aqueous solution presumably exists in equilibrium with its hydrated, cyclic form (132),[109] might have arisen from the starting alkene (93) directly by acid catalysed hydrolysis (Scheme 43, path a), as 6-deoxyhex-5-enopyranose derivatives are known to be, in general, susceptible to solvolysis in this way in acidic media.[107,149] In the present case this seems improbable, since the alkene (93) had been shown, by t.l.c., to be converted specifically into the mercurial (130) [or (129)], and in a control experiment it did not decompose to any extent when subjected to dilute hydrochloric acid of appropriate concentration in aqueous acetone at



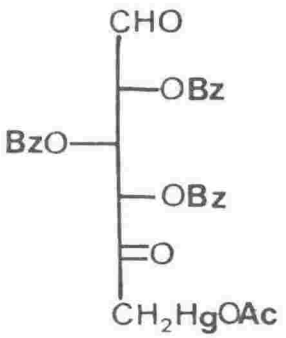
Scheme 43

room temperature for several weeks. It is thought more likely that acid promoted deoxymercuration of compound (130) led to the unsaturated species (133) which was hydrated to the by-product (132) (Scheme 43, path b); or, alternatively, a direct mercurinium chloride cation-proton exchange, as proposed by Lehmann, might have taken place (Scheme 43, path c).[150] Regardless of the exact mechanism, a decisive role in promoting this side reaction was played by the hydrochloric acid released in the hydroxymercuration step.

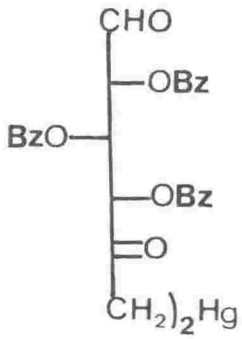
T.l.c. analysis had indicated that the same by-product [(131) or (132)] was produced also during the preparation of the cyclohexanone derivative (91) with mercury(II) chloride at elevated temperature (*cf.* Section A). The unfractionated product mixture of this reaction was shown by ^{1}H n.m.r. spectroscopy to contain, after thorough drying, *ca.* 30% ketoaldehyde (131), and it was felt that the presence of this compound not only affected the yield but also prevented crystallisation of the main product (91). In an attempt to inhibit this hydrolysis, the mercury(II) salt of a weak acid was used instead of mercury(II) chloride. Accordingly, when the alkene (93) was heated under reflux in aqueous acetone in the presence of mercury(II) acetate for 5 h the carbocyclic triester was obtained crystalline, without chromatography, in over 90% yield.

Somewhat surprisingly, the rearrangement was considerably slower with mercury(II) acetate than with mercury(II) chloride. An examination of the room temperature reaction between the hex-5-ene (93) and mercury(II) acetate - carried out and monitored in the same way as the corresponding reaction with the chloride - revealed that the hydroxymercuration was actually faster (0.25 h to reach maximal optical rotation with the acetate, 6 h with the chloride). However, the ring-closure step was very much slower, only traces of deoxyinososе (91) being detectable after one week. The intermediate, isolated after a reaction time of 1 h, was shown by ^{1}H n.m.r. spectroscopy not to be the expected acetate (134), since it lacked an acetoxy resonance. It was therefore thought to be the dialkyl mercurial (135), an assumption which was supported by mercury analysis.

The sluggishness of the mercury(II) acetate catalysed reaction might be associated with the dimeric nature of the hydroxymercuration product or, alternatively, it might be due to the absence of chloride ions which, by coordination with the mercury atom, facilitate scission of the carbon-metal bond. The observation that addition of sodium chloride to the reaction solution, once the hydroxymercuration was complete, greatly increased the rate of carbocyclic product formation, pointed strongly towards



(134)



(135)

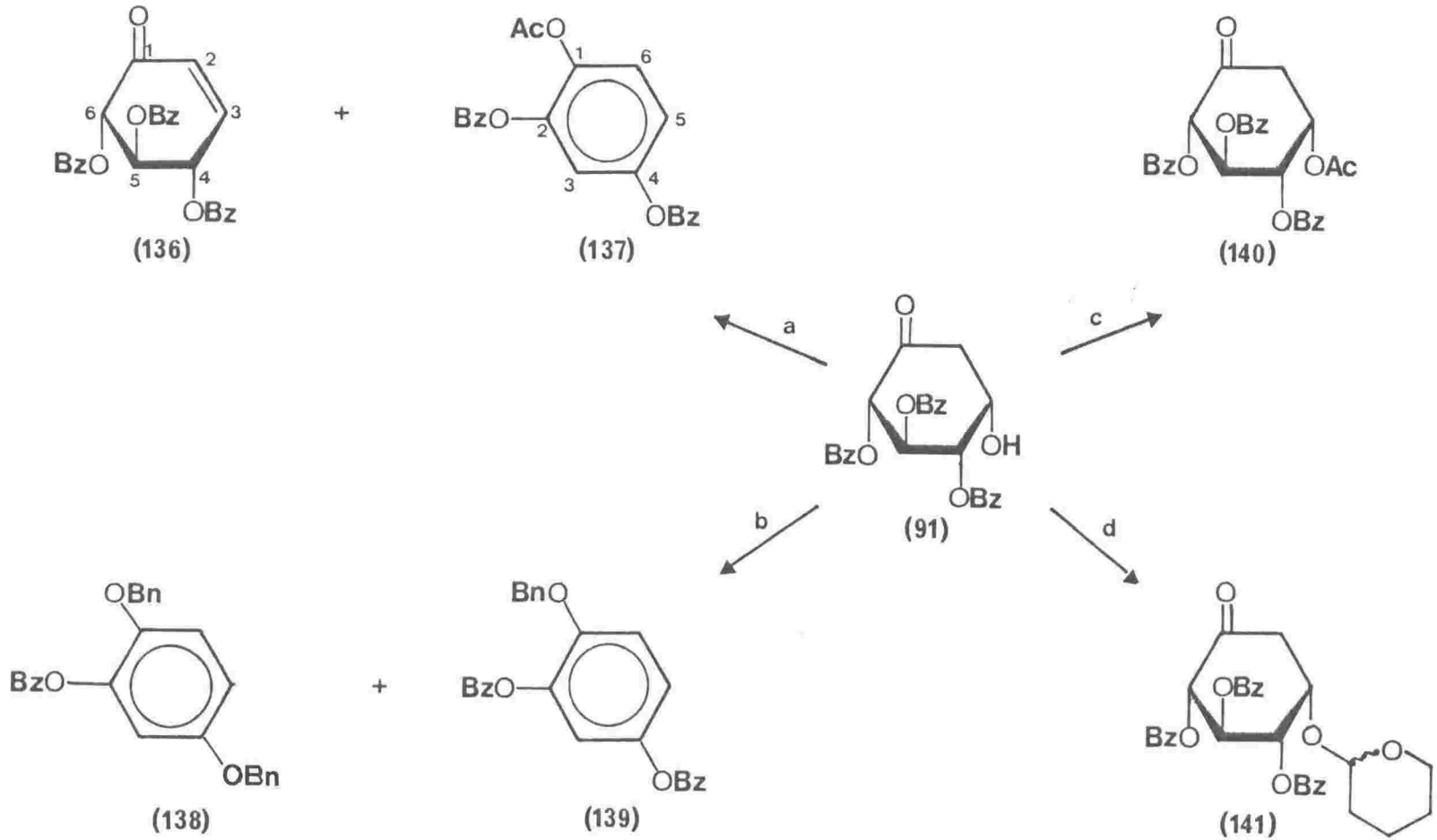
the latter explanation. Thus, when sodium chloride was added to a solution of alkene (93) and mercury(II) acetate in aqueous acetone which had been heated for 5 min., the rearrangement was complete after a total reaction time of 10 min.; the crystalline product (91) was obtained directly, after extractive work-up, but in lower yield (63%) than by the earlier procedure requiring heating for 5 h.

REACTIONS OF TRI-O-ACYL-TETRAHYDROXYCYCLOHEXANONES (91) AND (92)

Those reactions which led either to fully protected deoxyinosose derivatives or to elimination products, summarised in Scheme 44, are considered here; the introduction of chain-branching will be dealt with in Chapters 5 and 6. Most of the work reported in the remainder of this chapter was carried out with the tribenzoate (91), the reason being at first that this derivative was easier to prepare in good yield than the triacetate (92). Later it was also found that the products in the benzoylated series were all crystalline, in contrast to their acetylated analogues which tended to resist crystallisation.

A. Reactions Leading to Elimination Products

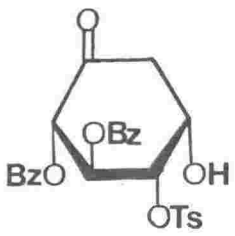
The preparation of fully protected derivatives from the monohydroxy-ketones (91) and (92) was seriously impeded by the readiness of these compounds to undergo elimination. It has been observed on many occasions[50,101,151,152] that in mildly alkaline media inosose peresters



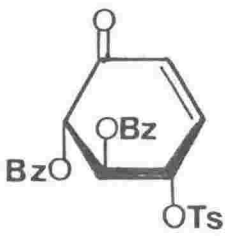
Reagents : a) Ac_2O/py ; b) AgO, BnBr/DMF ; c) Ac_2O, BF_3-Et_2O ; d) DHP, H^+

Scheme 44

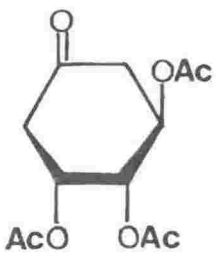
lose one molecule of carboxylic acid. The tosylated deoxyinosose (82), for example, gave the conjugated enone (142) on attempted acetylation with acetic anhydride in pyridine,[101] and the triacetoxycyclohexanone (143) was converted to the diastereoisomeric diacetoxycyclohexenones (144) not only



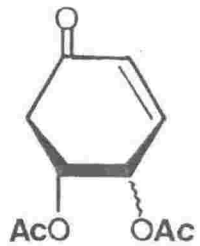
(82)



(142)

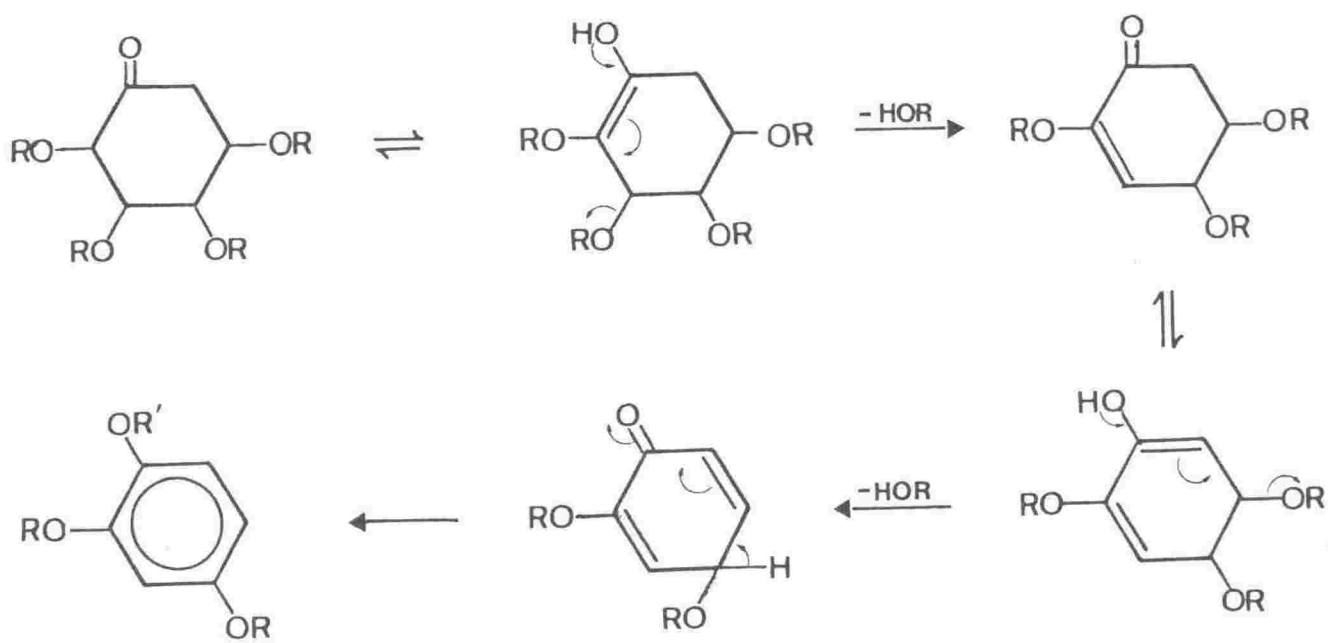


(143)



(144)

under basic (sodium hydrogen carbonate), but also under weakly acidic conditions (silica gel/methanol).[152] On contact with stronger base, peracylated as well as perbenzylated inososes have been found to suffer aromatisation.[101,153,154] A mechanism for this process involving two successive β-eliminations was first proposed by Isbell[155] in 1943, and it is outlined in Scheme 45 as applied to deoxyinosose derivatives. (The



R = Bz, Ac, or Bn
R′ see text

Scheme 45

nature of the group R' in the final product depends on the reaction conditions; see Scheme 44 for two examples).

Treatment of the hydroxybenzoate (91) with acetic anhydride in pyridine gave as the main product the enone (136) in 60% yield by direct crystallisation On standing for several days at -10°C the mother liquors deposited the phenolic compound (137) (28% isolated) (Scheme 44). The ^{1}H n.m.r. spectrum of the enone (136) showed one of the vinylic protons (H-3) as a doublet with J = 11 Hz at δ 7.02, the other one (H-2) resonated together with the three ring protons bonded to saturated carbon at higher field (δ 5.9-6.4) as an unresolved multiplet.

Attempted benzylation of the tribenzoate (91) with benzyl bromide in DMF in the presence of silver oxide[156] led to complete aromatisation (Scheme 44). The two crystalline benzene derivatives (138) and (139) were obtained in 29 and 31% yield, respectively, after column chromatography. The presence of the benzoate resonances precluded an analysis of the splitting patterns for the three aromatic ring protons in the ^{1}H n.m.r. spectra of these two compounds and of the acetoxy-dibenzoate (137). The 1,2,4-substituted structures were assigned to them on mechanistic grounds (*cf.* Scheme 45) and by analogy to the fully characterised aromatisation product of the tosylated derivative (82).[101] Compounds (137)-(139) all showed the appropriate ^{1}H n.m.r. signals for their protecting groups, and in the mass spectrometer they gave molecular ions with m/e 376, 410, and 424, respectively, and fragment ions characteristic for loss of ketene and benzoyl- and benzyl-radicals, as expected.

B. Preparation of Fully Protected Derivatives

Obviously, for successful protection of the C-5 hydroxyl group of compounds (91) and (92) reactions proceeding under non-basic conditions were required. Acetylation of the benzoylated derivative (91) in acetic anhydride with boron trifluoride etherate as catalyst afforded the crystalline acetate (140) in 50-85% yield (Scheme 44). Concurrent formation of the enone (136) - isolated in 20% crystalline yield from the mother liquors when the acetylation was performed at room temperature - could be inhibited by working at 0 — -10°C. The ^{1}H n.m.r. spectrum of compound (140) (Table 4, p.52), showing an acetoxy resonance at δ 2.13, was consistent with the assigned structure. The signal for H-5, which in the spectrum of the starting material (91) appeared at δ 4.60, had been shifted downfield by

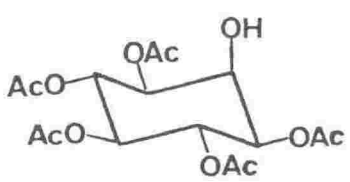
1.3 p.p.m., in keeping with the replacement of the hydroxyl group at C-5 by an acetoxy group, and resonated with H-2 and H-4 as an unresolved multiplet at δ 5.7-5.95. As in the precursor (91), H-3 resonated at somewhat lower field (δ 6.34) as a triplet with large coupling ($J_{2,3}$ = $J_{3,4}$ = 10 Hz).

The triacetate (92) gave under the same acetylation conditions a tetraacetate (^{1}H n.m.r. evidence) which could, however, not be crystallised. During attempted purification by chromatography on silica gel it underwent β-elimination in similar fashion to the triacetoxyketone (143) mentioned above.[152]

The tetrahydropyranyl ethers (141) were obtained in high yield (93%) on treatment of compound (91) with 2,3-dihydropyran with a trace of toluene-p-sulphonic acid as catalyst (Scheme 44). In the ^{1}H n.m.r. spectrum (Table 4, p.52) H-3, having the 1,3-diaxial relationship with the substituent at C-5, gave rise to two triplets of roughly equal intensity, centred at δ 6.32 and 6.44, indicating that the product (141) was a *ca.* 1:1 mixture of two diastereoisomeric compounds, as introduction of the protecting group created a new asymmetric centre on the tetrahydropyranyl ring. In all other aspects the spectra of the two isomers were identical and very similar to that of their precursor (91). In spite of being a mixture of diastereoisomers, product (141) crystallised after column chromatography, and when very pure starting material (91) was used, directly from a concentrated chloroform solution.

An attempt to prepare the 5-methyl ethers of compounds (91) and (92) by use of diazomethane in the presence of boron trifluoride etherate[157] proved unsuccessful. This was, however, not unexpected, since Angyal and Melrose[158] reported that myo-inositol 1,3,4,5,6-pentaacetate (145) which also has an axial hydroxyl group, could not be methylated with this reagent.

(145)

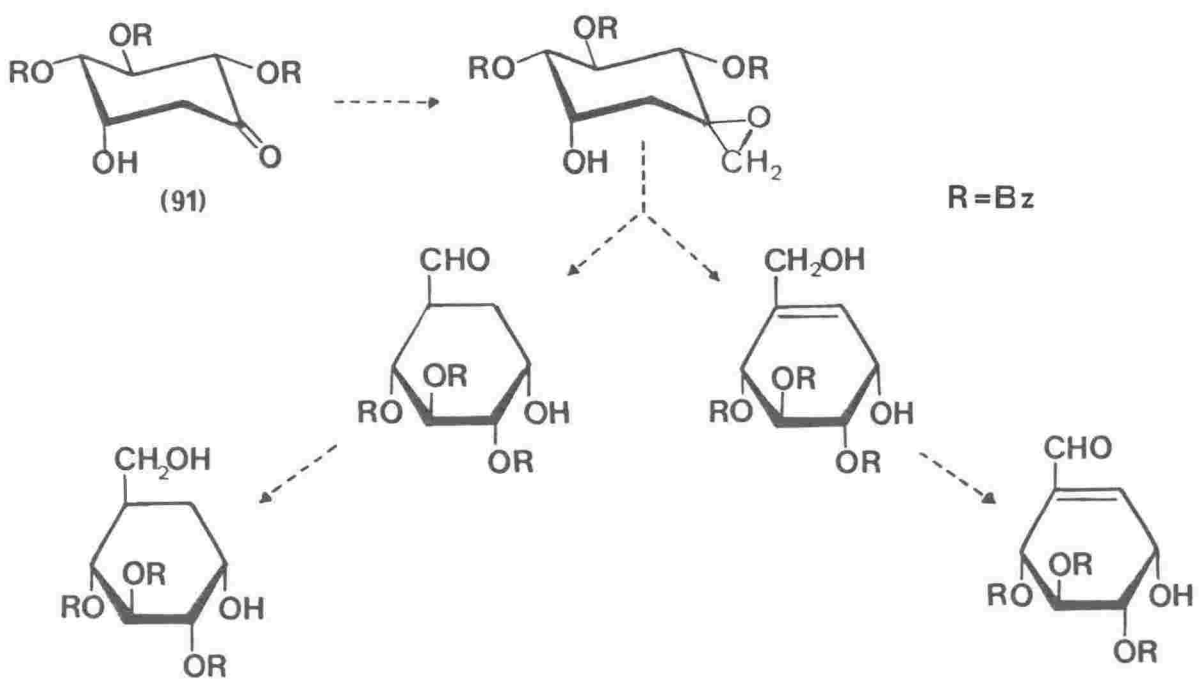


CHAPTER FIVE

INTRODUCTION OF CHAIN BRANCHING INTO TETRA HYDROXYCYCLOHEXANONE DERIVATIVES BY USE OF DIAZOMETHANE

With the 2-deoxyinososе tribenzoate (91), its 5-acetate (140), and its 5-tetrahydropyranyl ether (141) in hand, the introduction of a one-carbon branch at the carbonyl centre could now be undertaken, the final objective being the synthesis of rancinamycin or pseudo-sugar derivatives (*cf.* Chapter 1, p.13). A great variety of methods are, in principle, available for this purpose. Most of them involve, however, reaction conditions incompatible with the base-labile nature of inosose esters. The two approaches considered most promising and discussed in Chapters 5 and 6, respectively, were: (i) epoxidation with diazomethane, and (ii) cyanohydrin formation.

Epoxidation of penta-O-acetyl-myo-inosose with diazomethane was accomplished by Posternak as early as 1944[159] and several applications of this method to other inosose derivatives have been reported since.[54-56,160] One could therefore expect the substituted cyclohexanone (91) to form with this reagent a spiro-epoxide, which on treatment with a Lewis acid - e.g. boron trifluoride - would rearrange[161,162] to an aldehyde or an allylic alcohol (Scheme 46). The former should then be convertible by reduction to a



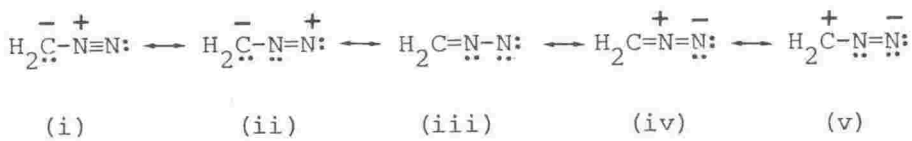
Scheme 46

pseudo-sugar, the latter by oxidation of the alcohol function to the tribenzoate of rancinamycin III.

THE REACTION OF (2,4,5/3)-TETRAHYDROXYCYCLOHEXANONE DERIVATIVES WITH DIAZOMETHANE

A. General Considerations

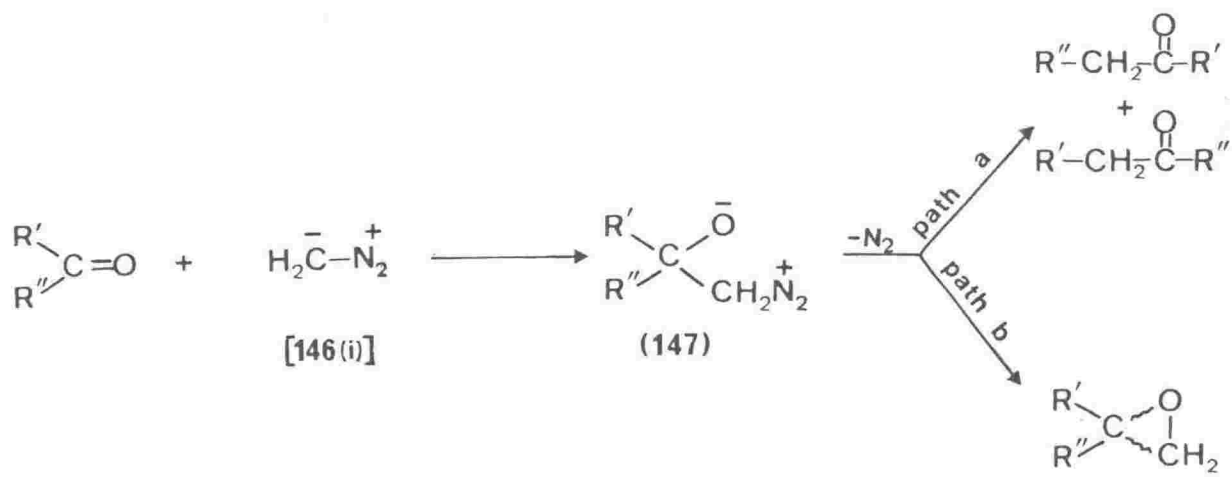
The differing modes of reaction of diazomethane are best understood by an inspection of its structure, which may be expressed by several canonical forms [146(i-v)]. It can act as a nucleophile, an electrophile, or a 1,3-



(i) (ii) (iii) (iv) (v)

(146)

dipole, and it has very weakly basic properties.[163] Its reaction with ketones[163,164] is thought to take the course outlined in Scheme 47.

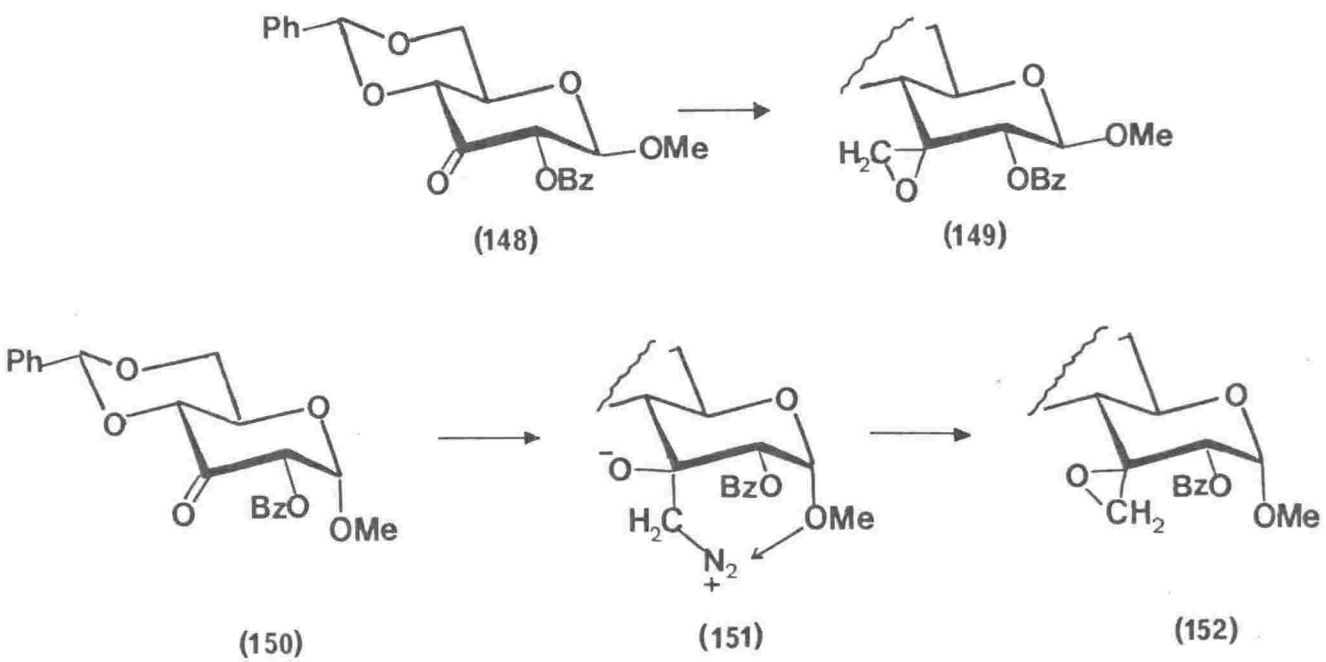


Scheme 47

Nucleophilic attack by diazomethane [146(i)] at the carbonyl carbon gives a zwitterion (147) which becomes stabilised with loss of nitrogen, either by migration of R′ or R″ to form homologous ketones (path a), or by ring-closure to give oxiranes (path b). Homologation is disfavoured when the ketone is sterically hindered and when electron-withdrawing substituents are present in the R-groups, and was therefore expected to be of little

significance in the case of the tribenzoate (91).

Information concerning the steric course of the epoxidation of substituted six-membered cyclic ketones with diazomethane is available from a considerable number of studies with inosose[54-56,159,160] and hexosulose[165-171] derivatives. As a rule the nucleophilic species [146(i)] approaches the ketone from the sterically less hindered side, *i.e.* in the absence of bulky, axial substituents in the α-positions from the equatorial direction.[172] However, axial, oxygen-containing substituents α or β to the carbonyl group can exert a directing influence by stabilising the zwitterion intermediate[168-170] [*e.g.* (151)]. Thus, on treatment with diazomethane, the methyl 3-uloside (148) gave the product of equatorial attack (149) in 90% yield (Scheme 48), while its anomer (150), which has an axial

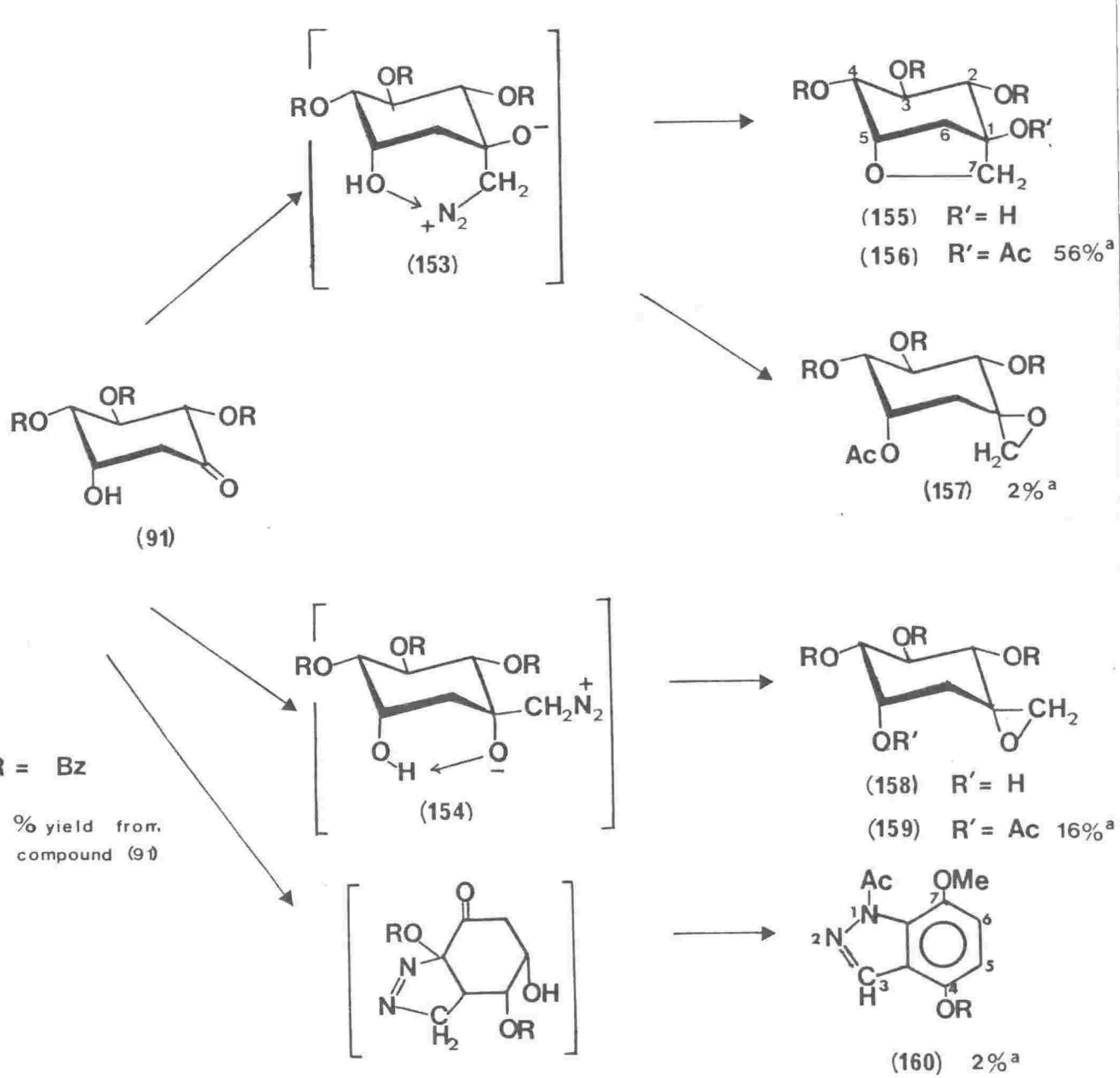


Scheme 48

methoxy group in the β-position, reacted via the oxygen-stabilised intermediate (151) to afford the product of axial attack (152) in 77% yield.[170] On this basis the predominant product from the reaction between 2-deoxyinosose (91) and diazomethane was expected to have the configuration shown in Scheme 46.

B. The Reaction of Tri-O-benzoyl-tetrahydroxycyclohexanone (91) with Diazomethane

When a solution of compound (91) in chloroform was treated with diazomethane in ether at +4° C, complete conversion of the starting material to two products was observed by t.l.c. after 48 h (Scheme 49). On trituration with methanol the major component crystallised in low yield (20%),



Scheme 49

and column chromatographic separation of the non-crystalline material gave a further quantity of the same compound (61% total) as well as the minor product in 15% crystalline yield. The latter was readily identified as a spiro-epoxide, its ^{13}C n.m.r. spectrum lacking a carbonyl resonance and showing instead signals at δ 47 and 56 which are characteristic of a methylene and a quarternary carbon atom, respectively, in an oxirane ring.[173] The stereochemistry at C-1 was not unambiguously determined, but considerations discussed on p.72 led to the assignment of structure (158). In the ^{1}H n.m.r. spectrum (Figure 1, see also Table 5) H-7 and H-7' resonated as an AB system at high field (δ 2.73 and 2.67) with geminal coupling of 4.5 Hz as is consistent with an exocyclic epoxide structure.[56,174,175] The two doublets of doublets at still higher field (δ 2.46 and 1.99) were attributed to H-6 and H-6' since their secondary splittings ($J_{5,6}$ = 3 Hz, $J_{5,6'}$ = 4 Hz) were removed on irradiation of H-5, leaving an AB pair of doublets with $J_{6,6'}$ = 15 Hz. With regard to the spectrum of the starting ketone (91), H-2 — H-5 had experienced slight shielding but their coupling constants ($J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 2.5 Hz) had remained essentially unchanged indicating that the shape of the cyclohexyl ring had not been affected by the replacement of the carbonyl group by a spiro-oxirane ring.

The ^{13}C n.m.r. spectrum of the major product contained, apart from resonances for three benzoyloxy groups, a signal at δ 39 and six signals between δ 71 and 79. Reaction had therefore taken place at the carbonyl centre with incorporation of a one-carbon unit, but neither an epoxide nor a ring-expanded ketone had been formed. These ^{13}C n.m.r. data, strongly supported by ^{1}H n.m.r. spectroscopic evidence, suggested a bicyclic structure (155) (Scheme 49). In the completely resolved 80 MHz ^{1}H n.m.r. spectrum of this compound (Figure 2, see also Table 6) the hydrogen atoms of the newly introduced C-7 methylene group gave rise to an AB pair of doublets at δ 4.33 and 3.69 with $J_{7,7'}$ = 8.5 Hz. The upfield one of these doublets showed small, secondary splittings (1.6 Hz), a double irradiation experiment revealing coupling with H-2; it was therefore assigned to the 7_{exo}-proton since H-2 and H-7_{exo} are separated by four bonds along a "planar W" path. Similar chemical shifts and geminal coupling constants of 7.5-8 Hz are reported for the C-6 protons of structurally related 1,6-anhydro-β-D-hexopyranoses,[176-178] long-range coupling of *ca.* 1 Hz between H-4 and H-6_{exo} being observable in the spectra of derivatives with axial hydrogen atoms at C-4. On comparing the spectrum of the bicyclic ether (155) (Figure 2) with that of the epoxide (158) (Figure 1) differences in the

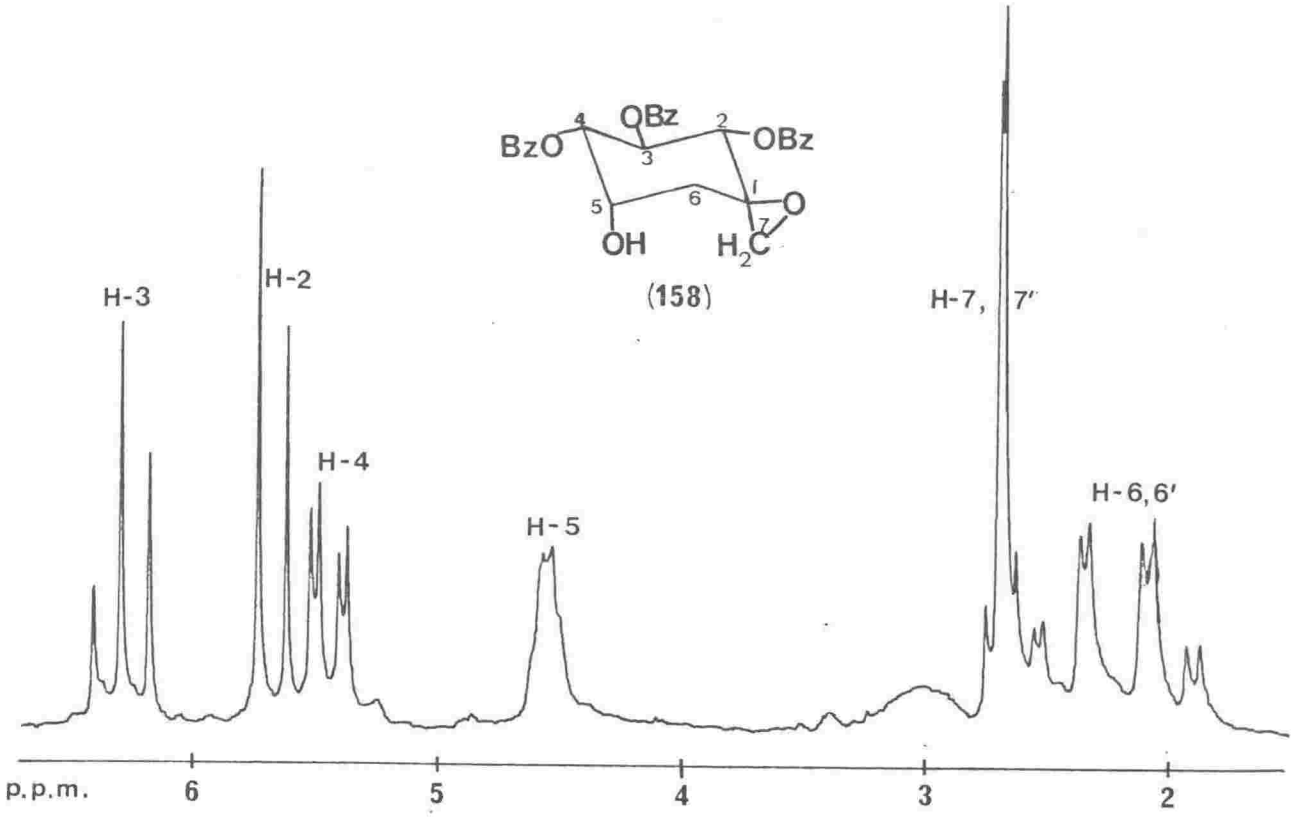


Figure 1

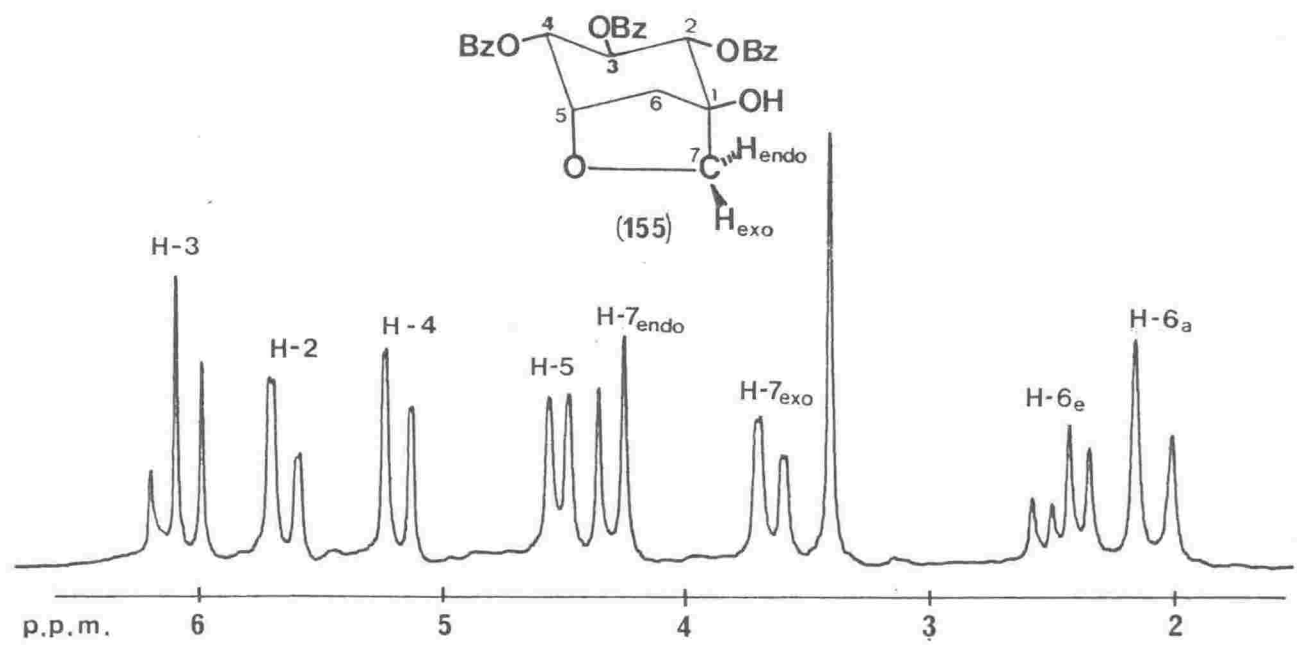


Figure 2

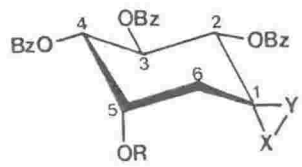
TABLE 5

^{1}H n.m.r. Spectral Data for Spiro-Epoxides

	Chemical Shifts (δ) in p.p.m. downfield from TMS[a]									Coupling Constants in Hz						
Compound	H-2	H-3	H-4	H-5	H-6	H-6'	H-7	H-7'	Others	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{7,7'}$
91[b]	5.83d	6.42t	5.77dd	4.60brs	◁——2.88m——▷		-	-		10	10	2.5	3[c]	4[c]	14[c]	-
158[b]	5.71d	6.34t	5.48dd	4.55brs	2.46dd	1.99dd	2.73d	2.67d	7.1-8.1 (3xOBz); ∿3.1 (OH)	9.5	9.5	2.5	3	4.5	15	4.5
159[b]	5.70d	6.29t	5.52dd	∿5.7m	◁——1.7-2.5——▷		2.71d	2.64d	7.1-8.1 (3xOBz); 2.17 (OAc)	9.5	9.5	3				4.5
157[b]	5.74d	6.11t	5.55dd	∿5.7m	2.45dd	1.96dd	3.13d	2.62d	7.1-8.1 (3xOBz); 2.11 (OAc)	9.5	9.5	3	3	4.5	14	4.5

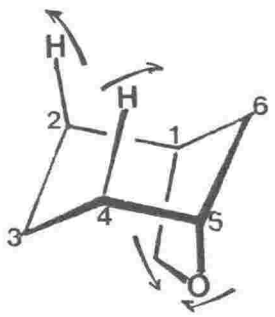
[a]Observed multiplicities: d, doublet; dd, pair of doublets; brs, broad singlet; t, triplet; m, multiplet.

[b]Measured at 80 MHz in $CDCl_3$. [c]Coupling constants determined in $(CD_3)_2CO$.



	R	X	Y
(158)	H	O	CH_2
(159)	Ac	O	CH_2
(157)	Ac	CH_2	O

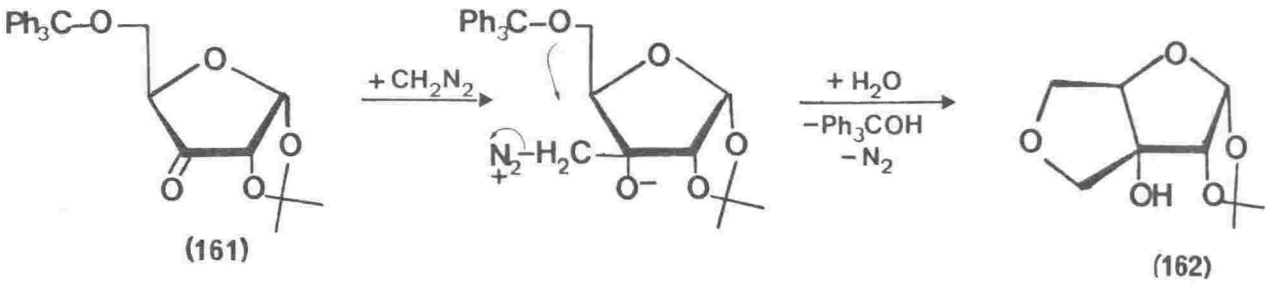
coupling constants were noticed, in particular the near zero coupling, for compound (155), between H-5 and its two axial, vicinal neighbours H-4 and $H\text{-}6_a$, indicating that the dihedral angles between H-5 and these two protons was close to 90°, consistent with increased puckering of the cyclohexyl ring due to its fusion to a five-membered ring; essentially zero couplings of the equatorial bridgehead proton (H-3) to the vicinal axial protons have been observed in the spectra of several 1,3-lactone-bridged cyclohexane derivatives.[179] The comparatively small values of 8.5 Hz for $J_{2,3}$ and $J_{3,4}$ might imply that H-2 and H-4, being α to the bridgehead positions and axially disposed are slightly tilted away from each other, in response to the constriction imposed on part of the six-membered ring by the carbon-oxygen



bridge between C-1 and C-5, as has been described for the substituents at the corresponding sites of bicyclo[3.2.1]octane derivatives.[180]

The formation of the bicyclic ether (155) as the main product is readily explained as resulting from participation of the C-5 hydroxyl group in the expulsion of nitrogen from the oxygen stabilised zwitterion (153) (Scheme 49). It cannot be ignored, however, that in the present case the alternative zwitterion (154) is also stabilised, by hydrogen bonding between the hydrogen atom of the hydroxyl group at C-5 and the negatively charged oxygen atom at C-1. The fact that the reaction via the species (153) is preferred seems to suggest that the steric course of the addition is governed not by the stability of the intermediate but rather by co-ordination of the approaching diazomethane molecule by the axial oxygen substituent prior to the formation of the zwitterion.

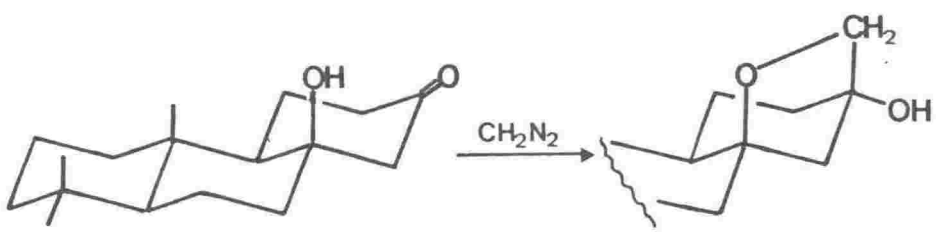
Neighbouring group participation in the reaction of ketones with diazomethane has been encountered before.[181,182] Considerable proportions (36%) of the tricyclic derivative (162) were, for instance, isolated when the pentos-3-ulose (161) was treated with this reagent[181] (Scheme 50).



(161) (162)

Scheme 50

A case very similar to the present one was reported by Temple,[182] who on treatment of 8-β-hydroxypodocarpan-13-one (163) with diazomethane obtained the ether (164) in 23% yield (Scheme 51). However, in both the above examples the major products were ring-expansion products.



(163) (164)

Scheme 51

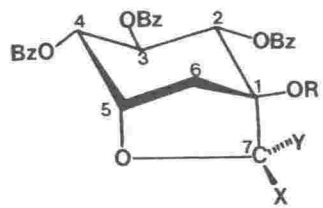
Compounds (155) and (158) were acetylated with acetic anhydride in pyridine to the corresponding acetates (156) and (159) in 92 and 93% yield, respectively (Scheme 49). Both products were crystalline and had ^{1}H n.m.r. spectra (Tables 5 and 6) consistent with the assigned structures. A striking feature in the spectrum of the acetylated bicyclic ether (156) was the down-field shift by 1 p.p.m. of H-6a with respect to its position in the spectrum of the unacetylated precursor (155), which suggests that the acetoxy group assumes the conformation shown, with H-6a in the deshielding zone of the ester carbonyl group.

TABLE 6

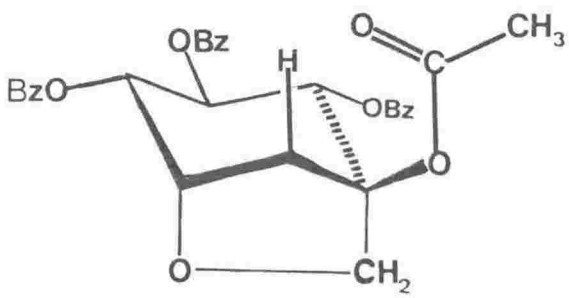
^{1}H n.m.r. Spectral Data for Bicyclic Derivatives

Compound	Chemical Shifts (δ) in p.p.m. downfield from TMS[a]									Coupling Constants in Hz							
	H-2	H-3	H-4	H-5	H-6$_e$	H-6$_a$	H-7$_{endo}$	H-7$_{exo}$	Others	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6_e}$	$J_{5,6_a}$	$J_{6,6'}$	$J_{7,7'}$	Others
91[b]	5.83d	6.42t	5.77dd	4.60brs	←2.88→		-	-	f	10	10	2.5	3[c]	4[c]	14[c]	-	
155[b]	5.63dd	6.16t	5.21d	4.58dd	2.46dd	2.13d	4.33d	3.69dd	∿3.2 (OH)[f]	8.5	8.5	0.5	6.5	0	12.5	8.5	$J_{2,7_{exo}}$ 1.6
156[b]	←6.1-6.2→		5.20d[e]	4.67d	2.51dd	3.08d	4.58d	3.85d	1.94 (OAc)[f]			0	6.5	0	12.5	8.5	
171[d]	←6.0-6.3→		5.25d	4.95d	←3.1→		6.82s	-	1.97 (OAc)[f]	7.5	7.5	0	5		-		
173[b]	5.80d	6.04t	5.21d	4.72d	2.61dd	2.12d	6.40s	-	3.1 (OH); 2.11 (OAc)[f]	8.5	8.5	0	7	0	12.5	-	
174[b]	←6.0-6.3m→		5.24d	4.89d	2.66dd	3.13d	6.70s	-	1.99 (OAc)[f]	7.5	7.5	0	7	0	13	-	
175[b]	←5.7-6.3m→		5.48dd[e]	5.13dd	3.42dd	2.69d	-	-	1.99 (OAc)[f]	8	8	1	7	0	12.5	-	

[a]Observed multiplicities: d, doublet; dd, pair of doublets; s, singlet; brs, broad singlet; t, triplet; m, multiplet. [b]Measured at 80 MHz in $CDCl_3$. [c]Coupling constants determined in $(CD_3)CO$. [d]Measured at 60 MHz in $CDCl_3$. [e]Virtual coupling. [f]The expected signals for 3 benzoate groups were also observed.



	R	X	Y
155	H	H	H
156	Ac	H	H
171	Ac	Br	H
173	Ac	OH	H
174	Ac	ONO_2	H
175	Ac	=O	

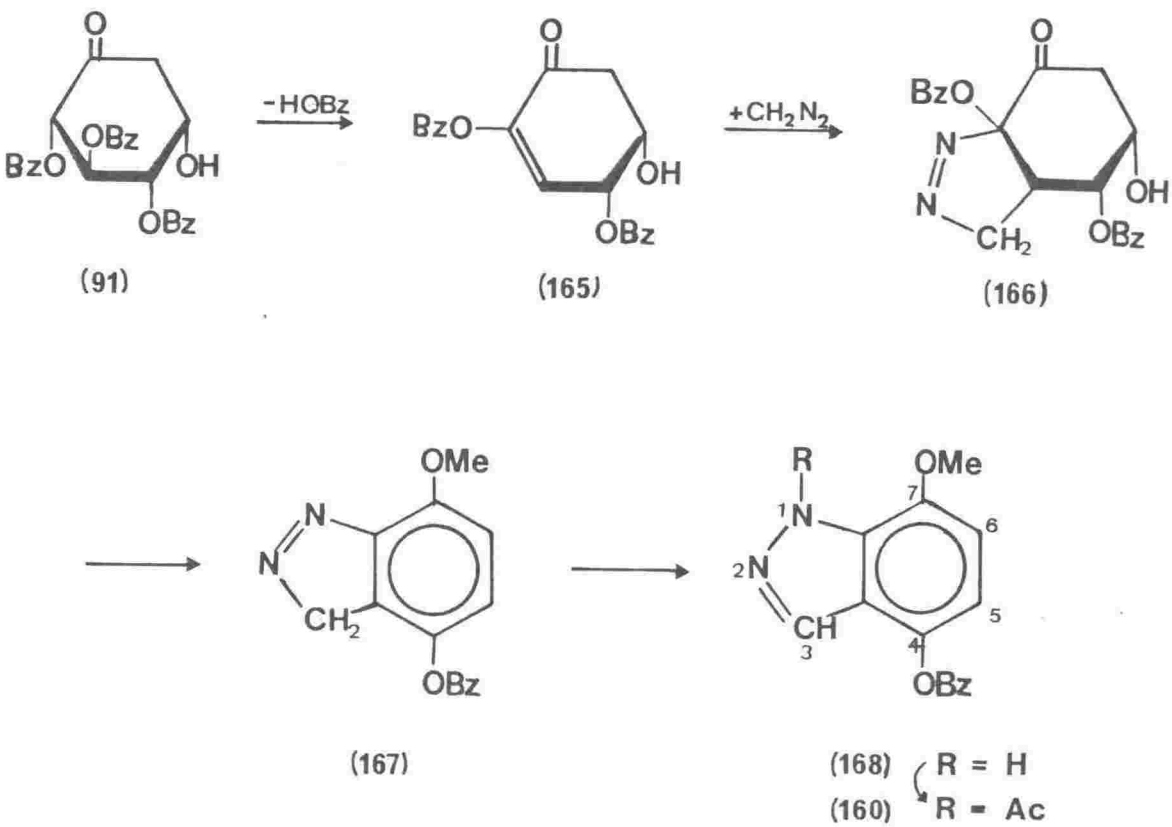


(156)

During the isolation of epoxide (158), crystallisation was very slow and inefficient. It was therefore decided to acetylate the combined mother liquors from repeated recrystallisations in order to recover some of the lost material in the form of the acetate (159). While the mother liquors had been essentially uniform by t.l.c., the acetylation product was however found to consist of several components with very similar, but distinctly different chromatographic mobilities. Fractionation on a column of silica gel, although incomplete, gave small amounts [2% each from the cyclohexanone derivative (91)] of three pure, crystalline products, which were identified as the acetylated epoxide (159), its epimer (157), and the 1H-indazole derivative (160) (Scheme 49). The ^{13}C n.m.r. spectrum of the acetate (157) showed the characteristic oxirane resonances at 49 and 56 p.p.m.,[173] and its ^{1}H n.m.r. spectrum (Table 5) differed from that of the alternative epoxide (159) only in the chemical shift of H-3 and of one of the oxirane methylene protons.

Tentative assignment of the (R) and (S) configurations to C-1 of the epoxides (157) and (159), respectively, was based on ^{1}H n.m.r. spectroscopy. In the spectrum of the epoxide (157) the two resonances of the downfield doublet of the AB system for H-7 and H-7' had widths at half height of *ca.* 3 Hz compared with a value of *ca.* 1.5 Hz for the resonances of the upfield doublet. This, according to Andrews *et al.*,[175] is indicative of a pseudo-axial methylene group in a spiro-epoxide fused to a cyclohexane ring. In the spectrum of the isomer (159) all four resonances for H-7 and H-7' had widths at half height of *ca.* 1 Hz. , Collins and Munashinghe[183] have used ^{13}C chemical shift differences to elucidate the configurations at tertiary alcoholic centres of branched chain pyranose derivatives. They found that

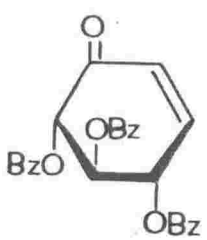
in geminally substituted compounds with equatorial hydroxyl groups and axial methyl or hydroxymethyl groups the exocyclic carbon atoms were shielded by 0.9-5.3 p.p.m. and the α, β, and γ ring carbon atoms were deshielded by 1.2-2.4 p.p.m. relative to the corresponding atoms of the epimers. Application of this method to the epoxides (157) and (159) gave inconclusive results, both C-6 and C-7 being more shielded (by 0.86 and 2.42 p.p.m., respectively) in isomer (159), C-1 having identical chemical shifts in both cases and the summation of the chemical shifts of the remaining ring carbon atoms (C-2—C-5) indicating that they were also more shielded in epoxide (159).



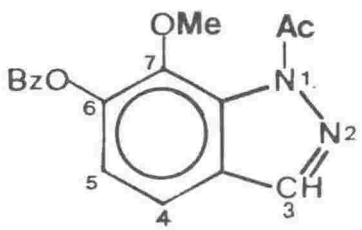
(91) (165) (166) (167) (168) (160)

Scheme 52

The indazole derivative (160) must have arisen from the 1,3-dipolar addition of diazomethane to an enone,[184] possibly enone (165), formed from the tribenzoate (91) by base-catalysed β-elimination of benzoic acid (*cf.* Chapter 4, p.59), with diazomethane acting as the base[163] (Scheme 52). It is thought that the initial addition product (166) aromatised by a mechanism similar to that shown in Scheme 45 (p.59), the resulting phenolic hydroxyl group being methylated by diazomethane, and that the 3H-indazole derivative (167) tautomerised to the stable 1H-isomer (168) which during treatment with acetic anhydride in pyridine was N-acetylated to the final product (160). The ^{1}H n.m.r. spectrum of this compound showed, in good agreement with published data for 1H-indazole,[185] an AB system for H-5 and H-6 at δ 7.02 and 6.90 with J_{AB} = 9 Hz consistent with an ortho-relationship, and a sharp singlet for H-3 at δ 7.99 , as well as the appropriate resonances for an acetoxy, a methoxy, and a benzoyloxy group. In the mass spectrum a consistent molecular ion with m/e 310 was observed. [1,3-Dipolar addition to enone (136) would, by a similar reaction sequence, afford the 1H-indazole derivative (169), which would fit the ^{1}H n.m.r. and mass spectral parameters equally well].



(136)



(169)

C. The Reaction of Diazomethane with the Fully Protected Tetrahydroxycyclohexanone Derivatives (140) and (141)

Because the free hydroxyl group at C-5 was able to participate in the reaction with diazomethane (*cf.* Scheme 49) only low yields of epoxides had been obtained from the tribenzoate (91). It was now hoped that epoxides would be available as the main products from the fully protected analogues (140) and (141). The tetrahydropyranyl derivatives (141) reacted extremely slowly with diazomethane in chloroform-ether but in the presence of methanol

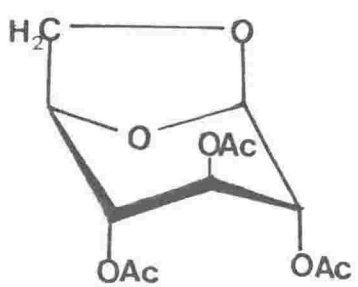
(10% v/v) - reported to accelerate the addition of diazomethane to ketones[164] - the reaction was complete after 24 h at +4 °C . As the main product (53% isolated), however, the bicyclic ether (155) was again obtained, showing that the acetal linkage within the protecting group was not stable under the conditions used.

The reaction of diazomethane with the 5-acetate (140), on the other hand, was very fast, all starting material being consumed within 2 h. T.l.c. showed that a mixture of at least five compounds had been formed, and the ^{1}H n.m.r. spectrum of the unfractionated products revealed that the acetoxy group was no longer present. It is thought that diazomethane, acting as a base,[163] had induced elimination to give an enone and, very likely, phenolic derivatives (*cf.* above and Chapter 4), which reacted further to give several products. An identical product mixture (by t.l.c.) was obtained when enone (136) was subjected to similar treatment with diazomethane.

FUNCTIONALISATION OF 1-O-ACETYL-5,7-ANHYDRO-2,3,4-TRI-O-BENZOYL-1-C-HYDROXYMETHYL-(1,3/2,4,5)-CYCLOHEXANEPENTOL (156) AT C-7

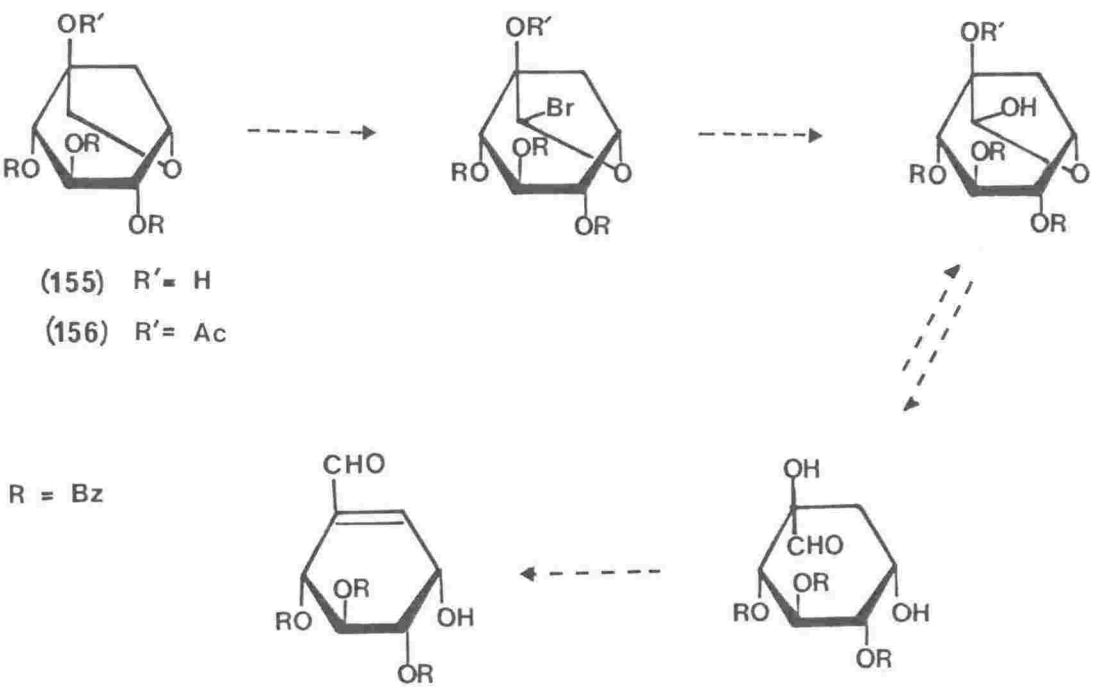
A. Photobromination

Since all the available cyclohexanone tribenzoates had failed to give spiro-epoxides in acceptable yields, the initial plan to prepare branched chain cyclitols by electrophilic ring-opening of epoxides (*cf.* Scheme 46) was abandoned and a way was sought instead to obtain the desired products via the cyclic ether (155) or its acetate (156). Ferrier and Furneaux[177] have found that tri-O-acetyl-1,6-anhydro-β-D-glucopyranose (170) can be functionalised at C-6 by photobromination and subsequent replacement of the bromine atom by a variety of nucleophiles. A similar reaction sequence involving bromination



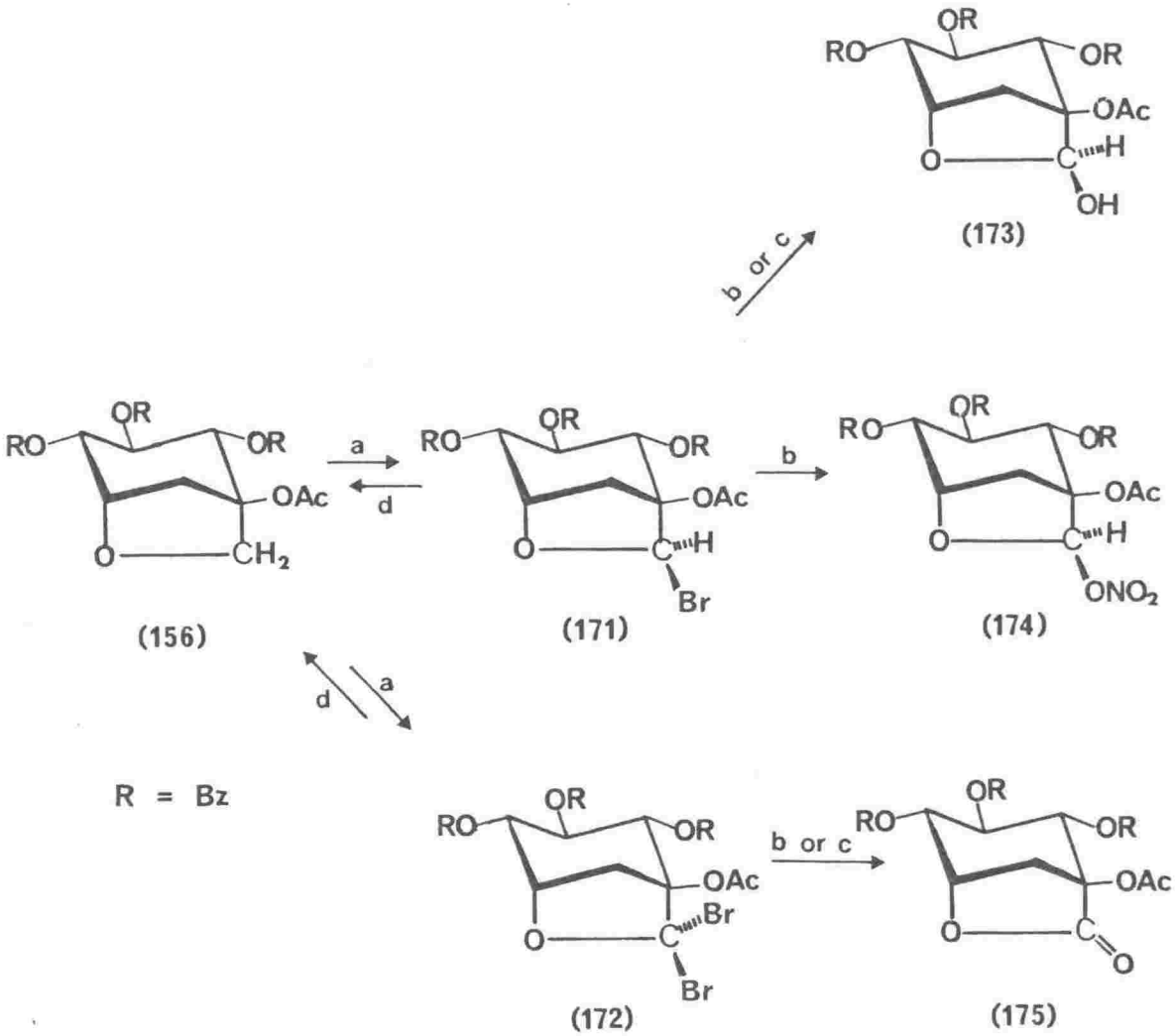
(170)

of the related bicyclic ethers (155) or (156) followed by hydrolysis would lead to intramolecular hemiacetals whose ring-opened forms on elimination of water or acetic acid would give a.rancinamycin III derivative (Scheme 53).



Scheme 53

Photobromination (*cf.* Chapter 3) of compound (155), which has a free hydroxyl group, gave no discrete product, but the acetate (156) was converted rapidly, by use of either bromine or NBS in carbon tetrachloride under bright, artificial light, to a chromatographically uniform and more mobile product, isolated as microcrystals in *ca.* 90% yield. This was shown by bromine analysis, and later by hydrolysis experiments (p.78), to consist of the bromide (171) and the dibromide (172) in a ratio of *ca.* 9:1 (Scheme 54). The dibromide could not be completely removed by recrystallisation or by column chromatrography, nor could its formation be prevented by changing the brominating conditions. (Prolonged reaction with a large excess of bromine increased the proportion of dibromide in the product to over 50%). The recrystallised bromination product gave a ^{1}H n.m.r spectrum (Table 6, p.71) in which resonances for the dibromide (172) were not



Reagents: a) Br_2 or NBS , hν ; b) $AgNO_3/H_2O$; c) SiO_2/H_2O ; d) Zn/HOAc

Scheme 54

apparent and which clearly showed that replacement of a hydrogen atom at C-7 had occurred, the remaining one being deshielded by 2.3 p.p.m., consistent with the introduction of a bromine atom at this site.[134,177] As the substitution had caused deshielding of H-5 and $H\text{-}6_e$ by 0.3 and 0.6 p.p.m., respectively, it is believed that the bromine atom occupied the 7-exo position, affecting the syn-related protons on the five-membered ring in a similar way as an axial bromine substituent in a six-membered ring affects the syn-axial

protons[109,130,177] (*cf.* Chapter 3). At the same time, the chemical shift of H-3 which, due to transannular interaction, would be affected by endo-substitution at C-7, had not changed on bromination, confirming the presence of an exo-bromide. In further support of the proposed (R) stereochemistry at C-7, the optical rotation of the bromination product was appreciably more positive ($[\alpha]_D$ +116°) than that of the starting material (156) ($[\alpha]_D$ +51°), the configuration at C-7 of the exo-bromide (171) being comparable to that at the anomeric centres of α-D- or β-L-furanosyl halides, which are known to be more dextrorotatory than their 1-deoxy analogues.[186] This photobromination thus proceeded in a manner very similar to that of the anhydro sugar (170)[177] by preferential abstraction - most likely - of the more accessible exo-hydrogen atom on the five-membered ring and substitution by bromine from the same side. Confirmation of the general structure of the bromination products (171) and (172) and proof that no rearrangement had occurred during the substitution followed from the generation of the starting material (156) on reduction with zinc-acetic acid.

B. Hydrolysis of the Photobromination Products

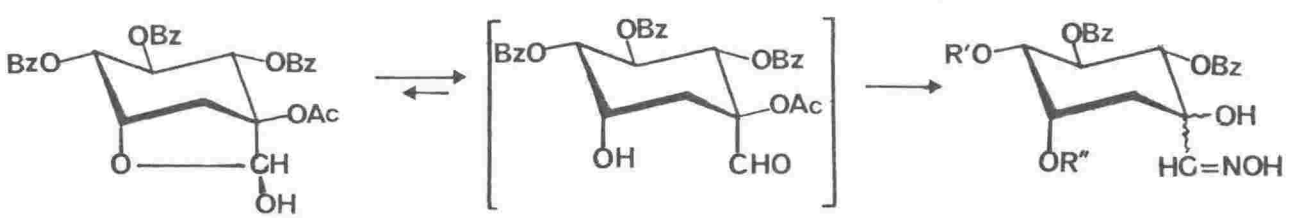
Treatment of the crude mixture of bromides (171) and (172) with silver nitrate in aqueous acetone gave three products (Scheme 54) which were separated by column chromatography. The two chromatographically less mobile compounds were the hemiacetal (173) and the lactone (175), *i.e.* the expected hydrolysis products. The former was obtained in 76% yield in microcrystalline form. Its ^{1}H n.m.r. spectrum (Table 6) showed a sharp singlet at δ 6.40. for the methine proton at C-7 and a broad singlet at δ 3.1, exchangeable with D_2O, for the hydroxyl group. The lactone (175), isolated as long needles in 10% yield, was identified by the lack of resonances for C-7 protons in its ^{1}H n.m.r. spectrum (Table 6) and by the occurrence of a strong absorption band at 1780 cm^{-1} in its i.r. spectrum which is characteristic of a γ-lactone. The third component was much faster on t.l.c. plates than the two hydrolysis products just described; it crystallised in a yield of 9% and had a ^{1}H n.m.r. spectrum (Table 6) very similar to those of the bromide (171) and the hydroxide (173) with a sharp singlet for H-7 at δ 6.70. A compound with the same bicyclic structure but with different functionality at C-7 was therefore indicated and the presence of a band at 1630 cm^{-1} in its i.r. spectrum and elemental analysis led to its identification as the nitric acid ester (174).

Compounds (173) and (174) were both assigned the (7S) (or exo-)

stereochemistry on the basis of their ^{1}H n.m.r. spectra [slight deshielding of H-5 and H-6_e with respect to their positions in the spectrum of the C-7-unsubstituted precursor (156), no change in the chemical shift of H-3] and their optical rotations {$[\alpha]_D$ +75° and +61°, respectively, *cf.* +51° for derivative (156)}; *i.e.* the substitution had taken place with retention of configuration at C-7.

The isolation of the nitrate (174) in appreciable proportions seemed at first surprising, since nitrate ions are, as a rule, considered too weakly nucleophilic to compete successfully with hydroxylic solvents in substitution reactions. However, given that in the present case an unusually small concentration of water was used ($[NO_3^-]/[H_2O]$ *ca.* 1:50, *cf.* Experimental) and assuming a nucleophilic reactivity of *ca.* 10, relative to water, for nitrate ions[187] (a value calculated from the relative rates of reaction of nitrates and water with methyl bromide) the formation of the nitrate (174) and the hydroxy derivative (173) in a ratio of 1:9 is not unexpected. In subsequent hydrolysis experiments silver carbonate or, alternatively, silica gel were used instead of silver nitrate; thus the desired hemiacetal (173) became available in 80% yield from the unpurified bromination products with the lactone (175) as the only by-product, separation from which, however, required chromatography.

That the hemiacetal (173) was in equilibrium with its ring-opened aldehydo form (176) (Scheme 55) - at least in alcoholic solution - became apparent when on addition of ethanolic 2,4-dinitrophenylhydrazine bright



(173) (176) (177) R' = H , R" = Bz
(178) R' = Bz , R" = H

Scheme 55

yellow crystals slowly deposited. These could be recrystallised only with difficulty, but the oximes (177) and (178), obtained as a *ca.* 1:1 mixture on heating compound (173) with hydroxylamine hydrochloride in refluxing ethanolic pyridine (Scheme 55), proved very satisfactory in this respect. From a hot, saturated solution in chloroform-ethanol the two isomers crystallised as a mixture, but slow crystallisation from a dilute ethanolic solution gave a small pure sample of derivative (177). Its ^{1}H n.m.r. spectrum (Table 7) showed two sharp singlets, one exchangeable with D_2O at δ 10.22 for the hydroxyl proton of the oximino group, the other at δ 7.99 for H-7. The coupling constants for the ring protons were very similar to those of the cyclohexanone derivative (91) and the epoxides (157)-(159) (Table 5) in keeping with the presence of an unbridged cyclohexyl ring. The lack of a three proton singlet near δ 2 indicated loss of the acetyl group, and from the appearance of a doublet of doublets at δ 4.44 with splittings of 10 and 3.5 Hz ($J_{3,4}$ and $J_{4,5}$, respectively) it was concluded that benzoyl migration from C-4 to C-5 had taken place. The signal at δ 4.44 (H-4) collapsed to a doublet on irradiation of the proton resonating at δ 5.7 (H-5), and at the same time the two double doublets of H-6 and H-6' were reduced to an AB system, confirming that O-5 and not O-4 was benzoylated. Acyl group migration in basic media, especially between an axial and an equatorial hydroxyl group, is a well known phenomenon in carbohydrate[188] as well as in inositol[189] chemistry.

The ^{1}H n.m.r. spectrum of the second product was obtained by subtracting the resonances for compound (177) from the spectrum of the mixed oximes. It contained sharp singlets for NOH and H-7 at δ 10.37 and 8.23, respectively. H-4 resonated at δ 5.54 and H-5 at δ 4.65, consistent with the unrearranged oxime structure (178).

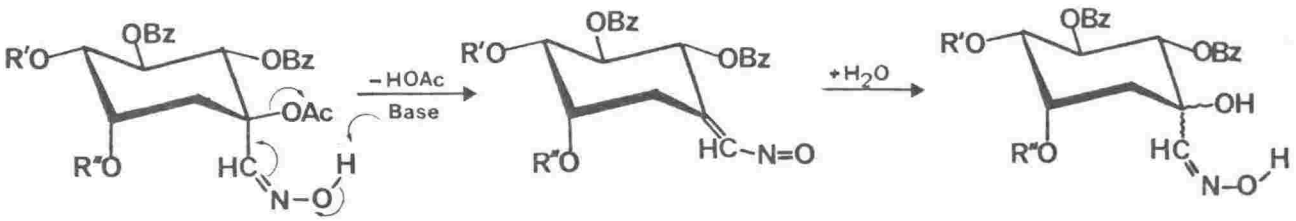
TABLE 7

^{1}H n.m.r. data for Oximes

	Chemical Shifts (δ) in p.p.m. from TMS[a,b,c]								Coupling constants in Hz					
Compound	H-2	H-3	H-4	H-5	H-6	H-6'	H-7	N-OH	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
177	5.69d	5.98t	4.44dd	5.7m	2.72dd	2.34dd	7.99s	10.22s	9.5	9.5	3.5	4	3	15
178	5.76d	6.14t	5.54dd	4.6brs	◁—— 2.41m ——▷		8.23s	10.37s	10	10	3			

[a]Observed Multiplicities: d, doublet; dd, pair of doublets; s, singlet; brs, broad singlet; t, triplet; m, multiplet. [b]Both spectra measured at 80 MHz in $(CD_3)_2CO$. [c]Additional resonances for both compounds: 7.1-8.1 (3xOBz); *ca.* 5.0 (2 X OH).

Loss of the tertiary acetyl group at C-1 might conceivably be the result of simple hydrolysis; the possibility of an alternative mechanism, shown in Scheme 56, must, however, also be considered.

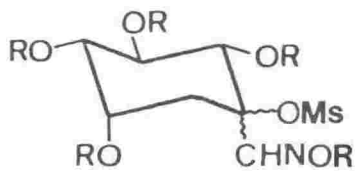


R' = H , R" = Bz, or
R' = Bz, R" = H

Scheme 56

Lemieux et al.[190] found that the 3-acetoxy groups of 2-deoxy-2-oximino-hexopyranose derivatives are susceptible to nucleophilic displacement by such an elimination-addition process involving a nitrosoalkene intermediate. The stereochemistry at C-1 of the oximes (177) and (178) is therefore uncertain.

Unfortunately, elimination of water from these oximes to form cyclohexenecarbaldehyde derivatives is not a viable proposition since under the reaction conditions necessary for dehydration (e.g. strong acid, $POCl_3$/pyridine) the oxime group undergoes the Beckmann rearrangement. A longer route via the pentabenzoate-mesylate (179) was contemplated, as was the trapping of the aldehyde (176) by reagents



R = Bz

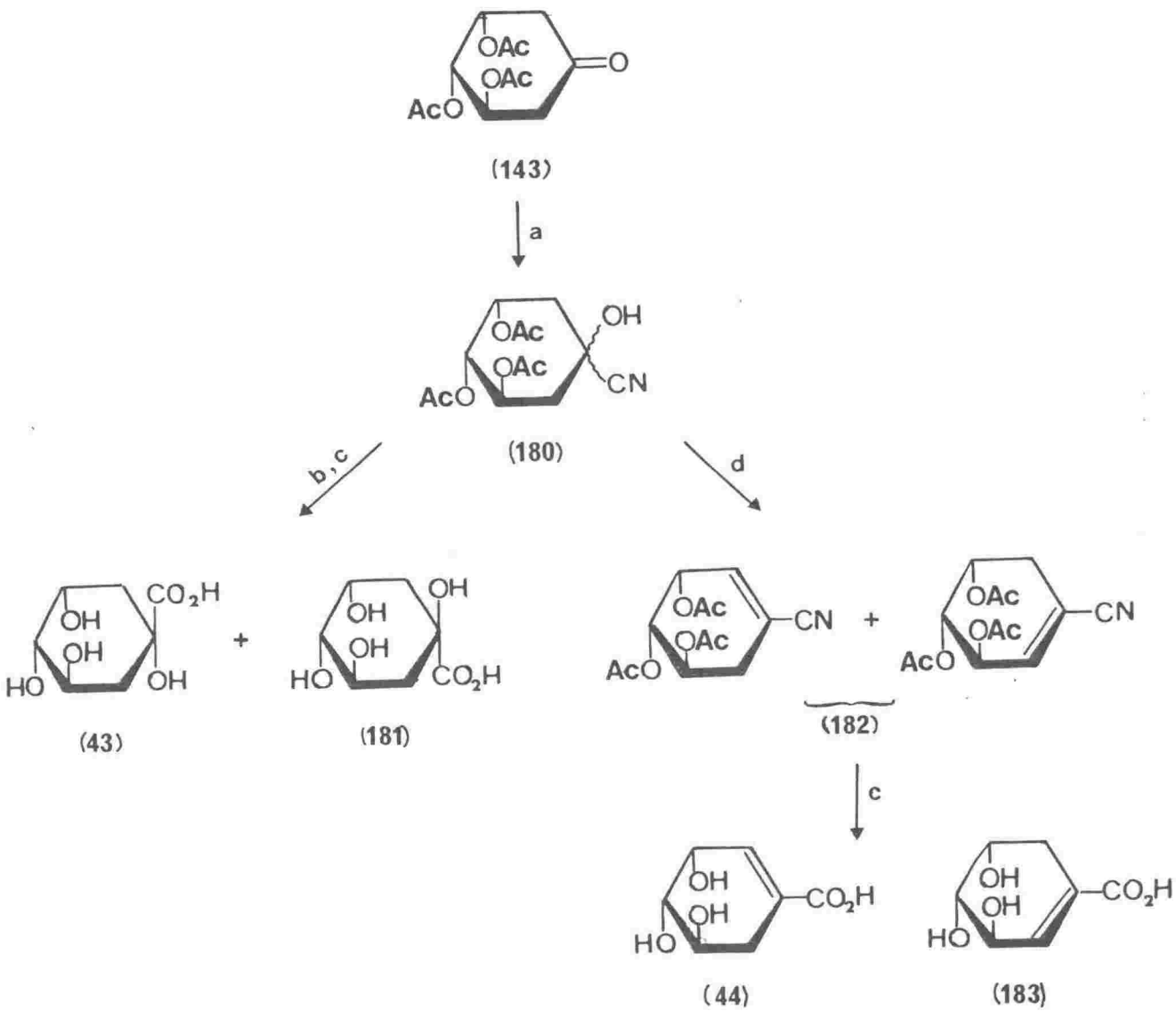
(179)

other than hydroxylamine hydrochloride (e.g. N,N-diphenyl-1,2-diamino-ethane). Preliminary tests for both alternatives were, however, not encouraging, and it seemed more worthwhile to investigate the introduction of chain-branching by different methods, especially by means of the cyanohydrin synthesis.

CHAPTER SIX

INTRODUCTION OF CHAIN BRANCHING INTO TETRAHYDROXYCYCLOHEXANONE DERIVATIVES BY WAY OF CYANOHYDRINS

The cyanohydrin addition reaction has been used to prepare derivatives of quinic acid (43) and shikimic acid (44) (*cf.* Chapter 1, p.13) from the triacetoxycyclohexanone (143) by Grewe and Vangermain[191] and several other authors.[192-194] A three step reaction sequence involving addition of hydrogen cyanide to the ketone (143), dehydration of the resulting cyanohydrins (180) to the cyclohexenecarbonitriles (182) and hydrolysis gave shikimic acid (44)

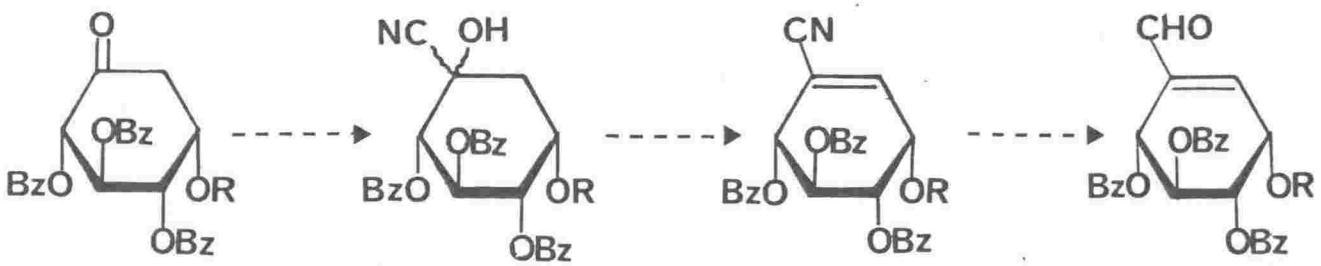


Reagents: a $NaHSO_3$, KCN; b Ac_2O/py; HBr/HOAc; N_2O_3; c KOH/H_2O; d TsCl or $SOCl_2$ or $POCl_3$/py

Scheme 57

and epi-shikimic acid (183); alternatively, the cyanohydrins (180) were hydrolysed to quinic acid (43) and epi-quinic acid (181) (Scheme 57). Claims that the hydrogen cyanide addition[190-192] as well as the elimination of water[191,193,195] were stereospecific, resulting in the formation of quinic acid (43) and shikimic acid (44) free of the corresponding epi-products (181) and (183), have been questioned by Snyder and Rapoport[194] who found in a detailed investigation that considerable proportions of the unwanted isomers were produced in both reaction steps.

A possible synthesis of rancinamycin derivatives (*cf.* Chapter 1, p.13) by a route similar to the above shikimic acid synthesis, from the 2-deoxy-inosose tribenzoates (140) and (141) is outlined in Scheme 58. Since the tertiary hydroxyl group of the cyanohydrin will subsequently be eliminated, the stereochemistry of the hydrogen cyanide addition is immaterial, and the presence of a benzoyloxy group at C-2 should disfavour the loss of a proton from that position, elimination in the required direction of C-6 thus being preferred.[196]



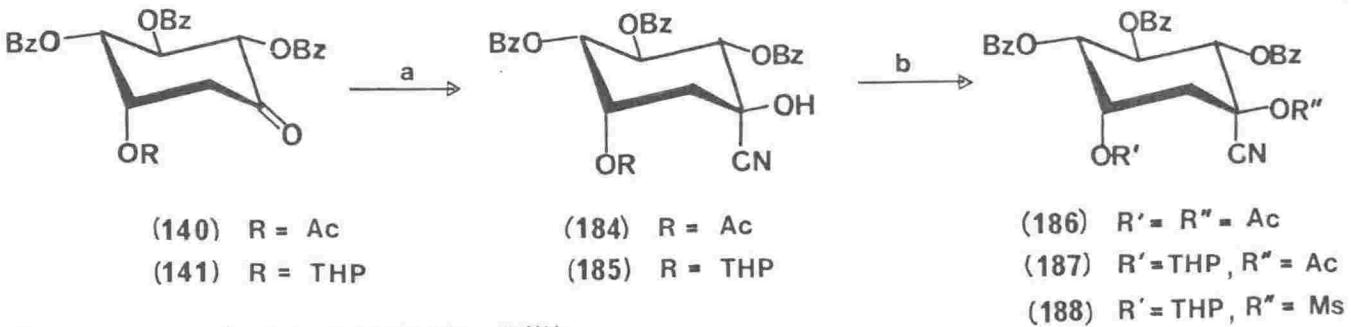
(140) R = Ac
(141) R = THP

Scheme 58

PREPARATION OF CYANOHYDRINS FROM THE 2-DEOXYINOSOSE DERIVATIVES (140) AND (141)

Grewe and Vangermain[191] prepared the cyanohydrins (180) in aqueous medium via the sodium bisulphite addition products, a method which was unsuitable for use with the water insoluble tribenzoates (140) and (141). However, hydrogen cyanide exchange with acetone cyanohydrin[197] gave good results, in particular with the tetrahydropyranyl ethers (141) which afforded a crystalline mixture of the cyanohydrins (185) in 80% yield after chromatography (Scheme 59). From the acetate (140), the corresponding product (184) was obtained in 60%

yield as a fine powder; t.l.c. indicated that in this case cyanohydrin formation was accompanied by a side reaction, probably β-elimination



(140) R = Ac
(141) R = THP

(184) R = Ac
(185) R = THP

(186) R' = R" = Ac
(187) R' = THP, R" = Ac
(188) R' = THP, R" = Ms

Reagents : a Acetone cyanohydrin, $EtNH_2$;
b Ac_2O or MsCl/py

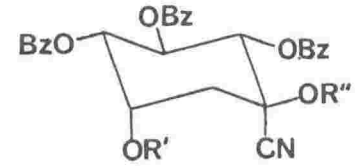
Scheme 59

(*cf.* Chapter 4, p.59) as slightly basic reaction conditions were required to catalyse the hydrogen cyanide exchange.

Neither of the two cyanohydrins (184) or (185) could be recrystallised; for better characterisation, they were therefore converted to the stable, recrystallisable tertiary acetates (186) and (187) by use of acetic anhydride in pyridine (Scheme 59). Although the i.r. spectra of compounds (184)-(187) were all devoid of absorption bands near 2240 cm^{-1}, which are characteristic of nitriles, the presence of this functional group was clearly indicated by ^{13}C n.m.r. spectroscopy, resonances appearing at δ 119 in the spectra of the cyanohydrins (184) and (185) and at δ 115 in those of their O-1-acetylated analogues (186) and (187). It has been pointed out by several workers,[198,199] that oxygen-containing substituents bonded to the α-carbon atoms can reduce the intensity of nitrile stretching absorptions below the limit of detection. The ^1H n.m.r. spectra of the derivatives (184) and (185) (Table 8) showed slight shielding of most ring protons with respect to their positions in the spectra of the starting ketones (140) and (141). In the spectra of the tertiary acetates (186) and (187), however, H-2 and $H\text{-}6_{axial}$ were deshielded by 0.3 and 0.6 p.p.m., respectively, which suggests the equatorial disposition of the acetoxy group. Similar deshielding of H-2 and of the axial H-6 was observed on acetylation of the equatorial, tertiary hydroxyl group at C-1 of the bicyclic ether (155) (*cf.* Chapter 5, p.70).

TABLE 8

^{1}H N.m.r. Spectroscopic Data for Cyanohydrins



Compound	R′	R″	Chemical Shifts (δ) in p.p.m. from TMS[a,b] H-2	H-3	H-4	H-5	H-6	H-6'	Others	Coupling Constants in Hz $J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
184	Ac	H	6.29t ◁——5.45-5.9——▷				2.94dd	2.25dd	7.1-8.1 (OBz); 2.21 (OAc)	10	10	2	4	2.5	15
185	THP	H	5.60d 5.59d	6.35t 6.27t	5.50dd 5.44dd	4.5m	2.86dd	2.20dd	7.1-8.1 (OBz)[c]	10	10	3	3.5	2.5	15
186	Ac	Ac	5.93d	6.31t	5.49dd	∿5.7	3.48dd	2.20dd	7.1-8.1 (OBz); 2.05, 2.21 (OAc)	10	10	3	4	3	15
187	THP	Ac	5.93d 5.90d	6.44t 6.36t	5.42dd	4.55m	3.53dd	2.15dd	7.1-8.1 (OBz); 2.05 (OAc)[c]	10	10	2.5	4	3	15
188	THP	Ms	5.92d 5.88d	6.39t 6.32t	5.45dd 5.42dd	4.55m	3.45dd	2.55dd	7.1-8.1 (OBz); 3.07 (OMs)[c]	10	10	3	4	2.5	15
140	Ac	-	6.34t ◁——5.7-5.95——▷				◁——2.99m——▷		2.13 (OAc)	10	10				
141	THP	-	5.87d	6.40t 6.32t	5.77dd	4.6m	◁——2.85m——▷			10	10	2			

[a]All spectra measured at 80 MHz in $CDCl_3$; [b]Observed multiplicities: d, doublet, dd, pair of doublets, m, multiplet, t, triplet. [c]The appropriate resonances for the tetrahydropyranyl group were also observed.

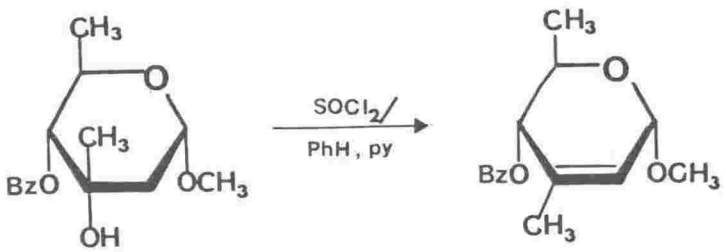
In addition, the crystalline methanesulphonates (188) were prepared in 88% yield from the cyanohydrins (185) by treatment with methanesulphonyl chloride and pyridine in dichloromethane. These derivatives were readily identified by a three-proton singlet at δ 3.07 in their ^{1}H n.m.r. spectrum (Table 8, p.86), which was otherwise very similar to that of the tertiary acetates (187), and by the characteristic sulphonate absorption bands at 1190 and 1380 cm^{-1} in the i.r. spectrum.

Compounds (185), (187), and (188) were each shown by t.l.c., ^{1}H and ^{13}C n.m.r. spectroscopy to consist of two components. These were thought to be isomers with different configurations at C-2 of the tetrahydropyranyl group, since they were derived from a mixture of two ketones with different stereochemistry in this ring. There is no evidence that further isomers, differing in their stereochemistry at C-1 of the cyclohexyl ring, were present. Consistent with this, the 5-O-acetylated analogues (184) and (186) were both homogeneous by t.l.c. and ^{1}H and ^{13}C n.m.r. spectroscopy. Under the reaction conditions used to prepare the cyanohydrins (184) and (185), formation of the thermodynamically more stable products may be assumed. As the steric requirements of the nitrile group are considerably smaller than those of the hydroxyl group (the reported values for the conformational free energies, *i.e.* the difference in free energy between an axially and an equatorially substituted cyclohexane derivative, are 0.8 and 2.5-3.8 kJ $mole^{-1}$, respectively, for CN and OH[200]) products with the (R) stereochemistry at C-1 are to be expected. (^{1}H N.m.r. spectroscopic evidence in support of this conclusion has been mentioned above). In keeping with this, a cyanohydrin with the *arabino*-configuration was formed exclusively from methyl-4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose under conditions of thermodynamic control.[201]

ATTEMPTED DEHYDRATION OF THE CYANOHYDRINS (184) AND (185)

Several dehydrating reagents have been used, with good results, in the synthesis of shikimic acid (44) from the cyanohydrins (180) (*cf.* Scheme 57). Dangschat and Fischer,[202] for example, used toluene-*p*-sulphonyl chloride at

+50°C, while Snyder and Rapoport[194] employed phosphorus oxychloride in pyridine at room temperature or, alternatively, sulphuryl chloride in pyridine at -78°C. In a similar way, Dyong and Schulte[196] prepared the alkene (190) from the tertiary alcohol (189) (Scheme 60) by means of thionyl chloride in benzene-pyridine at +5°C. When applied to the present cyanohydrins



(189) (190)

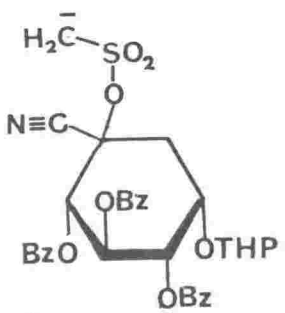
Scheme 60

(184) and (185), all these reagents failed to give the desired dehydration products. At the specified reaction temperatures and after considerable times, the unchanged starting materials were recovered, whereas use of more forcing conditions (higher temperatures, longer reaction times) led to degradation without formation of discrete products. Similarly, on heating the acetate (184) in benzene in the presence of toluene-*p*-sulphonic acid with azeotropic removal of water, no reaction, or, with higher concentrations of acid, complete decomposition took place.

Since the tertiary alcohols (180) and (189) were dehydrated smoothly by the above reagents, the stability of the cyanohydrins (184) and (185) under identical conditions must be due to the simultaneous presence of a nitrile group at C-1 and a benzoyloxy group at C-2.

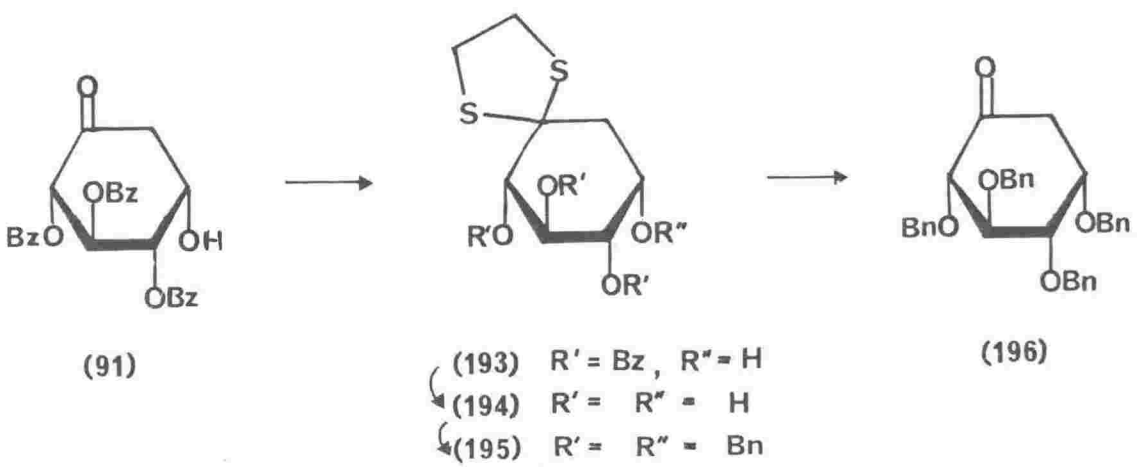
Possibly, the substituent at C-2 blocks the access of the reagents to the hydroxyl groups at C-1, thereby impeding their conversion into good leaving groups. Evidence in support of this argument is provided, for example, by the recovery of starting material, rather than formation of a tosylate, under the elimination conditions of Dangschat and Fischer[202] (toluene-*p*-sulphonyl chloride/pyridine at 50°C). However, the mesylates (188), whose preparation presented no difficulties, were stable when heated in pyridine at +80°C for three days. This seems to indicate that failure to eliminate is related to the strongly electronegative properties of the nitrile and benzoyloxy groups which prevent the formation of carbonium ions at C-1.

When the mesylates (188) were treated with DBU in DMF at room temperature for 16 h, the THP-ethers (191) of a single product were obtained. These lacked resonances for methanesulphonyl groups in their ^{1}H n.m.r. spectrum and for nitrile carbons in their ^{13}C n.m.r. spectrum. The remainder of both spectra indicated, however, that a saturated cyclohexyl ring with oxygen substituents at C-2—C-5 and with, essentially, the same conformation as that of the precursors, was still present. Elemental analysis for C, H, N, and S showed that, formally, addition of water to the starting material had taken place. It is believed that the base (DBU) abstracted a proton from the methanesulphonyl group to form the carbanion (192) which then attacked the nitrile group, but the exact nature of the final product has not been established. Fraser-Reid *et al.*[203] reported similar deprotonation of methanesulphonate ester derivatives of carbohydrates.



(192)

Throughout this work, progress has been hampered by side-reactions, most of which might be prevented by replacement of the ester protecting groups on the ring hydroxyls by less electronegative, less base-labile functions. It is therefore proposed to repeat some of the work described in Chapters 5 and 6 using the perbenzylated tetrahydroxycyclohexanone (196), which ought to be available from the tribenzoate (91) via the dithianes (193)-(195) (Scheme 61).



(91)

(193) R' = Bz, R" = H
(194) R' = R" = H
(195) R' = R" = Bn

(196)

Scheme 61

CHAPTER SEVEN

EXPERIMENTAL

GENERAL METHODS

Melting points were determined using a Reichert Thermopan apparatus and are uncorrected.

Optical rotations were measured for solutions within the concentration range 0.5-2.0 g/100 cm^3 in chloroform (unless otherwise stated) in a 1 dm tube using a Hilger standard polarimeter.

Elemental analyses (C, H, N, S) were performed by Professor A.D. Campbell and associates, University of Otago.

Total bromide was determined by heating the compounds with silver nitrate and fuming nitric acid in a sealed tube at 240°C for 24 h.[204] After dilution of the reaction mixture with water, the precipitated silver bromide was collected and weighed. Ionisable bromide was determined by addition of ethanolic silver nitrate solution (2%) to solutions of the bromo compounds in ethanol and weighing of the precipitated silver bromide.

Mercury was determined by passing hydrogen sulphide gas through a solution of the mercury(II) compounds in benzene or chloroform and weighing of the precipitated mercury(II) sulphide.

Infrared spectra were recorded in nujol mulls, in dichloromethane, or as thin films on Unicam SP 200 or SP3 100 spectrophotometers.

Nuclear magnetic resonance spectra were determined in deuterochloroform (unless otherwise specified) with TMS as an internal standard on a Hitachi-Perkin Elmer R20 60 MHz (^1H) or on a Varian FT-80A (79.56 MHz for ^1H, 20 MHz for ^{13}C) instrument. Chemical shifts are reported as δ values in parts per million relative to TMS (δ 0.00).

Low resolution mass spectra were recorded on a Micromass 12F instrument at 70 eV (unless otherwise stated).

Organic solutions were dried after processing over sodium sulphate and evaporated under reduced pressure at T <50°C.

Solvents were dried and purified according to the methods given by Perrin *et al.*;[205] the light petroleum used was the fraction with boiling range 60-68°C.

Chromatography

Chromatography columns were packed with Merck silica gel 60 (70-230 mesh) or Riedel de Haen silica gel S (0.063-0.2 mm).

Preparative thin layer chromatography was performed on 1 m X 20 cm glass plates coated to a thickness of 0.75 mm with Merck silica gel GF_{254}; for analytical thin layer chromatography (t.l.c.) glass plates of 10 cm length were used, coated to a thickness of 0.25 mm with Merck silica gel GF_{254}. Components were located under an ultraviolet lamp at 254 nm and/or by spraying with ethanol-sulphuric acid-anisaldehyde (93:5:2) followed by heating.

The following solvent mixtures (v/v) were employed:

A	light petroleum-ether	1:1
B	light petroleum-ether	1:2
C	light petroleum-ether	1:3
D	light petroleum-ethyl acetate	2:1

Photobrominations

(a) With bromine. The substrate and bromine were heated in refluxing carbon tetrachloride over one to three (depending on the volume of the solution) 275 W heat lamps. After the specified reaction time the solvent and excess bromine were removed under reduced pressure.

(b) With NBS. The substrate and NBS were heated in refluxing carbon tetrachloride over heat lamps as above. The cooled reaction mixture was filtered and the filtrate was washed with small volumes (x2) of water. The organic phase was dried and the solvent was removed under reduced pressure.

Reduction with zinc and acetic acid

To a stirred solution of sodium acetate (2x g) in aqu. acetic acid (10x cm^3, 1:1) at 0°C a solution of copper sulphate (0.2x g) in a small volume of water was added, followed by zinc dust (2x g) and a solution of the bromo compound (x g) in acetic acid (5x cm^3). Stirring was continued at room temperature for the specified time. The reaction mixture was filtered, the filtrate was extracted with three portions of chloroform, and the chloroform

extracts were washed successively with water, saturated sodium hydrogen carbonate, and water, dried and evaporated.

Acetylations

Unless otherwise stated, acetylations were performed with acetic anhydride in pyridine at room temperature for 16 h. The reaction mixtures were poured onto ice and the products, if solid, were collected by filtration. Oily products were isolated by extraction into chloroform. The chloroform extracts were washed with water (3x) and dried. After removal of the solvent toluene was added and removed under reduced pressure.

Diazomethane

Solutions of diazomethane in ether were prepared from *N*-nitrosomethylurea[206] following the procedure of Arndt[207] but were used undistilled after drying over potassium hydroxide pellets for several hours. Solution of diazomethane in dichloromethane were prepared in an analogous manner.

PREPARATION OF COMPOUNDS

1,2,3,4,6-Penta-O-benzoyl-β-D-glucopyranose (101) was prepared by the method of Ness *et al.*[208]

1,2,3,4,6-Penta-O-acetyl-β-D-glucopyranose (102) was prepared by the method of Fischer.[209]

Methyl 2,3,4-tri-O-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside (98).- To a cooled, stirred solution of methyl-α-D-glucopyranoside (97) (9.0 g) and NBS (16.5 g, 2.0 mol. equiv.) in dry DMF (450 cm^3), triphenyl phosphine (24.0 g, 2.0 mol. equiv.) was added in portions over 1 h. The light yellow solution was kept at 50°C for 2.5 h, cooled to room temperature and evaporated to a thick syrup, which was dissolved in chloroform (150 cm^3) and extracted with water (3x 50 cm^3). The aqu. extract was neutralised with 1R 45 (OH^-) ion exchange resin and evaporated. The crude product obtained was acetylated with acetic anhydride (40 cm^3) in pyridine (60 cm^3). Recrystallised (x2) from ethanol the acetylated bromide (98) (9.8 g, 61%) had m.p. 114-116°C, $[\alpha]_D$ + 126.3° [Lit.,[210] m.p. 117°C, $[\alpha]_D$ + 126° (pyridine)]. A sample further recrystallised had m.p. 117-118°C; its ^1H n.m.r. spectrum was in good agreement with published data.[111]

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (99).- Methyl tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside (98) (5.0 g) and sodium iodide (25 g, 5.7 mol. equiv.) were heated in refluxing acetone (150 cm^3) for 16 h. The solvent was removed and the residue was dissolved in chloroform (150 cm^3). After washing with saturated aqu. sodium thiosulphate (2x 20 cm^3), the solution was dried and evaporated to a solid which was recrystallised (x2) from methanol to give the iodide (99) (5.1 g, 90%), m.p. 147-149°C, $[\alpha]_D$ + 116° (lit.,[107] m.p. 150-151°C, $[\alpha]_D$ + 116.2°); ^1H n.m.r. δ 2.00, 2.05, and 2.07 (9 H, 3 s, 3x OAc), 3.0-3.4 (2 H, m, H-6,6'), 3.48 (3 H, s, OMe), 3.79 (1 H, m, H-5), 4.75-5.1 (3 H, m, H-1,2,4), 5.47 (1 H, t, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3).

Methyl 2,3,4-tri-O-acetyl-6-deoxy-α-D-xylo-hex-5-enopyranoside (96).- (a) *By dehydroiodination with silver fluoride.* Methyl tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (99) (0.50 g) and silver fluoride (0.75 g, 5 mol. equiv.) in dry pyridine (3 cm^3) were stirred for 24 h at room temperature. Ether (60 cm^3, in 3 portions) was added to extract the organic material. The filtered solution was washed with aqu. sodium thiosulphate (20 cm^3) and water (2x 20 cm^3) and dried over sodium sulphate. Removal of the ether gave a yellow oil which crystallised from light petroleum. The product (96) (2.7 g, 75%), recrystallised (x2) from the same solvent, had m.p. 97-98°C, $[\alpha]_D$ + 116° [lit.,[107] m.p. 100-101°C, $[\alpha]_D$ + 117°]; its ^1H n.m.r. spectrum was identical to that published.[108,111]

(b) *By dehydroiodination with DBU.* A solution of the iodide (99) (3.0 g) and DBU (2.0 g, 2 mol. equiv.) in dry DMF was left at room temperature for 3 days. The solvent was evaporated, the oily residue was dissolved in chloroform (75 cm^3), and the chloroform extract was washed with water (20 cm^3), dil. hydrochloric acid (20 cm^3), water (2x 10 cm^3), and dried. Removal of the solvent gave a thick syrup which was extracted with boiling light petroleum (4x 25 cm^3). The alkene (96) (1.50 g, 71%) crystallised on concentration of the light petroleum extract to *ca.* 30 cm^3. Recrystallised (x2) from the same solvent it had m.p. 97-100°C, $[\alpha]_D$ + 117°.

Methyl 2,3,4-tri-O-acetyl-6-O-[(benzylthio)thiocarbonyl]-α-D-gluco-pyranoside (100).- A solution of methyl α-D-glucopyranoside (97) (6.0 g) in dry pyridine (25 cm^3) was added to a stirred suspension of powdered sodium hydroxide (1.4 g, 1.1 mol. equiv.) in dry pyridine (25 cm^3). The mixture was heated under reflux for 4 h, cooled to 0°C and treated with carbon

disulphide (3.1 g, 1.3 mol. equiv.). After 16 h stirring at room temperature, benzyl bromide (5.3 g, 1 mol. equiv.) and, after a further 3 h, acetic anhydride (15 cm^3) were added. The resulting dark brown solution was kept at room temperature for 24 h and then poured onto ice (200 g); the mixture was extracted with chloroform (3x 50 cm^3), the chloroform extract was washed with dil. hydrochloric acid, water, aqueous sodium bicarbonate, and water (25 cm^3 each), dried and evaporated to a dark syrup. This was dissolved in ethanol, treated with charcoal and seeded with crystals obtained by preparative t.l.c. (R_F 0.5-0.6, eluting with solvent D). Recrystallised (x2) from ethanol, the dithiocarbonate (100) (3.0 g, 20%) had m.p. 105-106°C, $[\alpha]_D$ + 106° [lit.,[108] m.p. 105-107°, $[\alpha]_D$ + 107°]; the ^1H n.m.r. spectrum was indentical to that published.[108]

From the preparative t.l.c. plate used to obtain the above seed crystals, the main by-product, methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (*ca.* 30%), was isolated. Recrystallised (x2) from aqu. methanol, it had m.p. 102-103°C [lit.[211] m.p. 101°C]; the ^1H n.m.r. spectrum was in good agreement with published data.[212]

Pyrolysis of methyl 2,3,4-tri-O-acetyl-6-O-[(benzylthio)thiocarbonyl]-α-D-glucopyranoside (100).- The dithiocarbonate (100) (0.20-0.24 g) was heated under vacuum in a metal bath. The crude reaction mixtures were examined by t.l.c. and by i.r. spectroscopy. Presence of an absorption band at 1660 cm^{-1} was taken as evidence of alkene formation. The results are summarised in Table 9.

TABLE 9

Pyrolysis of Dithiocarbonate (100)

Bath temp. (°C)	Pressure (mm Hg)	Duration (h)	Observations
190	20	5.5	No change[a,b,c]
205	20	5.0	Mainly starting material, some alkene formed[b]
220	20	5.5	Decomposition products[d], some starting material, trace of alkene[b]
210	1	6.0	Starting material distilled without composition[b,c]
245	1	4.0	Decomposition products[d] no starting material, trace of alkene[b]

[a]Starting material recovered in 90% yield. [b]t.l.c. and i.r. evidence. [c]Identified by m.p. and mixed m.p. [d]Chromatographically very immobile compounds.

1,2,3,4,6-Penta-O-benzoyl-5-bromo-β-D-glucopyranose (103).- Penta-*O*-benzoyl-β-D-glucopyranose (101) (10.0 g) was photobrominated with bromine (6.0 g, 2.7 mol. equiv.) in carbon tetrachloride (300 cm^3) for 3 h. To a solution of the crude reaction product in chloroform (20 cm^3), ethanol (100 cm^3) was added in small portions to precipitate the crystalline bromide (103) (8.9 g, 80%). Recrystallised from ethanol-chloroform, the product had m.p. 170-171°C, $[\alpha]_D$ - 10.5° [lit.,[109,131] m.p. 171-172°C, $[\alpha]_D$ - 12°]. The ^1H n.m.r. spectrum was identical to that published.[109,131]

1,2,3,4-Tetra-O-benzoyl-6-deoxy-β-D-xylo-hex-5-enopyranose (93).- A solution of the bromide (103) (6.0 g) in acetone (300 cm^3) was treated with zinc-acetic acid for 48 h. The acetone was removed before the extractive work-up; this gave a syrup which crystallised on trituration with ethanol. Recrystallised (x3) from ethanol-chloroform (20:1) the alkene (3.0 g, 68%) had m.p. 126-128°C, $[\alpha]_D$ - 8° (*c* 4) [lit.,[109] m.p. 129-131°C, $[\alpha]_D$ - 8° (*c* 4)]; the ^1H n.m.r. spectrum was identical to that published.[109]

1,2,3,4,6-Penta-O-acetyl-α-L-threo-hex-4-enopyranose (107).- A solution of DBU (0.40 g) in DMF (10 cm^3) was slowly added to a cooled, stirred solution of penta-*O*-acetyl-5-bromo-β-D-glucopyranose (104) (0.58 g) in the same solvent (20 cm^3). After heating at 50°C for 75 min., the dark brown reaction mixture was diluted with water (50 cm^3) and extracted with chloroform (3x 25 cm^3). The chloroform extracts were washed with water, aqu. sodium hydrogen carbonate, and water (10 cm^3 each), dried and evaporated to a thick, black oil, which was extracted with boiling light petroleum (4x 20 cm^3). On removal of the solvent an almost colourless oil was obtained. Trituration with ethanol gave the crystalline *endocyclic alkene* (107) (0.31 g, 65%); recrystallised (x2) from ethanol it had m.p. 99-100°C, $[\alpha]_D$ + 50° (*c* 0.5) (Found: C, 49.5; H, 5.3. $C_{16}H_{20}O_{11}$ requires C, 49.5; H, 5.2%); for ^1H n.m.r. data see Table 1, p.34.

Zinc-acetic acid reduction of 1,2,3,4,6-penta-O-acetyl-5-bromo-β-D-glucopyranose (104). Preparation of 1,2,3,4-tetra-O-acetyl-6-deoxy-β-D-xylo-hex-5-enopyranose (94) and isolation of elimination by-products.- The crude product obtained by photobromination of β-D-glucose pentaacetate (102) (3.3 g) with NBS (6.6 g) (see p.97) was reduced with zinc-acetic acid to give, after work up, a light brown syrup which on trituration with ethanol gave the crystalline title compound (94). Recrystallised from ethanol (x3) this

product (1.32 g, 47%) had m.p. 115-117°C, $[\alpha]_D$ - 35° [lit.,[107] m.p. 119°C, $[\alpha]_D$ - 35°]; for ^{1}H n.m.r. data see Table 1, p.34.

A portion (0.7 g) of the non-crystalline product (1.03 g) was resolved on a silica gel column (solvent A). Fraction (i) (from ethanol, x2) alkene (94) (0.23 g, 12% , total 59%), m.p. 115-117°C, $[\alpha]_D$ - 34°, i.r. and ^{1}H n.m.r. data identical to those of the main product.

Fraction (ii) (from ethanol, x3) was 1,2,3,6-*tetra*-O-*acetyl*-4-*deoxy*-α-L-threo-*hex*-4-*enopyranose* (105) (0.29 g, 15%), m.p. 79-81°C, $[\alpha]_D$ + 20° (Found: C, 50.8; H, 5.5. $C_{14}H_{18}O_9$ requires C, 50.9; H, 5.5%); for ^{1}H n.m.r. data see Table 1, p.34.

Fraction (iii) (from methanol, x3) was 1,2,3,4,6-*penta*-O-*acetyl*-β-D-xylo-*hex*-5-*enopyranose* (106), m.p. 138-139°C, $[\alpha]_D$ -45° (Found: C, 49.1; H, 5.3. $C_{16}H_{20}O_{11}$ requires C, 49.5, H, 5.2%); for ^{1}H n.m.r. data see Table 1, p.34.

Small-scale photobromination of β-D-*glucose pentaacetate* (102). *Preparation of* 1,2,3,4,6-*penta*-O-*acetyl*-5-*bromo*-β-D-*glucopyranose* (104).-

(a) With NBS. The pentaacetate (102) (0.20 g) was photobrominated with NBS (0.40 g, 4.4 mol. equiv.) in carbon tetrachloride (15 cm^3) for 2 h. T.l.c. (solvent B) indicated that all starting material (R_F 0.35) had been replaced by mainly one product (R_F 0.52). Purification of the crude, syrupy reaction product on a column of silica gel (solvent A) gave the *5-bromide* (104) (0.20 g, 80%) which on recrystallisation (x2) from dry ether at -10°C had m.p. 119-120°C, $[\alpha]_D$ - 90° (Found: C, 41.1; H, 4.5; Br, 16.0. $C_{16}H_{21}BrO_{11}$ requires C, 41.0; H, 4.5; Br, 17%); for ^{1}H n.m.r. data see Table 3, p.44. This product was obtained crystalline in *ca.* 50% yield without column chromatographic purification.

(b) With bromine. The pentaacetate (102) (0.20 g) was photobrominated with bromine (0.20 g, 2.4 mol. equiv.) in carbon tetrachloride (15 cm^3) for 45 min. Purification by column chromatography, as above, gave the 5-bromide (104) (0.20 g, 80%) which was identical by optical rotation, t.l.c., and ^{1}H n.m.r. spectroscopy with the initial product obtained by using NBS.

Large-scale photobromination of β-D-*glucose pentaacetate* (102).-

(a) Preparation of 1,2,3,4,6-*penta*-O-*acetyl*-5-*bromo*-β-D- *glucopyranose* (104) *and isolation of bromination by-products.*

(a.i.) With NBS. The pentaacetate (102) (5.0 g) was photobrominated with NBS (10.0 g, 4.2 mol. equiv.) in carbon tetrachloride (300 cm^3) for 16 h

to give a light brown syrup (6.0 g), a portion of which (2.0 g) was fractionated on a silica gel column (solvent A). Fraction (i) (R_F 0.72, solvent B) was a mixture (111) of derivatives of penta-*O*-acetyl-5-bromo-β-D-glucopyranose containing approximately four bromine substituents in the acetyl groups (0.47 g, *ca.* 14%), $[\alpha]_D$ + 1° (Found: ionisable Br, 10.0; total Br, 53.1. $C_{16}H_{17}Br_5O_{11}$ requires for one ionisable Br, 10.2; total Br, 50.9%); see discussion, p.40, for ^{1}H n.m.r. data. Treatment with zinc-acetic acid converted this material (0.24 g) to a mixture of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-β-D-*xylo*-hex-5-enopyranose (94) and 1,2,3,6-tetra-*O*-acetyl-4-deoxy-α-L-*threo*-hex-4-enopyranose (105) (0.088 g, 84%, 4:1, by ^{1}H n.m.r. analysis). Small amounts of 1,2,3,4,6-penta-*O*-acetyl-β-D-*xylo*-hex-5-enopyranose (106) were also detected in the spectrum (see p.).

Fraction (ii) (R_F 0.52) was the 5-bromide (104) (1.30 g, 65%). Recrystallised from dry ether at -10°C, it had m.p. 119-120°C, $[\alpha]_D$ - 90°, and i.r. and ^{1}H n.m.r. spectra identical to those of the earlier sample.

(a.ii.) With bromine, in the absence of base. The pentaacetate (102) (10.0 g) was photobrominated with bromine (10.0 g, 2.5 mol. equiv.) in carbon tetrachloride (350 cm^3) for 4 h. T.l.c. (solvent B) showed that all starting material (R_F 0.35) had been replaced by a major product (R_F 0.52) and two minor compounds (R_F 0.55 and 0.75). A portion (2.6 g) of the syrup obtained (13.0 g) was fractionated on a silica gel column (solvent A).

Fraction (i) (R_F 0.75) was 2,3,4,6-*tetra-O-acetyl-5-bromo-β-D-glucopyranosyl bromide* (118) (0.31 g, 13%), $[\alpha]_D$ -90° (Found: ionisable Br, 31.2. $C_{14}H_{18}Br_2O_9$ requires Br, 32.6%); for ^{1}H n.m.r. data see Table 3, p.44. Treatment of the dibromide (0.19 g) with zinc-acetic acid gave 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-D-*threo*-hexa-1,5-dienitol (121) (0.58 g, 70%) as a light yellow oil, $[\alpha]_D$ -180° (*c* 0.6) [lit.[137,213] $[\alpha]_D$ -198° and -177°]. The ^{1}H n.m.r. spectrum was consistent with published data.[213]

Fraction (ii) (R_F 0.55) was 2,3,4,6-*tetra-O-acetyl-1-bromo-D-glucopyranosyl bromide* (119) (0.41 g, 17%), $[\alpha]_D$ +98° (Found: ionisable Br, 29.5. $C_{14}H_{18}Br_2O_9$ requires Br 32.6%); for ^{1}H n.m.r. data see Table 3, p.44. On reductive elimination with zinc-acetic acid this dibromide (0.22 g) was converted to tri-*O*-acetyl-D-glucal (122) (0.08 g, 66%) which crystallised from ethanol. Recrystallised from light petroleum it had m.p. and mixed m.p. 51-55°C, $[\alpha]_D$ -13° (ethanol) [lit.,[214] m.p. 54-55°C, $[\alpha]_D$ -15.5° (ethanol)]; the ^{1}H n.m.r. spectrum was identical to that of an authentic[115] sample.

After treatment of the 1,1-dibromide (119) (0.14 g) with ethanolic silver nitrate and removal of the precipitated silver bromide, the filtrate was

taken to dryness to leave a residue which was extracted with chloroform (3x 10 cm^3). The chloroform extract was washed with water (2x 5 cm^3), dried and evaporated to give syrupy ethyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate (123) (0.68 g, 62%), $[\alpha]_D$ +22° (*c* 0.5) [lit.[139] $[\alpha]_D$ + 19°]; the ^1H n.m.r. spectrum was in good agreement with published data.[139] Acetylation of the tetraacetate (123) (0.058 g) with acetic anhydride (1 cm^3) in pyridine (2 cm^3) gave ethyl 2,3,4,5,6-penta-*O*-acetyl-D-gluconate (124) (0.046 g, 71%), which crystallised from ethanol. Recrystallised from this solvent it had m.p. and mixed m.p. 103-104°C, $[\alpha]_D$ +18° (*c* 0.5) [lit.,[140] m.p. 103-104°C, $[\alpha]_D$ +20.5°]. The ^1H n.m.r. and i.r. spectra were consistent with published data,[140] and identical to those of an authentic sample prepared from calcium D-gluconate by acetylation[215] followed by treatment with phosphorus pentachloride and then ethanol.[140]

Fraction (iii) (0.56 g, *ca.* 23%) was re-fractionated on a silica gel column to give the 1,1-dibromide (119) (0.04 g, 1.6%) identical by t.l.c., ^1H n.m.r., and i.r. to the material isolated above, and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (120) (R_F 0.55, 0.06 g, 3%) which, crystallised from ether, had m.p. and mixed m.p. 83-87°C, $[\alpha]_D$ +170° [lit.,[216] m.p. 87-88°C, $[\alpha]_D$ +199°] and ^1H n.m.r. and i.r. spectra identical to those of an authentic sample.[142] The remaining fractions (0.39 g) comprised mixtures of these compounds and 5-bromide (104).

Fraction (iv) (R_F 0.52) was 1,2,3,4,6-penta-*O*-acetyl-5-bromo-β-D-glucopyranose (104). Crystallised from dry ether at -10°C, it had m.p. 119-121°C, $[\alpha]_D$ -91° and gave an ^1H n.m.r. spectrum identical to that of the authentic material.

(b) With bromine in the presence of potassium carbonate. Preparation of 1,2,3,4-tetra-O-acetyl-β-D-xylo-hex-5-enopyranose (94) and isolation of elimination by-products.

The photobromination of the pentaacetate (102) (10.0 g) with bromine was repeated under the same conditions as above but in the presence of dry potassium carbonate (5.0 g). The syrup obtained was reduced with zinc-acetic acid to give a mixture of alkenes from which on trituration with ethanol at 0°C, 1,2,3,4 tetra-*O*-acetyl-6-deoxy-β-D-*xylo*-hex-5-enopyranose (94) crystallised (3.2 g, 38%). Recrystallised (x2) from ethanol it had m.p. 115-117°C, $[\alpha]_D$ -34° and gave a ^1H n.m.r. spectrum identical to that of the earlier sample.

A portion (0.7 g) of the non-crystalline product (2.65 g) was resolved on a silica gel column (solvent A) to give four fractions. Fraction (i)

(R_F 0.83, solvent B) was 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-D-*threo*-hexa-1,5-dienitol (121) (0.020 g, 1.5%), $[\alpha]_D$ -188°, identical by t.l.c., ^{1}H n.m.r., i.r., and mass spectrometry to the previous sample.

Fraction (ii) (R_F 0.62) was tri-*O*-acetyl-D-glucal (122) (0.110 g, 5%); recrystallised (x2) from light petroleum, it had m.p. 53-54°C, $[\alpha]_D$ -15° (*c* 1.2, ethanol), and was identical by t.l.c., ^{1}H n.m.r. and i.r. spectroscopy to the previous sample.

Fraction (iii) (R_F 0.58) was 1,2,3,4-tetra-*O*-acetyl-6-deoxy-β-D-*xylo*-hex-5-enopyranose (94) (0.196 g, 9%, total 47%); recrystallised (x2) from ethanol, it had m.p. 115-117°C, $[\alpha]_D$ +34°, its ^{1}H n.m.r. and i.r. spectra were identical to those of the main product.

Fraction (iv) (R_F 0.50) was 1,2,3,6-tetra-*O*-acetyl-4-deoxy-α-L-*threo*-hex-4-enopyranose (105); recrystallised (x3) from ethanol, it had m.p. 81-82°C, $[\alpha]_D$ +20.5°, its ^{1}H n.m.r. and i.r. spectra were identical to those of the earlier sample.

Photobromination of penta-O-acetyl-α-D-idopyranose (125).- The idose ester (125) (0.20 g) was photobrominated with NBS (0.40 g, 4.4 mol. equiv.) in carbon tetrachloride (15 cm^3) for 2 h to give an unstable syrup, $[\alpha]_D$ +70°, with an ^{1}H n.m.r. spectrum identical to that of the product derived from penta-*O*-acetyl-β-D-glucopyranose (102) under exactly the same conditions ($[\alpha]_D$ -66°). The ^{1}H n.m.r. spectra further indicated that these products were almost entirely penta-*O*-acetyl-5-bromo-glucopyranose [compound (104) and its enantiomer (127)].

Attempted photobromination of acetobromoglucose (120).-

(a) With bromine. Acetobromoglucose (120) (0.40 g) was treated with bromine (0.40 g, 2.5 mol. equiv.) in carbon tetrachloride (40 cm^3) under photobrominating conditions. After 6 h only unreacted starting material was detected by t.l.c. (solvent B, R_F 0.55) and by ^{1}H n.m.r. spectroscopy of a processed sample. After 24 h a small amount of a chromatographically more mobile product (R_F 0.70) had been formed, which by t.l.c. and ^{1}H n.m.r. spectroscopy was neither the 1,5-dibromide (118) nor the 1,1-dibromide(119).

(b) With NBS. Acetobromoglucose (120) (0.40 g) was treated with NBS (0.80 g, 4.6 mol. equiv.) in carbon tetrachloride (35 cm^3) under photobrominating counditions for 24 h. A syrup was obtained which by t.l.c. and ^{1}H n.m.r. spectroscopy contained only unchanged starting material.

Treatment of β-D-*glucose pentaacetate (102) with hydrobromic acid.*- A solution of the pentaacetate (102) (0.5 g) in carbon tetrachloride (30 cm^3), through which was passed a slow stream of hydrogen bromide gas, was heated under reflux for 2 h. T.l.c. and ^1H n.m.r. spectroscopy of the residue, after removal of the solvent, showed only starting material.

The experiment was repated but, after heating for 2 h, bromine (0.3 g) was added. Heating was continued for 15 min., then all volatile material was removed to give a syrup which by t.l.c. and ^1H n.m.r. spectroscopy, was acetobromoglucose (120).

(2S)-2,3,4-Tri-O-benzoyl-2,4,5/3-tetrahydroxycyclohexanone (91).-

(a) From alkene (93). *(a.i.) With mercury(II) chloride.* A solution of the hex-5-enopyranose (93) (1.0 g) and mercury(II) chloride (2.0 g, 4.3 mol. equiv.) in aqu. acetone (100 cm^3, 2:5) was heated under reflux for 3 h. The acetone was removed, the aqueous suspension obtained was extracted with chloroform (3x 50 cm^3) and the chloroform extracts were washed with water (2x 10 cm^3), dried and evaporated to a foam. Purification on a column of silica gel (solvent B) gave the crystalline *cyclohexanone tribenzoate* (91) (0.45 g, 55%) which, after recrystallisation (x4) from light petroleum-chloroform, had m.p. 186-187°C, $[\alpha]_D$ -4° (Found: C, 68.4; H, 4.7. $C_{27}H_{22}O_8$ requires C, 68.4; H, 4.7%); for ^1H n.m.r. data see Table 4, p.52; ^{13}C n.m.r. δ 43.36 (C-6), 66.89, 70.37, 74.64, 77.20 (C-2,3,4,5), 197.07 (C-1).

(a.ii.) With mercury(II) acetate. A solution of the alkene (93) (1.0 g) and mercury(II) acetate (1.0 g, 1.8 mol. equiv.) in aqu. acetone (100 cm^3,

as above, to give the crystalline cyclohexanone derivative (91) (0.52 g, 63%) which had m.p. 184-186°C, $[\alpha]_D$ -4° after recrystallisation (x2) from light petroleum-chloroform.

(b) From the chloromercury derivative (129). Through a solution of freshly prepared chloromercury ketoaldehyde (129) (1.41 g) (see p.103) in dry benzene (50 cm^3), hydrogen sulphide was passed for 10 min. The precipitated mercury(II) sulphide was filtered off, the filtrate was washed with water (2x 10 cm^3), dried and evaporated to a foam (0.91 g). Purification on a column of silica gel (solvent B) gave the cyclohexanone derivative (91) of m.p. 184-186°C $[\alpha]_D$ -4°. Its i.r. and ^1H n.m.r. spectra were identical to those of the material previously obtained.

(2S)-2,3,4-Tri-O-acetyl-2,4,5/3-tetrahydroxycyclohexanone (92).-

(a) From 1,2,3,4-tetra-O-acetyl-6-deoxy-β-D-xylo-hex-5-enopyranose (94). *(a.i.) With mercury(II) chloride.* A solution of the alkene (94) (2.5 g) and mercury(II) chloride (5.0 g, 2.4 mol. equiv.) in aqu. acetone (250 cm^3, 1:2) was heated under reflux for 1.5 h. The acetone was removed and the aqu. suspension obtained was extracted with chloroform (3x 10 cm^3). The extracts were washed with water (2x 5 cm^3), dried and evaporated. Purification on a column of silica gel (eluted with ether) gave the crystalline *triacetylated cyclohexanone derivative* (92) (1.30 g, 60%) as fine needles. Recrystallised (x3) from light petroleum-chloroform, it had m.p. 142-144°C, $[\alpha]_D$ -5.5° (Found: C, 49.6; H, 5.5. $C_{12}H_{16}O_8$ requires C, 50.0; H, 5.6%); for ^1H n.m.r. data see Table 4, p.52.

(a.ii.) With mercury(II) acetate. A solution of the alkene (94) (1.0 g) and mercury(II) acetate (1.0 g, 1.03 mol. equiv.) in aqueous acetone (100 cm^3, 1:2) was heated under reflux for 3 h. The reaction solution was processed as above to give the cyclohexanone derivative (92) (0.65 g, 75%). Recrystallised (x2) from light petroleum-chloroform, it had m.p. 142-144°C, $[\alpha]_D$ -5.5° (*c* 4) and was identical by i.r. and ^1H n.m.r. spectroscopy to the material obtained above. Lower yields (50-60%) were obtained when column chromatographic purification was delayed for more than a few h.

(b) From methyl 2,3,4-tri-O-acetyl-6-deoxy-α-D-xylo-hex-5-enopyranoside (96). A solution of the alkene (96) (0.36 g) and mercury(II) chloride (0.72 g, 2.2 mol. equiv.) in aqueous acetone (30 cm^3, 1:2) was heated under

reflux for 1.5 h. The solution was processed as above to give the cyclohexanone derivative (92) (0.23 g, 66%). Recrystallised from light petroleum-chloroform it had m.p. 142-144°C, $[\alpha]_D$ -5°, and i.r. and ^{1}H n.m.r. spectra identical to those of the material obtained above.

Reaction of alkene (93) with mercury(II) chloride at room temperature.-

*(a) Isolation of 2,3,4-tri-O-benzoyl-6-chloromercury-6-deoxy-*D*-xylo-hexos-5-ulose* (129). A solution of the hex-5-enopyranose (93) (1.6 g) and mercury(II) chloride (3.2 g, 3.6 mol. equiv.) in aqu. acetone (60 cm^3, 1:5) was left at room temperature for 6 h, when all starting material (R_F 0.70, solvent B) had been replaced by a chromatographically less mobile product (R_F 0.07, bright yellow spot). The optical rotation of the solution had changed from -0.26° to +3.08° (6 h, constant). After removal of the acetone under reduced pressure, benzene (50 cm^3) and water (20 cm^3) were added. The benzene extract was washed with water (3x 20 cm^3), dried over sodium sulphate and evaporated to give the *chloromercury compound* (129) as a foam (1.49 g, 75%), $[\alpha]_D$ +53° (*c* 3, benzene) (Found: Cl, 4.7; Hg 25.4. $C_{27}H_{21}ClHgO_8$ requires Cl, 5.0; Hg, 28.2%); ^{1}H n.m.r. δ 2.88 (2 H, m, H-6,6'), 5.73 and 5.81 (2 H, 2 d, $J_{2,3} = J_{3,4}$ = 4 Hz, H-2 and H-4), 6.21 (1 H, t, H-3), 7.2-8.1 (15 H, m, 3x OBz), 9.58 (1 H, s, H-1).

Re-extraction of all washings with benzene gave a further quantity of less pure product (0.44 g, 97% total).

*(b) Isolation of 2,3,4-Tri-O-benzoyl-6-deoxy-*D*-xylo-hexos-5-ulose* (131). A solution of the alkene (93) (0.16 g) and mercury(II) chloride (0.30 g, 4.0 mol. equiv.) in aqueous acetone (10 cm^3, 1:5) was left at room temperature for 8 days. T.l.c. (solvent B) indicated that two products had been formed (R_F 0.20 and 0.35). The solvents were removed under reduced pressure, the residue was stirred with dry benzene (2x 20 cm^3) and the benzene evaporated. The ^{1}H n.m.r. spectrum of the crude product showed the cyclohexanone derivative (91) and the hydrolysis product (131) to be present in a ration of *ca.* 3:2. Hydrogen sulphide was passed through a solution of this product in benzene, and after removal of the precipitated mercury(II) sulphide and of the solvent, the minor product (131) was isolated by preparative t.l.c. [solvent B, extraction of the band with R_F 0.20-0.30 with acetone (3x 50 cm^3)]. After heating in refluxing benzene with azeotropic removal of water, the *1,5-dicarbonyl compound* (131) (0.32 g, 25%) was obtained as a colourless oil, $[\alpha]_D$ -8.5° (*c* 1, benzene); ^{1}H n.m.r. δ 2.26 (3 H, s, H-6); 5.77 and 5.86

(2 H, 2 d, $J_{2,3} = J_{3,4}$ = 4.5 Hz, H-2 and H-4); 6.24 (1 H, t, H-3), 7.1-8.1 (15 H, m, 3x OBz); 9.63 (1 H, s, H-1).

Reaction of alkene (93) with mercury(II) acetate at room temperature. Isolation of di-(2,3,4-tri-O-benzoyl-6-deoxy-D-xylo-hexos-5-ulos-6-yl) mercury (135).- A solution of the alkene (93) (0.15 g) and mercury(II) acetate (0.30 g, 3.6 mol. equiv.) in aqu. acetone (15 cm^3, 1:5) was left at room temperature for 1 h. [α = -0.08° → +0.90° (0.25 h, constant)]. After removal of the acetone under reduced pressure, dichloromethane (20 cm^3) and water (10 cm^3) were added. The organic phase was separated, washed with water (3x 5 cm^3), dried over molecular sieve and taken to dryness. Benzene (2x 10 cm^3) was added to the residue and evaporated to give the *mercurial* (135) (0.15 g, 100%) as a foam. (Found: Hg, 18.8. $C_{54}H_{42}HgO_{16}$ requires Hg 17.5%); ^{1}H n.m.r. δ 3.03 (2 H, m, H-6,6') 5.84 and 6.00 (2 H, 2 d, $J_{2,3} = J_{3,4}$ = 4 Hz, H-2 and H-4), 6.35 (1 H, t, H-3), 7.2-8.1 (15 H, m, 3x OBz), 9.69 (1 H, s, H-1).

(4S)-Tri-O-benzoyl-4,6/5-trihydroxycyclohex-2-enone (136).- The 5-hydroxy compound (91) (0.45 g) was dissolved in a mixture of pyridine (10 cm^3) and acetic anhydride (7 cm^3). After 16 h at room temperature the solution was poured onto ice and the precipitate was filtered off (0.41 g). Recrystallisation (x3) from methanol gave the *enone* (136) (0.26 g, 60%) of m.p. 149-151°C, $[\alpha]_D$ +106° (Found: C, 70.9; H, 4.3. $C_{27}H_{20}O_7$ requires C, 71.0; H, 4.4%); ^{1}H n.m.r. δ 5.9-6.4 (4 H, m, H-2,4,5,6), 7.02 (1 H, d, $J_{2,3}$ 11 Hz, H-3), 7.1-8.1 (15 H, m, 3x OBz).

From the mother liquors 2,4-*dibenzoyloxyphenyl acetate* (137) (0.10 g, 28%) crystallised at -10°C. Recrystallised (x3) from methanol it had m.p. 139-140°C, $[\alpha]_D$ = 0° (Found: C, 70.2; H, 4.4. $C_{22}H_{16}O_6$ requires C, 70.2; H, 4.3%), ^{1}H n.m.r. δ 2.16 (3 H, s, OAc), 7.1-8.2 (13 H, m, H-2,3,5, 2x OBz), m/e 376 (M^+, 15%), 334 (M-CH_2CO, 100), 230 (M + 1-CH_2CO-PhCO, 3).

Attempted benzylation of tribenzoate (91).- To a stirred solution of the 5-hydroxy tribenzoate (91) (0.40 g) in dry DMF (4 cm^3) and benzyl bromide (2 cm^3), silver oxide (0.67 g) was added in several portions over 1 h. Stirring at room temperature was continued for 16 h, the solids were removed by filtration and washed with DMF (4 cm^3) and chloroform (4 cm^3). Water (30 cm^3) was added to the combined filtrate and washings, and the mixture was extracted with chloroform (3x 15 cm^3). The chloroform extracts were washed

with water (3x 10 cm^3), dried and evaporated (70°C, 1 mm Hg) to a thick brown syrup. T.l.c. (solvent B) showed two main products with R_F values of 0.70 and 0.65. Separation on a silica gel column (solvent A) gave as the faster component *2,4-dibenzyloxyphenyl benzoate* (138) (0.10 g, 29%). Recrystallised (x2) from methanol it had m.p. 82-84°C, $[\alpha]_D$ 0° (Found: C, 79.4; H, 5.5. $C_{27}H_{22}O_4$ requires C, 79.0; H, 5.4%); ^{1}H n.m.r. δ 4.92 and 4.96 (4 H, 2 s, 2x CH_2), 6.6, 6.9-7.5, and 7.9-8.2 (8 H, 3 m, H-3,5,6, OBz), 7.13 and 7.25 (10 H, 2 s, 2x Ph), m/e 410 (M^+, 96%), 319 (M-$PhCH_2$,12), 105 (PhCO, 100), ($PhCH_2$, 79).

The slower product was 2,4-*dibenzoyloxyphenyl benzyl ether* (139) (0.11 g, 31%). Recrystallised (x2) from methanol it had m.p. 139-140°C, $[\alpha]_D$ 0° (Found: C, 76.1; H, 4.9. $C_{27}H_{20}O_5$ requires C, 76.4; H, 4.8%); ^{1}H n.m.r. δ 5.03 (2 H, s, CH_2), 6.9-7.7 and 8.0-8.25 (13 H, 2 m, H-3, H-5, and H-6, 2x OBz), 7.17 (5 H, s, Ph), m/e 424 (M^+, 100%), 105 (PhCO, 60), 91 ($PhCH_2$, 8).

(2S)-5-O-Acetyl-2,3,4-tri-O-benzoyl-2,4,5/3-tetrahydroxycyclohexanone (140).- To a cooled, stirred solution of the 5-hydroxy compound (91) (0.50 g) in acetic anhydride (15 cm^3) boron trifluoride etherate (0.2 cm^3) was added dropwise. After stirring for 1 h at 0°C, the reaction mixture was poured on ice. On stirring at room temperature for 1.5 h, a solid white precipitate was obtained which was filtered off and washed thoroughly with water. Recrystallised (x2) from methanol, the *acetate* (140) (0.48 g, 85%) had m.p. 149-151°C, $[\alpha]_D$ +42.5° (Found: C, 67.4; H, 4.8. $C_{29}H_{24}O_9$ requires C, 67.4; H, 4.7%); for ^{1}H n.m.r. data see Table 4, p.52.

When the same reaction [0.99 g starting material (91)] was carried out at room temperature, the acetate (140) was obtained in lower yield (0.53 g, 50% after recrystallisation from methanol), m.p. 149-150°C, $[\alpha]_D$ +42°. From the concentrated mother liquors the enone (136) crystallised after several days at -10°C (0.19 g, 20%). Recrystallised (x2) from methanol it had m.p. 149-150°C, $[\alpha]_D$ +107°, its i.r. and ^{1}H n.m.r. spectra were identical to those of the earlier product.

(2S)-2,3,4-Tri-O-benzoyl-5-O-(tetrahydropyran-2-yl)-2,4,5/3-tetra hydroxycyclohexanones (141).- A suspension of the 5-hydroxy derivative (91) (1.0 g) in dry benzene (20 cm^3) and 2,3-dihydropyran (2.0 g), containing toluene-*p*-sulphonic acid (0.002 g) was stirred at room temperature for 16 h. Anhydrous potassium carbonate (0.25 g) was added to the solution and stirring was continued for another 30 min. The solids were removed by filtration and

the filtrate was evaporated to a colourless oil. After purification on a silica gel column (solvent A) the *THP ethers* (141) (1.08 g, 93%) crystallised from the eluate on standing at room temperature unsealed for 4 days. A sample purified on a second column had m.p. 156-160°C, $[\alpha]_D$ +8° (Found: C, 69.0; H, 5.5. $C_{32}H_{30}O_9$ requires C, 68.8; H, 5.4%); for ^{1}H n.m.r. data see Table 4, p.52.

Reaction of the tetrahydroxycyclohexanonetribenzoate (91) with diazomethane.- A solution of compound (91) (1.0 g) in chloroform (20 cm^3) was treated with a solution of diazomethane [prepared from *N*-nitrosomethylurea (5.0 g)] in ether (50 cm^3) at +4°C for 2 days. The solution was evaporated to a light yellow oil from which *(1R)-5,7-anhydro-2,3,4-tri-O-benzoyl-1-C-hydroxymethyl-(1,3/2,4,5)-cyclohexanepentol* (155) (0.21 g, 20%) crystallised on trituration with methanol. Recrystallised (x4) from ethanol it had m.p. 178-179°C, $[\alpha]_D$ +50.5° (Found: C, 68.7; H, 5.0. $C_{28}H_{24}O_8$ requires C, 68.8; H, 5.0%); for ^{1}H n.m.r. data see Table 6, p.71; ^{13}C n.m.r. δ 38.72 (C-6), 71.28, 72.49, 76.35, 77.58, 77.70, 78.41 (C-1,2,3,4,5,7).

Separation of the concentrated mother liquors on a silica gel column (solvent B) gave a further quantity of the bicyclic ether (155) (0.42 g, 61% total) (R_F 0.50, solvent C). Recrystallised (x2) from ethanol it had m.p. 177-179°C, $[\alpha]_D$ +50°, the i.r. and ^{1}H n.m.r. spectra were identical to those of the above material.

A slow fraction (R_F 0.35, 0.22 g) gave the crystalline *(1S)-1,7-anhydro-2,3,4-tri-O-benzoyl-1-C-hydroxymethyl-(1,2,4,5/3)-cyclohexanepentol* (158) (0.15 g, 15%) from methanol after several weeks at -10°C. Recrystallised from the same solvent (x4) it had m.p. 151-154°C, $[\alpha]_D$ -5° (Found: C, 68.7; H, 5.0. $C_{28}H_{24}O_8$ requires C, 68.8; H, 5.0%); for ^{1}H n.m.r. data see Table 5, p.68; ^{13}C n.m.r. δ 34.50 (C-6), 47.20 (C-7), 56.42 (C-1), 67.76 70.08, 70.31, 74.80 (C-2,3,4,5).

(1R)-1-O-Acetyl-5,7-anhydro-2,3,4-tri-O-benzoyl-1-C-hydroxymethyl-(1,3/2,4,5)-cyclohexanepentol (156).-

(a) From the 1-hydroxy derivative (155). The 1-hydroxy bicyclic ether (155) (0.52 g) was acetylated with acetic anhydride (5 cm^3) in pyridine (10 cm^3) for 40 h at room temperature. The solid product (0.52 g, 91%) was recrystallised (x3) from ethanol to give the *acetylated bicyclic ether* (156), m.p. 157-157.5°C, $[\alpha]_D$ +50° (Found: C, 67.9; H, 5.1. $C_{30}H_{26}O_9$ requires C, 67.9; H, 5.0%); for ^{1}H n.m.r. data see Table 6, p.71.

(b) From the 7-bromide (171). The 7-bromide (171) (0.26 g) in acetone (5 cm^3) was reduced with zinc-acetic acid to give a colourless oil (0.25 g). Purification on a silica gel column (solvent A) gave the crystalline acetate (156) (0.14 g, 61%). Recrystallised from ethanol it had m.p. and mixed m.p. 156-157.5°C, $[\alpha]_D$ +50°; its ^1H n.m.r. spectrum was identical to that of the above material.

(1S)-5-O-Acetyl-1,7-anhydro-2,3,4-tri-O-benzoyl-1-C-hydroxymethyl-(1,2,4,5/3)-cyclohexanepentol (159).- The hydroxy epoxide (158) (0.080 g) was acetylated with acetic anhydride (1 cm^3) in pyridien (2 cm^3) for 20 h at room temperature to give a crystalline product (0.081 g, 93%). Recrystallised (x2) from methanol the *acetylated* (1S)*-epoxide* (159) had m.p. 160-161°C, $[\alpha]_D$ -7° (Found: C, 67.9; H, 5.0. $C_{30}H_{26}O_9$ requires C, 67.9; H, 5.0%); for ^1H n.m.r. data see Table 5, p.68; ^{13}C n.m.r. δ 21.04 (Ac), 32.22 (C-6), 47.15 (C-7), 55.67 (C-1); 68.89, 69.95, 70.31, 71.96 (C-2,3,4,5).

Acetylation of the mother liquors from the epoxide (158).- The concentrated mother liquors (0.4 g) from the crystallisation of the (1S)-hydroxy epoxide (158) [prepared from 5.9 g cyclohexanone derivative (91)] were acetylated with acetic anhydride in pyridine for 18 h at room temperature. Fractionation of the oily product on a silica gel column (solvent B) gave three pure fractions. The slowest fraction was the acetylated (1S)-epoxide (159) [0.12 g, 2% based on 5.9 g cyclohexanone (91)]. Recrystallised from methanol it had m.p. 159-160°C, $[\alpha]_D$ -5°; the ^1H n.m.r. spectrum was identical to that of the material obtained before.

The second fraction was 1-*acetyl-4-benzoyloxy-7-methoxy-*(1H)*-indazole* (160) (0.075 g, 2%). Recrystallised (x3) from methanol it had m.p. 173-175°C (sealed tube), $[\alpha]_D$ 0° (Found: C, 65.4; H, 4.6; N, 9.2. $C_{17}H_{14}N_2O_4$ requires C, 65.8; H, 4.6; N, 9.0%); ^1H n.m.r. δ 2.36 (3 H, s, Ac), 6.90 and 7.02 (2 H, dd, $J_{5,6}$ 9 Hz, H-5 and H-6), 7.79 (1 H, s, H-3), 7.3-8.3 (5 H, m, OBz); m/e 310 (M^+, 10%), 268 (M-CH_2O; 38), 163 (M-CH_2O-PhCO; 2), 105 (PhCO; 100); 77 (C_6H_5, 4).

The fastest fraction was (1R)*-5-O-acetyl-1,7-anhydro-2,3,4-tri-O-benzoyl-1-C-hydroxymethyl-(1,3/2,4,5)-cyclohexanepentol* (157) (0.10 g, 2%). Recrystallised (x4) from methanol, it had m.p. 163-165°C, $[\alpha]_D$ +26.5° (Found: C, 67.6; H, 4.9. $C_{30}H_{26}O_9$ requires C, 67.9; H, 5%); for ^1H n.m.r. data see Table 5, p.68; ^{13}C n.m.r. δ 20.82 (Ac), 33.08 (C-6), 49.57 (C-7), 55.67 (C-1), 67.91, 69.95, 70.81, 72.17 (C-2,3,4,5).

Reaction of the tetrahydropyranyl ethers (141) with diazomethane.- A solution of derivatives (141) (0.090 g) in chloroform (10 cm^3) and methanol (3 cm^3) was combined with a solution of diazomethane [prepared from *N*-nitrosomethylurea (5.0 g)] in ether (20 cm^3). After 24 h at +4°C the solvents were removed and the residue, shown by t.l.c. (solvent B) to contain two products, was fractionated on a silica gel column (solvent A). The faster product (R_F 0.75, 0.030 g) was not identified, the slower fraction (R_F 0.30, 0.048 g, 53%) was the cyclic ether (155). Recrystallised (x2) from ethanol, it had m.p. 174-177°C, $[\alpha]_D$ +50°, its ^1H n.m.r. spectrum was identical to that of previously obtained bicyclic ether (155).

Reaction of the acetate (140) with diazomethane.- A solution of the cyclohexanone derivative (140) (0.12 g) in chloroform (2 cm^3) was combined with a solution of diazomethane [prepared from *N*-nitrosomethylurea (1g)] in ether (10 cm^3). After 2 h at +4°C the reaction mixture was evaporated to a bright yellow syrup. T.l.c. showed at least 5 products, and ^1H n.m.r. spectroscopy indicated that the acetyl group had been lost. When the reaction was repeated at lower temperature(-10°C) and in different solvents (ether only, ether-dichloromethane, benzene) similar complex reaction mixtures were obtained. These were not further investigated.

Photobromination of the bicyclic ether (156).-

(a) With bromine. Compound (156) (0.30 g) was photobrominated with bromine (0.18 g, 2.0 mol. equiv.) in carbon tetrachloride (10 cm^3) for 30 min. to give a white foam which crystallised on trituration with light petroleum (0.31 g, *ca.* 90%, microcrystalline). T.l.c. (solvent B) showed only one product, chromatographically slightly more mobile than the starting material. Hydrolysis experiments (see p.109) indicated, however, the presence of a *ca.* 9:1 mixture of *(1S,7R)-5,7-anhydro-5-O-acetyl-2,3,4-tri-O-benzoyl-7-bromo-1-C-hydroxymethyl-(1,3/2,4,5)-cyclohexanepentol* (171) and the 7,7-dibromide (172) [Found: Br, 13.8%. A mixture (9:1) of $C_{30}H_{25}BrO_9$ requires Br, 14.1%]. Recrystallised from light petroleum-benzene, the 7-bromide (171), which was not free of dibromide (172), had m.p. 104-106°C, $[\alpha]_D$ +116° (benzene); for ^1H n.m.r. data see Table 6, p.71.

(b) With NBS. Photobromination of compound (156) (0.30 g) with NBS (0.30 g, 3.0 mol. equiv.) in carbon tetrachloride (10 cm^3) for 60 min. gave

a similar mixture (9:1) of 7-bromide (171) and 7,7-dibromide (172) (0.30 g, *ca.* 90%) as was obtained by use of bromine.

Hydrolysis of the bromides (171) and (172). Preparation of (1S,7S)-5,7-anhydro-5-O-acetyl-2,3,4-tri-O-benzoyl-7-hydroxy-1-C-hydroxymethyl-(1,3/2,4,5)-cyclohexanepentol (173).-

(a) With silver nitrate. A solution of the unpurified bromide (171) [0.95 g, containing *ca.* 10% dibromide (172)] in acetone (30 cm^3) was treated with silver nitrate (0.4 g) in water (2.0 cm^3). After stirring for 30 min., the precipitated silver bromide was filtered off and washed with several portions of acetone. The filtrate and washings were combined and evaporated to a thick aqueous suspension which was extracted with chloroform (3x 30 cm^3). The chloroform extracts, after washing with water (2x 10 cm^3), drying and evaporation left a syrup which was separated on a silica gel column (solvent B) to give three products. Fraction (i) [R_F 0.70 (solvent C), 0.77 g, 8.5%] was *(1S,7S)-5,7-anhydro-5-O-acetyl-2,3,4-tri-O-benzoyl-1-C-hydroxymethyl-7-nitrato-(1,3/2,4,5)-cylohexanepentol* (174). Recrystallised (x3) from light petroleum-acetone, it had m.p. 109-110°C, $[\alpha]_D$ +61 ° (Found: C, 61.1; H, 4.4; N, 2.2. $C_{30}H_{25}NO_{12}$ requires C, 60.9; H, 4.3; N, 2.4%); for ^1H n.m.r. data see Table 6, p.71.

Fraction (ii) (R_F 0.40, 0.080 g, 9.7%) was *(1S)-1-O-acetyl-2,3,4-tri-O-benzoyl-(1,3/2,4,5)-pentahydroxycyclopentanecarboxylic acid-5-lactone* (175). Recrystallised (x3) from light petroleum-acetone it had m.p. 214-215°C, $[\alpha]_D$ +44° (Found: C, 66.1; H, 4.6. $C_{30}H_{24}O_{16}$ requires C, 66.2; H, 4.5%); for ^1H n.m.r. data see Table 6, p.71.

Fraction (iii) (R_F 0.15, 0.61 g, 72%) was the *bicyclic hemiacetal* (173). Recrystallised (x3) from ethanol (microcrystalline) it had m.p. 163-164°C, $[\alpha]_D$ +75° (Found: C, 65.7; H, 5.0. $C_{30}H_{26}O_{10}$ requires C, 65.9; H, 4.8%); for ^1H n.m.r. data see Table 6, p.71.

(b) With silica gel. To a solution of the unpurified bromide (171) [0.31 g, containing *ca.* 10% dibromide (172)] in aqu. acetone (30 cm^3, 10:1) silica gel (Merck, G, 0.5 g) was added. After 48 h at room temperature, the silica gel was removed by filtration. The filtrate was processed as above to give, after column chromatography, (i) the lactone (175) (0.027 g, 10%). Recrystallised from light-petroleum-acetone it had m.p. 214-215°C, $[\alpha]_D$ +40°, its i.r. spectrum was identical to that of the lactone (175) described above,

and (ii) the hemiacetal (173) (0.25 g, 80%). Recrystallised (x2) from ethanol it had m.p. 162-164°C, $[\alpha]_D$ +74°; its ^{1}H n.m.r. spectrum was identical to that of the material obtained with silver nitrate.

(1R)-2,3,5- and 2,3,4-Tri-O-benzoyl-(1,3/2,4,5)-pentahydroxycyclohexanecarbaldehyde oximes* (177) and (178).- A solution of the hemiacetal (173) (0.65 g) and hydroxylamine hydrochloride (0.40 g) in ethanol (5 cm^3) and pyridine (5 cm^3) was heated under reflux for 3 h. The cooled solution was evaporated, treated with toluene (10 cm^3) and evaporated again. On trituration with water the mixed *oximes* (177) and (178) (0.65 g, 95%) crystallised. Recrystallised (x3) from chloroform-ethanol (0.44 g, 65%) they had m.p. 206-212°C, $[\alpha]_D$ -44° (acetone) (Found: C, 65.1; H, 4.9; N, 2.8. $C_{28}H_{25}NO_9$ requires C, 64.8; H, 4.9; N, 2.7%); for ^{1}H n.m.r. data see Table 7, p.81. Crystallisation from a dilute ethanolic solution gave a small sample of pure oxime (177) m.p. 209-211°C, $[\alpha]_D$ -48° (acetone). For ^{1}H n.m.r. data see Table 7, p. 81.

(1R)-5-O-Acetyl-2,3,4-tri-O-benzoyl-(1,3/2,4,5)-pentahydroxycylohexanecarbonitrile (184).- A solution of the acetate (140) (0.20 g) in methanol (1 cm^3) and acetone cyanohydrin[217] (2 cm^3) at room temperature was treated with ethylamine until just alkaline (3-4 drops). After 1 h the solution was poured into ice-cold, dilute aqu. acetic acid (15 cm^3). The fine precipitate formed was filtered off, washed with water and dried in a desiccator. Purification on a column of silica gel (solvent B) gave the powdery *cyanohydrin* (184) (0.13 g, 60%) of m.p. 150-155°C, $[\alpha]_D$ -12°. This compound could not be purified to give a satisfactory elemental analysis; for ^{1}H n.m.r. data see Table 8, p.86; ^{13}C n.m.r. δ 20.71 (Ac), 36.92 (C-6), 66.68, 69.04, 69.76, 71.70 (C-2,3,4,5), 76.33 (C-1), 118.48 (CN).

(1R)-2,3,4-Tri-O-benzoyl-5-O-(tetrahydropyran-2-yl)-(1,3/2,4,5)-pentahydroxycyclohexanecarbonitriles (185).- A solution of the tetrahydropyranyl ethers (141) (0.85 g) in methanol (4 cm^3) and acetone cyanohydrin[217] (4 cm^3) was treated with ethylamine until just alkaline (*ca.* 5 drops). After 1 h at room temperature the solution was poured into ice-cold, dilute, aqueous acetic acid (30 cm^3). The fine precipitate formed was filtered off, washed with water and dried in a desiccator. After purification on a column of silica gel (solvent B), the cyanohydrins (185) (0.55 g, 63%) were obtained as

or

* (1S)-(3/1,2,4,5)

long needles from the slowly evaporating eluate. Evaporation of the mother liquors gave a further quantity of the same product (0.16 g, total 80%) as a foam. An analytical sample, prepared by purification on a second column of silica gel, had m.p. 186-191°C $[\alpha]_D$ -7° (Found: C, 67.3, H, 5.5, N, 2.4. $C_{33}H_{31}NO_9$ requires C, 67.7; H, 5.3; N, 2.4%); for ^1H n.m.r. data see Table 8, p.86; ^{13}C n.m.r. δ 36.15 and 39.27 (C-6), 61.10 and 62.35; 67.88 and 69.97; 69.37; 70.27 and 70.52; 76.82 and 77.25 (C-1,2,3,4,5) 118.92 (CN).

(1R)-1,5-Di-O-acetyl-2,3,4-tri-O-benzoyl-(1,3/2,4,5)pentahydroxycyclohexanecarbonitrile (186).- Acetylation of the cyanohydrin (184) (0.38 g) with acetic anhydride (2 cm^3) in pyridine (2 cm^3) for 60 h gave the *diacetate* (186) (0.36 g, 87%) as a crystalline solid. Recrystallised (x3) from ethanol-chloroform it had m.p. 249-251°C, $[\alpha]_D$ -45° (Found: C, 65.4; H, 4.8; N, 2.4. $C_{32}H_{27}NO_{10}$ requires C, 65.6; H, 4.7; N, 2.4%); for ^1H n.m.r. data see Table 8, p.86; ^{13}C n.m.r. δ 20.50, 20.86 (2x Ac), 33.72 (C-6); 66.06, 68.65, 71.37, 72.33, 72.71 (C-1,2,3,4,5), 115.01 (CN).

(1R)-1-O-Acetyl-2,3,4-tri-O-benzoyl-5-O-(tetrahydropyran-2-yl)-(1,3/2,4,5)-pentahydroxycyclohexanecarbonitriles (187).- The cyanohydrins (185) (0.25 g) were acetylated with acetic anhydride (2 cm^3) in pyridine (2 cm^3) for 60 h to give the title compounds (187) (0.23 g, 86%). Recrystallised (x2) from ethanol-chloroform they had m.p. 245-248°C, $[\alpha]_D$ -61° (Found: C, 66.9; H, 5.6; N, 2.3. $C_{35}H_{33}NO_{10}$ requires C, 67.0; H, 5.3; N, 2.2%); for ^1H n.m.r. data see Table 8, p.86; ^{13}C n.m.r. δ 21.03 (OAc), 32.41 and 35.77 (C-6), 67.68 and 70.20; 68.94; 72.92 and 73.04; 73.26; 73.44 and 73.67 (C-1,2,3,4,5), 115.16 (CN).

(1R)-1-O-Methanesulphonyl-2,3,4-tri-O-benzoyl-5-O-(tetrahydropyran-2-yl)-(1,3/2,4,5)-pentahydroxycyclohexanecarbonitriles (188).- To a stirred suspension of the cyanohydrins (185) (0.15 g) in dichloromethane (0.5 cm^3) at 0°C, pyridine (0.15 cm^3) and, after a few minutes, methanesulphonyl chloride (0.15 g) were added. After 48 h at +4°C, the slightly darkened solution was poured onto ice. The solid precipitate (0.15 g, 88%) was removed by filtration, washed, and dried in a desiccator. Recrystallised (x3) from ethanol-chloroform, the *methanesulphonates* (188) had m.p. 188-189°C, $[\alpha]_D$ -33° (Found: C, 61.9; H, 5.2; N, 2.1; S, 4.8. $C_{34}H_{33}NO_{11}S$ requires C, 61.5; H, 5.0; N, 2.1; S, 4.8%); ν_{max} 1190, 1380 cm^{-1}; for ^1H n.m.r.

data see Table 8, p.86; ^{13}C n.m.r.* δ 18.18, 25.45, 30.22 (C-3',4',5')' 38.08 (C-6; 40.16 (OMs); 61.90 (C-6'); 68.85, 70.03, 73.46, 78.99 (C-1,2,3,4,5); 100.60 (C-2'); 114.66 (CN).

Attempted dehydration of cyanohydrins (184) *and* (185).-

*(a) With toluene-*p*-sulphonyl chloride in pyridine.* The cyanohydrin (185) (0.020 g) and toluene-*p*-sulphonyl chloride (0.020 g) were dissolved in pyridine (0.5 cm^3) and kept at 50°C under nitrogen for 5 days. The solution was poured onto ice and the precipitate formed was removed by filtration, washed with water and dried (0.015 g). T.l.c. and ^1H n.m.r. spectroscopy indicated that this was starting material.

(b) With phosphorus oxychloride in pyridine. To separate solutions of the cyanohydrins (184) and (185) (0.025 g) in pyridine (0.5 cm^3) phosphorus oxychloride (0.2 cm^3, freshly distilled) was added. After 2 h the solutions were poured onto ice and the precipitates formed were collected by filtration, washed with water and dried. T.l.c. and ^1H n.m.r. spectroscopy indicated that no reaction had taken place.

(c) With sulphuryl chloride in dichloromethane-pyridine. To separate, stirred solutions of the cyanohydrins (184) and (185) (0.040 g) in dichloromethane (0.75 cm^3) and pyridine (0.5 cm^3) under nitrogen at -78°C freshly distilled sulphuryl chloride (0.1 cm^3) was added. The solutions were allowed to warm to -10°C over a period of 2 h. After 30 min. at this temperature they were poured onto ice. The precipitates formed were filtered off, washed with water and dried. T.l.c. showed these to be the almost pure starting materials.

(d) With thionyl chloride in benzene-pyridine. To a stirred solution of the cyanohydrins (185) (0.010 g) in dry benzene (0.5 cm^3) and pyridine (0.2 cm^3) at 0°C, freshly distilled thionyl chloride (0.2 cm^3) was added dropwise. After 3 h at room temperature, water (5 cm^3) was slowly added. The mixture was extracted with chloroform (3x 10 cm^3) and the extracts were washed with water (3x 5 cm^3), dried, and evaporated to a foam. T.l.c. and

*This sample was obtained by fractional crystallisation and contained only one isomer.

^{1}H n.m.r. spectroscopy showed this to be the unreacted starting materials.

(e) With toluene-p-sulphonic acid in benzene. A solution of the cyanohydrin (184) (0.025 g) and toluene-*p*-sulphonic acid (0.005 g) in benzene (10 cm^3) was heated under reflux with azeotropic removal of water for 48 h. T.l.c. showed that no reaction had taken place.

When the reactions *(b)-(d)* were repeated at higher temperatures (50-80°C) and/or with longer reaction times (2-5 days), complex reaction mixtures (t.l.c. evidence) were obtained.

When reaction *(e)* was carried out with 0.02 g toluene-*p*-sulphonic acid, slow degradation without formation of a discrete product took place.

Treatment of the cyanohydrins (188) *with base.-*

(a) With pyridine. A solution of the cyanohydrins (188) (0.050 g) in pyridine (0.5 cm^3) was kept at 80°C for 3 days. On pouring onto ice, a solid precipitate was obtained which was collected by filtration, dried and recrystallised from ethanol (0.040 g). T.l.c. and ^{1}H n.m.r. spectroscopy showed this to be starting material.

(b) With DBU in DMF. A solution of the methanesulphonates (188) (0.20 g) and DBU (0.20 g) in dry DMF (2 cm^3) was kept at room temperature for 16 h. The dark brown solution was poured into ice-cold, dil. hydrochloric acid, and the precipitate formed was removed by filtration and dried (0.15 g 75%). Recrystallised from ethanol (x3) the unidentified product (191) had m.p. 150-152°C, $[\alpha]_D$ +2° (Found: C, 59.8; H, 5.2; N, 1.9; S, 4.8. $C_{34}H_{35}NO_{12}S$* requires C, 59.9; H, 5.2; N, 2.1; S, 4.7%); ν_{max} 1210, 1340 cm^{-1}; ^{1}H n.m.r., δ 1.1-1.9 (6 H, m, THP), 2.31 (1 H, dd, $J_{6,6'}$ 15 Hz, $J_{5,6'}$ 4 Hz, H-6'), 2.81 (1 H, dd, $J_{5,6}$ 6 Hz, H-6), 3.1-3.8 (2 H, m, THP), 4.38 (1 H, d, $J_{2,3}$ 7.5 Hz, H-2), 4.5-4.8 (2 H, m, H-5 and THP) 5.48 (1 H, dd, $J_{3,4}$ 7.5 Hz, H-4), 6.01 (1H, t, H-3), 7.1-8.1 (15 H, m, 3x OBz), 9.93 (1 H, brs, exchangeable, unassigned) ^{13}C n.m.r.** δ 19.90, 24.65, 30.14, 35.77 (4 t, C-3',4',5' and C-6); 64.09 (d, C-6'); 70.64, 71.04, 73.28 (3 d, C-2,3,4,5) 89.77 (s, unassigned); 101.34 (d, C-2'); 105.68 (d, unassigned); 145.49 (s, unassigned).

*This formula corresponds to the product of addition of water to the starting material (188).

**This sample was prepared from fractionally recrystallised starting material and contained mostly one isomer.

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