Microbial Oxidation of Aromatics in Enantiocontrolled Synthesis. Part 1.[1] Expedient and General Asymmetric Synthesis of Inositols and Carbohydrates *via* an Unusual Oxidation of a Polarized Diene with Potassium Permanganate[2]

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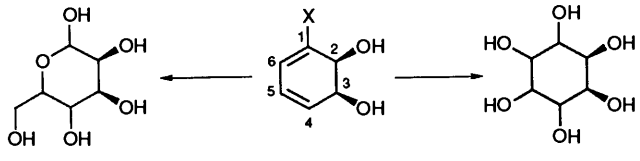
This paper reports on the details of a general design of carbohydrates and cyclitols from biocatalytically derived synthons. Homochiral 1-halogenocyclohexa-4,6-diene-2,3-diols **1a** and **1b** have been generated from chloro- and bromo-benzene, respectively, by means of bacterial dioxygenase of *Pseudomonas putida* 39D. These chiral synthons have been manipulated to cyclitols and carbohydrates by further stereoselective functionalizations. The preparation of D-*chiro*-inositol, *neo*-inositol, *muco*-inositol, and *allo*-inositol exemplifies their use in enantiocontrolled synthesis. A novel oxidation of polarized dienes with $KMnO_4$ resulted in the synthesis of α-halogeno epoxy diols, which proved unexpectedly stable. A mechanism is proposed for this transformation and placed in context with the only four reported examples of this reaction in the literature. In addition to the application of this new chemistry to the synthesis of cyclitols, chloro epoxy diol **21a** has been transformed into a series of cyclitol synthons by reductive or hydrolytic operations. Reaction of **21a** with ammonia led to the preparation of highly oxygenated pyrazines, whose structures were proven by X-ray crystallography. The use of **21a** in the preparation of D-*chiro*-3-inosose, a hitherto unreported cyclitol derivative, is also reported. In addition, chloro epoxy diol **21a** was transformed into D-erythruronolactone, completing the synthesis of this important chiral pool reagent in two operations from chlorobenzene. Oxidative cleavage of tetrol **20** yielded D-mannosolactone identical with an authentic sample.

Stereospecific hydroxylation of aromatic rings facilitated by enzymes from procaryotic organisms is a reaction that has as yet no equivalent in synthetic methodology. The versatility of substituted homochiral cyclohexadiene *cis*-diols such as **1** in organic synthesis has become evident in recent years through many applications of these richly endowed synthons in enantiocontrolled synthesis.[3]

In this manuscript, we focus on a general and systematic application of the chemistry of diols **1** in cyclitol and carbohydrate synthesis [eqn. (1)]. The conversion of diene **1**



3 Carbohydrates — **1a** X = Cl, **1b** X = Br — **2** Inositols

Eqn. (1)

into polyhydroxylated cyclohexanes (inositols) **2** is achieved by further stereoselective oxidation whereas pyranoses (or their lower homologues) of type **3** are attained by cleavage of the ring with controlled scission of two, one, or no carbon atoms. Placement of additional peripheral heteroatoms onto the diene unit in **1** prior to the oxidative scission of the C(1)–C(6) double bond changes the carbon content of the resulting carbohydrate and leads to aza analogues of pyranoses as well.[1a]

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Placement of an exocyclic nitrogen atom without subsequent ring scission then leads to aminoconduritols and lycoricidine alkaloids.[1b] Fig. 1 describes the design of the four major classes of carbohydrates from *cis*-1-chlorocyclohexadiene diol **1** further substituted with appropriate heteroatom functionalities.

Parallel to the execution of efficient design of the carbohydrate derivatives we embarked on a general synthetic approach to inositols. Instead of oxidative cleavage of the cyclohexane ring in **1**, this approach relies on precise stereodefined functionalization, which can yield all of the known inositols, including their homochiral derivatives (*i.e.*, desymmetrized through selective protection of specific hydroxy groups). In this report the achievement of selective syntheses of both cyclitols and carbohydrates is exemplified by the preparation from chlorobenzene of D-*chiro*-inositol, *neo*-inositol, *muco*-inositol, *allo*-inositol, D-mannose, and D-erythruronolactone. In other reports[1a,b] the synthesis of aza sugars by means of oxidative cleavage of nitrogen-substituted intermediates of type **4** and that of conduramines by cycloadditions of acylnitroso derivatives to protected forms of **1** are described.

Several of the isomers of inositol (all nine are shown in Fig. 2) have been implicated in important cellular functions,[5] but only three—*myo*-, *scyllo*-, and *epi*-inositols—are commercially available (Sigma). One, D-*chiro*-inositol **15**, has invoked recent interest as a potential antidiabetic agent.[6] We therefore embarked on a programme to furnish not only D-*chiro*-inositol but also as many of the other isomers as possible through a systematic synthetic design employing efficient and environmentally sound protocols.

The biooxidation of aromatic compounds with mutant strains of *Pseudomonas putida*, discovered by Gibson in 1968[7] and studied by Ribbons,[8a] Dalton and Boyd,[8b–d] has been applied extensively to the synthesis of natural products beginning with Ley's preparation of racemic pinitol in 1987,[9a] which followed, by 4 years, the disclosure of biocatalytic

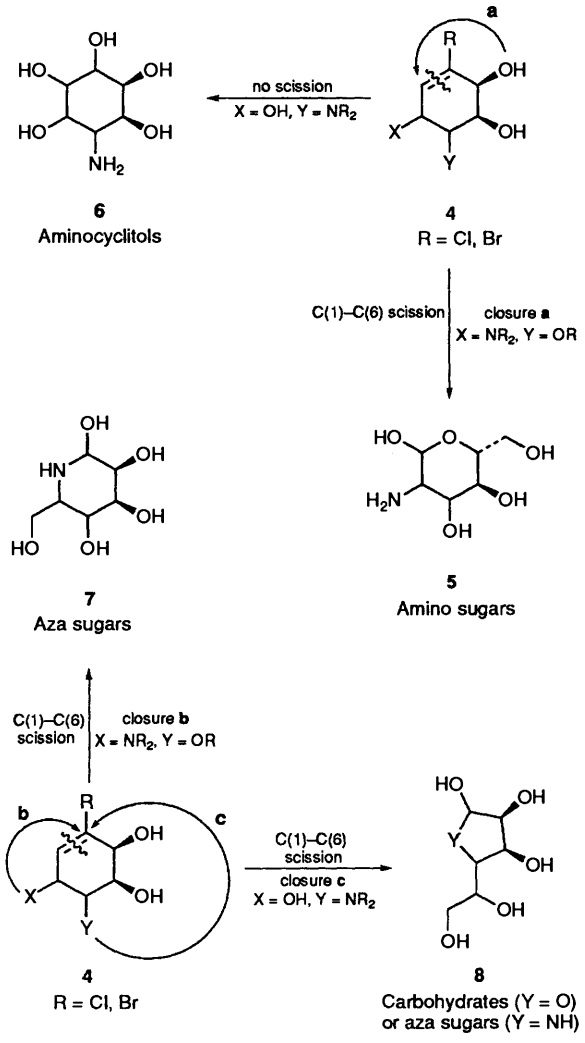


Fig. 1 Divergent design of carbohydrate topology from peripherally functionalized diols

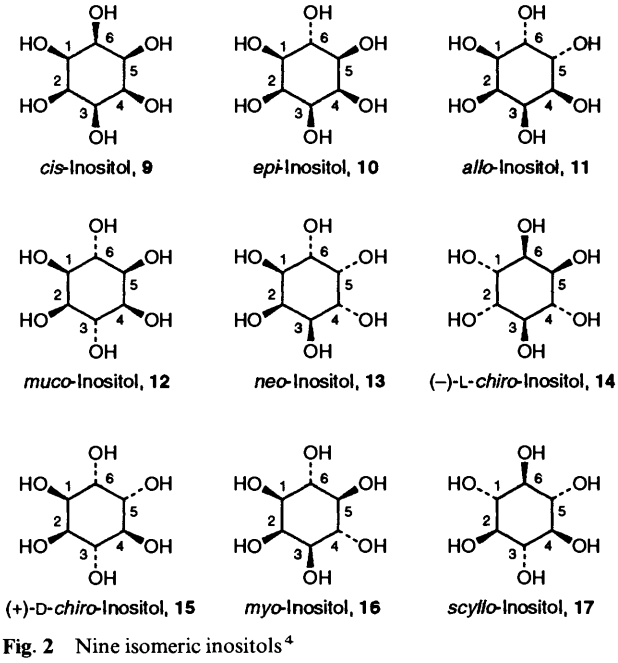


Fig. 2 Nine isomeric inositols[4]

synthesis of polyphenylene from benzene by Taylor.[9b] Since that time we have used a combination of biocatalysis and synthesis to achieve efficient preparations of such important compounds as (+)- and (−)-pinitols,[10] conduramine A1,[11] (+)-lycoricidine,[12] mannojirimycin,[13] kifunensine,[14] specionin,[15] a partial skeleton of morphine,[16] as well as other compounds. The applications of *cis*-cyclohexadiene diols **1** in enantiocontrolled synthesis continue to appear at a rapid rate from our laboratories and from those of Banwell, Boyd, Carless, Johnson, Ley, Roberts, and others,[3] and these applications are likely to continue as these versatile synthons gain further recognition.

After the introduction of chirality through the microbial oxidation step, the homochiral *cis*-cyclohexadiene diols **1** are subjected to a precisely defined sequence of stereospecific transformations with brevity and enantiodivergence as the ultimate objectives of the synthetic endeavour. The successful realization of this goal as described in the published examples listed above has resulted in the preparation of target compounds with efficiency far exceeding that of classical methods that use commercially available sugars, amino acids, or terpenoids.[17] The advantage of using optically pure *cis*-diols over sugars as chiral pool synthons is that the number of protective and deprotective operations found in the carbohydrate manipulations is reduced significantly.[18] Through strategic planning, any combination of stereocentres is available through further functionalization of the diols. The subsequent oxidation of the diene unit in **1** or **18** to yield the cyclitols has been accomplished by epoxidation or osmylation, as shown in Scheme 1. The absolute stereochemistry of the first centre introduced after enzymatic oxidation is controlled either by the *syn*-directing effect of free diol **1** or by the *anti*-directing effect of the rigid acetonide **18**. Depicted in Fig. 3 are minimized

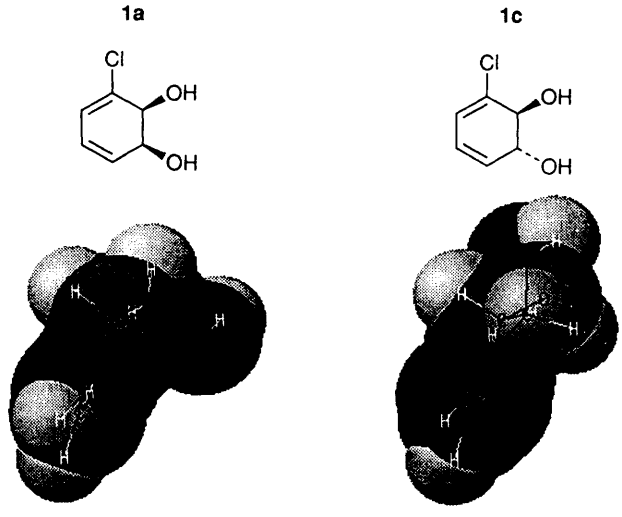
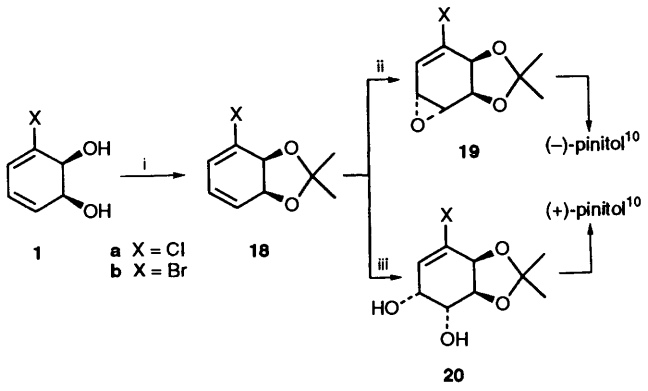


Fig. 3 MM2 structures of *cis*-diol **1a** and its *trans* isomer **1c**

structures (CAChe modelling system) of *cis*-diol **1a** and the corresponding *trans*-derivative **1c** as might be available from the hydrolysis of arene oxides produced by the action of more highly evolved oxygenases (cytochrome P450, for example) on aromatic compounds. It is clear that the definition of *exo* and *endo* surfaces begins to take place in **1a** but is absent in the *trans* derivative. Thus the *endo*-directing effects are expected from the free *cis*-diols in those reactions known for hydrogen-bonded delivery of reagents. Extension of the bowl-shaped surface by acetonide or ester protection hinders the *endo* face and allows the attachment of the reacting entity to the *exo* face of the molecule. This simple tactic is responsible for complete diastereoisomeric control in all subsequent operations.

The subsequent centres can, therefore, be set in any desired configuration. The stereospecifically synthesized epoxide **19** and diol **20** were utilized in the recent synthesis of both enantiomers



Scheme 1 Stereocontrolled oxygenation of *cis*-diols[10] *Reagents:* i, DMP/H$^+$; ii, *m*-CPBA; iii, OsO_4

of pinitol [C-4 and C-5 methyl ethers of (+)- and (−)-*chiro*-inositol, respectively] in four steps each.[10]

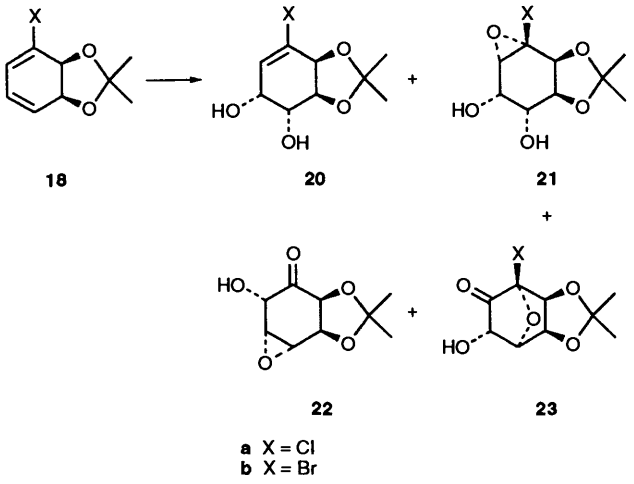
Our aim to use environmentally benign methods led us to search for a reasonable substitute for osmium tetroxide in hydroxylation of olefins. In this manuscript we report on the features of an unusual oxidation of conjugated chloro- and bromo-dienes in **1** and **18** with permanganate. The oxidation products, halogeno epoxy diols **21a** and **21b**, were used in extremely efficient preparations of four of the nine inositols, including D-*chiro*-inositol. In addition **18** has been converted into D-mannose and to D-erythruronolactone, which has also been attained from **21a** in just two operations.

Results and Discussion

Most reported syntheses of cyclitols and sugars from *cis*-cyclohexadiene diols have relied on further oxygenations, including ozonolysis, singlet oxygen additions, hydroxylation by osmium tetroxide, peracid-mediated epoxidation, or Sharpless titanium-catalysed processes.[3] We sought to develop preparative methods of oxidation, applicable to large-scale synthesis, that are academically pleasing yet efficient and offering waste-conscious principles of operation. We chose to reinvestigate the permanganate oxidation of olefins, a well known reagent whose potential has been greatly under-utilized in synthetic chemistry, as evidenced by a recent review of its chemistry.[19]

Permanganate Oxidation of Halogeno Dienes **18**.—The oxidation of olefins with permanganate is well documented, but it is not commonly used as a preparative method because of its typically low selectivity.[19–23] It is, however, recognized as a less costly and less toxic alternative to osmium tetroxide.[2,19] We chose to examine the oxidation of acetonides **18** with permanganate with the intent of producing diols **20**, previously made through osmylation, on a large scale. Initial treatment of **18a** with $KMnO_4$ (0.85 equiv., 25 °C, water–acetone) gave a complex mixture of products from which diols **21a** and **20a** were isolated in low yields. To our surprise, under milder conditions (2.3 equiv. $KMnO_4$ in the presence of $MgSO_4$,[21] 0 °C, water–acetone), a 1:1 mixture of chloro epoxy diol **21a** and diol **20a**, as well as several minor compounds that together accounted for only 10–15% of the product, were obtained in an isolated yield of 60%, Scheme 2.[2]

Inosose epoxide **22**, whose structure was confirmed by X-ray analysis, was the only minor product characterized at this stage of research. Because the unusual course of the permanganate oxidation of **18** could ultimately lead to a more efficient source of oxygenated compounds, we decided to optimize the conditions of this reaction in order to manufacture either **21a** or **20a** selectively. The product distribution was found to be



Scheme 2 Oxidation of halogeno dienes with potassium permanganate. *Reagents:* To obtain **21**, **20**, **22**: $KMnO_4$, $MgSO_4$, H_2O–acetone, −5 °C; to obtain **21**, **20**, **23**: $KMnO_4$, H_3PO_4, TEAC, CH_2Cl_2–H_2O, −5 °C

highly sensitive to reaction conditions.* With lower concentrations of permanganate (limiting amount of 0.75 equiv.), higher temperature range, and slower addition of dilute solution of the reagents, monoglycol **20a** was the major product, with a yield of *ca.* 40%. Higher concentrations of reagents, simultaneous mixing of reagents then addition of the solution of the protected diol to a solution of permanganate and magnesium sulfate, low temperatures and short reaction times favoured formation of chloro epoxy diol **21a**. Surprisingly, when the reaction was carried out in acetone containing a small amount of water at −78 °C, no significant change in the reaction velocity or in the composition of products was found. Similar results have been obtained with bromo diene **18b**.[2]

Further optimization of reaction conditions led to the use of tetraethylammonium chloride (TEAC) as a phase-transfer catalyst (PTC) and phosphoric acid instead of magnesium sulfate, conditions resulting in a 52% yield of a mixture containing 80% chloro epoxide **21a** as well as inosose epoxide **22** and a new by-product, the unusual bicyclic ether **23a**. Diol **20a** was not detected. The presence of **23** was later detected (*vide* NMR) to the extent of *ca.* 5% in reaction mixtures available from oxidations of dienes **18** that were run under the less optimal conditions of earlier experiments. The absence of diol **20a**, whose separation from **21a** is problematic, and the significantly lower amount of water in the PTC reaction mixtures simplified the isolation of chloro epoxy diol **21a**—only an extraction and a single recrystallization were necessary to provide a pure product.

Our results were surprising in view of the general belief that permanganate oxidations of conjugated dienes cannot be easily

* Product distribution from the oxidation of **18a** with potassium permanganate:

T/°C	$KMnO_4$ (equiv.)	Method	% **20a**	% **21a**	% **22**
−5	0.85	A	45	45	10
25	0.85	A	60	30	10
−5	2.10	A	30	60	10
−10	2.10	B	10	80	10
−5	2.30	C	10	80	10
−78	2.30	B	15	75	10

Method A: $KMnO_4$–$MgSO_4$ solution was added to a solution of **18a**. Method B: Simultaneous mixing of both reagents (see Experimental section for details). Method C: A solution of **18a** was added to a suspension of reagents.

controlled and yield the products of full oxidative cleavage in most cases.[22] The literature contains examples of oxidation of 1,5-dienes with concomitant ring closure to dihydrofurans[23] as well as four examples of a controlled oxidation of 1,3-dienes to epoxy diols, albeit in yields of only about 30%. Occidentalol **24** yielded epoxy diol **25**[24] with potassium permanganate, whereas a milder reagent, zinc permanganate, furnished epoxy diol **26** from cyclopentadiene.[25] A third example involved the potassium permanganate oxidation of β-ionone **27** to α-hydroxy lactone **28**.[26a] In this transformation, the epoxy diol **29** may have been an intermediate, which would suffer further oxidative cleavage and an epoxide–ketone rearrangement under the reaction conditions (Fig. 4). In the fourth example epoxy diol **31** was generated from a steroidal diene **30**.[26b]

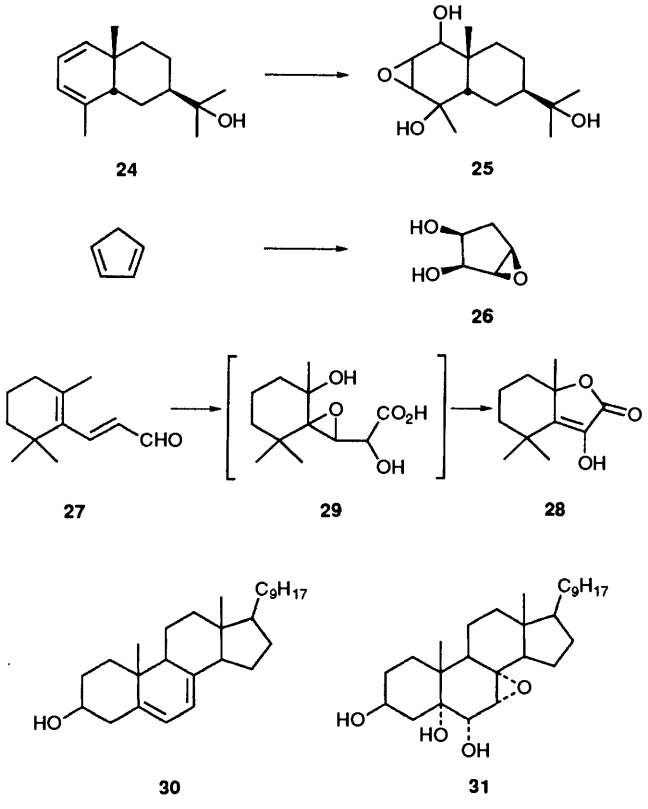


Fig. 4 Reported oxidations of 1,3-dienes with permanganate

Also surprising was the observation that the chloro epoxy diols **21** appeared to be remarkably stable. Such compounds, although commonly reported in the literature, are generally unstable and rearrange easily unless they are substantially stabilized by substituent effects. In general, α-halogeno epoxides are prone to rearrangements that lead to α-halogeno ketones and should be handled with care.[27] The racemic chloro epoxide **32** reported by Gasteiger rearranges at room temperature.[28] The halogeno epoxides **33** and **34**, prepared by Berchtold *via* peroxidation of the corresponding vinyl halides, are also unstable at room temperature.[29] Also α-halogeno epoxide **35** and its derivatives (Fig. 5), have been reported by Hanzlik

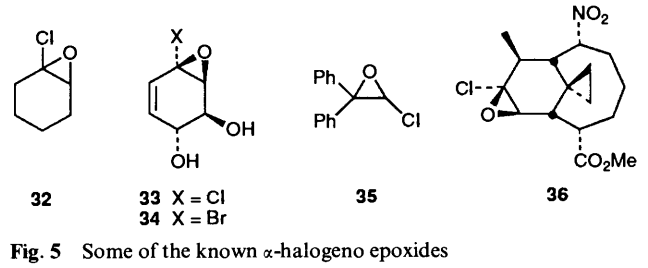


Fig. 5 Some of the known α-halogeno epoxides

and shown to rearrange to α-halogeno ketones.[30] Another interesting α-halogeno epoxide, **36**, was recently reported during a synthetic investigation of taxane diterpenes by Cha, who has commented on its unusual stability.[31]

Mechanistic Interpretations.—For the conversion of a 1,3-diene into an epoxy diol, Sable proposed a rearrangement (either concerted or stepwise) of allylic manganese(v) ester **37** to an 'anhydride' of mixed oxidation states such as **38** (Fig. 6).[25a]

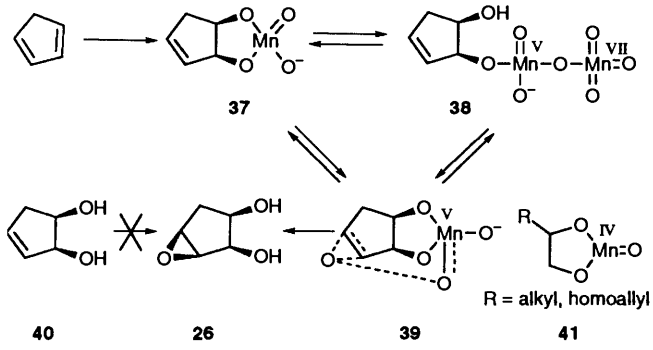


Fig. 6 Sable's mechanism of diene oxidation[25]

The introduction of the epoxide in Sable's example was compared mechanistically with the oxidation of allylic alcohols by means of perbenzoic or pertungstenic acid. At the time of Sable's investigation no hard evidence for species such as **38** or **39** was available, but in a later report[25b] Sable confirmed that allylic diol **40** was *not* an intermediate in the formation of **26**. Species such as **38** and **39** as well as cyclic manganese(IV) esters of type **41**, have been proposed by Wolfe, Ingold and Lemieux[32] for the 'normal' oxidation of olefins[32a] and 1,5-dienes.[32b]

To explain the formation of **20**, **21**, **22** and **23** we propose a mechanism involving a '1,4-addition' of permanganate to the polarized diene in **18** as shown in Fig. 8. Although no hard evidence is available concerning the precise mechanism of permanganate oxidation of polyolefinic compounds, it is not improbable that such a 1,4-interaction can occur. There are two arguments in favour of this mechanism. The first comes from observations made by Rojahn[23] in 1965 and Ingold[32b] in 1981 concerning $KMnO_4$ oxidation of 1,5-dienes such as **42** to tetrahydrofuran-2,5-diols or their methyl-substituted analogues (Fig. 7).

A plausible explanation of this process may indeed involve

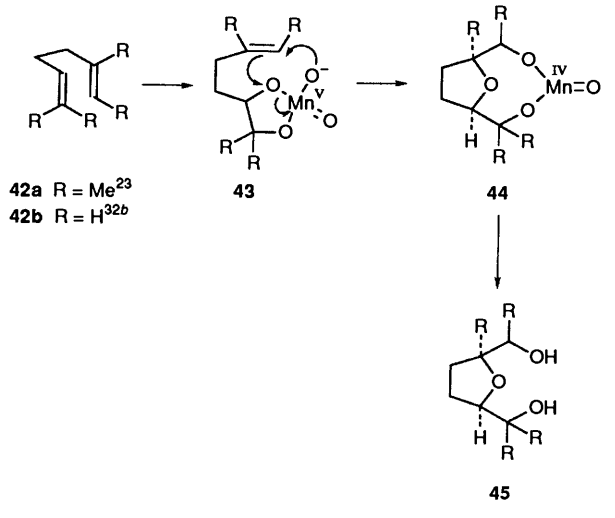


Fig. 7 Oxidation of 1,5-dienes

the internal migration and concomitant reduction of the initial adduct **43** to **44**, which is then hydrolysed to the product. The second argument involves the polarization of the diene moiety in **18** as shown by AM1 calculations[1b,10] as well as the ease and the regioselectivity with which it undergoes 4 + 2 cycloadditions.[3,11,12,33] The mechanism proposed in Fig. 8 accounts

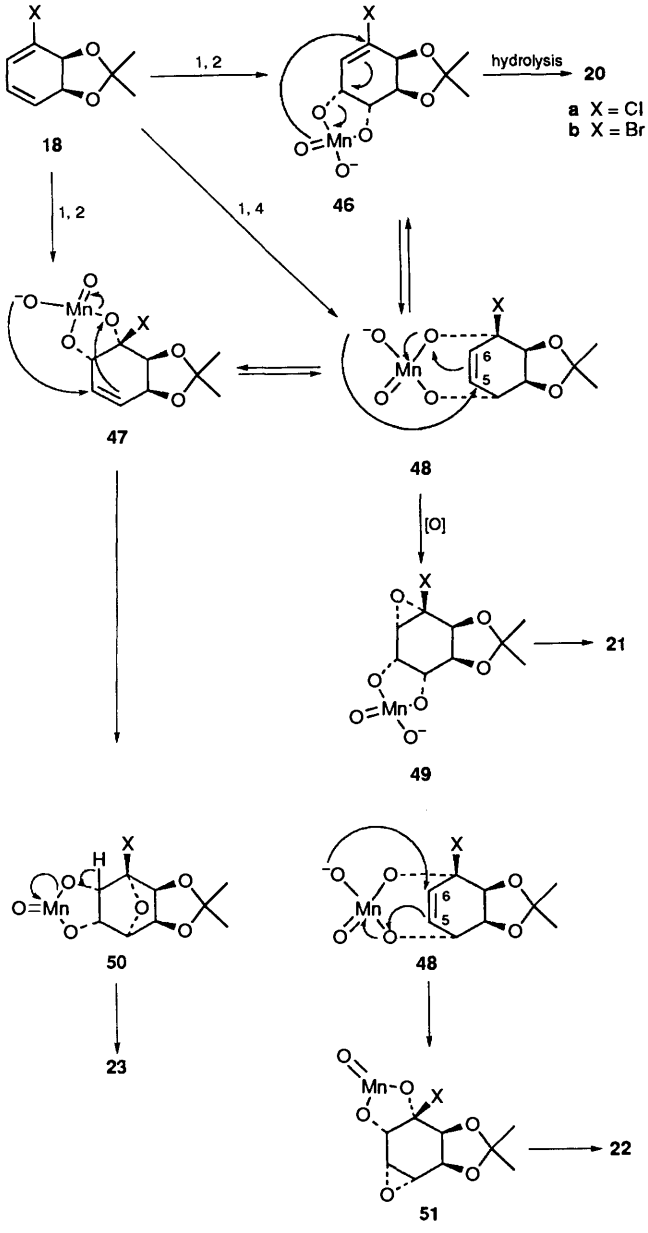


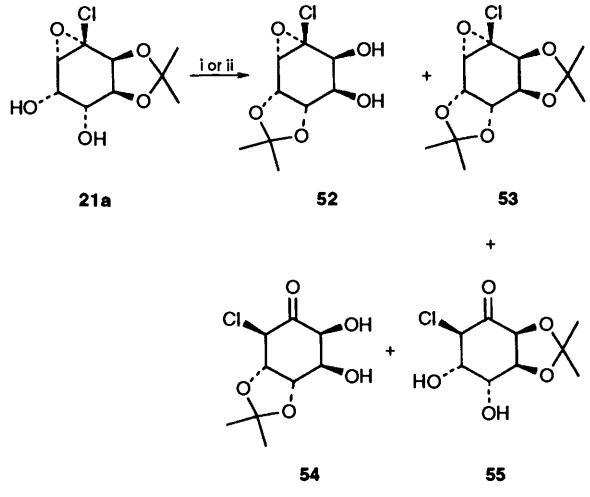
Fig. 8 Proposed mechanism of oxidation of halogeno dienes **18** with permanganate

for the formation of all products observed in the oxidations of **18a** and **18b**.

The interpretation of these results suggests a kinetic 1,4-addition of permanganate to the highly polarized diene in **18** to form intermediate **48**, which can rearrange to either of the normal 1,2-adducts **46** or **47**, formed also by addition of the permanganate ion to either of the two double bonds. The ratios of products from reaction of **18** under different conditions may reflect the competition between the two pathways. The collapse of the 1,4-adduct also requires further oxidation, which can be accomplished under the reaction conditions with a second equivalent of oxidant (Fig. 8). Molecular modelling suggests that one of the oxygen atoms in **48** lies directly over the π-system of the C(5)–C(6) olefin thus facilitating a possible sigmatropic rearrangement to **49**. Compounds **21** and **22** may, therefore, result from a non-regiospecific sigmatropic rearrangement of adduct **48** at C-5 and C-6, respectively, as shown in Fig. 8. Diol **20** is a product of the 'normal' 1,2-addition of permanganate to the more electron-rich C(4)–C(5) olefin. The adduct of permanganate at the C(1)–C(6) double bond would lead, through a sigmatropic migration similar to that postulated for **48** to **50**, which suffers a redox process to generate the C-6 carbonyl.

Further studies will investigate the validity of these processes by direct monitoring of reaction aliquots by ^{1}H, ^{13}C and ^{55}Mn NMR spectroscopy. The rearrangement pathway or the regiochemical competition of 1,2-oxidations of the two olefins is supported by the isolation of minor products **22** and **23**, but a more precise definition of the mechanism must await further study. As an extension of the initial mechanistic studies by Sable[25b] we monitored these reactions for the intermediacy of diol **20a**. Independent experiments established that this material is *not* converted into chloro epoxide **21a** under the reaction conditions, thus confirming Sable's observation.

Reactivity and Dehalogenation Studies of Halogeno Epoxides.—In view of the literature precedent, the observed stability of **21a** ($t_{\frac{1}{2}}$ in toluene at 110 °C is *ca.* 50 h) was puzzling. Furthermore, heating of the neat chloro epoxy diol **21a** to 116 °C under argon led to either complete decomposition with a rather violent release of HCl or, after 5 min, to an unexpected intra- as well as inter-molecular migration of the acetonide moiety with the retention of the chloro epoxide (Scheme 3).*



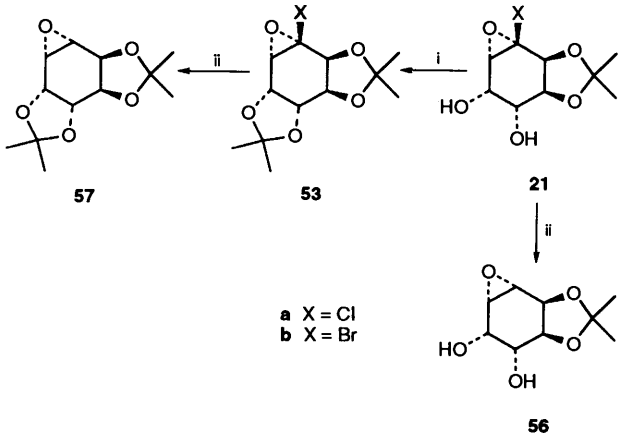
Scheme 3 Thermolysis of chloro epoxy diol **21a**. *Conditions:* i, 100 °C; ii, 116 °C.

From this reaction mixture, chloro epoxy diols **52** (57%), fully protected **53** (14%) and chloro ketone **54** (2%) as well as 10% starting material were identified (Scheme 3). The completely deprotected chloro epoxide tetrol was not detected in the mixture by ^{1}H NMR. Optical rotation of **53** was identical with that obtained from the protection of **21a** with dimethoxypropane (DMP) under acid catalysis. This fact coupled with structure confirmation for **52** by X-ray crystallography served as additional proof of the identity of **21a**. Careful heating of **21a** at 100 °C for 20 min led to complete conversion of chloro epoxy diol **21a** into chloro epoxide **52** (75%) and chloro ketone **55**

* The intermolecular migration of the acetonide moiety was also observed in the mother liquor from recrystallizations of the crude permanganate oxidation products. After 3 months at −20 °C, *ca.* 30% conversion of diols **20** and **21** into their fully protected counterparts was observed.

(25%). Chloro epoxy diol **52** was found to melt at a temperature more than 30 °C higher than the parent compound **21a** and was significantly less soluble in organic solvents, most probably because of the hydrogen bonding between the chlorine atom and the hydrogen atom of the adjacent hydroxyl. The dehalogenation of halogeno epoxides **21** and **53** was studied, and they were converted to known epoxy diols **56**[2,10] and **57**,[34] respectively.

A systematic search for the efficient reduction protocol led to some new discoveries.* The successful reduction of the α-chloro epoxide moiety to the epoxide was achieved by the reduction of the fully protected chloro epoxide **53** by tributyltin hydride (TBTH) and azoisobutyronitrile (AIBN) in a yield of 54%.[35] The best results in the mono protected series, **21**, were obtained with tris(trimethylsilyl)silane (TTMS) and AIBN by an adaptation of a known reduction procedure[36] (Scheme 4).

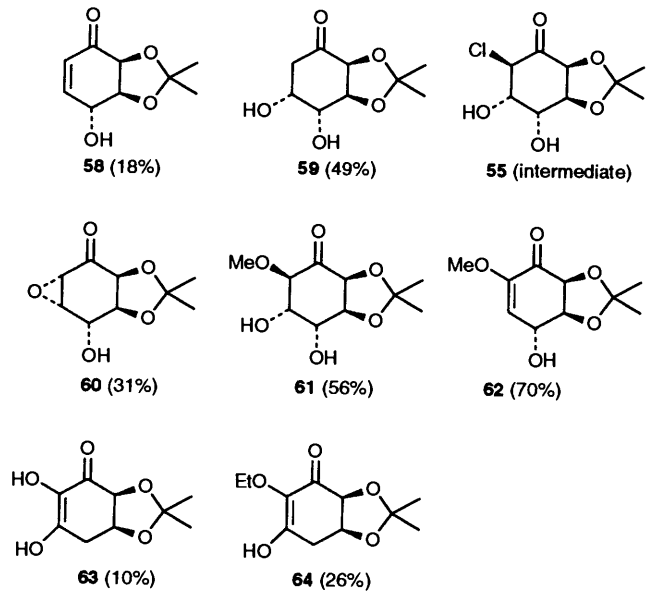


57 **53** **21** **56**

Scheme 4 Reduction of halogeno epoxides **21** and **53**. *Reagents:* i, DMP/PTSA; ii, TTMSS/AIBN or TBTH/AIBN.

However, scale-up was problematic, and the product had to be purified by chromatography [in the case of **21a** (42%), chloro ketone **55** was isolated as a by-product (5%); in the case of **21b** (48%), ketone **59** was isolated]. In one experiment (see footnote,* section I of the Supplementary Material) the bicyclic ether **23** was isolated along with **56** and **59**.* The problem was solved by extraction of the crude mixture with water and use of the aqueous solution directly in further conversion of **56** to inositols.[2] Preliminary accounts of hydrolysis of this compound to several inositols including D-*chiro*-inositol, have appeared.[2,37]

During the various attempts at an effective preparation of **56**, some interesting reactive tendencies of **21a** and **21b** were observed. For example, treatment of chloro epoxide **21a** with SmI_2 in THF–MeOH for 30 min furnished enone **58**[10b,38a] isolated in 18% yield, a chiral synthon used previously in the preparation of conduritol C, conduritol A, and dihydroconduritol A,[38a,10b] as well as other compounds.[38b] Unless its preparation by this method can be optimized, the previously published procedure[10b] is superior and has been found reproducible by other investigators.[38b] The major product, ketone **59**, was isolated in 49% yield. Chloro ketone **55** was identified in the reaction mixture by careful monitoring and found to provide epoxy ketone **60** (31%) upon alkaline work-up (Fig. 9). It would appear likely that the rearrangement of **21a** to



58 (18%) **59** (49%) **55** (intermediate)

60 (31%) **61** (56%) **62** (70%)

63 (10%) **64** (26%)

Fig. 9 Products obtained from reductive and hydrolytic reactions of epoxides **21**

chloro ketone **55** is the primary process in the samarium-mediated reduction of **21a**.[28,30,39] Attempted zinc-mediated reduction of chloro epoxide **21a** in refluxing methanol provided after 2 h mostly ketone **61**, isolated in 56% yield, which was further transformed to the ultimate product of this reaction, methoxy enone **62**, isolated after 30 h in 70% yield.

Attempted generation of amino inososes from **21a** by reaction with benzylamine in THF at −25 °C and conversion of the product into its salt at low temperature gave an impure solid whose recrystallization from 95% ethanol furnished through nucleophilic displacement of the amino group and elimination, enones **63**† and **64** in 10 and 26% yields, respectively. NMR evidence (HETCOR) suggested that **63** exists as two distinct enol tautomers.

These oxygenated synthons are potentially useful in the general syntheses of cyclitols and their derivatives (see the section on inositol an inosose syntheses). The reactivity of the α-chloro epoxide[27,29] and the oxygenation of the ring provide multiple options during reductive or nucleophilic operations. No aromatic by-products were detected in any reaction mixtures, and all of the ketones shown in Fig. 9 are stable to handling.[40] Experimental and spectral data for these compounds reported in our preliminary paper[40] are listed in the Experimental section.

Oxygenated Dimers containing the Pyrazine Nucleus.—An interesting observation was made during an attempted generation of amino-3-inosose by aminolysis of **21a**. In ammonia or in $CHCl_3$ saturated with ammonia, **21a** undergoes the expected epoxide opening followed by *in situ* dimerization to dihydropyrazine, which undergoes aromatization and further reactions to furnish the dimers shown in Fig. 10. Neither amino 3-inosose **65** nor dimer **66** have been detected in reaction mixtures even with careful monitoring. It appears that the initial adduct **66** leads, through tautomerization of one of the imines, to a β-hydroxy enamine **67**. This compound can be detected by NMR

* For specific conditions and description of compounds not contained in this manuscript consult the Supplementary materials section (I. Dehalogenation and aminolysis of chloro and bromo epoxides **21** and their derivatives. II. Hydrolytic studies and optimization of conditions for the synthesis of D-*chiro*-inositol from epoxide **56**. III. Hydrolysis of epoxide **21a**. IV. Reduction of **80**).

† The enone **63** was also observed as a product of decomposition of epoxy ketone **22** during column chromatography on silica gel. To confirm this observation, epoxy ketone **22** was exposed to 10% deactivated silica gel in hexane–ethyl acetate mixture for 2 h at ambient temperature. Nearly 20% conversion to the enone **63** was observed (*vide* NMR).

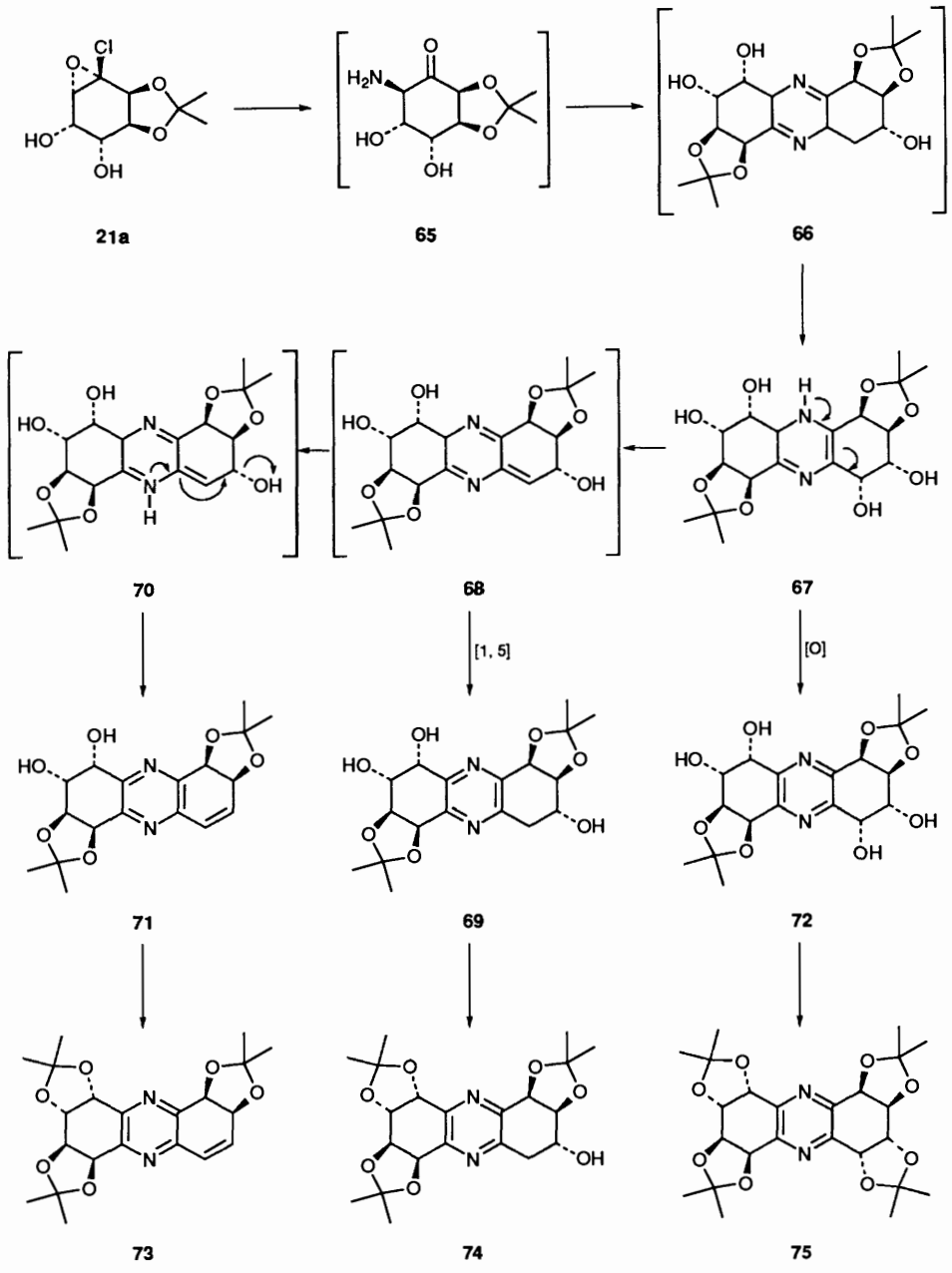


Fig. 10 Oxygenated aminoinososes dimers containing the pyrazine nucleus

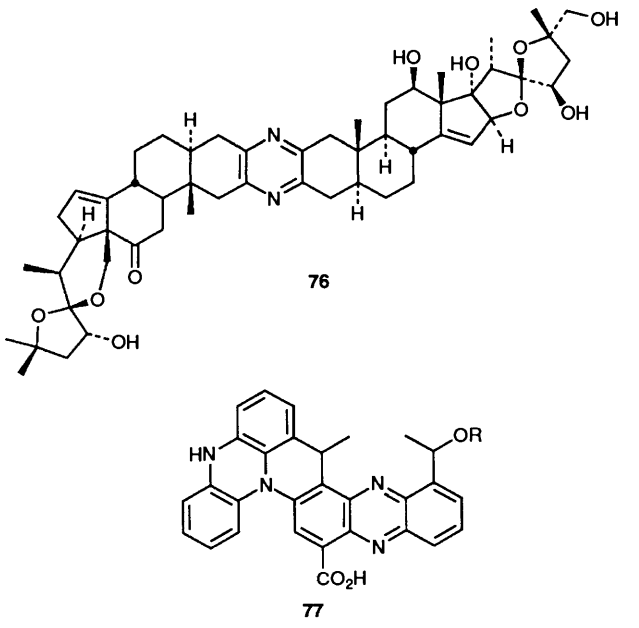
as the only product when the reaction and work-up are carried out below 0 °C and under an inert atmosphere, but it is unstable to further manipulation. Dehydration of enamine **67** yields **68** and provides either **69** *via* a [1,5]-shift or leads to the tautomer **70**, which undergoes further elimination to **71**. The formation of **72** is best explained by air oxidation of the initial adduct.

The tendency of aminocarbonyl compounds to dimerize with concomitant aromatization is well known.[41] For better separation, the crude dimerized mixture was treated with DMP/PTSA to obtain the fully protected **73** (42%), **74** (22%), and the highly crystalline symmetrical **75** (5%), whose structure was determined by X-ray crystallography.

Compounds **69**, **71** and **72** are structurally related to the antibiotic cephalostatin **76**, which has shown antiviral properties.[42,43] Recently studies of the biosynthesis of pyrazine-containing esmeraldin-type antibiotics **77** has implicated dimerization of dehydroamino shikimates by a mechanism similar to the one suggested here.[43b] Deprotected and hydrogenated forms of the oxygenated dimers will be subjected to standard antiviral screening.* In the deprotected form they may exhibit interesting chelating properties, especially if the pyrazine ring is fully saturated and, therefore, having defined *exo* and *endo* surfaces. Further investigations of the molecular properties of these compounds will be pursued.

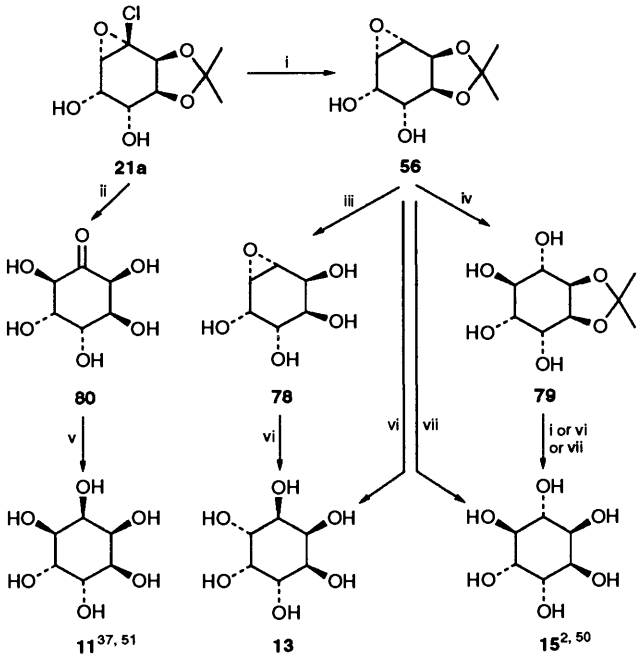
Synthesis of Inositols and Inososes.—Epoxy diol **56** is an ideal substrate for the synthesis of inositols and conduramines. In a preliminary account, we have already suggested a possible mechanism for conversion of epoxide **56** into D-*chiro*-inositol **15**, *muco*-inositol **12**, and *neo*-inositol **13**.[37] We have subsequently discovered an error in our assignment of *muco*-inositol, prepared by other means.[44] A variety of reaction conditions (see Supplementary publication) was investigated to optimize the hydrolysis of **56** and to understand the series of

* An agreement for testing of these materials has been established with Genencor International, Inc.



Structures **76** and **77**

Payne rearrangements[37,45] that some of these cyclic hydroxy epoxides seemed to undergo. Exposure of **56** to acidic ion-exchange resin at ambient temperature or hydrolysis in 10% acetic acid at 80 °C led to epoxide **78** (the enantiomer of conduritol E epoxide reported by Carless)[34] with selectivity of *ca.* 95 and in > 80% yield (Scheme 5).

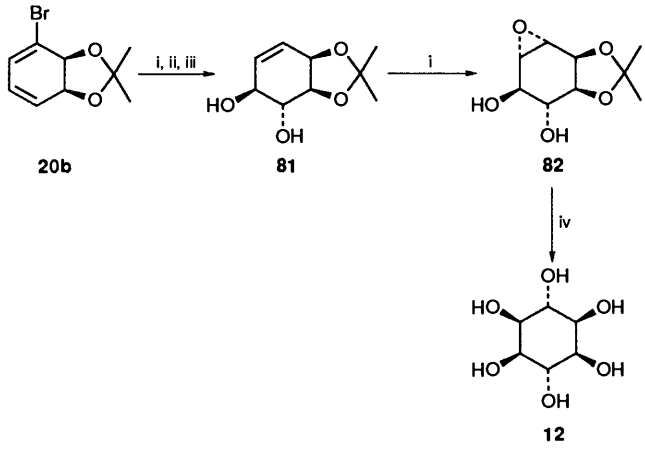


Scheme 5 Synthesis of inososes and inositols from epoxy diol **21a**. *Reagents and conditions:* i, TTMSS/AIBN; ii, H_2O/Al_2O_3/80 °C; iii, H_2O/Amberlyst 15/25 °C or 10% AcOH/80 °C; iv, H_2O/Amberlyst A21 and Amberlite IRA 904 (1:1)/100 °C; v, H_2/Ra-Ni/MeOH; vi, H_2O/Amberlite IR 118/100 °C or H_2O/100 °C; vii, H_2O/sodium benzoate/100 °C.

D-*chiro*-Inositol **15** was obtained with greater than 95% selectivity by hydrolysis of **56** under mildly basic conditions (sodium salts of weak organic acids) *via* D-*chiro*-inositol acetonide **79**. When sodium benzoate was used as a base, a nearly quantitative yield of **15** was obtained. The use of stronger bases led to the isolation of pure **79** (88%), which could be hydrolysed in water or with acid catalysis. *neo*-Inositol **13** is prepared by hydrolysis of epoxide **56** (as a 30–40% mixture with D-*chiro*-inositol) in water or in the presence of strongly acidic resins at 95–100 °C *via* epoxide **78**, which could be isolated then hydrolysed in water at 100 °C (as a 40% mixture with D-*chiro*-inositol). It is isolated with *ca.* 50% recovery by a single recrystallization from such reaction mixtures because of its significantly lower solubility than D-*chiro*-inositol.

Treatment of the chloro epoxy diol **21a** with water led to mixtures containing inosose **80** in various proportions based on the reaction condition * (Scheme 5). After careful optimization,* the best hydrolytic conditions proved to be catalysis with aluminium oxide or simply refluxing **21a** in water. When inorganic acids or bases were used, products were dark, very complex, and difficult to isolate. The highest stereoselectivity (< 95%) was achieved with aluminium oxide; however, from a preparative point or view, the best results were obtained when water alone was used in spite of lower selectivity (90%). When the reaction mixture was neutralized with a basic ion exchange resin before the work-up, **80** was obtained in nearly 85% yield; otherwise, the reaction mixtures and products were very unstable and decomposed during work-up to dark, acidic by-products. The use of activated charcoal as a decolourizing agent was avoided since it decreased the quality of the product. Finally, *allo*-inositol was prepared by reduction of *chiro*-3-inosose **80** by several approaches, including hydride reductions and resin-supported borohydrides; metal reductions did not give satisfactory selectivity and yield.* Catalytic hydrogenation over Raney nickel was the most successful method, which led to *allo*-inositol **11** with 90% selectivity and in 80% yield.

To confirm our error in the preliminary report,[37,44] *muco*-inositol **12** was synthesized as shown in Scheme 6 by adapting



Scheme 6 Synthesis of *muco*-inositol. *Reagents:* i, *m*-CPBA; ii, H_2O/NaOH; iii, TBTH/AIBN; iv, H_2O/sodium benzoate.

our procedure for the synthesis of pinitols[10] and D-*chiro*-1-inositol.[2] Hydrolysis of **56** was repeated under the originally reported conditions;[37] careful analysis of the products indicated the presence of *muco*-inositol to the extent of 5%, thus corroborating the conclusions regarding the consecutive Payne rearrangements reached in the preliminary report.[37,44] Thus three of the nine inositols were prepared in a selective fashion from a single enantiomer of α-chloro epoxide **21a**, whereas

* For specific conditions and description of compounds not contained in this manuscript consult the Supplementary materials section (I. Dehalogenation and aminolysis of chloro and bromo epoxides **21** and their derivatives. II. Hydrolytic studies and optimization of conditions for the synthesis of D-*chiro*-inositol from epoxide **56**. III. Hydrolysis of epoxide **21a**. IV. Reduction of **80**).

muco-inositol was derived from acetonide **20b** by epoxidation, hydrolysis, and reduction *via* the known *trans*-diol **81**[38a] (the acetonide of (−)-conduritol F) and the hydrolysis of its epoxide **82**. The synthesis of these inositols was executed in a manner that would allow the preparation of the homochiral protected derivatives of the *meso* compounds by adjustments in the choice of protecting groups or nucleophiles used. Their short syntheses compare more than favourably with those currently in the literature.[3a,5f]

Carbohydrate Synthesis.—We have discussed the potential of *cis*-cyclohexadiene diols in generating simple tetroses, pentoses and hexoses by a controlled scission of two, one, or no carbon atoms from **18**.[3d,10] The availability of epoxides **21** allowed us to prepare in just two steps D-erythruronolactone **83** (Fig. 11),

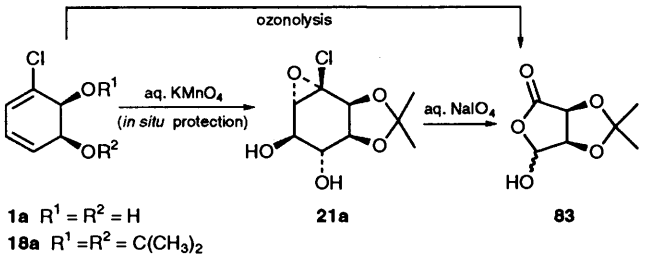


Fig. 11 Synthesis of D-erythruronolactone by sequential oxidation of chlorobenzenediol

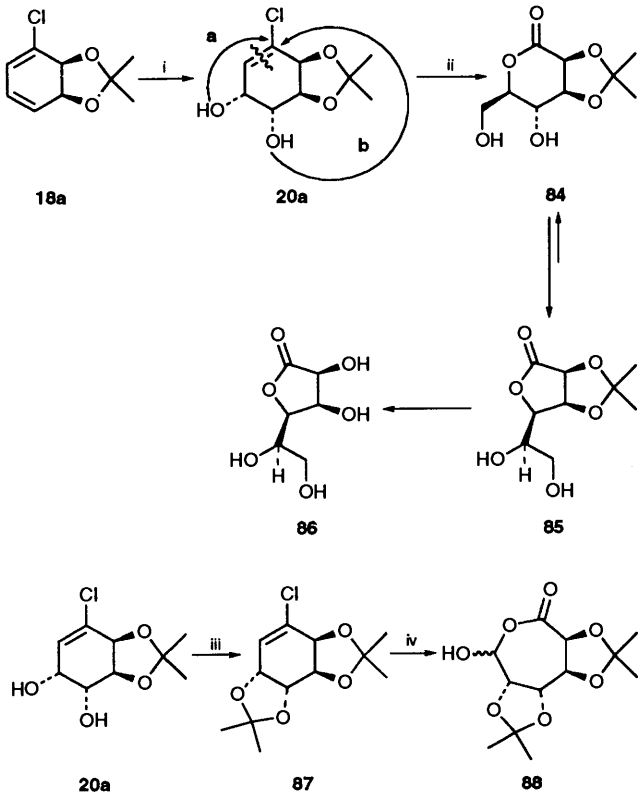
previously made by ozonolysis of **18** and which served as a source of both enantiometers of erythrose[46] and ribonolactone.[47] Oxidation of **21a** with 2 equiv. of periodate provides **83** in an overall yield comparable to that obtained from ozonolysis.[48]

A plausible mechanism of formation of **83** using 2 equiv. of periodate has been proposed in our published disclosure of this synthesis.[49] This transformation allows for a large-scale synthesis of this intermediate, completely avoiding ozone (and the necessary cooling) in the process, and allows the entire transformation to take place in a one-pot sequence from **18a** (or **1a**, with *in situ* protection of the diol) in 51% yield.[49]

For the preparation of higher carbohydrates of the hexose type (pyranose or furanose) we chose mannose to demonstrate the feasibility of oxidative cleavage of the C(1)–C(6) olefin in **18** and the concomitant trapping of the C-1 carboxylate by a peripherally located nucleophile. The transformations of **18a** and **20a** to mannose-like-synthons are shown in Scheme 7.

Ozonolysis of **20a** in the presence of $NaHCO_3$ followed by hydrogenation afforded cleanly the protected mannosolactone **85**. Removal of the acetonide group provided sugar **86**, which was identical with an authentic sample of L-mannosolactone (Aldrich) in all respects except optical rotation. The six-membered ring form of mannosolactone **84** is present in the reaction mixture but is not stable to isolation. Only the γ-lactone was isolated *via* the cyclization of C-4-hydroxyl in contrast to a similar cyclization of amino alcohol which produced a six-membered lactam.[1a] Similarly, ozonolysis at room temperature and non-reductive work-up of completely protected olefin **87** produced the hydroxy lactone of mannonic acid aldehyde **88**. This strategy has also been applied to the preparation of aza analogues of carbohydrates.[1a]

Conclusions.—The attainments of several inositols and a hexose concludes that part of the program aimed at concise preparation of carbohydrates and cyclitols from chiral synthons derived from bacterial dioxygenation of chlorinated aromatics. The design of synthesis for such compounds from chloro dienediols offers many advantages: first, the preparations are



Scheme 7 Synthesis of mannose derivatives from olefin **20a**. *Reagents:* i, $KMnO_4/MgSO_4$; ii, $O_3/NaHCO_3$; $H_2/Pd(C)$; iii, DMP/PTSA; iv, O_3, then $DMS/NaHCO_3$; v, CF_3CO_2H/H_2O.

short and environmentally sound; second, the stereochemistry of almost any sugar derivative can easily be incorporated into the periphery of dienediol though short sequences of stereoselective transformations, and third, the modes of cyclization of peripheral substituents onto carbonyl groups derived *via* oxidative cleavage can be controlled by a judicious choice of protective groups.

Experimental

General.—All nonhydrolytic reactions were conducted in oven-dried or flame-dried glassware under atmospheres of dry argon. All solvents were reagent grade. Anhydrous solvents were dried immediately before use. Ether and THF were distilled from sodium benzophenone ketyl. Dichloromethane, diisopropylethylamine, pyridine, hexamethyldisilazane, chlorotrimethylsilane, triethylamine, dimethylformamide, and *tert*-butyldimethylsilyl chloride were distilled from CaH_2.

Ozonolysis was carried out with an OREC apparatus, model 03V10-0. Dry oxygen containing about 2.5% ozone was introduced at a speed of 4 dm^3 min^{-1} into the solution of a substrate.

Analytical TLC was performed on silica gel Merck Kieselgel 60 F_{254} (0.25 mm thickness) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution or phosphomolybdic acid solution (EtOH 95%) followed by warming on a hot plate. Flash chromatography was carried out on Merck Kieselgel 60 silica gel (230–400 mesh). Mass spectra were recorded on a Varian MAT-112 instrument (low resolution) or on a double focussing VG 7070 E-HF instrument (exact mass). IR spectra were recorded on Perkin-Elmer 283B or 710B instruments. NMR spectra were recorded on a Bruker WP-270 instrument. ^1H NMR chemical shifts are reported in parts per million (ppm) relative to TMS as were carbon chemical shifts; *J*-values are reported in Hz. Rotations were recorded on a Perkin-Elmer 241

digital polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Melting points were obtained on a Thomas–Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., PO Box 2288, Norcross, GA 30091.

The following experimental procedures have been published in preliminary reports: D-*chiro*-inositol **15**,[2] *allo*-inositol **11**,[37] chloro epoxy diol **21a**,[2] bromo epoxy diol **21b**,[2] D-*chiro*-3-inososse **80**,[2] erythruronolactone **83**.[49] Updated experimentals for **59** and **60**[40] and a new procedure for the preparation of **21a**[2] are listed in this section.

muco-*Inositol* **12**.—A solution of **82** (66 mg, 0.33 mmol) and sodium benzoate (3 mg, 0.02 mmol) in water (2 cm^3) was heated in darkness under argon to 105 °C for 40 h. Evaporation of the mixture and recrystallization of the product from ethanol–water furnished crystalline **12** (45 mg, 77%): m.p. 285–300 °C (lit.,[52] m.p. 280–300 °C; ν_{max}(KBr)/cm^{-1} 3300, 2945, 2900, 1460, 1390, 1340, 1145, 1115, 1085 and 1070; $\delta_H(D_2O)$ 3.89 (br t, *J* 5.8, 2 H), 3.76 (br d, *J* 6.8 Hz, 4 H); $\delta_C(D_2O)$ 72.5 (CH, double intensity) and 70.4 (CH).

neo-*Inositol* **13**.—A mixture of epoxide **56** (0.69 g, 3.4 mmol), Amberlyst IR-118® (1.5 g) and water (10 cm^3) was stirred at 100 °C for 30 min and then filtered. The solution was filtered again through charcoal and then concentrated to give a mixture (0.54 g, 87%) containing D-*chiro*-inositol **15** (70%) and **13** (30%). Recrystallization of this product from aqueous ethanol furnished *neo*-inositol **13** (96 mg), m.p. > 300 °C (lit.,[53] m.p. 315 °C); $\delta_H(D_2O)$ 3.94 (br s, 2 H) and 3.65 (br s, 4 H).

(1R,2S,3S,4R,5S,6S)-1-*Chloroisopropylidenedioxy*-1,2-*epoxycyclohexane*-3,4-*diol* **21a**.*—To a stirred solution of **1a** (9.0 g, 62 mmol) in a mixture of chloroform (100 cm^3) and DMP (15.1 cm^3, 123 mmol) at 10 °C was added PTSA·7H$_2$O (0.8 g, 4 mmol). After the reaction mixture had been stirred for 20 min it was washed with 0.1 mol dm^{-3} aqueous NaOH. The resulting solution was added dropwise, over a period of 10 min, to a vigorously stirred mixture of water (300 cm^3), KMnO$_4$ (24.8 g, 0.157 mol), chloroform (150 cm^3), H$_3$PO$_4$ (11 cm^3, 0.19 mol) and tetraethylammonium chloride (0.2 g, 1.2 mmol), precooled to 0 °C. The reaction temperature during the addition was < 5 °C. Sodium hydrogensulfite was then added to the mixture until the remaining permanganate was reduced, after which it was stirred at 5–10 °C for 15 min. The mixture was filtered to remove precipitated MnO$_2$ after which the latter was washed with water and chloroform. The filtrate was extracted (× 10) with chloroform and the combined extracts were dried (MgSO$_4$) and evaporated to give an almost colourless solid (7.6 g, 52%), which was recrystallised from benzene–hexane to furnish **21a** (5.1 g, 35%). The mother liquor was evaporated to leave a solid residue (2.4 g) containing **21a** (30%), **22** (30%) and **23** (40%), which was quickly chromatographed (10% deactivated silica gel, CHCl$_3$–MeOH, 99:1) to furnish **23** (260 mg, 2%).

(2S,3R,4R,5S,6S)-2-*Hydroxy*-5,6-*isopropylidenedioxy*-3,4-*epoxycyclohexanone* **22**.—The filtrate from the preparation of **21b**[2] was saturated with NaCl and extracted with EtOAc. Drying and concentration of the extract yielded crude crystalline product (3.3 g), recrystallization (EtOAc/hexane/Et$_2$O) of which gave **21b** (1.63 g, 22%). The mother liquor was concentrated under reduced pressure, and the residue was purified by flash chromatography (10% deactivated silica gel, CHCl$_3$–MeOH, 95:5) to furnish **21b** (90 mg, 1.3%), the bromo derivative **20b**[10] (380 mg, 3.8%) and **22** (55 mg, 1.1%); m.p. 126–127 °C; $[\alpha]_D^{20}$ +61.1 (*c* 1, CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3515, 3005, 2965, 1735, 1390, 1385, 1245, 1205, 1090 and 1055; $\delta_H(CDCl_3)$ 5.13 (dd, *J* 5.8, 1.4, 1 H), 4.86 (ddd, *J* 5.9, 1.4, 1.4, 1 H), 4.42 (dd, *J* 5.9, 1.5, 1 H), 3.67 (ddd, *J* 3.8, 1.4, 1.4, 1 H), 3.39 (ddd, *J* 3.8, 1.4, 1.4, 1 H), 3.31 (br d, *J* 5.8, 1 H), 1.60 (s, 3 H) and 1.39 (s, 3 H); $\delta_C(CDCl_3)$ 202.4 (C), 113.2 (C), 78.2 (CH), 77.4 (CH), 70.0 (CH), 59.5 (CH), 54.0 (CH), 27.3 (CH$_3$) and 25.3 (CH$_3$); *m/z* (CI) (rel. intensity) 201 (M + 1, 100), 143 (12), 125 (14) and 111 (14) (Found: C, 53.8; H, 6.0. Calc. for $C_9H_{12}O_5$: C, 54.00; H, 6.04%).

(1S,3S,5R,6S)-1-*Chloro*-3-*hydroxy*-5,6-*isopropylidenedioxy*-7-*oxabicyclo*[2.2.1]*heptan*-2-*one* **23**.—M.p. 104–106 °C; $[\alpha]_D^{25}$ −38.6 (*c* 1, CHCl$_3$); ν_{max}(CHCl$_3$)/cm^{-1} 3540, 3040, 1750, 1395, 1375, 1210, 1095 and 1085; $\delta_H(CDCl_3)$ 5.14 (dd, 5.7, 1.2, 1 H), 4.88 (dd, 5.9, 1.6, 1 H), 4.46 (d, 5.9, 1 H), 3.93 (dd, 1.6, 1.2, 1 H), 3.29 (d, 5.8, 1 H), 1.65 (s, 3 H) and 1.43 (s, 3 H); δ_C([$^2H_6$]acetone) 200.7 (C), 113.9 (C), 80.6 (CH), 78.6 (CH), 76.2 (C), 69.5 (CH), 67.8 (CH), 26.8 (CH$_3$) and 25.0 (CH$_3$); *m/z* (CI) (rel. intensity) 235 (100, M + 1), 219 (15), 199 (15), 189 (10), 171 (25), 159 (10), 149 (10), 129 (20), 113 (15) and 101 (20) [Found (HRMS, CI): 235.0362. Calc. for $C_9H_{11}ClO_5$: 235.0373].

(1S,2S,3R,4R,5S,6S)-1-*Chloro*-4,5-*isopropylidenedioxy*-1,6-*epoxycyclohexane*-2,3-*diol* **52**.—Epoxide **21a** (neat; 450 mg, 1.90 mmol) was heated under argon to 120 °C for 4 min. The resulting dark solid was dissolved in acetone, and the solution filtered through charcoal and concentrated. The residue was chromatographed (10% deactivated silica gel, CHCl$_3$–MeOH, 3:97) to furnish **53** (75 mg, 14%), **52** (210 mg, 47%), starting material **21a** (45 mg, 10%) and **54** (10 mg, 2%).

For **52**: m.p. 147–148 °C; $[\alpha]_D^{25}$ −128.7 (*c* 0.5, MeOH); ν_{max}(KBr)/cm^{-1} 3400, 2990, 2915, 2540, 2495, 1370, 1260, 1200, 1130 and 1060; $\delta_H(CDCl_3)$ 4.72 (dd, *J* 7.9, 2.9, 1 H), 4.45 (dd, *J* 3.2, 2.1, 1 H), 4.17 (t, *J* 7.9, 1 H), 3.86 (ddd, *J* 7.9, 6.4, 3.3, 1 H), 3.78 (d, *J* 2.9, 1 H), 2.72 (br d, *J* 2.1, 1 H), 2.44 (br d, *J* 6.4, 1 H), 1.50 (s, 3 H) and 1.37 (s, 3 H); $\delta_C(CD_3OD)$ 110.2 (C), 80.2 (C), 77.5 (CH), 74.7 (CH), 73.6 (CH), 72.9 (CH), 60.3 (CH), 27.2 (CH$_3$) and 24.7 (CH$_3$); *m/z* (CI) (rel. intensity) 237 (20, M + 1) 221 (50), 201 (15), 179 (10), 161 (40), 143 (60), 133 (35), 125 (60) and 115 (65) [Found (HRMS, CI): 237.0488. Calc. for $C_9H_{13}ClO_5$ (M + 1): 237.0530].

For (2R,3S,4S,5R,6S)-2-*chloro*-5,6-*dihydroxy*-3,4-*isopropylidenedioxycyclohexanone* **54**, m.p. 121–125 °C; $[\alpha]_D^{25}$ +84.5 (*c* 0.3, CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3300, 2995, 2920, 1740, 1640, 1370, 1240, 1220 and 1050; $\delta(CDCl_3)$ 4.55 (d, *J* 5.3, 1 H), 4.48 (ddd, *J* 5.4, 4.0, 1.7, 1 H), 4.42 (br d, *J* 4.3, 1 H), 4.20 (br t, *J* 4.1, 1 H), 3.60 (dd, *J* 1.5, 0.6, 1 H), 2.93 (br s, 1 H), 2.42 (br s, 1 H), 1.47 (s, 3 H) and 1.38 (s, 3 H); $\delta_C(CDCl_3)$ 174.1 (C), 110.8 (C), 70.4 (CH), 68.7 (CH), 68.2 (CH), 63.6 (CH), 30.9 (CH), 27.41 (CH$_3$) and 25.45 (CH$_3$); *m/z* (CI) (rel. intensity) 237 (25, M + 1), 221 (65), 201 (45), 161 (35), 143 (80), 133 (35), 125 (45) and 115 (65) [Found (HRMS, CI): 237.0537. Calc. for $C_9H_{13}ClO_5$ (M + 1): 237.0530].

(1S,2S,3S,4R,5R,6S)-1-*Chloro*-3,4;5,6-*bis*(*isopropylidenedioxy*)-1,2-*epoxycyclohexane* **53**.—To a stirred solution of **21a** (1.14 g, 4.82 mmol) in dichloromethane (6.0 cm^3) and 2,2-dimethoxypropane (1.8 cm^3, 14.6 mmol) was added PTSA·7H$_2$O (10 mg, 0.053 mmol). After 2.5 h, sat. aq. Na$_2$CO$_3$ (0.5 cm^3) and water (25 cm^3) were added to the reaction mixture which was then extracted with light petroleum. The extract was dried and evaporated to give colourless crystalline **53** (1.24 g, 93%), m.p. 59–62.5 °C; $[\alpha]_D^{25}$ +23.1 (*c* 1, CHCl$_3$); ν_{max}(KBr)/cm^{-1} 2981, 2930, 1378, 1261, 1214, 1162, 1072 and 1053; $\delta_H(CDCl_3)$ 4.62 (m, 3 H), 4.35 (ddd, *J* 6.3, 1.7, 1.0, 1 H), 3.64 (ddd, *J* 1.8, 1.0,

* Another method for the synthesis of **21a** has been previously reported.[2]

1.0, 1 H), 1.48 + 1.47 (s, 6 H), 1.40 (s, 3 H) and 1.36 (s, 3 H); $\delta_C(CD_3OD)$ 111.0 (C), 110.6 (C), 79.0 (C), 76.2 (CH), 74.7 (CH), 74.2 (CH), 72.1 (CH), 62.2 (CH), 27.4 (CH_3), 26.8 (CH_3), 25.8 (CH_3) and 25.3 (CH_3); *m/z* (CI) (rel. intensity) 277 (M + 1, 63), 261 (80), 245 (10), 219 (15), 183 (40), 161 (43), 143 (72), 133 (62), 125 (45) and 115 (75) (Found: C, 52.2; H, 6.2. Calc. for $C_{12}H_{17}ClO_5$: C, 52.09; H, 6.19%).

(1R,2S,3S,4S,5R,6S)-1,6-*Isopropylidenedioxy*-2,3-*epoxycyclohexane*-4,5-*diol* **56**.—*Method A*. A solution of **21a** (103 mg, 0.435 mmol), tris(trimethylsilyl)silane (130 mg, 0.522 mmol) and AIBN (25 mg, 0.152 mmol) in toluene (1.5 cm^3) was degassed with argon and heated for 6 h to 105 °C. The reaction mixture was concentrated then chromatographed (10% deactivated silica gel, $CHCl_3$–MeOH, 95:5) to yield **56**[10] (37.1 mg, 42%) and **55** (3.9 mg, 5%). (When **21b** was used, the yield of **56** was 48%).

For (2R,3S,4R,5S,6S)-2-*chloro*-5,6-*isopropylidenedioxycyclohexane* **55**, m.p. 105–108 °C; $[\alpha]_D^{25}$ +110.5 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3500, 2990, 2915, 1740, 1365, 1225, 1150 and 1065; $\delta_H(CDCl_3)$ 4.93 (dd, *J* 10.7, 0.7, 1 H), 4.63 (d, *J* 5.2, 1 H), 4.56 (dd, *J* 2.9, 2.6, 1 H), 4.53 (dd, *J* 5.2, 2.9, 1 H), 3.97 (dd, *J* 10.7, 2.6, 1 H), 2.93 (br s, 2 H) and 1.41 + 1.40 (s, 6 H); $\delta_C(CD_3OD)$ 201.7 (C), 117.3 (C), 86.8 (CH), 79.7 (CH), 74.9 (CH), 70.8 (CH), 66.3 (CH), 27.6 (CH_3) and 26.2 (CH_3); *m/z* (CI) (rel. intensity) 237 (M + 1, 100), 219 (55), 201 (20), 193 (15), 185 (15), 179 (13), 161 (50), 143 (35), 127 (70) and 115 (25) [Found (HRMS, CI): 237.0534. Calc. for $C_9H_{14}ClO_5$ (M + 1): 237.0530].

Method B. A mixture of **21a** (4 g, 16.9 mmol), tris(trimethylsilyl)silane (4.72 g, 18.98 mmol), and AIBN (0.4 g, 2.44 mmol) in toluene (25 cm^3) was degassed with argon; it was then stirred at 70 °C until all the material dissolved whereupon it was heated at reflux for 5 h. The cooled mixture was extracted with water (×4), and the combined aqueous extracts were mixed with alumina (1 g) and activated charcoal (1 g) and then filtered with suction through Celite. Evaporation gave a solid (3.37 g) containing **56** (65%).

(1S,2R,3R,4S,5S,6R)-3,4; 5,6-*Bis*(*isopropylidenedioxy*)-1,2-*epoxycyclohexane* **57**.—A solution of **53a** (60.0 mg, 0.239 mmol), tributyltin hydride (76.3 mg, 0.262 mmol), and AIBN (19.6 mg, 0.119 mmol) in benzene (1.5 cm^3) was heated for 2.5 h under argon to 75 °C. The reaction mixture was then diluted with light petroleum (5 cm^3) and filtered through 10% deactivated silica gel. Washing of the silica gel with EtOAc and evaporation of the eluent gave waxy crystalline product (75 mg), whose chromatography (10% deactivated silica gel, hexane–EtOAc, 7:1) furnished **57** (25 mg, 43%), m.p. 109–110 °C; $[\alpha]_D^{25}$ −13.6 (*c* 1, MeOH) (lit.,[36] +13.5 for *ent*-**57**); ν_{max}(KBr)/cm^{-1} 2980, 2930, 1370, 1360, 1225, 1210 and 1050; $\delta_H(CDCl_3)$ 4.57 (m, 3 H), 4.34 (br d, *J* 6.5, 1 H), 3.34 (m, 2 H), 1.52 (s, 3 H), 1.41 (s, 3 H) and 1.37 (s, 6 H); $\delta_C(CDCl_3)$ 109.3 (C), 108.9 (C), 74.5 (CH), 72.5 (CH), 71.5 (CH), 69.9 (CH), 55.1 (CH), 52.3 (CH), 27.4 (CH_3), 26.5 (CH_3), 25.8 (CH_3) and 25.0 (CH_3); *m/z* (CI) (rel. intensity) 243 (M + 1, 37), 227 (50), 185 (100), 169 (10) and 127 (40) (Found: C, 59.6; H, 7.5. Calc. for $C_{12}H_{18}O_9$: C, 59.49; H, 7.49%).

(2S,3S,4R,5R)-4,5-*Dihydroxy*-2,3-*isopropylidenedioxycyclohexanone* **59**.—To a solution of **21a** (52.1 mg, 0.220 mmol) in a mixture of THF (1 cm^3) and MeOH (0.3 cm^3) under argon at −90 °C was added dropwise over a period of 30 min a solution of SmI_2 in THF (0.1 mol dm^{-3}; 2.5 cm^3, 0.230 mmol). The mixture was stirred for 1 h without cooling after which sat. aq. K_2CO_3 (1 cm^3) was added to it and stirring continued for an additional 15 min. The mixture was extracted with EtOAc and the extract dried and evaporated under reduced pressure to give the crude product as a solid. Flash chromatography (10% deactivated silica gel, $CHCl_3$–MeOH, 95:5, then 9:1) of this furnished **58** (7.2 mg, 18%)[41a] and **59** (22 mg, 49%); m.p. 87–88 °C; $[\alpha]_D^{25}$ +39.2 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400, 3030, 2995, 2935, 1735, 1385 and 1330; $\delta_H(CDCl_3)$ 4.55 (dd, *J* 6.5, 3.9, 1 H), 4.49 (br d, *J* 6.6, 1 H), 4.28 (m, 1 H), 4.16 (m, 1 H), 3.20 (br d, *J* 3.1, 1 H), 2.94 (br d, *J* 4.7, 1 H), 2.79 (dd, *J* 15.6, 8.2, 1 H), 2.67 (dd, *J* 15.6, 5.2, 1 H), 1.44 (s, 3 H) and 1.39 (s, 3 H); $\delta_C(CDCl_3)$ 206.4 (C), 110.5 (C), 78.2 (CH), 77.0 (CH), 70.9 (CH), 68.1 (CH), 42.6 (CH_2), 26.7 (CH_3) and 25.1 (CH_3); *m/z* (CI) (rel. intensity) 203 (M + 1, 70), 187 (35), 159 (15), 145 (30) and 127 (100) (Found: C. 53.25; H, 6.9. Calc. for $C_9H_{14}O_5$: C, 53.46; H, 6.98%).

(2R,3S,4R,5S,6S)-4-*Hydroxy*-5,6-*isopropylidenedioxy*-2,3-*epoxycyclohexanone* **60**.—Analogous treatment as described for **59**, with **21a** (420 mg, 1.78 mmol) in a mixture of THF (10 cm^3) and MeOH (3 cm^3), with the period of addition of SmI_2 (0.1 mol dm^{-3} in THF; 18.0 cm^3, 1.95 mmol) within 2 min, yielded after chromatography (10% deactivated silica gel, $CHCl_3$–MeOH, 95:5) **59** (77 mg, 22%) and a complex mixture of products (190 mg). Chromatography (10% deactivated silica gel, EtOAc–hexane 1:1) of this mixture furnished **60** as an oil (110 mg, 31%); $[\alpha]_D^{25}$ −84 (*c* 1.6, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3500, 3020, 2990, 1740, 1385 and 1220; $\delta_H(CDCl_3)$ 4.75 (br d, *J* 9.1, 1 H), 4.53 (dd, *J* 9.1, 6.6, 1 H), 4.10 (dd, 6.5, 4.3, 1 H), 3.65 (ABq, *J* 4.6, 4.4, 2 H), 2.75 (m, 1 H), 1.49 (s, 3 H) and 1.37 (s, 3 H); $\delta_C(CDCl_3)$ 201.1 (C), 109.8 (C), 78.0 (CH), 76.0 (CH), 71.5 (CH), 58.6 (CH), 54.9 (CH), 26.3 (CH_3) and 23.9 (CH_3); *m/z* (CI) (rel. intensity) 201 (M + 1, 100), 185 (20), 143 (15) and 125 (15) [Found (HRMS, CI): 201.0747. Calc. for $C_9H_{13}O_5$ (M + 1): 201.0762].

(2R,3S,4R,5S,6S)-2-*Methoxy*-5,6-*isopropylidenedioxycyclohexane*-3,4-*diol* **61**.—A mixture of **21a** (141 mg, 0.596 mmol), Zn powder (100 mg) and MeOH (5 cm^3) was heated at reflux under argon for 1.5 h, after which the solid was filtered off and washed with EtOAc. To the filtrate was added Na_2CO_3 (sat'd. solution; 0.5 cm^3) and water, and the mixture was extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated to furnish the crude product (110 mg), the chromatography (10% deactivated silica gel, $CHCl_3$– MeOH, 95:5) of which yielded **61** (77 mg, 56%), **62** (27 mg, 21%) and starting material **21a** (8 mg, 6%).

For **61**: $[\alpha]_D^{25}$ +191.6 (*c* 1, $CHCl_3$); $\nu_{max}(CDCl_3)$/cm^{-1} 3460, 2989, 2936, 1742, 1384, 1226, 1158 and 1078; $\delta_H(CDCl_3)$ 4.59 (br d, *J* 4.9, 1 H), 4.51 (m, 2 H), 4.19 (br d, *J* 10.4, 1 H), 3.93 (br d, *J* 10.3, 1 H), 3.56 (s, 3 H), 2.92 (br s, 2 H) and 1.39 (s, 6 H); $\delta_C(CD_3OD)$ 207.8 (C), 129.3 (CH), 111.6 (C), 85.1 (CH), 79.5 (CH), 73.2 (CH), 69.7 (CH), 59.7 (CH_3), 27.4 (CH_3) and 26.1 (CH_3); *m/z* (CI) (rel. intensity) 233 (M + 1, 12), 215 (15), 201 (12), 183 (63), 174 (25), 157 (70), 143 (90) and 125 (100) (Found: C, 51.6; H, 7.0. Calc. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94%).

For (4R,5S,6S)-4-*hydroxy*-5,6-*isopropylidenedioxy*-2-*methoxycyclohex*-2-*enone* **62**: m.p. 75–77 °C; $[\alpha]_D^{25}$ −16.3 (*c* 1, $CHCl_3$); $\nu_{max}(CDCl_3)$/cm^{-1} 3500, 3010, 2955, 1700, 1635, 1375, 1225, 1160, 1140 and 1075; $\delta_H(CDCl_3)$ 5.80 (dd, *J* 5.4, 1.2, 1 H), 4.79 (ddd, *J* 5.5, 5.0, 3.0, 1 H), 4.59 (d, *J* 5.5, 1 H), 4.51 (ddd, *J* 5.3, 3.0, 1.2, 1 H); 3.69 (s, 3 H), 2.22 (br s, *J* 5.0, 2 H), 1.42 (s, 3 H) and 1.39 (s, 3 H); $\delta_C(CD_3OD)$ 192.4 (C), 151.9 (C), 115.5 (CH), 111.2 (C), 80.0 (CH), 76.6 (CH), 65.0 (CH), 55.8 (CH_3), 27.0 (CH_3) and 26.0 (CH_3); *m/z* (CI) (rel. intensity) 215 (M + 1, 10), 197 (75), 169 (20), 157 (100), 139 (100) and 127 (100) (Found: C, 55.95; H, 6.6. Calc. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59%).

(5S,6S)-2-*Ethoxy*-3-*hydroxy*-5,6-*isopropylidenedioxycyclohex*-2-*enone* **64**.—A mixture of **21a** (375 mg, 1.59 mmol) and benzylamine (340 mg, 3.17 mmol) in THF (2 cm^3) was stirred at −25 °C for 10 h. Acetone (6 cm^3) was then added to the mixture

and the precipitated benzylamine hydrochloride was filtered off at −25 °C. To the filtrate at −20 °C was added oxalic acid (142 mg, 1.59 mmol); after 10 min the white solid (430 mg) that formed was filtered off. This solid (188 mg) was then heated to reflux in ethanol (5 cm^3). Precipitated benzylamine oxalate was filtered off, and the filtrate was evaporated to yield the crude product (110 mg) whose chromatography (10% deactivated silica gel, $CHCl_3$–MeOH, 95:5) furnished **64** (46.8 mg, 26%) and **63** (13.5 mg, 10%).

For **64**: m.p. 107–110 °C; $[\alpha]_D^{25}$ +76.2 (*c* 0.5, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3010, 2995, 1650, 1630, 1380, 1300 and 1210; $\delta_H(CDCl_3)$ 5.51 (br s, 1 H), 4.89 (d, *J* 8.4, 1 H), 3.83 (ddd, *J* 11.4, 8.4, 5.2, 1 H), 3.75 (dq, *J* 9.2, 7.1, 1 H), 3.64 (dq, *J* 9.3, 7.1, 1 H), 2.93 + 2.41 (ABq, *J* 16.8, 11.5, 5.2, 2 H), 1.69 (s, 3 H), 1.60 (s, 3 H) and 1.24 (t, *J* 7.0, 3 H); $\delta_C(CDCl_3)$ 189.9 (C), 148.0 (C), 126.3 (C), 117.9 (C), 80.3 (CH), 77.1 (CH), 65.6 (CH_2), 39.2 (CH_2), 26.6 (CH_3), 24.3 (CH_3) and 15.3 (CH_3); *m/z* (CI) (rel. intensity) 229 (M^+, 100), 183 (30), 170 (20), 143 (25) and 127 (10) (Found: C, 58.0; H, 7.0. Calc. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07%).

For (5S,6S)-2,3-*dihydroxy*-5,6-*isopropylidenedioxycyclohex*-2-enone **63**: m.p. 153–154 °C; $[\alpha]_D^{25}$ +102.0 (*c* 0.5, MeOH); ν_{max}(KBr)/cm^{-1} 3250, 3105, 3040, 1700, 1610, 1390, 1380, 1315, 1155, 1120 and 1070; $\delta_H(CDCl_3)$ 5.45 (br s, 1 H), 4.85 (d, *J* 8.3, 1 H), 4.18 (ddd, *J* 11.6, 8.4, 5.4, 1 H), 2.88 + 2.49 (ABq, *J* 16.7, 11.6, 5.4, 1 H), 2.43 (br s, 1 H), 1.69 (s, 3 H) and 1.61 (s, 3 H); $\delta_C([^2H_6]DMSO)$ 200.1 (C), 159.5 (C), 136.4 (C), 125.8 (C), 90.3 (CH), 78.9 (CH), 52.7 (CH_2), 36.3 (CH_3) and 33.8 (CH_3); *m/z* (CI) (rel. intensity) 201 (M + 1, 100), 183 (15), 143 (20), 127 (15) and 97 (15) [Found (HRMS, CI): 201.0753. Calc. for $C_{21}H_{28}N_2O_7$ (M + 1): 201.0763].

(1R,2S,3R,6R,7S,8R,9R)-1,2;6,7-*Bis*(*isopropylidenedioxy*)-1,2,3,4,6,7,8,9-*octahydrophenazine*-3,8,9-*triol* **69**.—Liquid ammonia (5 cm^3) was added to a solution of chloro epoxide **21a** (1.5 g, 6.3 mmol) in chloroform (50 cm^3), cooled to −5 °C under argon; the mixture was stirred at room temperature for 3 h. Filtration and evaporation of the filtrate gave a solid (1.37 g) whose chromatography (10% deactivated silica gel, $CHCl_3$–MeOH, 95:5 to 80:20) furnished **69** (794 mg, 66%) and **71** (50 mg, 4.4%), which were recrystallized from benzene.

For **69**: m.p. 136–140 °C; $[\alpha]_D^{25}$ +137.7 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 3020, 3000, 2930, 1385, 1360 and 1055; $\delta_H(CDCl_3)$ 5.34 (d, *J* 6.6, 1 H), 5.32 (d, *J* 6.8, 1 H), 4.97 (d, *J* 2.4, 1 H), 4.68 (dd, *J* 6.8, 3.2, 1 H), 4.51 (dd, *J* 6.2, 4.7, 1 H), 4.45 (dd, *J* 2.5, 2.4, 1 H), 4.41 (br s, 1 H), 4.35 (br m, 1 H), 3.34 (dd, *J* 16.7, 2.5, 1 H), 3.05 (dd, *J* 16.7, 5.7, 1 H), 2.87 (br s, 1 H), 2.53 (br d, *J* 2.9, 1 H), 1.51 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 3 H) and 1.37 (s, 3 H); $\delta_C(CD_3OD)$ 151.6 (C), 150.8 (C), 150.3 (C), 148.8 (C), 147.5 (C), 110.1 (C), 109.9 (C), 77.7 (CH), 76.1 (CH), 75.5 (CH), 75.4 (CH), 72.3 (CH), 69.0 (CH), 67.7 (CH), 35.1 (CH_2), 27.4 (CH_3), 27.2 (CH_3), 25.1 (CH_3) and 24.9 (CH_3); *m/z* (CI) (rel. intensity) 381 (M + 1, 100), 365 (15), 323 (20) and 305 (15) (Found: C, 56.9; H, 6.4; N, 7.3. Calc. for $C_{18}H_{24}N_2O_7$: C, 56.83; H, 6.36; N, 7.37%).

For (1R,2S,6R,7S,8R,9R)-1,2,6,7-*bis*(*isopropylidenedioxy*)-1,2,6,7,8,9-*hexahydrophenazine*-8,9-*diol* **71**, m.p. 172–173 °C; $[\alpha]_D^{25}$ +216 (*c* 0.7, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3030, 3005, 2950, 1425, 1385, 1375, 1155 and 1050; $\delta_H(CDCl_3)$ 6.73 (dd, *J* 10.1, 1.3, 1 H), 6.29 (ddd, *J* 10.0, 2.8, 0.7, 1 H), 5.34 (d, *J* 6.8, 1 H), 5.21 (dd, *J* 7.2, 0.8, 1 H), 5.14 (ddd, *J* 7.2, 2.8, 1.3, 1 H), 5.01 (br d, *J* 2.8, 1 H), 4.71 (dd, *J* 6.8, 3.3, 1 H), 4.62 (br s, 1 H), 4.52 (br dd, *J* 3.3, 2.7, 1 H), 1.53 (s, 3 H), 1.46 (s, 3 H), 1.43 (s, 3 H) and 1.37 (s, 3 H); $\delta_C(CDCl_3)$ 148.5 (C), 147.8 (C), 146.2 (C, double intensity), 133.5 (CH), 126.6 (CH), 109.8 (C), 108.1 (C), 75.0 (CH), 74.8 (CH), 73.9 (CH), 73.5 (CH), 71.1 (CH), 67.7 (CH), 27.0 (CH_3), 26.5 (CH_3), 25.5 (CH_3) and 24.0 (CH_3); *m/z* (CI) (rel. intensity) 363 (M + 1, 100), 347 (20), 305 (100), 287 (15), 247 (20), 229 (15) and 201 (15) [Found (HRMS, CI): 363.1573. Calc. for $C_{18}H_{23}N_2O_6$ (M + 1): 363.1556].

(1R,2S,3R,4R,6R,7S,8R,9R)-1,2;6,7-*Bis*(*isopropylidenedioxy*)-1,2,3,4,6,7,8,9-*octahydrophenazine*-3,4,8,9-*tetraol* **72**.—Liquid ammonia (5 cm^3) was added to a solution of chloro epoxide **21a** (0.80 g, 3.4 mmol) in chloroform (50 cm^3) cooled to 0 °C, and the mixture was stirred at 0 °C for 2 h. After O_2 had been bubbled through the mixture at 0 °C for 2 h, it was filtered and evaporated to give a solid (530 mg). Chromatography of this product (10% deactivated silica gel, $CHCl_3$–MeOH, 95:5) furnished crystalline **72** (354 mg, 53%), m.p. 118–120 °C; $[\alpha]_D^{25}$ +86.1 (*c* 0.4, MeOH); ν_{max}(KBr)/cm^{-1} 3400, 2900, 2850, 1380, 1260, 1205, 1150 and 1050; $\delta_H([^2H_6]DMSO)$ 5.05 (br s, 2 H), 5.32 (d, *J* 7.0, 2 H), 5.25 (br s, 2 H), 4.75 (br d, *J* 2.5, 2 H), 4.53 (dd, *J* 7.0, 4.4, 2 H), 4.05 (br dd, *J* 4.3, 2.6, 2 H), 1.40 (s, 6 H) and 1.30 (s, 6 H); $\delta_C(CDCl_3)$ 149.9 (C), 146.9 (C), 109.9 (C), 74.8 (CH), 74.5 (CH), 71.1 (CH), 65.6 (CH), 26.5 (CH_3) and 24.0 (CH_3); *m/z* (CI) (rel. intensity) 397 (M + 1, 10), 337 (25), 309 (100), 199 (30) and 171 (15) [Found (HRMS, CI): 397.1604. Calc. for $C_{18}H_{25}N_2O_8$ (M + 1): 397.1604].

(1R,2S,6R,3R,4R,7S,8R,9R)-1,2,6,7,8,9-*Tris*(*isopropylidenedioxy*)-1,2,6,7,8,9-*hexahydrophenazine* **75**.—Liquid ammonia (10 cm^3) was added to a solution of chloro epoxide **21a** (1.5 g, 6.3 mmol) in chloroform (50 cm^3), and the mixture was stirred overnight at room temperature. It was then filtered and evaporated to give a foamy solid (1.25 g), containing (by NMR) 80% of intermediate **67**, plus 10% each of **69** and **72**. To a solution of this solid (1.25 g) in chloroform (50 cm^3) was added dimethoxypropane (5.0 cm^3, 41 mmol) and PTSA·$7H_2O$ (0.20 g, 1.1 mmol), and the mixture was stirred at ambient temperature for 16 h. It was then washed with 0.5 mol dm^{-3} aqueous NaOH, dried (Na_2SO_4) and evaporated to give a foamy solid. Chromatography (10% deactivated silica gel, $CHCl_3$–MeOH, 98:2) of this product furnished a mixture of **75** and **73** (0.74 g) and **74** (0.29 g, 22%). The mixture of **75** and **73** was then recrystallized from benzene–hexane to give **75** (72 mg, 5%); the mother liquor was chromatographed (10% deactivated silica gel, CH_2Cl_2–MeOH, 98:2) to furnish **73** as a foamy solid (0.53 g, 42%); $[\alpha]_D^{25}$ +267.2 (*c* 1, $CHCl_3$); $\nu_{max}(CDCl_3)/cm^{-1}$ 2995, 2945, 1660, 1420, 1380, 1365, 1150 and 1065; $\delta_H(CDCl_3)$ 6.75 (dd, 10.2, 1.4, 1 H), 6.29 (ddd, 10.1, 2.8, 1.1, 1 H), 5.31 (d, *J* 4.9, 1 H), 5.27 (dd, *J* 6.9, 1.0, 1 H), 5.24 (d, *J* 4.8, 1 H), 5.13 (ddd, *J* 6.9, 2.8, 1.5, 1 H), 4.82 (m, 2 H), 1.49 (s, 3 H), 1.45 (s, 6 H), 1.42 (s, 3 H) and 1.15 (s, 3 H); $\delta_C(CDCl_3)$ 147.5 (C), 147.2 (C), 147.1 (C), 144.7 (C), 134.7 (CH), 126.1 (CH), 109.7 (C), 109.6 (C), 107.9 (C), 73.7 (CH), 73.6 (CH), 73.5 (CH), 73.3 (CH), 73.1 (CH), 73.0 (CH), 27.4 (CH_3), 27.3 (CH_3), 26.7 (CH_3), 25.4 (CH_3) and 25.3 (CH_3, double intensity); *m/z* (CI) (rel. intensity) 403 (M + 1, 35), 387 (30), 373 (15), 345 (100), 329 (20), 315 (15), 287 (60) and 271 (25) [Found (HRMS, CI): 403.1913. Calc. for $C_{21}H_{27}N_2O_6$ (M + 1): 403.1870].

For (1R,2S,3R,4R,6R,7S,8R,9R)-1,2;3,4;6,7;8,9-*tetrakis*(*isopropylidenedioxy*)-1,2,3,4,6,7,8,9-*octahydrophenazine* **75**, m.p. 261–264 °C; $[\alpha]_D^{25}$ +173.2 (*c* 0.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2970, 2935, 1405, 1360, 1355, 1190, 1165 and 1025; $\delta_H(CDCl_3)$ 5.39 (m, 4 H), 4.84 (m, 4 H), 1.43 (s, 12 H) and 1.05 (s, 12 H); $\delta_C(CDCl_3)$ 148 (C), 109.9 (C), 73.6 (CH, double intensity), 27.4 (CH_3) and 25.7 (CH_3); *m/z* (CI) (rel. intensity) 477 (M + 1, 100), 461 (55), 419 (20), 403 (20), 389 (15), 361 (50), 345 (30), 303 (30), 245 (35) and 217 (25) [Found (HRMS, CI): 477.2213. Calc. for $C_{24}H_{33}N_2O_8$ (M + 1): 477.2237].

For (1R,2S,3R,6R,7S,8R,9R)-1,2;6,7;8,9-*tris*(*isopropylidenedioxy*)-1,2,3,4,6,7,8,9-*octahydrophenazine*-3-*ol* **74**, m.p. 193–195 °C; $[\alpha]_D^{25}$ +183.9 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3327, 2986, 2936, 1416, 1376, 1235 and 1059; $\delta_H(CDCl_3)$ 5.43 (d, *J* 6.6, 2 H), 5.32 (d, *J* 4.8, 1 H), 5.24 (d, *J* 4.8, 1 H), 4.80 (d, *J* 5.0,

2 H), 4.49 (dd, *J* 5.6, 5.5, 1 H), 4.35 (ddd, *J* 6.2, 5.0, 3.4, 1 H), 3.41 (dd, *J* 16.7, 3.3, 1 H), 3.08 (dd, *J* 16.6, 6.2, 1 H), 1.95 (br d, *J* 2.9, 1 H), 1.48 (s, 3 H, 1.45 (s, 3 H), 1.43 (s, 3 H) and 1.15 (s, 6 H); $\delta_C(CDCl_3)$ 151.6 (C), 148.9 (C), 147.3 (C), 145.6 (C), 109.9 (C, double intensity), 78.0 (CH), 75.2 (CH), 74.2 (CH), 73.8 (CH), 73.6 (CH), 73.5 (CH), 68.3 (CH), 35.5 (CH_2), 27.4 (CH_3, double intensity), 27.0 (CH_3), 25.6 (CH_3, double intensity) and 24.7 (CH_3); *m/z* (CI) (rel. intensity) 421 (M + 1, 100), 405 (55), 391 (15), 363 (60), 345 (35), 305 (100), 289 (25) and 247 (35) [Found (HRMS, CI): 421.1985. Calc. for $C_{21}H_{29}N_2O_7$ (M + 1): 421.1975].

(1R,2S,3S,4S,5S,6S)-1,2-*Epoxycyclohexane*-3,4,5,6-*tetraol* **78**.—A mixture of epoxide **56** (0.58 g, 2.86 mmol), Amberlyst 15 (wet; 0.66 g) in water (20 cm^3) was stirred at room temperature for 24 h. After filtration, the solution was filtered through charcoal and the filtrate evaporated to give a colourless product (0.43 g, 83%) containing >90% of **78**. Recrystallization of the crude product from aqueous ethanol furnished **78** (0.34 g), m.p. 210–213 °C (lit.,[34] m.p. not given); $[\alpha]_D^{25}$ −148 (*c* 1, H_2O) [lit.,[34] +153 (*c* 0.5, H_2O) for *ent*-**78**].

(1S,2R,3R,4R,5S,6R)-1,6-*Isopropylidenedioxycyclohexane*-2,3,4,5-*diol* **79**.—A mixture of epoxide **56** (0.392 g, 1.94 mmol), water (5 cm^3), and Amberlyst IRA 904 (0.3 g) was stirred under argon for 4 days at 110 °C. The resin was filtered off, and the filtrate was evaporated to give crystalline **79** (0.376 g, 88%), m.p. 157–158 °C; $[\alpha]_D^{25}$ +87.9 (*c* 1, H_2O); ν_{max}(KBr)/cm^{-1} 3400, 2995, 2905, 1365, 1210 and 1100; $\delta_H([^2H_6]DMSO)$ 4.99 (d, *J* 4.6, 1 H), 4.87 (d, *J* 5.0, 1 H), 4.72 (d, *J* 4.4, 1 H), 4.69 (d, *J* 4.6, 1 H), 4.07 (dd, *J* 6.2, 4.5, 1 H), 3.88 (dd, *J* 7.7, 6.3, 1 H), 3.82 (m, 1 H), 3.39 (m, 1 H), 3.32 (m, 1 H), 3.23 (m, 1 H), 1.37 (s, 3 H) and 1.25 (s, 3 H); $\delta_C(D_2O)$ 111.1 (C), 79.5 (CH), 77.9 (CH), 76.2 (CH), 72.5 (CH), 72.4 (CH), 69.7 (CH), 28.0 (CH_3) and 25.9 (CH_3); *m/z* (CI) (rel. intensity) 221 (M + 1, 100), 205 (20), 163 (50), 145 (30), 127 (55), 109 (40), 99 (18), 85 (20) and 81 (15) (Found: C, 49.1; H, 7.3. Calc. for $C_9H_{16}O_6$: C, 49.09; H, 7.32%).

(1S,2R,3S,4R,5S,6S)-2,3-*Isopropylidenedioxy*-1,6-*epoxycyclohexane*-4,5-*diol* **82**. To a solution of **81**[41a] (0.49 g, 2.6 mmol) in dichloromethane (10 cm^3) was added *m*-CPBA (50–60%, Aldrich; 2 g), and the mixture was stirred for 30 h at room temperature. Then water, sodium hydrogen carbonate, and sodium hydrogen sulfate were added to the mixture which was then extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to furnish crystalline **82** (0.31 g, 59%), m.p. 103–105 °C; $[\alpha]_D^{25}$ +28.4 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)$ 3400, 2990, 2930, 1380, 1240 and 1220; $\delta_H(CDCl_3)$ 4.65 (dd, *J* 5.5, 0.5, 1 H), 4.42 (dddd, *J* 5.5, 4.4, 0.9, 0.8, 1 H), 4.16 (br m, 1 H), 4.02 (br d, *J* 9.6, 1 H) 3.53 (dddd, *J* 3.4, 3.1, 1.3, 0.5, 1 H), 3.30 (dd, *J* 3.4, 0.8, 1 H), 3.14 (br d, *J* 10.2, 1 H), 2.65 (br d, *J* 10.6, 1 H), 1.51 (s, 3 H) and 1.39 (s, 3 H); $\delta_C(CDCl_3)$ 109.9 (C), 75.4 (CH), 70.5 (CH), 67.7 (CH), 66.8 (CH), 55.3 (CH), 52.8 (CH), 27.6 (CH_3) and 25.1 (CH_3); *m/z* (CI) (rel. intensity) 203 (M + 1, 33), 187 (85), 145 (15), 127 (35), 109 (95), 99 (78) and 81 (100) [Found (HRMS, CI): 203.0907. Calc. for $C_9H_{15}O_5$ (M + 1): 203.0920].

(3R,4R,5R,6R)-1-*Chloro*-3,4;5,6-*bis*(*isopropylidenedioxy*)-*cyclohex*-1-*ene* **87**.—To a solution of **20a** (2.25 g, 10.2 mmol) in dichloromethane (40 cm^3) was added DMP (1.69 g, 16.3 mmol) and PTSA·$7H_2O$ (95 mg, 0.5 mmol). The mixture was stirred for 4 h at ambient temperature and then washed with 0.5 mol dm^{-3} aqueous NaOH, dried (Na_2SO_4), and evaporated to give **87** as a colourless oil (2.61 g, 99%); $[\alpha]_D^{25}$ +67.6 (*c* 2.5, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2980, 2935, 2900, 1365, 1220, 1200 and 1060; $\delta_H(CDCl_3)$ 5.84 (d, 2.9, 1 H), 4.66 (dd, *J* 5.2, 2.9, 1 H), 4.63 (dd, *J* 3.0, 1.4, 1 H), 4.57 (ddd, *J* 5.0, 3.0, 1.0, 1 H), 4.51 (br d, *J* 5.0, 1 H), 1.41 (s, 6 H) and 1.38 (s, 6 H); $\delta_C(CDCl_3)$ 132.9 (C), 125.3 (CH), 110.2 (C), 109.9 (C), 74.3 (CH), 73.6 (CH), 73.0 (CH), 72.0 (CH), 28.0 (CH_3), 27.7 (CH_3), 26.6 (CH_3) and 26.5 (CH_3); *m/z* (EI) (rel. intensity) 261 (M^+, 5), 247 (100), 187 (100), 145 (100), 115 (60) and 101 (100) (Found: C, 55.2; H, 6.6. Calc. for $C_{12}H_{17}ClO_4$: C, 55.28; H, 6.57).

2,3-*Isopropylidenedioxy*-D-*mannono*-γ-*lactone* **85** and D-*mannono*-γ-*lactone* **86**.—A mixture of O_2/O_3 was bubbled for 10 min through a solution of **20a** (280 mg, 1.27 mmol) and $NaHCO_3$ (213 mg, 2.54 mmol) in MeOH (10 cm^3) at −78 °C until a blue colour persisted. After removal of the excess of O_3 at −78 °C, the mixture was warmed to ambient temperature and transferred to a hydrogenator. The mixture (containing 30 mg of 10% Pd/C) was hydrogenated for 3 days at 45 lb in^{-2}. At this time, the progress of the reduction was checked by TLC, and additional Pd/C was added (150 mg total added). After a total of 5 days, the mixture was filtered through Celite, evaporated and purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 92:8) to afford **85** (32%, 90 mg); R_F 0.375 (CH_2Cl_2–MeOH, 93:7); $\nu_{max}(CHCl_3)$/cm^{-1} 3450, 3030, 3000, 1790, 1385, 1375, 1210, 1085 and 750; $\delta_H(CDCl_3)$ 4.96 (dd, *J* 5.5, 3.8, 1 H), 4.86 (d, *J* 5.5, 1 H), 4.51 (dd, *J* 9, 3.8, 1 H), 4.0 (m, H), 3.94 (dd, *J* 11.6, 2.9, 1 H), 3.80 (dd, *J* 11.6, 4.7, 1 H), 2.79 (OH), 2.20 (OH), 1.49 (s, 3 H) and 1.44 (s, 3 H). The lactone **85** was deprotected when stored for several days at room temperature or in 75% aqueous trifluoroacetic acid to afford the lactone **86** superposable by ^1H NMR (in D_2O or CD_3OD) to the commercially available enantiomer L-mannono-γ-lactone. An analytical sample was recrystallized in CH_2Cl_2–MeOH; m.p. 152–153 °C; $[\alpha]_D^{25}$ +50.9 (*c* 1.01, H_2O) (Found: C, 40.49; H, 5.67. Calc. for $C_6H_{10}O_6$: C, 40.45; H, 5.65%).

(3S,4S,5R,6R,7R,S)-7-*Hydroxy*-3,4;5,6-*bis*(*isopropylidenedioxy*)-1-*oxacycloheptane*-2-*one* **88**.—A mixture of O_2/O_3 was bubbled for 90 min at ambient temperature through a solution of **87** (500 mg, 1.92 mmol) in EtOAc (50 cm^3). Then $NaHCO_3$ (650 mg, 7.67 mmol), dimethyl sulfide (477 mg, 7.67 mmol) and water (40 cm^3) were added to the mixture which was then stirred for 2 h. The aqueous layer was separated, adjusted to pH 2 (6 mol dm^{-3} HCl) and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to give a viscous product (0.32 g). Chromatography (10% deactivated silica gel, $CHCl_3$–MeOH, 96:4) of this product furnished crystalline **77** (132 mg, 25%), m.p. 176–179 °C; $[\alpha]_D^{25}$ +15.9 (*c* 0.7, MeOH); $\nu_{max}(CDCl_3)$/cm^{-1} 3500, 2995, 2950, 1780, 1375, 1260, 1205, 1120, 1095 and 1060; $\delta_H(CDCl_3)$ 5.52 (d, 2.6, 1 H), 4.88 (dd, *J* 5.8, 3.5, 1 H), 4.66 (d, *J* 9.5, 1 H), 4.65 (d, *J* 5.9, 1 H), 4.47 (dd, *J* 9.5, 3.5, 1 H), 3.42 (d, *J* 2.6, 1 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.50 (s, 3 H) and 1.36 (s, 3 H); $\delta_C(CDCl_3)$ 171.6 (C), 113.0 (C), 111.5 (C), 102.1 (CH), 84.9 (CH), 80.1 (CH), 78.3 (CH), 71.3 (CH), 27.4 (CH_3), 26.5 (CH_3), 26.0 (CH_3) and 24.8 (CH_3); *m/z* (CI) (rel. intensity) 275 (M + 1, 25), 257 (60), 245 (7), 217 (100), 199 (30), 189 (60), 171 (40) and 159 (20) [Found (HRMS, CI): 275.1140. Calc. for $C_{12}H_{19}O_7$ (M + 1): 275.1131].

Supplementary Material Section

Further experimental details and reaction engineering are described for several reactions mentioned in the Discussion section in a Supplementary publication [Sup. No.: 57011 (4 pp.)].*

* For details of the Supplementary publications scheme see 'Instructions for Authors (1994),' *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

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References

1 This paper is the first of a three-part series. For parts 2 and 3 see: (*a*) T. Hudlicky, J. Rouden, H. Luna and S. Allen, *J. Am. Chem. Soc.*, 1994, **116**, 5099; (*b*) T. Hudlicky, H. F. Olivo and B. McKibben, *J. Am. Chem. Soc.*, 1994, **116**, 5108.

2 Preliminary account of the synthesis of D-*chiro*-inositol has been published: M. Mandel, T. Hudlicky, L. D. Kwart and G. M. Whited, *J. Org. Chem.*, 1993, **58**, 2331.

3 For comprehensive reviews of arene *cis*-diol chemistry see: (*a*) S. M. Brown and T. Hudlicky, in *Organic Synthesis: Theory and Practice*; ed. T. Hudlicky, JAI Press, Greenwich, CT, 1992, vol. 2 p. 113; (*b*) D. A. Widdowson, D. A. Ribbons and S. D. Thomas, *Janssen Chimica Acta*, 1990, **8**, 3; (*c*) H. A. J. Carless, *Tetrahedron: Asymm.* **1992**, 795; (*d*) T. Hudlicky and J. W. Reed, in *Advances in Asymmetric Synthesis*, ed. A. Hassner, JAI Press, Greenwich, CT, 1994; in press.

4 The numbering system is that described in Index Guide, *Chem. Abstr.*, 1990, 1001.

5 (*a*) T. Posternak, *Les cyclitols*, Hermann, Paris, 1962, p. 10, p. 283; (*b*) R. H. Mitchell, A. H. Drummond and C. P. Downess, *Inositol Lipids in Cell Signalling*, Academic, San Diego, 1989; (*c*) G. Legler and E. Bause, *Carbohydrate Res.*, 1973, **28**, 45; (*d*) G. Legler and W. Lotz, *Hoppe-Seyler's Z. Physiol. Chem.*, 1973, **354**, 243; (*e*) *Inositol Phosphates and Derivatives: Synthesis, Biochemistry, and Therapeutic Potential*, ed. A. B. Reitz, ACS Symposium Series 463, American Chemical Society, Washington, DC, 1991; (*f*) For a recent compilation of cyclitol and conduramine data see: T. Hudlicky and M. Cebulak, *Cyclitols and Their Derivatives: A Handbook of Physical, Spectral and Synthetic Data*, VCH, New York, 1993; (*g*) M. J. Bevridge and R. F. Irvine, *Nature*, 1989, **341**, 197; (*h*) D. C. Billington, *Chem. Soc. Rev.*, 1989, **18**, 83. For recent syntheses of cyclitols and their glycosides see: (*i*) O. Arjona, A. Candilejo, A. de Dios, R. Fernández de la Pradilla and J. Plumet, *J. Org. Chem.*, 1992, **57**, 6097; (*j*) J. L. Aceña, O. Arjona, R. Fernández de la Pradilla, J. Plumet and A. Viso, *J. Org. Chem.*, 1992, **57**, 1945; (*k*) O. Arjona, R. Fernández de la Pradilla, E. García, A. Martín-Domenech and J. Plumet, *Tetrahedron Lett.*, 1989, **30**, 6437; (*l*) O. Arjona, R. Fernández de la Pradilla, A. Mallo, J. Plumet and A. Viso, *Tetrahedron Lett.*, 1990, **31**, 1475; (*m*) C. Jaramillo, R. Fernández de la Pradilla and M. Martín-Lomas, *Carbohydr. Res.*, 1991, **209**, 296; (*n*) C. Jaramillo and M. Martín-Lomas, *Tetrahedron Lett.*, 1991, **32**, 2501.

6 (*a*) A. S. Kennington, C. R. Hill, J. Craig, C. Bogardus, I. Raz, H. K. Ortmeyer, B. C. Hansen, G. Romero and J. Larner, *New England J. Med.*, 1990, **323**, 373; (*b*) L. C. Huang, L. Zhang and J. Larner, *FASEB*, 1992, A1629, Abstr. 4009; (*c*) Y. Pak L. C. Huang and J. Larner, *FASEB*, 1992, A1629, Abstr. 4008; (*d*) J. Larner, L. C. Huang, C. F. W. Schwartz, A. S. Oswald, T.-Y. Shen, M. Kinter, G. Tang and K. Zeller, *Biochem. Biophys. Res. Commun.*, 1988, **151**, 1416.

7 (*a*) D. T. Gibson, G. R. Koch and R. E. Kallio, *Biochemistry*, 1968, **7**, 2653; (*b*) D. T. Gibson, M. Hensley, H. Yoshioka and J. J. Mabry, *Biochemistry*, 1970, **9**, 1626.

8 For latest publications by leading authors in this field see: (*a*) D. W. Ribbons and J. O. Williams, *Advances in Nat. Prod. Chem.*, in press; (*b*) D. R. Boyd, N. D. Sharma, R. Boyle, J. F. Malone, J. Chima and H. Dalton, *Tetrahedron: Asymm.*, 1993, **4**, 1307; (*c*) D. R. Boyd, N. D. Sharma, M. R. J. Dority, M. V. Hand, R. A. S. McMordie, J. F. Malone, H. P. Porter, H. Dalton, J. Chima and G. N. Sheldrake, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1065; (*d*) D. R. Boyd, N. D. Sharma, R. Boyle, T. T. McMurray, T. A. Evans, J. F. Malone, H. Dalton, J. Chima and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1993, 49; (*e*) P. J. Geary, R. J. Pryce, S. M. Roberts, G. Ryback and J. A. Winders, *J. Chem. Soc., Chem. Commun.*, 1990, 204; (*f*) K. H. Engesser, G. Auling, J. Busse and H. J. Knackmuss, *Arch. Microbiol.*, 1990, **153**, 193.

9 (*a*) S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **28**, 225; (*b*) D. G. H. Ballard, A. Courtis, I. M. Shirley and S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1983, 954.

10 (*a*) T. Hudlicky, J. D. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, 1990, **112**, 9439; (*b*) T. Hudlicky, R. Fan, T. Tsunoda, H. Luna, C. Andersen and J. D. Price, *Isr. J. Chem.*, 1991, **31**, 229.

11 T. Hudlicky and H. F. Olivo, *Tetrahedron Lett.*, 1991, **32**, 6077.

12 T. Hudlicky and H. F. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694.

13 T. Hudlicky, J. Rouden and H. Luna, *J. Org. Chem.*, 1993, **58**, 985.

14 T. Hudlicky and J. Rouden, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1095.

15 T. Hudlicky and M. G. Natchus, *J. Org. Chem.*, 1992, **57**, 4740.

16 T. Hudlicky, C. H. Boros and E. E. Boros, *Synthesis*, 1992, 174.

17 *Asymmetric Synthesis*, eds. R. A. Aitken and S. N. Kilenyi, University Press, Cambridge, 1992.

18 (*a*) S. Hanessian, *Total Synthesis of Natural Products: The 'Chiron' Approach*, Pergamon, Oxford, 1983; (*b*) Z. J. Witczak, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, vol. 3, part B, pp. 209–232.

19 A. J. Fatiadi, *Synthesis*, 1987, 85.

20 M. Hudlicky, *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, 1990, p. 86.

21 D. G. Lee, *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open Court, La Salle, 1980.

22 K. Gollnick, G. Schade and S. Schroeter, *Tetrahedron*, 1966, **22**, 139.

23 E. Klein and W. Rojahn, *Tetrahedron*, 1965, **21**, 2353.

24 E. von Rudloff, *Tetrahedron Lett.*, 1966, 993.

25 (*a*) H. Z. Sable, T. Anderson, B. Tolbert and T. Posternak, *Helv. Chim. Acta*, 1963, **46**, 1157; (*b*) H. Z. Sable, K. A. Powell, H. Katchian, C. B. Niewoehner and S. B. Kadlec, *Tetrahedron*, 1970, **26**, 1509.

26 (*a*) C. J. W. Brooks, G. Eglinton and D. S. Magrill, *J. Chem. Soc.*, 1961, 308; (*b*) M. Anastasia, A. Fiecchi and A. Scala, *J. Org. Chem.*, 1979, **44**, 3657.

27 (*a*) R. N. McDonald, in *Mechanisms of Molecular Migrations*, ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1971, vol. 3, p. 68; for specific references on epoxidation–rearrangement of vinyl chlorides see: (*b*) R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, 1963, **85**, 820, 4004; (*c*) R. N. McDonald and T. E. Tabor, *J. Am. Chem. Soc.*, 1967, **89**, 6573.

28 (*a*) J. Gasteiger and C. Herzig, *Tetrahedron*, 1981, **37**, 2607; (*b*) J. Gasteiger and C. Herzig, *J. Chem. Res.*, 1981 (*S*), 113; (*M*), 1101.

29 M. V. Ganey, R. E. Padykula and G. A. Berchtold, *J. Org. Chem.*, 1989, **54**, 2787.

30 R. P. Hanzlik and J. M. Hilbert, *J. Org. Chem.*, 1978, **43**, 610.

31 J. Oh, J.-R. Choi and J. K. Cha, *J. Org. Chem.*, 1992, **57**, 6664. This compound exhibited exceptional stability to hydrolytic conditions (J. K. Cha, personal communication).

32 (*a*) S. Wolfe, C. F. Ingold and R. U. Lemieux, *J. Am. Chem. Soc.*, 1981, **103**, 938; (*b*) S. Wolfe and C. F. Ingold, *J. Am. Chem. Soc.*, 1981, **103**, 940.

33 (*a*) T. Hudlicky, E. E. Boros, H. F. Olivo and J. S. Merola, *J. Org. Chem.*, 1992, **57**, 1026; (*b*) C. A. Pitoll, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sick and J. O. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1160; (*c*) S. V. Ley, A. J. Redgrave, S. C. Taylor, S. Ahmed and D. W. Ribbons, *Synlett*, 1991, 741.

34 H. A. J. Carless, *Tetrahedron Lett.*, 1992, **33**, 6379.

35 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.

36 C. Chatgilialoglu, D. Griller and M. Lesage, *J. Org. Chem.*, 1988, **53**, 3641.

37 M. Mandel and T. Hudlicky, *J. Chem. Soc., Perkin Trans. 1*, 1993, 741. See corrigendum ref. 44*a*.

38 (*a*) T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent and J. D. Price, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2907; (*b*) This enone has also been used in recent total syntheses of shikimic acid and lycorane alkaloids by C. R. Johnson and W. Oppolzer (personal communications).

39 J. A. Soderquist, *Aldrichimica Acta*, 1991, **24**, 15.

40 A preliminary account of this work has appeared: M. Mandel and T. Hudlicky, *Synlett*, 1993, 418.

41 O. Wallach and A. Wiessenborn, *Ann.*, 1924, **437**, 148.

42 G. R. Pettit, Y. Kamano, C. Dufresne, M. Inoue, N. Christie, J. M. Schmidt and D. L. Doubek, *Can. J. Chem.*, 1989, **67**, 1509.

43 (*a*) S. C. Smith and C. H. Heathcock, *J. Org. Chem.*, 1992, **57**, 6379; (*b*) C. W. Van't Land, U. Mocek and H. G. Floss, *J. Org. Chem.*, 1993, **58**, 6576.

44 (*a*) Corrigendum for ref. 37: M. Mandel and T. Hudlicky, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1537; see also: (*b*) H. A. J. Carless, *Tetrahedron Lett.*, 1992, **33**, 6379; (*c*) After the publication of our synthesis of four inositols, a manuscript appeared describing their preparation in racemic fashion from *meso*-cyclohexadiene-*cis*-diol by previously published methods: see H. A. J. Carless, K. Busia and O. A. Oak, *Synlett*, 1993, 672.
45 (*a*) G. H. Payne, *J. Org. Chem.*, 1962, **27**, 3819; (*b*) S. J. Angyal, V. Bender and J. H. Curtin, *J. Chem. Soc. C*, 1966, 798; for earlier examples see: (*c*) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 1957, 3691; (*d*) J. G. Buchanan, *J. Chem. Soc.*, 1958, 995, 2511.
46 T. Hudlicky, J. Luna, J. D. Price and F. Rulin, *Tetrahedron Lett.*, 1989, **30**, 4053.
47 T. Hudlicky and J. D. Price, *Synlett*, 1990, 159.
48 T. Hudlicky, H. Luna, J. D. Price and F. Rulin, *J. Org. Chem.*, 1990, **55**, 4683.
49 M. Mandel, T. Hudlicky, L. D. Kwart and G. M. Whited, *Collect. Czech. Chem. Commun.*, 1993, **58**, 2517.
50 P. P. Collins, in *Carbohydrates*, Chapman and Hall, New York, 1987, p. 289.
51 S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 1958, 375.
52 M. Nakajima, I. Tomida, N. Kurihara and S. Takai, *Chem. Ber.*, 1959, **92**, 173.
53 S. J. Angyal and N. K. Matheson, *J. Am. Chem. Soc.*, 1955, **77**, 4343.

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