Studies on the role of conformation and of hydrogen-bonding on the dihydroxylation of cyclic allylic alcohols: application to the synthesis of conduritol D

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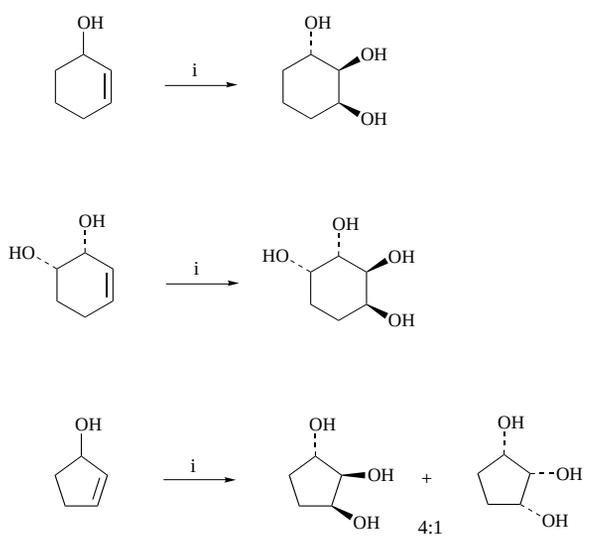
A study on the dihydroxylation of a series of conformationally 'locked' cyclohexenols is reported. The orientation of the hydroxy group (*i.e.* equatorial or axial) is crucial in determining the degree of diastereoselectivity observed during oxidation. In some cases, the use of hydrogen-bonding enables the stereoselective synthesis of *syn* triols and tetraols. This effect has been utilised in the synthesis of conduritol D: X-ray crystal structure analysis provided a method of assigning the relative and absolute stereochemistry of an advanced synthetic intermediate.

Introduction

The use of osmium tetraoxide to transform an alkene into a stereochemically defined vicinal diol has proven to be effective for the construction of complex organic molecules.[1] Seminal studies by Kishi and co-workers on the dihydroxylation of allylic alcohols showed that a hydroxy group was capable of influencing the facial selectivity of an oxidation step (Scheme 1).[2]



Scheme 1 *Reagents:* i, OsO_4 (cat.), NMO, acetone, H_2O

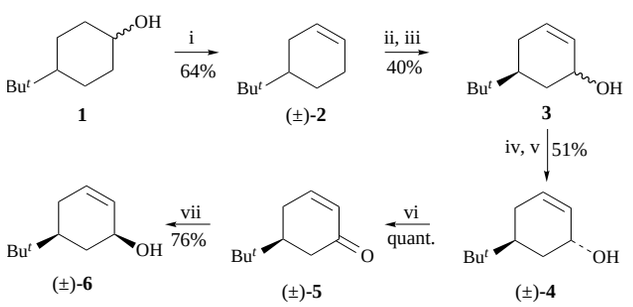
When acyclic substrates were oxidised, the level of stereochemical control depended upon the substitution pattern of the alkene; however, the dihydroxylation of cyclic allylic alcohols (especially six-membered ones) provided an opportunity to effect a considerable degree of stereocontrol during the oxidation reaction (Scheme 1).

The high level of diastereoselectivity in the oxidation of cyclohex-2-enol was puzzling, as it seemed unlikely that an allylic hydroxy group would provide a significant steric block to one face of the alkene. We have recently communicated the results of a study on the dihydroxylation of conformationally 'locked' cyclic allylic alcohols which we now discuss in detail, and which shed some light onto the above reaction.[3] In addition, we are interested in reversing the inherent *anti* diastereofacial selectivity of cyclic allylic alcohols by encouraging hydrogen-bonding between OsO_4 and a hydroxy group. The outcome would be a *syn* selective dihydroxylation of cyclic allylic alcohols, which would be a worthwhile addition to synthetic methodology, as it is currently difficult to achieve in a succinct manner.

Results and discussion

Dihydroxylation of cyclohexenol derivatives

We decided to investigate the oxidation of cyclohexenol derivatives that were substituted with a *tert*-butyl group so as to provide reasonable conformational restriction and enable us to study the dihydroxylation of alkenes adjacent to both an axially and an equatorially 'locked' hydroxy group. Consequently, the *cis* and *trans* isomers of 5-*tert*-butylcyclohex-2-enol were synthesised from commercially available 4-*tert*-butylcyclohexanol **1** (Scheme 2).[4] The *trans* isomer of the *p*-nitrobenzoate derivative



Scheme 2 *Reagents:* i, $KHSO_4$, heat; ii, NBS; iii, aq. K_2CO_3; iv, *p*-$NO_2C_6H_4COCl$ then crystallise; v, aq. NaOH; vi, CrO_3, H_2SO_4; vii, $LiAlH_4$, Et_2O, −78 °C

of **3** can be obtained in diastereoisomerically pure form by crystallisation of the crude reaction mixture (Scheme 2). The *cis* isomer **6** can be obtained in greater than 97% purity by (axial) reduction of enone **5** with lithium aluminum hydride at low temperature.

Armed with these derivatives, we determined the ratios of vicinal diols that were formed from reaction with osmium tetraoxide under a variety of conditions. The dihydroxylation of 4-*tert*-butylcyclohexene **2** was also investigated to examine

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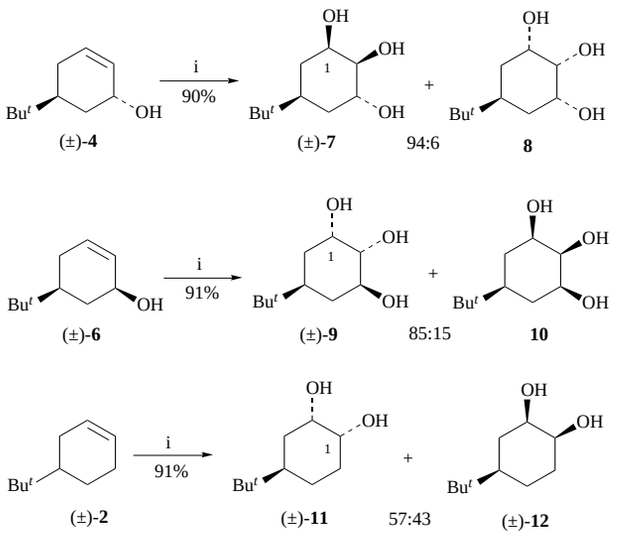
the steric influence of the *tert*-butyl group. When the three alkenes **2**, **4** and **6** were oxidised with catalytic osmium tetraoxide in aqueous acetone with *N*-methylmorpholine *N*-oxide (NMO) as re-oxidant, a clear picture emerged (Scheme 3).

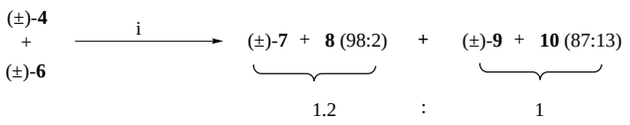


Scheme 3 *Reagents:* i, cat. OsO_4, NMO, acetone, H_2O

Each allylic alcohol was oxidised to give predominantly the *anti*/*syn* isomer, with good to excellent diastereoselectivity. The diastereoisomeric triols were separated by reversed phase HPLC or by flash column chromatography of their isopropylidene derivatives (see Scheme 7). The identity of each of the diastereoisomeric triols was confirmed (with diastereoisomerically pure material) by ^{1}H NMR spectroscopy. Coupling constants between the three C*H*OH protons were consistent with the proposed structures. For example, the (C-2) C*H*OH resonance for **9** was identified by a ^{1}H COSY NMR experiment and had a coupling of 3.2 Hz (axial–equatorial) and 9.3 Hz (axial–axial). These data are consistent with the triol adopting a chair conformation with the hydroxy groups on C-2 and C-3 equatorial and the hydroxy groups on C-1 axial. In addition, the minor oxidation products, *syn*/*syn* triols **8** and **10**, were shown to have a plane of symmetry by careful examination of their ^{1}H and ^{13}C NMR spectra.

When 4-*tert*-butylcyclohexene **2** was oxidised under analogous conditions, little selectivity was observed and two vicinal diols were obtained in a 57:43 ratio. The major isomer was presumed to have an *anti* relationship between the hydroxy groups and the *tert*-butyl group, although this was not proven. Such a result rules out the possibility that the *tert*-butyl group within alcohols **4** and **6** is directly responsible for the diastereofacial selectivity that they exhibit upon oxidation, and implies that control originates from the allylic hydroxy group. Although the reasons for this *anti* selectivity are undoubtedly complex, a steric argument can be put forward to partly rationalise these results, as both an axially or equatorially oriented hydroxy group provides steric differentiation between the faces of the adjacent alkene. In addition, there may be electrostatic repulsion between the hydroxy group and the oxidant which contributes to the *anti* facial selectivity.[5] While these arguments provide a rationale for the *anti* selectivity displayed by each isomer, one must be careful when comparing the oxidation of **4** with the oxidation of **6** as the differences in selectivities are small. However, an axial hydroxy group is likely to provide more of a steric bias to the olefin than an equatorial hydroxy group, which fits with the fact that oxidation of **4** is more selective than oxidation of **6**. We do not wish to exclude the possibility that the reaction may proceed *via* conformations other than the standard half-chair, such as the boat.

A competition rate experiment was undertaken using compounds **4** and **6** as models for the axial and equatorial conformers of cyclohex-2-enol. An equimolar mixture of **4** and **6** was oxidised with osmium tetraoxide (NMO as re-oxidant) in aqueous acetone (Scheme 4). However, in order to avoid mass-



Scheme 4 *Reagents:* i, OsO_4 (1 mol%), NMO (6 mol%), acetone, H_2O

action effects, the amount of osmium tetraoxide was limited (1 mol%) as was the re-oxidant (6 mol%). Therefore, we assume that these conditions accurately duplicate those described in Scheme 3 whilst limiting the amount of dihydroxylation that can be achieved. The crude reaction mixture was analysed by ^{1}H NMR spectroscopy and by GC, which enabled determination of the relative amounts of the four triols present.

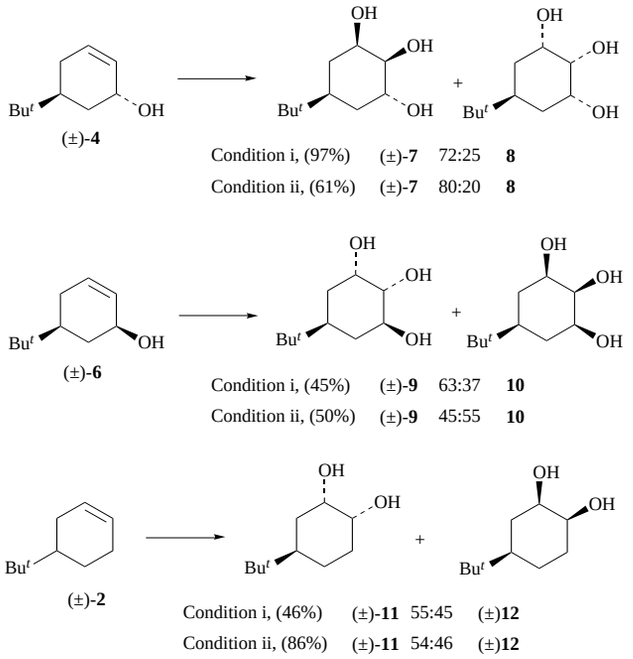
The results outlined above show that the axially 'locked' diastereoisomer **4** is 1.2 times more reactive towards dihydroxylation than the equatorially 'locked' alcohol **6** (average of three experiments). Reassuringly, each alcohol displayed similar diastereofacial selectivity to that we had observed earlier and the recovered mass of triol products was >90% of the theoretical amount, Scheme 4. Although this rate difference is rather small, we were surprised that the axial alcohol **4** was the more reactive. We tentatively attribute the rate difference to [A]^{1,2} strain between the C-2 vinylic hydrogen and the equatorial substituent at C-1. This effect will destabilise the transition state leading to oxidation (*anti*) of **6** (equatorial hydroxy) relative to **4** (equatorial hydrogen).[6] These results suggest that the axial conformer of cyclohex-2-enol is likely to be both more reactive and exhibit a more stereoselective dihydroxylation reaction than the equatorial one. Interestingly, it is also likely that the axial conformer of cyclohex-2-enol is more stable than the equatorial one.[7] The combination of all these effects would give rise to Kishi's observation on the stereoselective (*anti*) oxidation of cyclohex-2-enol, Scheme 1.§

Although the results presented here form a self consistent picture of the oxidation of cyclohex-2-enol, some caution is called for. In particular, we are not able to discount participation from other conformations (easily accessible in energy terms) of the cyclohexene ring which may prove to be more reactive than those derived from the half-chair.

An investigation into methods for reversing the *anti* selectivity described above was undertaken. The most obvious method of achieving this goal was to encourage hydrogen-bonding between the hydroxy group and the osmium tetraoxide, and in this regard we performed the dihydroxylation reactions of alkenes **2**, **4** and **6** in an inert (for hydrogen-bonding) solvent.[6b,8] In order to reduce complicating factors, stoichiometric amounts of osmium tetraoxide were employed initially (Condition i, Scheme 5). However, we also investigated methods of duplicating the selectivity observed under 'hydrogen-bonding' conditions using only catalytic amounts of osmium tetraoxide. Conditions originally reported by Poli[6] (1 mol% OsO_4 in dichloromethane with $Me_3NO{\cdot}2H_2O$) seemed to be ideal. Indeed, when the three alkenes **2**, **4** and **6** were oxidised using this method, some interesting results were obtained (Condition ii, Scheme 5).

The facial selectivities observed upon dihydroxylation under the action of stoichiometric osmium tetraoxide, as outlined above, reveal a reduction of the *anti* facial selectivity described earlier in aqueous acetone (Scheme 3). We ascribe this to competing hydrogen-bonding directed hydroxylation which opposes

§ We have found that cyclohex-2-enol was oxidised with a selectivity of 92:8 (94% yield) in favour of the *anti*/*syn* isomer, under the aqueous acetone conditions outlined in Scheme 3.



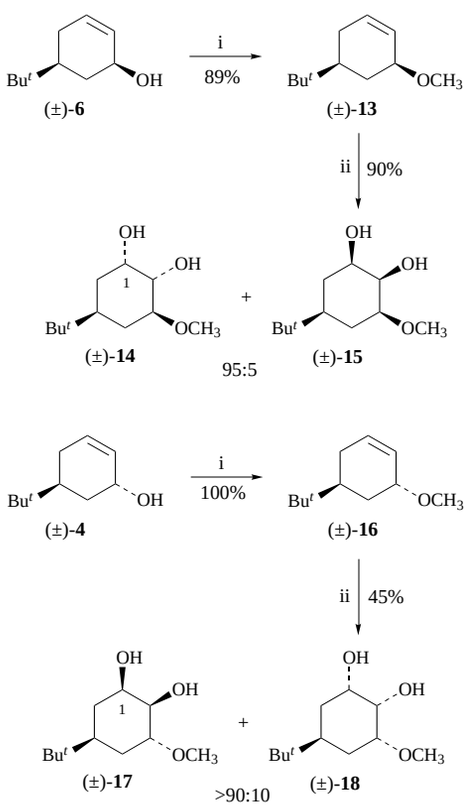
Scheme 5 *Reagents:* i, OsO_4, CH_2Cl_2; ii, OsO_4 (1 mol%), $Me_3NO\cdot 2H_2O$ (1.3 equiv.), DCM

the steric effect exerted by the allylic alcohol. Indeed, the observation of such phenomena in the oxidation of allylic and homoallylic alcohols has been reported before.[8] Apparently, the strength of this hydrogen-bonding is not as great as in other synthetically useful reactions such as epoxidation or cyclopropanation, and cannot overcome the steric effect of the hydroxy group.[9] It is unclear whether this is a consequence of the steric requirements of osmium tetraoxide or whether the transition metal compound has an inherent inability to act as an effective hydrogen-bond acceptor. The equatorially 'locked' alcohol **6** gives more of the *syn* triol product than its axially 'locked' counterpart, **4**. This may be a consequence of the smaller steric bias that has to be overcome in the *syn* selective dihydroxylation of **6**, whatever the reactive conformation; it may also be the case that an equatorial hydroxy group is more effectively aligned to provide hydrogen-bonding in the transition state than an axial hydroxy group (this effect has been noted in hydrogen-bonding directed epoxidation and cyclopropanation).[9] Under conditions that were catalytic in osmium tetraoxide, a similar trend in facial selectivity was observed. The oxidation of *trans* alcohol **4** was moderately *anti* selective with a facial selectivity that approximated to the ratio observed under stoichiometric conditions in dichloromethane. We were delighted to find that the *cis* alcohol **6** was oxidised with (albeit modest) *syn* selectivity under these conditions. Interference from the *tert*-butyl group was ruled-out by the non-selective oxidation of **2**.

The difference in selectivity between the stoichiometric and catalytic conditions is unusual and at this stage it is not possible to rationalise these results fully without further study. However, we believe that trimethylamine (liberated from the reduction of trimethylamine *N*-oxide) is at least partly responsible for the enhanced *syn* selectivity in the oxidation of **6**, the 45 : 55 ratio of diastereoisomers may represent the facial selectivity displayed by an amine–osmium tetraoxide adduct.¶[10] Under catalytic conditions, operation of the 'second cycle' may be relevant, as it is possible that a different oxidant is operational [*i.e.* osmium tetraoxide with stoichiometric oxidant in dichloromethane and a trioxo osmium(VIII) glycolate ester with catalytic osmium tetraoxide in dichloromethane].[11]

The yield of triol products from oxidation of **6** was only 45–50%, despite complete consumption of starting material and numerous attempts at reductive osmate ester hydrolysis (Na_2SO_3, H_2S *etc.*). This puzzling fact was subsequently explained by the observation (TLC) and eventual isolation of volatile enone **5** from the reaction mixture. This fact may be taken as circumstantial evidence of some kind of association between osmium and the allylic alcohol, prior to osmate ester formation. Of course, an axial hydrogen atom is removed during the alcohol to ketone transformation, which raises the possibility of C–H orbital overlap with the alkene π-electrons in the transition state.

Support for hydrogen-bonding under aprotic conditions was sought in the dihydroxylation of methyl ethers **13** and **16** (Scheme 6). After methylation of alcohols **4** and **6** with methyl



Scheme 6 *Reagents:* i, NaH, MeI; ii, OsO_4, CH_2Cl_2

iodide, the resulting ethers were dihydroxylated with stoichiometric amounts of osmium tetraoxide in dichloromethane (Scheme 6).

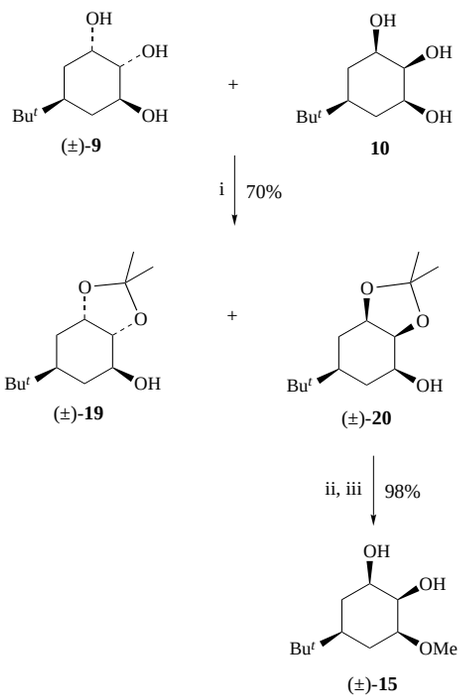
The diastereoselectivity displayed by the equatorially locked methyl ether was remarkably high (90% de) and was determined by ^{1}H and ^{13}C NMR spectroscopy of the crude reaction mixture and confirmed by GC [these experiments were performed with an authentic sample of the minor (all *cis*) diastereoisomer **15** for comparison, see Scheme 7]. The major diastereoisomer **14** was readily identified as being *anti*/*syn* by ^{1}H NMR spectroscopy of its diacetate derivative: the C*H*OH resonance on C-2 had two couplings, $J = 3$ and 11 Hz, which were consistent with a chair conformation with the C-2 hydrogen atom axially oriented and coupled to one axial (C-3) and one equatorial (C-1) hydrogen.

Moreover, the axially 'locked' methyl ether **16** gave essentially a single product upon oxidation (analysed by ^{1}H, ^{13}C NMR spectroscopy and GC) and this was subsequently shown (^{1}H NMR spectroscopy of the diacetate) to be the *anti*/*syn* product

¶ Oxidation of **6** in CH_2Cl_2 (saturated with trimethylamine) with a stoichiometric amount of osmium tetraoxide gave a 48 : 52 ratio of **9** and **10** (32% yield).

17: in this instance we did not have an authentic sample of the *syn*/*syn* diastereoisomer **18** for comparison and the ratio **17**:**18** was conservatively estimated at >90:10.

This stereoselectivity has obvious implications for the results presented in Scheme 5 and is a clear factor supporting hydrogen-bonding in those systems. Indeed, we were slightly surprised at the high degree of facial selectivity displayed by the methyl ether **13** (which cannot act as a hydrogen-bond donor). Electrostatic repulsion between the OMe and osmium tetraoxide, which is prevalent in a non-polar solvent, may explain this result.[5] As alluded to earlier, an authentic sample of the *syn*/*syn* diol **15** was required for analysis of the reaction mixture from dihydroxylation of ether **13**. This was prepared as outlined in Scheme 7 and the inefficiency of the chosen route is testament

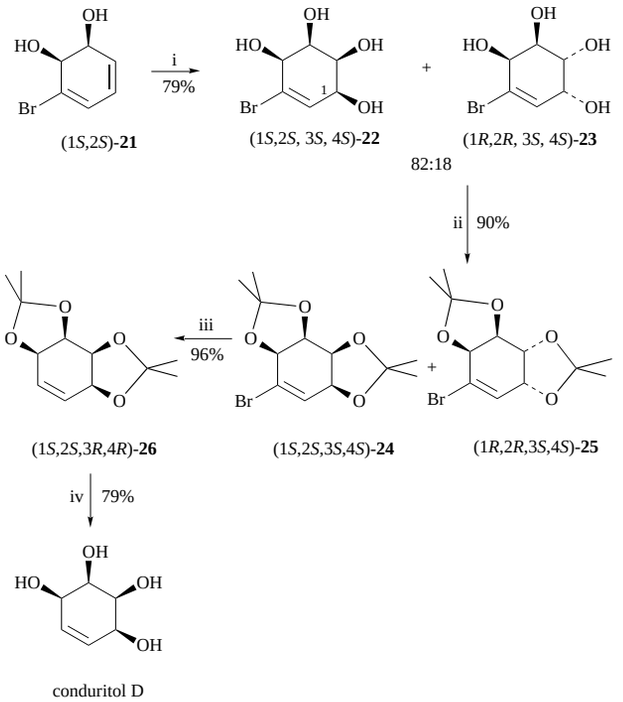


Scheme 7 *Reagents:* i, $CH_3C(OCH_3)_2CH_3$, PTSA; ii, NaH, MeI, THF; iii, H_3O^+

to the lack of viable methods to achieve the *syn* dihydroxylation of cyclic allylic alcohols. The triol products (**9** and **10**) from the oxidation of **6** were not separable by flash chromatography (although separation could be achieved by reversed phase HPLC) and so a 78:22 (*anti*:*syn*) mixture was treated with 2,2-dimethoxypropane under acidic conditions: the resulting isopropylidenes were separated by chromatography on silica gel and the minor compound **20** identified by acidic hydrolysis back to symmetrical triol **10**. Methylation of **20** was followed by aqueous acid deprotection of the acetal protecting group to yield **15** unambiguously, Scheme 7.

Synthesis of conduritols

An investigation into the application of this methodology to biologically important molecules ensued. The conduritols are a series of cyclohexene tetraols bearing a descriptor A–F depending on their stereochemistry: each of them poses a unique and interesting problem to synthetic organic chemists.[12] Conduritol D (Scheme 8) has proven to be one of the most difficult isomers to prepare and use of a hydrogen-bonding directed dihydroxylation reaction presented itself as an ideal method for the synthesis of this compound. Studies on the dihydroxylation of cyclohexadienediols (obtained from the oxidation of benzene and its derivatives by mutant strains of *Pseudomonas putida*) were undertaken. Many syn-



Scheme 8 *Reagents:* i, OsO_4 (1 mol%), $Me_3NO{\cdot}2H_2O$ (1.3 equiv.), CH_2Cl_2; ii, $CH_3C(OCH_3)_2CH_3$, PTSA; iii, Bu_3SnH, AIBN; iv, H_3O^+

thetic routes which utilise these diols make use of an *anti* selective dihydroxylation of their isopropylidene derivatives.[13] A *syn* selective dihydroxylation would appear to be unprecedented in this area and was viewed as a potentially useful reaction.

A series of cyclohexadienediols has already been subjected to the dihydroxylation reaction, reported by Carless *et al.*,[14] and in each case the *anti* diastereoisomer of a tetraol product predominated (although the degree of stereofacial discrimination was not always large). However, the reaction conditions involved aqueous acetone as solvent with NMO as re-oxidant. We suspected that dihydroxylation of these derivatives under aprotic conditions would result in preferential formation of the *syn* tetraol. When bromocyclohexadienediol (*S*,*S*)-**21** was dihydroxylated in dichloromethane with one equivalent of osmium tetraoxide only very low yields (<30%) of tetraols were obtained: we reasoned that the tetraol products were not compatible with the vigorous reductive work-up (heating at reflux with aqueous sodium sulfite) and opted instead for a protocol that involved oxidative cleavage of the osmate ester. When bromodiene (*S*,*S*)-**21** was oxidised under *catalytic* conditions in dichloromethane with trimethylamine *N*-oxide as a re-oxidant, we were delighted to observe a *syn* selective dihydroxylation (82:18, *syn*:*anti*, Scheme 8). The major compound from this reaction was easily identified as (*S*,*S*,*S*,*S*)-**22** and was identical to the minor compound formed by oxidation of **21** in aqueous acetone. Presumably, the remaining alkene unit in both tetraols **22** and **23** is both sterically hindered and electronically deactivated towards further oxidation.[15]

Unfortunately, we were not able to separate the tetraol products **22** and **23** and resorted to formation of their diisopropylidene derivatives.[14] Derivatisation was readily accomplished under the reaction conditions specified in Scheme 8. The two diastereoisomeric products thus formed had remarkably different polarity and were easily separated by chromatography on silica gel. The major compound, **24**, was confirmed as having all *cis* stereochemistry by X-ray crystallography, Fig. 1. In addition, the presence of a heavy atom made confirmation of the absolute stereochemistry of the compound possible (as drawn).

The synthesis of conduritol D was achieved using radical

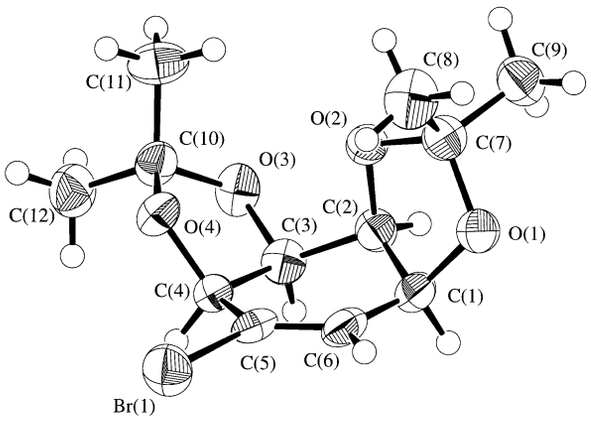
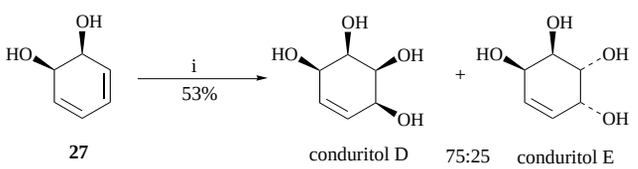


Fig. 1 X-Ray crystal structure of (1*S*,2*S*,3*S*,4*S*)-5-bromo-1,2:3,4-di-*O*-isopropylidenecyclohex-5-ene-1,2,3,4-tetraol **24**

debromination to give compound **26**, followed by acetal hydrolysis:[14] the material produced in this manner had three resonances in its ^{13}C NMR spectrum which were in accord with the literature values, Scheme 8.[16]

A much simpler route to conduritol D was completed *via* the dihydroxylation of unsubstituted diene **27** using catalytic 'hydrogen-bonding' conditions; again the major compound formed was the *syn* tetraol, which corresponds to conduritol D, (75 : 25, *syn* : *anti*, Scheme 9). This oxidation represents a reversal



Scheme 9 *Reagents:* i, OsO_4 (1 mol%), $Me_3NO{\cdot}2H_2O$ (1.3 equiv.), DCM

in the direction of stereochemical control when compared to dihydroxylation of the same substrate in acetone–water (Carless reported a 25 : 75 *syn* : *anti* ratio).[14] Unfortunately, the *anti* tetraol (conduritol E) could not be removed directly from the reaction mixture and this required formation of diisopropylidenes, which were easily separated by chromatography on silica gel. As such this approach represents an extremely short route to conduritol D and, as the diene **27** is commercially available, could easily be adapted to produce substantial amounts of material.

Our ability to produce the directed dihydroxylation products (*syn* tetraols) as the major components of oxidation is significant. The enhanced *syn* selectivity observed in the oxidation of the two cyclohexadienediols when compared to the dihydroxylation of cyclohexenols is interesting. Puckering of the cyclohexadiene ring may enable it to position one of its two hydroxy groups in a pseudo-equatorial position from where it is especially effective in directing the oxidant to the proximal alkene. Moreover, the dienes possess a second potentially directing hydroxy group at the homoallylic position. There is a clear trend which correlates enhanced *syn* selectivity during 'hydrogen-bonding' directed dihydroxylation with low *anti* selectivity in aqueous acetone solution.

In conclusion, we have investigated the factors responsible for the highly stereoselective dihydroxylation of cyclohex-2-enol in aqueous acetone solvent by utilising two conformationally 'locked' cyclohexenol derivatives. The results from this study enabled the development of a hydrogen-bonding delivered dihydroxylation using either stoichiometric or catalytic amounts of osmium tetraoxide and this reaction has been applied to the synthesis of conduritol D. This approach to the stereoselective synthesis of triols and tetraols holds promise for the preparation of naturally occurring compounds and is currently under investigation.

Experimental

General details

Melting points were determined with an 'Electrothermal' capillary melting point apparatus and are uncorrected. IR Spectra were measured with an ATI Mattison Genesis Series FTIR as KBr discs or neat oils as appropriate. The ^{1}H (500 and 200 MHz) NMR and ^{13}C (125 and 50 MHz) NMR spectra were obtained on Varian Unity 500 and Varian Gemini 200 spectrometers in deuteriated chloroform, deuterium oxide or deuteriated methanol with trimethylsilane as the internal standard at room temperature. *J* Values are given in Hz. Elemental analyses were performed in-house. Mass spectra were obtained on a Kratos Concept Mass Spectrometer using the electron impact mode (70 eV) or chemical ionisation. Preparative reversed phase HPLC was carried out with a Gilson Computerised apparatus using a Gilson 131 Refractive Index Detector. GC studies were performed using a CP-Chirasil DEXCB column (25 m × 0.32 mm, 0.28 μ) controlled by a Shimadzu Cromatopac R4AX unit. All solvents were purified by following standard literature methods. Thin layer chromatography (TLC) was performed on Polygram 0.25 mm silica gel pre-coated plastic sheets and visualised with UV light (254 nm) and/or phosphomolybdic acid in ethanol, *p*-anisaldehyde in glacial acetic acid or basic potassium permanganate as appropriate. Chromatography was performed on silica gel (Merck 60). $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to the fraction with bp 40–60 °C.

General dihydroxylation methods

Method A: catalytic osmium tetraoxide in aqueous acetone. To a solution of the alkene (0.01 M) in acetone–water (4 : 1, v : v, respectively), was added *N*-methylmorpholine *N*-oxide (4 equiv.) followed by a catalytic amount of osmium tetraoxide (5 mol%). The reaction mixture was then stirred at room temperature until complete (TLC analysis). Sodium sulfite (0.5 g) was added and the reaction was stirred for a further 0.5 h. The resulting mixture was poured into saturated aqueous sodium chloride (40 cm^3) and extracted with excess ethyl acetate (3 × 200 cm^3, to ensure complete removal of the product). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The products were purified by flash chromatography or preparative HPLC as appropriate.

Method B: stoichiometric osmium tetraoxide in anhydrous dichloromethane. To a solution of the alkene (0.01 M), in anhydrous dichloromethane, was added a stoichiometric amount of osmium tetraoxide (1.05 equiv.). The reaction mixture was then stirred under a dry nitrogen atmosphere at room temperature until complete (TLC analysis). The dichloromethane was removed on a hot oil bath and replaced with saturated aqueous sodium sulfite and THF (1 : 1, v : v, 20 cm^3). The resulting black mixture was heated at reflux overnight and then allowed to cool to room temperature. This mixture was poured into saturated aqueous sodium chloride (40 cm^3) and extracted with excess ethyl acetate (3 × 200 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered through a plug of Celite and concentrated under reduced pressure.

Method C: catalytic osmium tetraoxide in anhydrous dichloromethane. To a solution of the alkene (0.05 M) in anhydrous dichloromethane was added trimethylamine *N*-oxide dihydrate (1.3 equiv.), followed by a catalytic amount of osmium tetraoxide (1 mol%). The reaction was stirred at room temperature under a dry nitrogen atmosphere until complete (TLC analysis). The resulting mixture was concentrated under reduced pressure and the products purified by flash chromatography where appropriate.

(1*RS*,2*SR*,4*RS*)- and (1*RS*,2*SR*,4*SR*)-4-*tert*-Butylcyclohexane-1,2-diol 11 and 12

Method A. 4-*tert*-Butylcyclohexene **2** (138 mg, 1 mmol) was submitted to the general dihydroxylation conditions described in method A. After 24 h the reaction mixture was worked-up as outlined to provide a colourless crystalline solid (156 mg, 91%). ^{1}H NMR Spectroscopy of the crude product showed an inseparable mixture of the diols **11** and **12** in a 57:43 ratio, that did not require any further purification, δ_H(200 MHz, $CDCl_3$) 4.15–4.20 (1 H, m, C*H*OH), 3.90–3.81 (1 H, m, C*H*OH), 3.61–3.42 (2 H, m, C*H*OH), 2.40–1.90 (2 H, m), 1.80–0.95 (12 H, m), 0.87 [9 H, s, C(CH_3)$_3$], 0.82 [9 H, s, C(CH_3)$_3$]; δ_C(50 MHz, $CDCl_3$) 73.21, 72.49, 70.32, 69.23, 46.89, 40.09, 32.81, 32.52, 32.33, 31.21, 30.46, 29.40, 27.99, 25.57, 20.14; ν_{max}(Nujol)/cm^{-1} 3373br s (OH stretch), 2924 (CH stretch), 1461 (C–O stretch); *m*/*z* (CI) 190 (M^+ + 18, 100%), 155 (M^+ − 18), 137 (M^+ − 35) [Found (EI): M^+, 172.1468. $C_{10}H_{20}O_2$ requires *M*, 172.1468; Found: C, 69.84; H, 11.78. $C_{10}H_{20}O_3$ requires C, 69.72; H, 11.70%].

Method B. 4-*tert*-Butylcyclohexene **2** (55 mg, 0.39 mmol) was submitted to the dihydroxylation conditions described in method B. After 24 h the reaction mixture was worked-up as outlined to give a grey solid residue. Flash chromatography (light petroleum–EtOAc, 4:1) gave a colourless solid (32 mg, 46%), being an inseparable mixture of the diastereoisomeric diols **11** and **12** (55:45, respectively).

Method C. 4-*tert*-Butylcyclohexene **2** (250 mg, 1.81 mmol) was submitted to the dihydroxylation conditions described in method C. After 48 h the reaction mixture was worked-up as outlined to give a colourless solid. Flash chromatography (light petroleum–EtOAc, 4:1) gave a colourless solid (267 mg, 86%), being an inseparable mixture of the diastereoisomeric diols **11** and **12** (54:46, respectively).

(1*RS*,3*RS*)-5-*c*-*tert*-Butylcyclohexane-*r*-1,*c*-2,*t*-3-triol 7 and (1*RS*,2*RS*,3*SR*,5*RS*)-5-*tert*-butylcyclohexane-1,2,3-triol 8

Method A. *trans*-5-*tert*-Butylcyclohex-2-enol **4** (222 mg, 1.44 mmol) was submitted to the conditions described in method A. After 48 h the reaction mixture was worked-up as outlined to provide a colourless, crystalline solid (244 mg, 90%). ^{1}H NMR Spectroscopy of the crude product showed triols **7** and **8** in a 94:6 ratio, that did not require any further purification. Preparative HPLC (MeOH–H_2O, 60:40) gave (1*RS*,3*RS*)-5-*c*-*tert*-butylcyclohexane-*r*-1,*c*-2,*t*-3-triol **7** as the first compound to be eluted, being a colourless, crystalline solid; mp 184–188 °C (decomp.); δ_H(200 MHz, D_2O) 4.05–4.15 (1 H, br m, 3-H), 3.83 (1 H, dt, *J* 11.2 and 3.4, 1-H), 3.74 (1 H, br t, *J* 2.8, 2-H), 1.80–1.50 (2 H, br m), 1.50–1.10 (3 H, br m), 0.82 [9 H, s, C(CH_3)$_3$]; δ_C(50 MHz, D_2O) 73.86 (CH, C-3), 73.46 (CH, C-1), 71.57 (CH, C-2), 42.35 (CH, C-5), 34.0 (C), 31.20 (CH_2), 29.62 (CH_2), 29.51 (3 × CH_3); ν_{max}(Nujol)/cm^{-1} 3331br s (OH stretch), 2952, 2924 and 2854 (CH stretch); *m*/*z* (CI) 206 (M^+ + 18, 100%) (Found: M^+, 188.1414. $C_{10}H_{20}O_3$ requires *M*, 188.1412; Found: C, 63.51; H, 10.36. $C_{10}H_{20}O_3$ requires C, 63.80; H, 10.7%). Further elution provided (1*RS*,2*RS*,3*SR*,5*RS*)-5-*tert*-butylcyclohexane-1,2,3-triol **8** as a colourless crystalline solid; mp 184–188 °C (decomp.); δ_H(200 MHz, D_2O) 4.04–4.07 (2 H, br m, 1-H and 3-H), 3.52 (1 H, t, *J* 3.1, 2-H), 2.00–1.85 (2 H, m), 1.70–1.55 (1 H, br m, 5-H), 1.40–1.20 (2 H, br m), 0.83 [9 H, s, C(CH_3)$_3$]; δ_C(50 MHz, D_2O) 74.38 (2 × CH, C-1 and C-3), 73.44 (CH, C-2), 36.05 (CH, C-5), 34.66 (2 × CH_2), 33.49 (C), 29.57 (3 × CH_3); ν_{max}(Nujol)/cm^{-1} 3361br s (OH stretch), 2952, 2924 and 2854 (CH stretch); *m*/*z* (CI) 206 (M^+ + 18, 100%) (Found: M^+ + 18, 206.1756. $C_{10}H_{20}O_3{\cdot}NH_4$ requires *M* + 18, 206.1756; Found: C, 63.74; H, 10.80. $C_{10}H_{20}O_3$ requires C, 63.80; H, 10.71%).

Method B. *trans*-5-*tert*-Butylcyclohex-2-enol **4** (85 mg, 0.55 mmol) was submitted to the conditions described in method B. After 24 h the reaction was worked-up as described to provide a colourless solid (99 mg, 97%). ^{1}H NMR Spectroscopy of this crude product showed triols **7** and **8** in a 75:25 ratio, respectively, that did not require any further purification.

Method C. *trans*-5-*tert*-Butylcyclohex-2-enol **4** (50 mg, 0.36 mmol) was submitted to the conditions described in method C. After 18 h the reaction mixture was concentrated under reduced pressure to give an off-white solid. ^{1}H NMR Spectroscopy of the crude product showed triols **7** and **8** in an 80:20 ratio, respectively. Flash chromatography (EtOAc) gave the single diastereoisomer **7** as a colourless solid (38 mg, 61%).

(1*RS*,3*RS*)-5-*t*-*tert*-Butylcyclohexane-*r*-1,*c*-2,*t*-3-triol 9 and (1*RS*,2*SR*,3*SR*,5*RS*)-5-*tert*-butylcyclohexane-1,2,3-triol 10

Method A. *cis*-5-*tert*-Butylcyclohex-2-enol **6** (142 mg, 0.92 mmol) was submitted to the procedure described in method A. After 48 h the reaction mixture was worked-up as described to give a colourless solid (157 mg, 91%). ^{1}H NMR Spectroscopy of the crude product showed triols **9** and **10** in a 85:15 ratio, respectively, that did not require any further purification. The diastereoisomers **9** and **10** were separated and characterised through conversion to their corresponding acetonides **19** and **20**, followed by subsequent deprotection, *vide supra*.

Method B. *cis*-5-*tert*-Butylcyclohex-2-enol **6** (66 mg, 0.43 mmol) was submitted to the conditions described in method B. After 24 h the reaction was worked-up as described to give a grey solid. ^{1}H NMR Spectroscopy of the crude product showed triols **9** and **10** in a 63:37 ratio, respectively. Flash chromatography (EtOAc) gave a colourless solid (34 mg, 45%), being an inseparable mixture of the triols **9** and **10**, in a ratio of 63:37, respectively.

Method C. *cis*-5-*tert*-Butylcyclohex-2-enol **6** (75 mg, 0.54 mmol) was submitted to the conditions described in method C. After 18 h the reaction mixture was concentrated under reduced pressure to a dark oil. ^{1}H NMR Spectroscopy of this oil showed triols **9** and **10** in a 45:55 ratio, respectively. Flash chromatography (EtOAc) gave a colourless solid (46 mg, 50%), being an inseparable mixture of alcohols **9** and **10** in a 45:55 ratio, respectively.

Competition experiment using the two isomers 4 and 6 of 5-*tert*-butylcyclohex-2-enol

To a solution of **4** (154 mg, 1 mmol) and **6** (154 mg, 1 mmol) in acetone–water (1:1, v:v, 100 cm^3), was added *N*-methylmorpholine *N*-oxide (7 mg, 6 × 10^{-5} mol) followed by osmium tetraoxide (2.5 mg, 1 × 10^{-5} mol). The reaction mixture was stirred at room temperature for 2 days. Solid sodium sulfite (0.5 g) was added and the mixture refluxed for 3 h. The reaction mixture was allowed to cool to room temperature then poured into saturated aqueous sodium chloride (20 cm^3). This aqueous solution was extracted with ethyl acetate (3 × 200 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered through a pad of Celite, then concentrated under reduced pressure to a colourless oil (280 mg). GC studies of this oil showed the oxidation products from alcohol **4** (triols **7** and **8**) and alcohol **6** (triols **9** and **10**) in a ratio of 1.2:1, respectively. This crude oil was dissolved in a mixture of diethyl ether (50 cm^3) and water (50 cm^3). After separation of the two layers the aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The organic extracts were back-washed with water (50 cm^3) and the combined aqueous extracts concentrated under reduced pressure to a colourless solid (13 mg). GC studies of this solid residue showed the oxidation products from alcohol **4** and alcohol **6** in a ratio of 1.2:1, respectively.

(3*RS*,5*RS*)-3-Methoxy-5-*tert*-butylcyclohex-1-ene 13

A solution of the alcohol **6** (90 mg, 0.58 mmol) in Me_2SO (3 cm^3) was treated with sodium hydride (60% dispersion in oil, 52 mg, 1.3 mmol) and the resulting solution stirred at room temperature under a dry nitrogen atmosphere for 1 h. Iodomethane (freshly filtered through anhydrous K_2CO_3, 0.2 cm^3, 3.2 mmol) was added and the reaction mixture was stirred at room tem-

perature for 3 h. Water (40 cm^3) was added and the resulting mixture extracted into dichloromethane (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to a pale yellow oil. Flash chromatography (light petroleum–Et_2O, 10:1) gave the methyl ether **13** (87 mg, 89%) as a colourless oil; δ_H(200 MHz, $CDCl_3$) 5.65–5.85 (2 H, m, 1-H and 2-H), 3.85–3.80 (1 H, br m, 3-H), 3.38 (3 H, s, OCH_3), 2.30–0.80 (5 H, m), 0.87 [9 H, s, $C(CH_3)_3$]; δ_C(50 MHz, $CDCl_3$) 130.03 (CH, C-1), 128.63 (CH, C-2), 78.15 (CH_3, OCH_3), 56.03 (CH, C-3), 43.33 (CH, C-5), 32.73 [C, $C(CH_3)_3$], 30.80 (CH_2), 27.53 [CH_3, $C(CH_3)_3$], 27.44 (CH_2); ν_{max}(neat)/cm^{-1} 2989 and 2818 (CH stretch), 1656 (C=C stretch); *m*/*z* (EI) 168 (M^+, 10%), 154 ($M^+ - 14$, 100) [Found (EI): M^+, 168.1505. $C_{11}H_{20}O$ requires *M*, 168.1514].

(1*RS*,2*RS*,3*RS*,5*RS*)-3-Methoxy-5-*tert*-butylcyclohexane-1,2-diol 14

The methyl ether **13** (85 mg, 0.5 mmol) was submitted to the conditions described in general hydroxylation method B. After 48 h the reaction mixture was worked-up as described to provide a colourless oil (100 mg, 99%). ^{1}H NMR Spectroscopy and GC studies on the crude reaction mixture showed a 95:5 mixture of the diastereoisomers **14** and **15**. Flash chromatography (light petroleum–ethyl acetate, 2:1) gave **14** as a colourless oil (91 mg, 90%); δ_H(200 MHz, $CDCl_3$) 4.18–4.14 (1 H, br m, 1-H), 3.40–3.30 (2 H, br m, 2-H and 3-H), 3.38 (3 H, s, OCH_3), 3.20–2.80 (2 H, br s, OH), 2.30–0.90 (5 H, m), 0.87 [9 H, s, $C(CH_3)_3$]; δ_C(50 MHz, $CDCl_3$) 80.85 (CH, C-1), 76.16 (CH_3, OCH_3), 69.60 (CH, C-2), 57.0 (CH, C-3), 39.75 (CH, C-5), 32.44 (CH_2), 31.61 (CH_2), 29.78 [C, $C(CH_3)_3$], 27.98 [CH_3, $C(CH_3)_3$]; ν_{max}(neat)/cm^{-1} 3390br s (OH stretch), 2965 and 2859 (CH stretch); *m*/*z* (CI) 220 (M^+ + 18, 70%), 177 ($M^+ - 25$, 100) (Found: M^+ + 18, 220.1909. $C_{11}H_{22}O_3{\cdot}NH_4$ requires *M* + 18, 220.1913).

(3*SR*,5*RS*)-3-Methoxy-5-*tert*-butylcyclohex-1-ene 16

A solution of the alcohol **4** (100 mg, 0.65 mmol) in anhydrous THF (4 cm^3) was added dropwise to a suspension of sodium hydride (60% dispersion in oil, washed with THF, 57 mg, 1.43 mmol) at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for a further 45 min. Iodomethane (89 μl, 202 mg, 1.43 mmol) was added to the reaction mixture, which was then refluxed with stirring for a further 1 h. The crude product was filtered through a pad of silica (eluting with light petroleum–EtOAc, 4:1). Concentration of the filtrate under reduced pressure provided the methyl ether **16** (110 mg, 100%) as a colourless oil; δ_H(200 MHz, $CDCl_3$) 6.10–5.79 (2 H, m, 1-H and 2-H), 3.80–3.70 (1 H, br m, 3-H), 3.37 (3 H, s, OCH_3), 2.30–0.9 (5 H, m), 0.87 [9 H, s, $C(CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 132.71 (CH, C-1), 125.50 (CH, C-2), 73.57 (CH_3 OCH_3), 56.03 (CH, C-3), 37.92 (CH, C-5), 29.72 [C, $C(CH_3)_3$], 28.17 (CH_2), 27.27 (CH_2), 27.17 [CH_3, $C(CH_3)_3$]; ν_{max}(neat)/cm^{-1} 3026 (C=CH stretch), 2961 and 2928 (CH stretch), 1656 (C=CH); *m*/*z* (EI) 168 (M^+, 10%), 154 ($M^+ - 14$, 100) [Found (EI): M^+, 168.1514. $C_{11}H_{20}O$ requires *M*, 168.1514].

(1*RS*,2*RS*,3*RS*,5*SR*)-3-Methoxy-5-*tert*-butylcyclohexane-1,2-diol 17

The methyl ether **16** (50 mg, 0.3 mmol) was submitted to the dihydroxylation conditions described in Method B. After 18 h the reaction mixture was worked-up in the described manner to give a colourless, crystalline solid (36 mg, 70%). ^{1}H NMR Spectroscopy and GC studies of the crude product showed diastereoisomer **17** only. Flash chromatography (light petroleum–EtOAc, 2:1) gave diol **17** (23 mg, 45%), as a colourless, crystalline solid; mp 74–76 °C; δ_H(200 MHz, $CDCl_3$) 3.96–3.80 (2 H, m, 2-H and 3-H), 3.64–3.56 (1 H, br m, 1-H), 3.30 (3 H, s, OCH_3), 2.6–2.4 (1 H, br m, OH), 2.30–2.10 (1 H, br m, OH), 1.90–1.60 (2 H, m), 1.40–1.20 (3 H, m), 0.87 [9 H, s, $C(CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 79.66 (CH, C-1), 69.58 (2 × CH, C-2, C-3), 56.54 (CH_3, OCH_3), 39.47 (CH, C-5), 31.93 [C, $C(CH_3)_3$], 29.49 (CH_2), 27.40 [CH_3, $C(CH_3)_3$], 24.17 (CH_2); ν_{max}(KBr)/cm^{-1} 3409br s (OH stretch), 2969 and 2929 (CH stretch); *m*/*z* (CI) 220 (M^+ + 18, 70%), 177 ($M^+ - 25$, 100) (Found: M^+ + 18, 220.1910. $C_{11}H_{22}O_3{\cdot}NH_4$ requires *M* + 18, 220.1913).

(1*RS*,2*SR*,3*RS*,5*SR*)-2,3-*O*-Isopropylidene-5-*tert*-butylcyclohexane-1,2,3-triol 19 and (1*RS*,2*RS*,3*SR*,5*SR*)-2,3-*O*-isopropylidene-5-*tert*-butylcyclohexane-1,2,3-triol 20

To a solution of the triols **9** and **10** (257 mg, 1.37 mmol, 78:22 ratio) in 2,2-dimethoxypropane (13 cm^3) and acetone (4 cm^3) at 0 °C with stirring, was added a small crystal of toluene-*p*-sulfonic acid. The solution was then stirred at room temperature for 90 min. Aqueous NaOH (10%, 4 cm^3), brine (4 cm^3) and diethyl ether (20 cm^3) were added. After stirring for a further 10 min the layers were separated and the aqueous layer extracted with diethyl ether (3 × 20 cm^3). The combined ethereal extracts were washed with brine (10 cm^3) and dried ($MgSO_4$). Filtration and concentration under reduced pressure gave a crude oil (326 mg). Flash chromatography (light petroleum–EtOAc, 4:1) gave (1*RS*,2*RS*,3*SR*,5*SR*)-2,3-*O*-isopropylidene-5-*tert*-butylcyclohexane-1,2,3-triol **20** (47 mg, 70%) as the first compound to be eluted, as a colourless oil; δ_H(200 MHz, $CDCl_3$) 4.25 (1 H, t, *J* 4.4, 2-H), 4.20–4.08 (1 H, m, 3-H), 3.81 (1 H, dt, *J* 10.6 and 4.4, 1-H), 220 (1 H, br s, OH), 1.52 [3 H, s, $C(CH_3)_2$], 1.37 [3 H, s, $C(CH_3)_2$], 2.20–0.90 (5 H, m), 0.87 [9 H, s, $C(CH_3)_3$]; δ_C(50 MHz $CDCl_3$) 109.27 [C, $C(CH_3)_2$], 76.15 (2 × CH, C-2 and C-3), 70.29 (CH, C-1), 42.12 (CH, C-5), 32.61 [C, $C(CH_3)_3$], 31.04 (CH_2), 30.72 (CH_3), 28.87 (CH_2), 27.85 [CH_3, $C(CH_3)_3$], 26.75 (CH_3); ν_{max}(neat)/cm^{-1} 3410br s (OH stretch), 2964 and 2870 (CH stretch), 1379 [$C(CH_3)_2$]; *m*/*z* (EI) 213 ($M^+ - 15$, 30%), 174 ($M^+ - 54$, 40), 105 ($M^+ - 123$, 100) [Found (CI): M^+ + 1, 229.1804. $C_{15}H_{27}O_5$ requires *M* + 1, 229.1803].

Further elution provided (1*RS*,2*SR*,3*RS*,5*SR*)-2,3-*O*-isopropylidene-5-*tert*-butylcyclohexane-1,2,3-triol **19** (170 mg, 70%) as a colourless crystalline solid; mp 59–60 °C; δ_H(200 MHz, $CDCl_3$) 4.38–4.30 (1 H, m, 3-H), 3.80–3.60 (2 H, m, 1-H and 2-H), 2.70–2.50 (1 H, br s, OH), 1.50 [3 H, s, $C(CH_3)_2$], 1.36 [3 H, s, $C(CH_3)_2$], 2.20–0.80 (5 H, m), 0.87 [9 H, s, $C(CH_3)_3$]; δ_C(50 MHz, $CDCl_3$) 109.09 [C, $C(CH_3)_2$], 82.39 (CH, C-3), 75.43 (CH, C-2), 74.20 (CH, C-1), 40.91 (CH, C-5), 32.94 (CH_2), 32.46 (CH_2), 29.02 (CH_3), 28.66 [C, $C(CH_3)_3$], 27.84 [CH_3, $C(CH_3)_3$], 26.86 (CH_3); ν_{max}(KBr)/cm^{-1} 3454br s (OH stretch), 2968 and 2874 (CH stretch), 1383 [$C(CH_3)_2$]; *m*/*z* (CI) 229 (M^+ + 1, 100%) [Found (CI): M^+ + 1, 229.1801. $C_{15}H_{27}O_5$ requires *M* + 1, 229.1803].

(1*RS*,3*RS*)-5-*t*-*tert*-Butylcyclohexane-*r*-1,*c*-2,*t*-3-triol 9

A solution of the acetonide **19** (20 mg, 8.81×10^{-5} mol) in dilute hydrochloric acid (2 M) and THF (1:1, v:v, 1 cm^3) was stirred at room temperature for 1 h. The reaction mixture was concentrated by azeotroping with toluene, then dried further under high vacuum to give triol **9** as a colourless, crystalline solid (16 mg, 97%); mp 166–168 °C; δ_H(200 MHz, CD_3OD) 4.02 (1 H, br q, *J* 2.9, 1-H), 3.70 (1 H, td, *J* 10.7 and 4.7, 3-H), 3.20 (1 H, dd, *J* 9.3 and 3.2, 2-H), 2.00–1.80 (2 H, m), 1.61 (1 H, tt, *J* 13 and 3, 5-H), 1.40–1.00 (2 H, m), 0.89 [9 H, s, $C(CH_3)_3$]; δ_C(50 MHz, CD_3OD) 78.56 (CH, C-1), 71.81 (CH, C-3), 71.62 (CH, C-2), 40.93 (CH, C-5), 35.80 (CH_2), 33.68 (CH_2), 32.85 (C), 28.24 (CH_3); ν_{max}(Nujol)/cm^{-1} 3343br s (OH stretch), 2859 (CH stretch), 1094 (C–O stretch); *m*/*z* (CI) 206 (M^+ + 18, 100%) (Found: M^+ + 18, 206.1753. $C_{10}H_{20}O_3{\cdot}NH_4$ requires *M* + 18, 206.1756; Found: C, 63.78; H, 10.41. $C_{10}H_{20}O_3$ requires C, 63.80; H, 10.71%).

(1*RS*,2*SR*,3*SR*,5*RS*)-5-*tert*-Butylcyclohexane-1,2,3-triol 10

A solution of the acetonide **20** (10 mg, 4.4×10^{-5} mol) in dilute hydrochloric acid (2 M) and THF (1:1, v/v, 1 cm^3) was stirred at

room temperature for 1 h. The reaction mixture was concentrated by azeotroping with toluene, then dried further under high vacuum to give triol **10** as a colourless, crystalline solid (8 mg, 100%); mp 170–172 °C; δ_H(300 MHz, D_2O) 3.86–3.88 (1 H, br m, 2-H), 3.57 (2 H, dt, *J* 11 and 3, 1-H and 3-H), 1.70–0.80 (5 H, m), 0.81 [9 H, s, C(CH_3)$_3$]; δ_C(50 MHz, D_2O) 75.08 (CH, C-2), 73.45 (2 × CH, C-1 and C-3), 44.45 (CH, C-5), 34.16 [C, *C*(CH_3)$_3$], 30.50 (CH_2), 29.67; ν_{max}(neat)/cm^{-1} 3396br s (OH stretch), 2959 and 2868 (CH stretch); *m*/*z* (CI) 206 (M^+ + 18, 100%) (Found: M^+ + 18, 206.1750. $C_{10}H_{20}O_3 \cdot NH_4$ requires *M* + 18, 206.1756).

(1*S*,2*S*,3*S*,4*S*)-5-Bromo-1,2:3,4-di-*O*-isopropylidenecyclohex-5-ene-1,2,3,4-tetraol 24 and (1*R*,2*R*,3*S*,4*S*)-5-bromo-1,2:3,4-di-*O*-isopropylidenecyclohex-5-ene-1,2,3,4-tetraol 25

A solution of the diol **21** (3 cm^3, 10% w/v) in EtOAc, was added to vigorously stirred light petroleum (36 cm^3) at 0 °C. The resulting precipitate was filtered under reduced pressure and dried *in vacuo*. To a solution of this freshly precipitated diol (300 mg, 1.57 mmol) in anhydrous dichloromethane (31 cm^3) was added trimethylamine *N*-oxide dihydrate (227 mg, 2.04 mmol), followed by a catalytic amount of osmium tetraoxide (4 mg, 1.57 × 10^{-5} mol). The reaction was then stirred under an atmosphere of nitrogen at room temperature for 48 h. The resulting mixture was concentrated under reduced pressure to provide a black oil. ^{1}H NMR Spectroscopy of this crude oil showed the tetraols **22** and **23** in a ratio of 82:18, respectively. Flash chromatography (EtOAc–MeOH, 9:1) gave an inseparable mixture of the tetraols **22** and **23**, in a ratio of 76:24 respectively, as a colourless, crystalline solid (276 mg, 79%).

To a solution of the above tetraols (200 mg, 0.88 mmol) in acetone (20 cm^3) and 2,2-dimethoxypropane (4 cm^3) at 0 °C was added a catalytic amount of trifluoroacetic acid (40 µl) and the mixture was stirred at 4 °C overnight. The reaction mixture was neutralised with triethylamine (0.2 cm^3) and concentrated under reduced pressure at 20 °C to a viscous oil. Flash chromatography (light petroleum–diethyl ether, 4:1) gave the acetonide **25** as a colourless oil (43 mg, 90%); $[\alpha]_D^{24}$ +81.2 (*c* 0.95 in $CHCl_3$) {lit,[14] $[\alpha]_D^{26}$ +82.2 (*c* 1.25 in MeOH)}; δ_H(200 MHz, $CDCl_3$) 6.08 (1 H, m, 6-H), 4.68–4.58 (4 H, m, 1-H, 2-H, 3-H and 4-H), 1.41 (6 H, s, 2 × CH_3), 1.38 (6 H, s, 2 × CH_3); δ_C(50 MHz, $CDCl_3$) 129.64 (CH, C-6), 124.80 (C, C-5), 110.56 [C, *C*(CH_3)$_3$], [C, *C*(CH_3)$_2$], 110.34 [C, *C*(CH_3)$_2$], 74.88, 74.50, 73.08 and 72.77 (all CH, C-1, C-2, C-3 and C-4), 28.32, 28.02, 26.97 and 26.83 (all CH_3); ν_{max}(neat)/cm^{-1} 2986 and 2934 (CH stretch), 1649 (C=CH stretch), 1371 [C(CH_3)$_2$]; *m*/*z* (CI) 322, 324 (M^+ + 18, 100%) [Found (CI): M^+ + 1, 305.0386, 307.0371. $C_{12}H_{17}BrO_4$ requires *M* + 1, 305.0389, 307.0369].

Further elution provided acetonide **24** (185 mg, 90%) as a colourless, crystalline solid; mp 119–121 °C (lit.,[14] mp 130–132 °C); $[\alpha]_D^{31}$ +8.5 (*c* 1.0 in $CHCl_3$) {lit.,[14] $[\alpha]_D^{26}$ −3.8 (*c* 0.5 in MeOH)}; δ_H(200 MHz, $CDCl_3$) 6.24 (1 H, d, *J* 3.5, 6-H), 4.61–4.54 (2 H, m, 1-H and 4-H), 4.47 (1 H, t, *J* 4.2, 2-H), 4.41 (1 H, t, *J* 4.8, 3-H), 1.53 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 1.42 [3 H, s, C(CH_3)$_2$], 1.39 [3 H, s, C(CH_3)$_2$]; δ_C(50 MHz, $CDCl_3$) 128.87 (CH, C-6), 124.81 (C, C-5), 111.64 [C, *C*(CH_3)$_2$], 75.99, 74.32, 73.17 and 72.41 (all CH, C-1, C-2, C-3 and C-4), 27.37 (CH_3), 26.89 (CH_3); ν_{max}(KBr)/cm^{-1} 3012 and 2931 (CH stretch), 1648 (C=CH stretch), 1376 [C(CH_3)$_2$]; *m*/*z* (CI) 322, 324 (M^+ + 18, 100%) [Found (CI): M^+ + 1, 305.0384, 307.0371. $C_{12}H_{17}BrO_4$ requires *M* + 1, 305.0389, 307.0369].

(1*S*,2*S*,3*R*,4*R*)-1,2:3,4-Di-*O*-isopropylidenecyclohex-5-ene-1,2,3,4-tetraol 26

Tributyltin hydride (124 µl, 0.46 mmol) was added to a solution of the bromide **24** (70 mg, 0.23 mmol) and AIBN (38 mg, 0.23 mmol) in anhydrous toluene (7 cm^3). The reaction mixture was headed at reflux overnight and then allowed to cool to room temperature. The solvent was removed under reduced pressure and flash chromatography (hexane then hexane–diethyl ether, 7:3) gave the diacetonide of conduritol D **26**, as a colourless oil (50 mg, 96%); δ_H(200 MHz, $CDCl_3$) 5.82 (2 H, d, *J* 1.4, 5-H and 6-H), 4.58–4.52 (2 H, m, 1-H and 4-H), 4.39 (2 H, dd, *J* 4.3 and 1.8, 2-H and 3-H), 1.48 [6 H, s, C(CH_3)$_2$], 1.38 [6 H, s, C(CH_3)$_2$]; δ_C(50 MHz, $CDCl_3$) 127.12 (CH, C-5 and C-6), 111.0 [C, *C*(CH_3)$_2$], 72.97 (CH, C-1 and C-4), 71.55 (CH, C-2 and C-3), 27.58 (CH_3), 26.93 (CH_3); ν_{max}(neat)/cm^{-1} 3035 (C=CH stretch), 2983 and 2932 (CH stretch), 1378 [C(CH_3)$_2$]; *m*/*z* (CI) 227 (M^+ + 1, 100%) [Found (CI): M^+ + 1, 227.1284. $C_{12}H_{19}O_4$ requires *M* + 1, 227.1283].

Conduritol D

A solution of the diacetonide **26** (45 mg, 0.2 mmol) in acetic acid (0.3 cm^3) and water (2.7 cm^3) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool, then concentrated under reduced pressure. Flash chromatography (EtOAc then EtOAc–MeOH, 9:1) gave conduritol D (23 mg, 79%) as a colourless, viscous oil; δ_H(500 MHz, CD_3OD) 5.99 (2 H, d, *J* 1.5, 5-H and 6-H), 4.29 (2 H, d, *J* 3.4, 1-H and 4-H), 4.0 (2 H, d, *J* 4.7, 2-H and 3-H); δ_C(125 MHz, CD_3OD) 130.37 (CH, C-5 and C-6), 72.04 (CH, C-1 and C-4), 69.16 (CH, C-2 and C-3) [lit.,[16] δ_C(CD_3OD) 130.4, 72.0 and 69.1]; ν_{max}(neat)/cm^{-1} 3325br s (OH stretch), 2914 (CH stretch), 1642 (C=C stretch); *m*/*z* (CI) 164 (M^+ + 18, 100%) [Found (CI): M^+ + 18, 164.0926. $C_6H_{10}O_4 \cdot NH_4$ requires *M* + 18, 164.0923].

Dihydroxylation of *cis*-cyclohexa-3,5-diene-1,2-diol 27

The diol **27** (400 mg, 3.57 mmol) was submitted to the dihydroxylation conditions described in method C. After 4 h the dark brown reaction mixture was concentrated at 20 °C under reduced pressure to a viscous red–brown oil. ^{1}H NMR Spectroscopy of this oil showed it to consist of a 78:22 mixture of conduritol D and conduritol E, respectively. Flash chromatography (EtOAc–MeOH, 9:1) gave conduritol D and conduritol E (276 mg, 53%) as an inseparable mixture of diastereoisomers, in a ratio of 82:18, respectively.

To a solution of the above tetraols (104 mg, 0.71 mmol) in 2,2-dimethoxypropane (3 cm^3) and acetone (1 cm^3) was added with stirring, at 0 °C a small crystal of toluene-*p*-sulfonic acid. After 1 h the reaction mixture was neutralised with triethylamine (0.05 cm^3) and the mixture concentrated under reduced pressure at 20 °C to a colourless solid. Flash chromatography (light petroleum–diethyl ether, 4:1) gave protected conduritol D **26** as a colourless oil (79 mg, 60%).

Crystal data for 24

$C_{12}H_{17}BrO_4$, *M* = 305.17, orthorhombic space group $P2_12_12_1$ (No. 19), crystal dimensions 0.07 × 0.15 × 0.26 mm, colourless crystal, *a* = 5.739(1), *b* = 9.036(2), *c* = 25.207(6) Å, *U* = 1307.2(4) Å^3, using the setting angles of 25 carefully centred reflections in the range 15.29 < 2θ < 19.76°, *Z* = 4, D_c = 1.551 g cm^{-3}, *F*(000) = 624.00. Rigaku AFC5R diffractometer, graphite monochromated Mo-Kα radiation (λ = 0.710 69 Å), μ(Mo-Kα) 31.54 cm^{-1}, 1403 unique reflections measured, maximum 2θ value of 50.1°, segment (+*h*, +*k*, +*l*), 1003 of these with $I > 3.00\,\sigma(I)$ used in refinement. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.83 to 1.00. The intensities of three representative reflections were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.3%. A linear correction factor was applied to account for this phenomenon. Solution by heavy atom method, hydrogen atoms included in idealised positions (C–H 0.95 Å) with isotropic thermal parameters 20% greater than the equivalent *B* value of the relevant carbon. The structure was refined [refinement on *F*, function minimised: $\Sigma\omega(|F_o| - |F_c|)^2$] to *R* = 0.032, R_w = 0.026, $w = 1/[\sigma^2(F_o) + 0.004F_o^2]$. $R = \Sigma||F_o| - |F_c||/$

$\Sigma|F_o|$, $R_w = \sqrt{\Sigma\ \omega(|F_o| - |F_c|)^2/\Sigma wF_o^2}$)]. Chirality determined both by comparison with inverted structure ($R = 0.052$, $R_w = 0.046$) and from the Flack[17] parameter: value = 0.004(4) (correct = 0, enantiomer = 1). Calculations performed using the TEXSAN[18] packages.‖

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‖ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/76.

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