Hydroxyl-directed Reduction of β-Hydroxycycloalkanones as a Stereoselective Route to 1,3-Diols: X-Ray Crystal Structure and Structural Features of (1*R**,2*R**,6*S**)-2-[Hydroxy(phenyl)methyl]cyclopentanol

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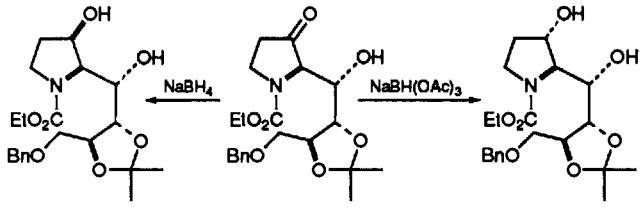
syn and *anti* Aldol adducts **4**/**5** and **6**/**7** undergo reduction using $NaBH(OAc)_3$ to give 1,3-diols with good to excellent levels of diastereoselectivity. Reduction using $NaBH_4$ is generally less selective but, in the cyclohexyl series, reduction of the *syn* aldol adduct **6** does afford a complementary stereochemical outcome in relation to the product 1,3-diols obtained, **12** *vs.* **13**. The structure of the diol **9** has been determined by X-ray crystallographic analysis, thereby providing proof of the stereochemical course of the reduction of the aldol **4**. Additionally, the diol **9** is shown to pack in the solid state as columnar stacks of independent hexamers with each pillar comprising a central $(OH)_6$ core, incorporating a network of hydrogen bonds, with a hydrophobic exterior.

Acyclic *syn*- and *anti*-1,3-diols may be generated efficiently by reduction of β-hydroxy ketones either *via* chelation control[1,2a] or internal hydride delivery,[1,2b] respectively. While these methodologies have been extensively applied to acyclic substrates, their utility towards reduction of ketones incorporated within a carbocyclic or heterocyclic framework has remained less well developed. As part of a programme focused on the construction of the castanospermine class of glycosidase inhibitors, the *anti* aldol adduct **1** (containing a pyrrolidin-3-one unit) was reduced using $NaBH_4$ and $NaBH(OAc)_3$ to give the *anti*- and *syn*-1,3-diols **2** and **3**, respectively with both reductions proceeding in a completely stereoselective manner (Scheme 1). The diols **2** and **3** were then carried through short synthetic sequences to give 1,8,8a-tri-*epi*- and 8,8a-di-*epi*-castanospermine, respectively.[3]



Scheme 1

In view of the complementary stereochemical results observed in the reduction of the pyrrolidinone **1** that is associated with the reagents used, we have carried out a more comprehensive examination of the reduction of β-hydroxy ketones using substrates derived from cycloalkanones. We were especially interested to evaluate the potential offered by hydroxyl-directed reductions in these systems and the results of this study, together with the outcome of the corresponding $NaBH_4$-mediated reductions, are described in this paper.†[4,5]

† The reduction of the cyclohexanone-derived *syn*- and *anti*-aldol adducts **6** and **7** has previously been examined using $NaBH_4$ (**6** only), $LiAlH_4$, $BH_3{\cdot}SMe_2$ and $LiAl(Bu^tO)_3$.[4] Reduction of the methoxy-substituted ketone **19** using $NaBH_4$ in ethanol gives a 65:35 mixture of the monoethers **20** and **21**.

Results and Discussion

Two sets of β-hydroxy ketones (aldol adducts), *syn*-**4** and *anti*-**5** (from cyclopentanone–PhCHO)[6] and *syn*-**6** and *anti*-**7** (from cyclohexanone–PhCHO)[7] were prepared. Each substrate was then reduced using (*i*) $NaBH_4$ (in MeOH) and (*ii*) $NaBH(OAc)_3$ (in CH_2Cl_2). The resulting 1,3-diols, **8**–**15**, were then characterised and the diastereoselectivity of each reduction sequence was determined by ^1H NMR analysis of the crude reaction mixture; the results of this study are summarised in Table 1. It should also be noted that equilibration of the aldol isomers (**4** ⇌ **5**; **6** ⇌ **7**) *did not* occur under either of the reducing conditions used.

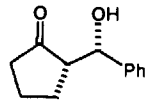
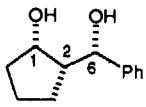
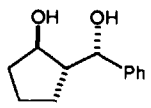
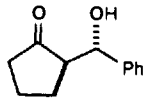
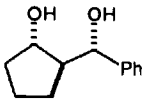
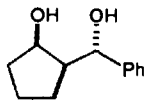
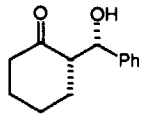
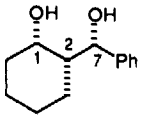
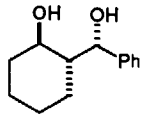
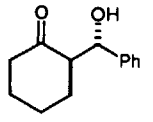
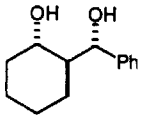
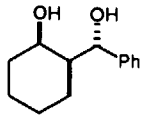
(a) *Reduction of Cyclopentanone-based Aldol Adducts.*—Reduction of the *syn* and *anti* aldol adducts **4** and **5** using $NaBH_4$ was essentially nonselective in both cases. However, use of $NaBH(OAc)_3$ resulted in complete control of stereochemistry leading to the *anti*- and *syn*-1,3-diols **9** and **10**, respectively. The structure of the diol **9** was established by X-ray crystallographic analysis (see below) which also served to confirm the stereochemistry of the initial aldol adduct **4** and hence **5**. The *syn*-1,3-diol relationship present in **10** was assigned by ^1H NMR analysis [based on coupling constants associated with H(1)], using data available from the diols **8**, **9** and **11**.‡

The results obtained using $NaBH(OAc)_3$[8a] are consistent with the accepted mechanism of hydroxyl group complexation to, and subsequent activation of the borane moiety towards, intramolecular delivery of hydride to the ketone function.[8b-e] It is important to note that the facial selectivity observed in this step is determined primarily by the stereochemistry at C(2) and not by that of the benzylic hydroxyl residue [at C(6)]. However, the influence that this benzylic stereocentre may exert should not be ignored (see below).

(b) *Reduction of Cyclohexanone-based Aldol Adducts.*—The cyclohexyl series based on the aldol adducts **6** and **7** showed a somewhat different trend. Using $NaBH_4$, the *syn* aldol adduct **6** gave a 3:1 mixture of the *syn*- and *anti*-1,3-diols **12** and **13**,

‡ ^1H NMR data for H(1): **8** δ_H 4.12 (m, $w_{\frac{1}{2}}$, *J* 6); **9** δ_H 3.95 (q, *J* 7); **10** δ_H 4.15 (q, *J* 7); **11** δ_H 4.41 (t d, *J* 5, 2.5). See also E. Ghera and S. Shoua, *J. Org. Chem.*, 1972, **37**, 1292.

Table 1

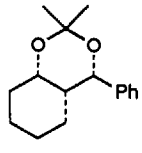
β-Hydroxy ketone	Reducing agent	Products (ratio)		Yield (%)
 *syn* - **4**		 **8**	 **9**	
	$NaBH_4$	1.1	1	79
	$NaBH(OAc)_3$	not observed	only product	74
 *anti* - **5**		 **10**	 **11**	
	$NaBH_4$	2	1	56
	$NaBH(OAc)_3$	only product	not observed	64
 *syn* - **6**		 **12**	 **13**	
	$NaBH_4$	3	1	85
	$NaBH(OAc)_3$	1	4	81
 *anti* - **7**		 **14**	 **15**	
	$NaBH_4$	4	1	85
	$NaBH(OAc)_3$	only product	not observed	68

respectively. With $NaBH(OAc)_3$, a *reversal* of this selectivity was obtained, with the *anti*-1,3-diol **13** predominating. In the case of the *anti* aldol adduct **7**, reduction with $NaBH_4$ showed a preference for axial delivery of hydride (to give the equatorial alcohol) leading to the *syn*-1,3-diol **14**. With $NaBH(OAc)_3$, the same product, diol **14**, was observed but a higher degree of selectivity was apparent and the *anti* diol **15** was not detected under these conditions.

Reduction of 2-substituted cyclohexanones with $NaBH_4$ usually favours axial attack[9] of hydride but with the *syn* aldol **6** the alternate pathway is preferred. This may be a consequence of chelate formation involving the ketone and adjacent hydroxyl unit, a process that would position the phenyl residue in a 1,3-axial orientation with respect to axial hydride attack required for formation of **13**. It would, however, be misleading to rationalise this modest level of selectivity (50% d.e.) given the sensitivity associated more generally with changes in substrate structure and in reaction conditions.

Using $NaBH(OAc)_3$, axial reduction of the aldol **6** did occur and, while this can be viewed as involving intramolecular hydride delivery, the modest selectivity (60% d.e.) likely reflects the bulk of the reagent involved, together with other steric demands imposed on the ketone by the environment about the benzylic stereocentre subsequent to complexation.

With the *anti* aldol adduct **7**, axial hydride attack (to give **14**) was observed with both $NaBH_4$ (60% d.e.) and ($NaBH(OAc)_3$ (100% d.e.) and it is apparent in this case that neither chelate formation nor internal hydride delivery would generate unfavourable steric interactions involving the phenyl residue and an incoming hydride nucleophile. Stereochemical assignments of the diols **12–14** were also based on their conversion into the corresponding acetonides **16–18**, respectively, followed by ^1H and ^{13}C NMR analysis.§



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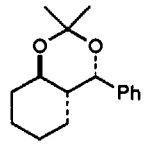

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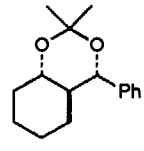
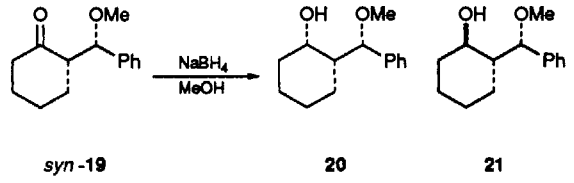


18

The importance of the hydroxyl group present in the aldols **4–7** to activate and direct reduction with $NaBH(OAc)_3$ has also been established. Reduction of the *syn*-β-methoxy keytone **19**[4] proceeds smoothly using $NaBH_4$ (in MeOH) to give a 4:1 mixture of the corresponding diol monoethers **20**[4] and **21**[4]

§ ^1H and ^{13}C NMR data for the acetonides **16** and **18** were characteristic of a chair conformation for the heterocyclic ring while the *anti*-1,3-diol gave a product **17** incorporating a twist boat.[10] While similar ^{13}C NMR correlations have been utilised extensively in acyclic systems,[11] its application to bicyclic variants, such as **16–18**, has been validated in a number of cases.[11a] Acetonides derived from the cyclopentyl-based diols **8–11** were not sufficiently stable to characterise.

(Scheme 2).¶ However, the ketone **19** was essentially inert to $NaBH(OAc)_3$ with < 5% conversion into **20** and **21** (as a 1 : 1 mixture) being observed (by ^1H NMR) after 24 h under our standard conditions ($MeCO_2H$, CH_2Cl_2, room temp.).



syn-**19** **20** **21**

Scheme 2

X-*Ray Crystal Structure of the anti-Diol* **9**.—Unambiguous structural assignment of the course of these reduction processes was felt to be essential and, given the problems encountered with derivatisation of the cyclopentyl-based diols **8**–**11**, the crystal structure of the diol **9** was solved. This served both to confirm the stereochemistry of the initial aldol adduct **4** and the outcome of the reduction study, but the structure of the diol **9** also contained several interesting structural features that merit further comment.

The asymmetric unit of the diol **9**, as illustrated in the ORTEP plot (Fig. 1), consists of three independent molecules, identical geometrically within the bounds of experimental error. However, the molecule containing the O(5) and O(6) hydroxyl groups, as presented, is an optical isomer of its twin sisters (Fig. 1).‖ Aside from the molecular structure of the diol **9**, the extended packing order is particularly interesting, as it is governed by a network of cylindrical hydrogen bonds which generate infinite tunnels within the lattice parallel to the *a*-axis. Consequently, there is a pseudo-hexagonal arrangement of molecules about the tunnel shaft when viewed perpendicular to the *bc* plane (Fig. 2). This pseudo-symmetry was clearly evident from early oscillation and Weissenberg photographs of the crystal.

The hydrogen bonding itself is a rigid 6-fold, 2-tier continuous system generated about those space group inversion centres having co-ordinates $x, \frac{1}{2}, \frac{1}{2}$ ($x = 0, \frac{1}{2}$). The strongest 'ring' of bonds results from an interaction between those hydroxyls attached to the 5-membered rings [O(1), O(3), O(5)] and their inversion equivalents [O(1)···O(3), O(3)···O(5), O(5)···O(1′); 2.668(5), 2.664(5), 2.668(3) Å, respectively]. The second 'ring' of bonds is encountered by moving along the *a* axis by *a*/2. In this case, the interaction is generated by

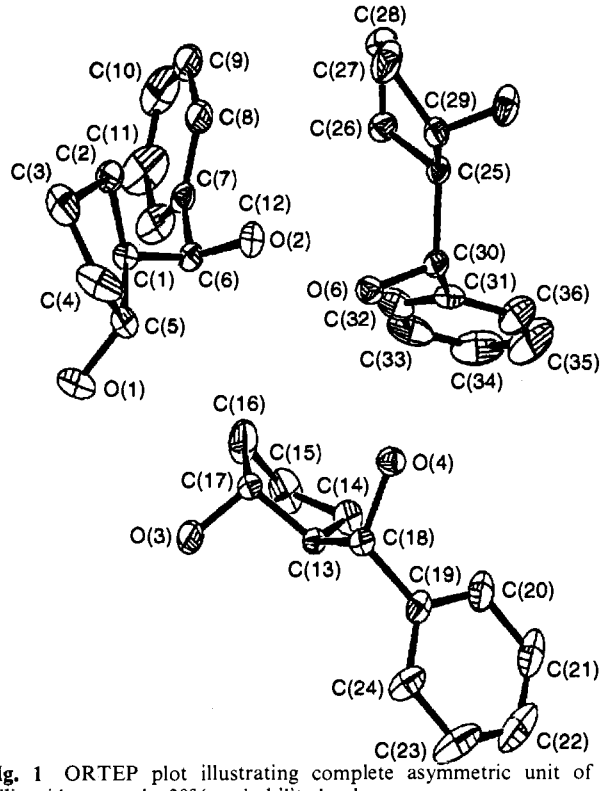


Fig. 1 ORTEP plot illustrating complete asymmetric unit of **9**. Ellipsoids are at the 30% probability level.

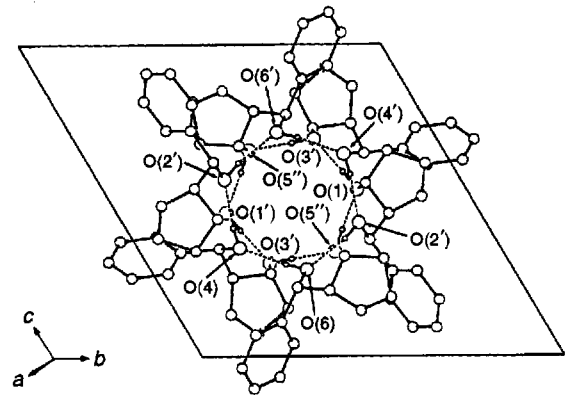


Fig. 2 Packing diagram of **9** viewed perpendicular to the *bc* plane. O(2′), O(4′), O(6′) are generated from O(2), O(4), O(6) *via* the 1-*x*, 1-*y*, 1-*z* operator. O(5″) is related to O(5) by the translation $-1 + x, y, z$ and O(1′), O(3′), O(5‴) are generated from O(1), O(3), O(5″) *via* the operator $-x, 1 - y, 1 - z$.

the alternative group of hydroxyls, O(2), O(4), O(6) and their symmetry partners [O(2)···O(4), O(4)···O(6), O(6)···O(2′); 2.929(3), 2.928(4), 2.926(3), respectively]. The hydrogen bonding network is further consolidated globally by the almost linear O–H–O units [O(1)–H(1)–O(3), 177(5); O(3)–H(3)–O(5), 175(5); O(5)–H(1)–O(1′), 178(4); O(2)–H(2)–O(6), 169(3); O(6)–H(4)–O(4), 171(3); O(4)–H(4)–O(2′), 170(3)°]. The interior diameter of the $(OH)_6$ rings, as estimated by the average of the three O, O′ separations, is thus smaller for the O(1), O(3), O(5) ring (5.24 Å) than its O(2), O(4), O(6) analogue (5.61 Å). Overall, the former chair-like arrangement of bonds leads to the formation of molecular hexamers, whereas the latter interaction, whilst itself generating a hexameric $(OH)_6$ ring, also serves to cement these hexamers together into pillars (Fig. 3). Each pillar contains a polar interior, sheathed by a hydrophobic exterior.

There has been considerable interest in recent years in the design of new host materials for selective guest inclusion, many of which are based on either phenolic compounds[14,15] or

¶ See footnote † on p. 379.

‖ A crystal of approximate dimensions 0.2 × 0.2 × 0.4 mm was used for data collection. *Crystal data*. $C_{12}H_{16}O_2$, M = 192.3 monoclinic, a = 9.897(2), b = 14.194(5), c = 14.188(5) Å, α = 114.80(2), β = 103.38(2), γ = 103.48(3)°, U = 1632.5 Å^3, space group $P\bar{1}$, Z = 6, D_c = 1.17 g cm^3, μ(Mo-Kα) = 0.70 cm^{-1}, F(000) = 612. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leqslant \theta \leqslant 22°$. 4145 Reflections were collected of which 2549 were unique with $I \geqslant 2\sigma(I)$. Data were corrected for Lorentz and polarization but not for absorption. The structure was solved by direct methods and refined using the SHELX[12,13] suite of programs. In the final least-squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions except in the instance of the hydroxyl groups, where the H(1)–H(6) were located in an advanced difference Fourier map and each refined at a distance of 0.94 Å from the relevant parent oxygen atom. Final residuals after 10 cycles of least squares were R = 0.0481, R_w = 0.0473, for a weighting scheme of $w = 2.6670/[\sigma^2(F) + 0.000\,297(F)^2]$. Max. final shift/esd was 0.001. The max. and min. residual densities were 0.08 and −0.06 e Å^{-3} respectively. Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles, together with tables of anisotropic temperature factors are available as supplementary data. The asymmetric unit is shown in Fig. 1, along with the labelling scheme used.

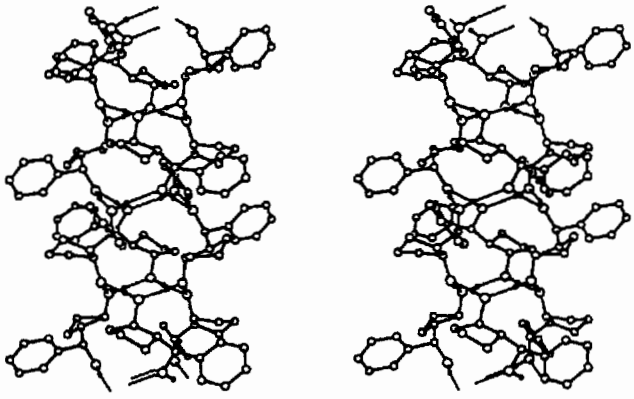
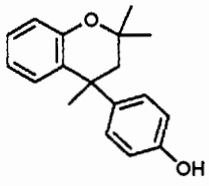


Fig. 3 Stereoview of packing diagram of **9** viewed perpendicular to the *bc* plane. Symmetry operators relating primed to unprimed atoms are as in Fig. 2.

alicyclic diols.[16] The lattice structure of the diol **9** is similar to that of Dianin's compound **22**,[17] one of the historically important molecules in this field. Like the diol **9**, Dianin's compound forms columnar stacks of independent hexamers with a central $(OH)_6$ core, a feature which is common to other host compounds such as quinol. Additionally, the stereochemistry within Dianin's compound alternates *R,S* around the ring, as in the diol **9**.[18] However, in contrast to **22** in which packing of hexamers alone generates columnar stacks, the additional hydroxyl group present in the diol **9** forms a second layer of $(OH)_6$ rings which directs the assembly of the pillars. The result of this is that cavity height, that is the spacing between alternate $(OH)_6$ rings, is approximately 4.9 Å (*a*/2), considerably smaller than in both Dianin's compound and more recent variations on this theme (*ca.* 11 Å).[15] The structural variations in the host lattices generated by acyclic diols have recently been reviewed, and it is noteworthy that the structural motif associated with the diol **9**, that is discrete columnar stacks of $(OH)_6$ hexamers, is not included.[16]



22

In summary, the use of hydroxyl activation coupled by internal hydride delivery, based on the use of $NaBH(OAc)_3$, provides a stereospecific method of producing 1,3-diols from aldol adducts derived from cycloalkanones. In those cases studied, use of $NaBH_4$ was less effective in terms of the level of stereocontrol that was achievable which is in marked contrast to our earlier observations (illustrated in Scheme 1) where $NaBH_4$ had provided a highly effective complement to $NaBH(OAc)_3$. However, in this latter situation the increased steric bias associated with the bulky 2-substituent of the aldol adduct **1** may play a more significant role in directing hydride delivery to the less hindered face of the five-membered ring, a factor that is less dominant in the case of the sterically less demanding PhCHO-based aldol adducts **8** and **9**.

Experimental

syn- and *anti*-2-[Hydroxy(phenyl)methyl]cyclopentanone **4** and **5** and *syn*- and *anti*-2-[hydroxy(phenyl)benzyl]cyclohexanone **6** and **7** were prepared using the procedures described by Seebach[6] and House,[7] respectively. ^1H NMR spectra were obtained at 270 MHz in $CDCl_3$ solution.

General Procedure for Reduction using Sodium Borohydride.—To a stirred solution of the β-hydroxy ketone (3 mmol) in methanol (15 cm^3) was added sodium borohydride (1.5 mmol), in portions, at ambient temperature. After 2 h, water (15 cm^3) was added slowly to the mixture which was then extracted with ethyl acetate (4 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give the crude diol mixtures. The mixtures could be separated by flash chromatography (silica gel, eluting with ethyl acetate–pentane, 1 : 1).

General Procedure for Reduction using Sodium Triacetoxyborohydride.—To a stirred solution of acetic acid (4 mmol) in dichloromethane (5 cm^3) at 0 °C (ice bath) was added sodium borohydride (0.6 mmol) in portions, and the mixture warmed to ambient temperature and stirred until effervescence ceased. A solution of the β-hydroxy ketone (0.5 mmol) in dichloromethane (2 cm^3) was then added and, after 6 h, the reaction mixture was poured onto saturated aqueous sodium hydrogen carbonate (5 cm^3) and extracted with dichloromethane (4 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give the diol mixtures. The mixtures could be separated by flash chromatography (silica gel, eluting with ethyl acetate–pentane, 1 : 1).

Spectroscopic and analytical data for the diols **8–15** are presented below. Yields and diastereoisomer ratios are displayed in Table 1. When mixtures of the diols **8–11** (derived from the cyclopentanone aldols **4** and **5**) were obtained these were not separated.

(1S*,2R*,6S*)- *and* (1R*,2R*,6S*)-2-[*Hydroxy(phenyl)methyl*]*cyclopentanol* **8** *and* **9**.—The mixture (from $NaBH_4$ reduction of **4**) was isolated as a colourless oil; ν_{max}/cm^{-1} (film) 3384; δ_H 7.30 (5 H, m, ArH, both isomers), 5.20 (1 H, d, *J* 3, C*H*Ph, **9**), 4.70 (0.55 H, d, *J* 6, C*H*Ph, **8**), 4.32 (1 H, m, $W_{\frac{1}{2}}$ 7, C*H*OH, **9**), 3.95 (1 H, q, *J* 7, C*H*OH, **8**), 3.40 (1 H, br s, OH, **9**) and 2.20–1.40 (7 H, m, both isomers, and OH of **8**).

(1R*,2R*,6S*)-2-[*Hydroxy(phenyl)methyl*]*cyclopentanol* **9**.—From reduction of **4** using $NaBH(OAc)_3$ as a colourless solid, mp 79–80 °C (Et_2O/light petroleum) (Found: C, 75.1; H, 8.7. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%); ν_{max}/cm^{-1} ($CHCl_3$) 3567; δ_H 7.30 (5 H, m, ArH), 4.70 (1 H, d, *J* 6 C*H*Ph), 3.95 (1 H, q, *J* 7, C*H*OH), 2.80 (1 H, s, OH) and 2.00–1.40 (8 H, m); *m*/*z* (CI) 207 $(M + H)^+$.

(1S*,2S*,6S*)- *and* (1R*,2S*,6S*)-2[*Hydroxy(phenyl)methyl*]*cyclopentanol* **10** *and* **11**.—The mixture (from $NaBH_4$ reduction of **5**) was isolated as a colourless oil; ν_{max}/cm^{-1} (film) 3415; δ_H 7.30 (5 H, m, ArH, both isomers), 4.75 (1 H, d, *J* 6, C*H*Ph, **11**), 4.45 (1 H, d, *J* 9, C*H*Ph, **10**), 4.40 (1 H, t d, *J* 5, 2.5, C*H*OH, **11**), 4.15 (1 H, q, *J* 7, C*H*OH, **10**), 3.10 (2 H, br s, OH both isomers) and 2.15–1.00 (7 H, m, both isomers).

(1S*,2S*,6S*)-2-[*Hydroxy(phenyl)methyl*]*cyclopentanol* **10**.—From reduction of **5** using $NaBH(OAc)_3$ as a colourless solid, mp 83 °C (Et_2O–light petroleum) (Found: C, 75.3; H, 8.7. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%); ν_{max}/cm^{-1} ($CHCl_3$) 3597; δ_H 7.30 (5 H, m, ArH), 4.45 (1 H, d, *J* 9, C*H*Ph), 4.15 (1 H, q, *J* 7 C*H*OH), 3.10 (2 H, br s, OH) and 2.20–1.20 (7 H, m); *m*/*z* (CI) 207 $(M + H)^+$.

(1S*,2R*,7S*)-2-[*Hydroxy(phenyl)methyl*]*cyclohexanol* **12**.—Isolated as colourless crystals, mp 97–98 °C (CCl_4–light petroleum) (lit.,[4] mp 97–98 °C); δ_H 7.30 (5 H, m, ArH), 5.05

(1 H, br s, C*H*Ph), 4.20 (1 H, br s, $W_{\frac{1}{2}}$ 6, C*H*OH), 3.30 (1 H, br s, OH), 2.50 (1 H, br s, OH) and 1.90–1.10 (9 H, m).

(1R*,2R*,7S*)-2-[*Hydroxy(phenyl)methyl*]*cyclohexanol* **13**. —Isolated as a colourless solid, mp 103–104 °C (CCl_4–light petroleum) (lit.,[4] mp 106–107 °C); δ_H 7.30 (5 H, m, ArH), 4.95 (1 H, br s, C*H*Ph), 3.50 (1 H, t d, *J* 10, 5, C*H*OH) and 2.00–0.90 (9 H, m).

(1S*,2S*,7S*)-2-[*Hydroxy(phenyl)methyl*]*cyclohexanol* **14**. —Isolated as a colourless solid, mp 124–125 °C (CCl_4–light petroleum) (lit.,[4] mp 125–126 °C); δ_H 7.30 (5 H, m, ArH), 4.55 (1 H, d, *J* 9, C*H*Ph), 3.60 (1 H, t d, *J* 9.7, 4.5, C*H*OH) and 2.00–0.80 (9 H, m).

(1R*,2S*,7S*)-2-[*Hydroxy(phenyl)methyl*]*cyclohexanol* **15**. —Only the minor component of a mixture was obtained with the diol **14**. Data corresponding to the isomer **15** is given: δ_H 4.60 (1 H, d, *J* 7, C*H*Ph), 4.20 (1 H, br s, OH), 3.75 (1 H, m, C*H*OH) and 2.75 (1 H, br s, OH).

General Procedure for Acetonide Formation.—A solution of the diol (1.2 mmol) in chloroform (30 cm^3) was treated with 2,2-dimethoxypropane (1.8 mmol) and toluene-*p*-sulfonic acid (0.1 mmol) and the mixture stirred at reflux; 10 cm^3 portions of solvent were removed (Dean–Stark apparatus) and replaced with fresh 10 cm^3 portions of chloroform. After 3 h, the mixture was cooled to ambient temperature, diluted with chloroform (15 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 10 cm^3) and brine (10 cm^3). The organic phase was dried (Na_2SO_4), evaporated and the residue purified by flash chromatography (silica gel, eluting with ethyl acetate–pentane, 1 : 19) to yield the acetonide derivatives **16–18**.

Acetonide **16**.—Isolated (from the diol **12**) as a pale yellow gum [Found: $(M + H)^+$, 247.1698. $C_{16}H_{23}O_2$ requires 247.1698]; ν_{max}/cm^{-1} ($CHCl_3$) 2900; δ_H 7.35 (5 H, m, ArH), 5.05 (1 H, d, *J* 5, C*H*Ph), 4.20 (1 H, br s, CHO), 1.85 (1 H, m), 1.56 (3 H, s, OCMe), 1.52 (3 H, s, OCMe) and 1.50–0.80 (7 H, m); δ_C(67.8 MHz, $CDCl_3$) 140.7 (C), 128.0 (CH), 126.7 (CH), 125.6 (CH), 98.9 (C_{quat}), 74.1 (CH), 68.1 (CH), 40.7 (CH), 31.9 (CH_2), 30.11 (CH_3), 25.2 (CH_2), 20.2 (CH_2), 19.7 (CH_3) and 19.1 (CH_2); *m*/*z* (CI) 247 $(M + H)^+$.

Acetonide **17**.—The acetonide formed from the diol **13** could not be isolated in sufficiently pure form for full characterisation and diagnostic data only are shown: ν_{max}/cm^{-1} ($CHCl_3$) 2900; δ_H 5.17 (1 H, d, *J* 9, C*H*Ph), 3.70 (1 H, t d, *J* 10, 5, CHO), 1.50 (3 H, s, OCMe) and 1.48 (3 H, s, OCMe); δ_C(67.8 MHz, $CDCl_3$) 100.1 (C_{quat}), 27.4 (CH_3) and 24.7 (CH_3); *m*/*z* (CI) 247 $(M + H)^+$.

Acetonide **18**.—Isolated (from the diol **14**) as a pale yellow gum [Found: $(M + H)^+$, 247.1698. $C_{16}H_{23}O_2$ requires 247.1698]; ν_{max}/cm^{-1} (KBr) 2900; δ_H 7.35 (5 H, m, ArH), 4.50 (1 H, d, *J* 10, C*H*Ph), 3.65 (1 H, d t, *J* 10, 4, CHO), 1.90 (1 H, m), 1.80 (1 H, m), 1.55 (3 H, s, OCMe), 1.48 (3 H, s, OCMe) and 1.40–0.80 (7 H, m); δ_C(67.8 MHz, $CDCl_3$) 140.2 (C), 128.2 (CH), 127.9 (CH), 127.4 (CH), 99.1 (C_{quat}), 77.6 (CH), 73.6 (CH), 47.7 (CH), 32.2 (CH_2), 30.4 (CH_3), 25.7 (CH_2), 25.3 (CH_2), 24.8 (CH_2) and 20.0 (CH_3); *m*/*z* (CI) 247 $(M + H)^+$.

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References

1 N. Greeves, *Comprehensive Organic Synthesis*, eds., B. M. Trost and I. Fleming, vol. 8, pp. 1–24, Pergamon, Oxford, 1991; M. Nógrádi, *Stereoselective Synthesis*, VCH, New York, 1986, pp. 131–148; T. Oishi and T. Nakata, *Acc. Chem. Res.*, 1984, **17**, 338.
2 (*a*) C. R. Sarko, I. C. Guch and M. DiMare, *J. Org. Chem.*, 1994, **59**, 705; (*b*) D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
3 T. Gallagher, M. Giles, R. S. Subramanian and M. S. Hadley, *J. Chem. Soc., Chem. Commun.*, 1992, 166; S. H. J. Thompson, R. S. Subramanian, J. K. Roberts, M. S. Hadley and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1994, 933.
4 A. Balsamo, P. Crotti and F. Macchia, *J. Chem. Soc., Perkin Trans. 1*, 1982, 3065.
5 For reductions leading to structurally related products see K. Shishido, O. Irie and M. Shibuya, *Tetrahedron Lett.*, 1992, **33**, 4589; M. Nakata, T. Tamai, T. Kamio, M. Kinoshita and K. Tatsuta, *Tetrahedron Lett.*, 1994, **35**, 3099.
6 E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson and D. Seebach, *Synthesis*, 1993, 1271. See also C. Mukai, W. J. Cho, I. J. Kim, M. Kido and M. Hanaoko, *Tetrahedron*, 1991, **47**, 3007.
7 H. O. House, D. S. Crumrine, A. Y. Teranishi and H. D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310.
8 (*a*) G. W. Gribble and D. C. Ferguson, *J. Chem. Soc., Chem. Commun.*, 1975, 535; (*b*) A. K. Saksena and P. Mangiaracina, *Tetrahedron Lett.*, 1983, **24**, 273; (*c*) C. F. Nutaitis and G. W. Gribble, *Tetrahedron Lett.*, 1983, **24**, 4287; (*d*) M. D. Turnbull, G. Hatter and D. E. Ledgerwood, *Tetrahedron Lett.*, 1984, **25**, 5449; (*e*) G. W. Gribble and C. F. Nutaitis, *Org. Prep. Proced. Int.*, 1985, **17**, 317. For a recent application of internal hydride delivery to a cycloalkanone, see R. E. McDevitt and B. Fraser-Reid, *J. Org. Chem.*, 1994, **59**, 3250.
9 D. C. Wigfield, *Tetrahedron*, 1979, **35**, 449; H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567. For reduction of simple 2-substituted cyclopentanones see also B. Caro, B. Boyer, G. Lamaty and G. Jaouen, *Bull. Soc. Chim. Fr.*, 1983, II-281.
10 J. Pawlak, K. Nakanishi, T. Iswashita and E. Borowski, *J. Org. Chem.*, 1987, **52**, 2896.
11 (*a*) J. G. Buchanan, A. R. Edgar, D. I. Rawson, P. Shahidi and R. H. Wightman, *Carbohydr. Res.*, 1982, **100**, 75; (*b*) S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945; (*c*) D. A. Evans, D. L. Rieger and J. R. Gage, *Tetrahedron Lett.*, 1990, **31**, 7099; (*d*) S. D. Rychnovsky, B. Rogers and G. Yang, *J. Org. Chem.*, 1993, **58**, 3511.
12 G. M., Sheldrick SHELX86, a computer program for crystal structure determination, University of Gottingen, 1986.
13 G. M., Sheldrick, SHELX76, a computer program for crystal structure determination, University of Cambridge, 1976.
14 *Inclusion Compounds*, eds. J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, London, 1984, vol. 2.
15 *Inclusion Phenomena and Molecular Recognition*, ed. J. L. Atwood, Plenum Press, New York, 1990.
16 R. Bishop, D. C. Craig, I. G. Dance, S. Kim, M. A. I. Malik, K. C. Pich and M. L. Scudder, *Supramolecular Chem.*, 1993, 1, 171.
17 A. P. Dianin, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1310.
18 W. Baker, A. S. Weaving and J. F. W. McOmie, *J. Chem. Soc.*, 1956, 2018.

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