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Total syntheses of glucosidase inhibitors, cyclophellitols

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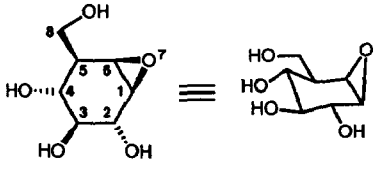
ABSTRACT

A β-D-glucosidase inhibitor, cyclophellitol [(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol, **1**] and its epoxide diastereomer, 1,6-epicyclophellitol (**2**) have been synthesized by using an intramolecular [3+2]-cycloaddition of a nitrile oxide to an alkene as a key step. 2,3,4-Tri-*O*-benzyl-6,7-dideoxy-D-*ido*-hept-6-enose (*E*,*Z*)-oxime (**6**) was prepared from L-glucose in 11 steps. Intramolecular cycloaddition of **6** was realized by NaOCl *via* an intermediary nitrile oxide to afford the isoxazoline, (1*S*,2*R*,3*S*,4*S*,5*R*)-3,4,5-tribenzyloxy-2-hydroxy-8-oxa-7-azabicyclo[4.3.0]non-6-ene (**7**). Hydrogenolysis of **7** followed by a 5-step sequence gave cyclophellitol (**1**). Compound **2** was synthesized from methyl α-D-galactopyranoside by using a conceptually similar route. The glycosidase-inhibiting activities of **2** were examined.

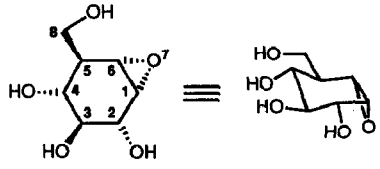
INTRODUCTION

Cyclophellitol[1] (**1**) is a novel β-D-glucosidase inhibitor isolated from culture filtrates of a mushroom, *Phellinus* sp. The absolute structure of **1** was established by X-ray crystallographic analysis which disclosed a fully oxygenated cyclohexane, corresponding to a carba analogue of D-glucopyranose.

We report in this full account[2,3] the details of the enantiospecific synthesis of cyclophellitol (**1**) and its unnatural epoxide diastereomer, 1,6-epicyclophellitol (**2**). The glycosidase-inhibiting activities of these compounds are also described to clarify their mode of action in glucosidase inhibition. Racemic **1** and **2** have already been prepared as blocked derivatives during a synthetic study on hydroxyvalidamine[4].



1 : Cyclophellitol



2 : 1,6-Epicyclophellitol

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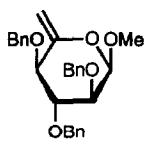
Our strategy for construction of these highly oxygenated cyclohexanes ("pseudo sugars"[5]) is an intramolecular cycloaddition of a nitrile oxide to an alkene. Recently, the synthesis of five- and six-membered carbocycles by an intramolecular nitrone cycloaddition[6] has been independently reported by applying the precedent of Bernet and Vasella[7].

RESULTS AND DISCUSSION

Our synthesis of cyclophellitol (**1**) began with the preparation of the *xylo*-hex-5-enopyranoside **3** from L-glucose according to the procedures of Gero *et al.*[8a] and Lipták *et al.*[8b] Stereoselective hydroboration of **3** with dicyclohexylborane in THF followed by oxidation with alkaline peroxide gave the two hydration products in 85 and 12% yields, respectively. As **4** appears to adopt a conformation having the three OBn groups in equatorial orientation and an axial hydroxymethyl substituent, the structure of the major product was determined to be **4** from its ^{1}H-n.m.r. spectrum ($J_{4,5}$ 5.6 Hz). The minor product was identical with methyl 2,3,4-tri-*O*-benzyl-α-L-glucopyranoside, the intermediate during the preparation[8] of **3**, by its R_F value and ^{1}H-n.m.r. spectrum. Swern oxidation of the desired alcohol **4** afforded the unstable aldehyde, which was subjected to Wittig alkenation with salt-free methylidenetriphenylphosphorane[9] in benzene to afford the alkene **5** in 75% yield. The $J_{4,5}$ coupling constant (5.8 Hz) in the ^{1}H-n.m.r. spectrum of **5** showed that the C-5 stereocenter remained unchanged through this transformation. This alkene **5** was hydrolyzed with aqueous HCl in 1,4-dioxane at 80° to an idopyranose derivative, which was treated with hydroxylamine hydrochloride in pyridine to give the oxime **6** in 80% yield. Intramolecular cycloaddition of **6** was realized by using NaOCl in CH_2Cl_2 at 25° *via* the intermediary nitrile oxide[10] to afford the isoxazoline **7** as a single product in 70% yield. The stereochemistry was confirmed by



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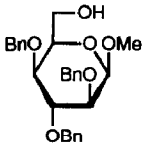

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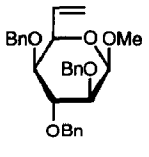

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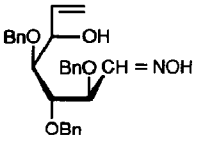

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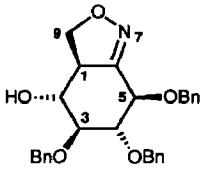

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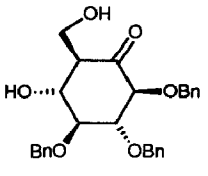

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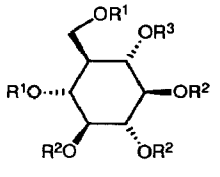
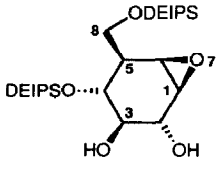


9 : R^1 = DEIPS, R^2 = Bn, R^3 = H
10 : R^1 = DEIPS, R^2 = Bn, R^3 = MS
12 : R^1 = R^2 = H, R^3 = Ms

DEIPS = Et_2Pr^iSi



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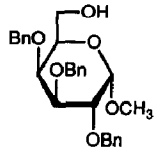
^{1}H-n.m.r. analyses of compounds **7–11** and, finally the completion of the synthesis presented next. The diastereoselectivity of this intramolecular nitrile oxide cycloaddition will be discussed later. This isoxazoline could be a key intermediate for the syntheses of highly oxygenated cyclohexanes.

The isoxazoline opening was achieved by treatment of **7** with 1 atm of H_2 and Raney Ni-W4 in aqueous 1,4-dioxane in the presence of acetic acid to afford the keto-diol **8** in 80% yield. After silylation of **8** with diethylisopropylsilyl triflate[11] and 2,6-lutidine in CH_2Cl_2, the resulting ketone was reduced with $BH_3 \cdot Me_2S$ to afford the desired α-alcohol **9** in 60% yield. The undesired β-alcohol, obtained in 20% yield, was recycled to the disilylated ketone of **8** by Swern oxidation. Although the ^{1}H-n.m.r. spectrum of **9** was too complicated for assignment, that of the β-alcohol clearly indicated ($J_{1,2} = J_{1,6} = 3.0$ Hz) that it has the C-1 hydroxyl group axially oriented, and thus the C-1 hydroxyl group of **9** is oriented equatorially. Mesylation of **9** with methanesulfonyl chloride in pyridine provided the labile mesylate **10** in 75% yield, which was subjected to brief hydrogenolysis using 1 atm of H_2 and $Pd(OH)_2$ in MeOH followed by epoxidation with sodium methoxide in $CHCl_3$ to give the labile epoxide **11**. Finally, deprotection of **11** with Bu_4NF in THF completed the synthesis, giving cyclophellitol (**1**) as colorless plates in 40% yield from **10**. The diethylisopropylsilyl protecting group was first developed by us[11] and selective removal of this group under mild acidic conditions was examined[12]. Recently, we found that this protecting group may be readily cleaved under hydrogenolysis conditions[13]. Therefore, the hydrogenolysis of **10** was re-examined and the deprotected mesylate **12** was in fact obtained following prolonged exposure of **10** to the hydrogenolysis conditions. Alkaline treatment of **12** provided cyclophellitol (**1**). The synthetic cyclophellitol (**1**) was identical with that obtained from natural sources by i.r. and ^{1}H-n.m.r. spectra, optical rotation, and biological activities (see later).

In order to provide additional insight into the mode of action of cyclophellitol (**1**), we synthesized the unnatural epoxide diastereomer of **1**, 1,6-epicyclophellitol (**2**). The synthesis of **2** was accomplished by a route conceptually similar to the synthesis of cyclophellitol (**1**). Swern oxidation of the readily available methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside[14] (**13**) gave the corresponding aldehyde, which was subjected to Wittig alkenation to afford the alkene **14** in 91% yield. Acetolysis of **14** with acetic anhydride in the presence of a catalytic amount of H_2SO_4, followed by *O*-deacetylation with NaOMe in MeOH led to the corresponding hemiacetal, which was treated with hydroxylamine hydrochloride in pyridine to give the oxime **15** in 90% overall yield.

This oxime **15**, submitted to intramolecular cycloaddition by the same procedure (NaOCl, CH_2Cl_2, 25°) as described in the preparation of **7** produced almost exclusively the undesired isoxazoline **17**. On the other hand, the desired isoxazoline **16** was obtained in 15% yield along with **17** (75%) when the oxime **15** was treated with NaOCl in toluene for 0.5 h at 100°. The stereochemistry was confirmed by ^{1}H-n.m.r. analyses of compounds **16–22** and **2** (see Experimental). The diastereoselectivity of this intramolecular nitrile oxide cycloaddition is discussed later. Fortunately, acidic hydrogenolysis of **17** with 1 atm of H_2 and Raney Ni-W4 in aqueous 1,4-dioxane gave the desired keto-



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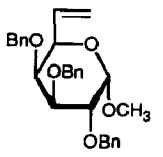

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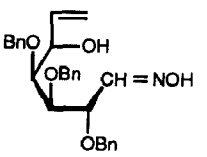

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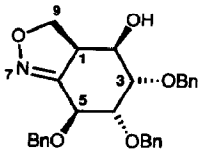

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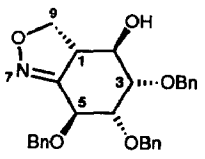

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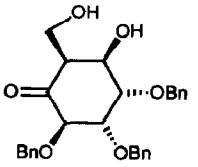

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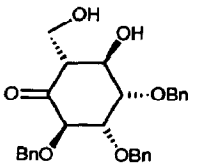

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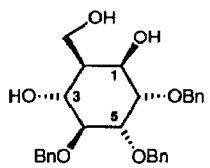
alcohol **18** as the major product in 70% yield along with the undesired keto-alcohol **19** (28%), while **16** was converted by similar hydrogenolysis into the keto-alcohol **18** in 75% yield as a single product. Further, treatment of the undesired keto-alcohol **19** with triethylamine in CH_2Cl_2 at 25° gave the desired keto-alcohol **18** in 65% yield, along with unchanged starting material (26%). It is not yet clear why the keto-alcohol **18** is more stable than the keto-alcohol **19** under epimerization conditions. The ketone **18** was stereoselectively reduced by $BH_3 \cdot Me_2S$ in THF at 0° to afford the alcohol **20** in 80% yield. Compound **20** contains three kinds of hydroxyl groups, namely, the primary, C-3 equatorial, and C-1 axial hydroxyl groups, which may be selectively protected. In fact, selective silylation of **20** with diethylisopropylsilyl chloride[11] and imidazole in DMF for 4 h at 0° gave the desired di-*O*-silylated compound **21** and the mono-*O*-silylated compound **22** in 60 and 39% yields, respectively.

The mono-*O*-silylated compound **22** was again silylated to afford **21** in 60% yield, along with unchanged starting material (30%). Mesylation of **21** afforded **23**, which was subjected to the hydrogenolysis using 1 atm of H_2 and $Pd(OH)_2$ in MeOH to generate the deprotected mesylate **24** in 90% yield from **21** as described in the synthesis of **12**.

Finally, treatment of **24** with NaOMe in MeOH afforded the crystalline 1,6-epicyclophellitol (**2**) in 80% yield.

The diastereoselectivity of the intramolecular cycloaddition from **6** to **7** *via* a nitrile oxide may be explained as follows. Two transition-state models are predicted, namely, transition-state model **A** which leads to the isoxazoline **7**, and the transition-



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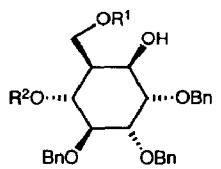
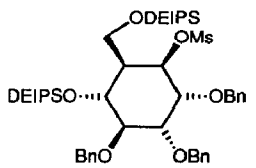


21 : $R^1 = R^2$ = DEIPS
22 : R^1 = DEIPS, R^2 = H
DEIPS = Et_2Pr^iSi



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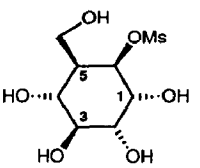

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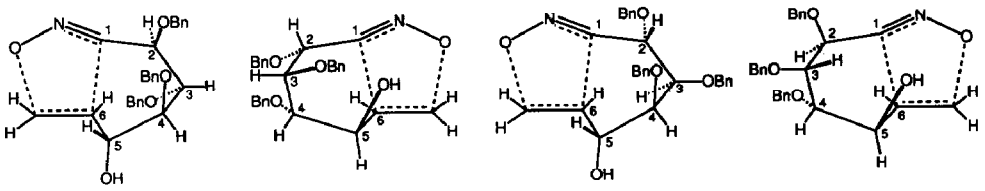


A B C D

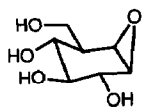
7 diastereomer of 7 17 16

state model **B** which leads to the diastereomer of **7**. The transition-state model **A** has one 1,3-interaction between the 2- and 4-OBn groups, whereas the transition-state model **B** has two 1,3-interactions between the 2- and 4-OBn groups and the 3-OBn and 5-OH groups.

In the transition-state model **A**, the 5-OH group and hydrogen lie *anti* and *inside*, respectively, with respect to the forming C-1–C-6 bond. On the other hand, in the transition-state model **B**, the 5-OH group lies *inside* and the hydrogen *anti*, and therefore, electronic repulsive interaction exists between the inside OH group and the 5-membered ring containing the C=N-O···C–C arrangement. From this explanation, it is reasonable that the transition-state model **A** is more favorable than model **B**, and results in the exclusive formation of **7**. Similarly, the diastereoselectivity of the intramolecular cycloaddition from **15** to **17** *via* a nitrile oxide is explained as follows. There are no significant differences around the C-2–C-4 skeleton between the transition-state models **C** and **D**, which lead to the isoxazoline **17** and **16**, respectively. As the C-5 stereochemistry of **C** and **D** are the same as **A** and **B**, respectively, the transition-state model **C** is more reasonable than model **D**, and results in the dominant formation of **17**.

The glycosidase-inhibiting activities of **2** were generally assayed according to the method reported by Saul *et al.*[15]. In dramatic contrast to natural cyclophellitol (**1**) which inhibited[1] only almond β-D-glucosidase activity by 50% at 0.8 μg/mL, the epi-epoxide **2** exhibited inhibiting activity only against baker's yeast α-D-glucosidase, at IC_{50} 10 μg/mL.

Structurally, cyclophellitol (**1**) has a quasi-equatorially oriented C-1–O bond, which corresponds to the equatorial C-1–O bond of β-D-glucopyranosides (**25β**), whereas epicyclophellitol (**2**) has a quasi-axial C-1–O bond corresponding to the axial C-1–O bond of α-D-glucopyranosides (**25α**). The glucosidase-inhibiting activities of **1** and **2** emphasized that the α- and β-D-glucosidases recognized especially the C-1 positions as corresponding to those of α- and β-D-glucopyranosides. Consequently, cyclophellitol (**1**) and its epi-epoxide, 1,6-epicyclophellitol (**2**) serve as antagonists of β- and α-D-glucopyranosides, respectively.



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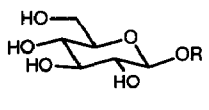
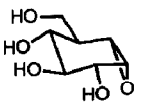


25β



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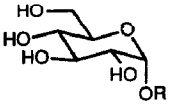

25α

EXPERIMENTAL

General methods. — Melting points were determined on a micro hot-stage Yanaco MP-S3 apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-360 photoelectric polarimeter in $CHCl_3$ at 25° unless otherwise noted. I.r. spectra were recorded on a Bio Rad Digilab FTS-65 spectrometer and ^{1}H-n.m.r. spectra were recorded on either a Jeol GSX270 or a Jeol GSX400 spectrometer for solutions in $CDCl_3$ using Me_4Si as the internal standard, unless otherwise noted. Silica gel t.l.c. and column chromatography were performed on Merck TLC 60F-254 and Merck Kieselgel 60, respectively. Air- and/or moisture-sensitive reactions were carried out under an argon atmosphere with oven-dried glassware. In general, organic solvents were purified and dried by the appropriate procedure, and evaporations and concentrations were performed under diminished pressure below 30°, unless otherwise noted.

Methyl 2,3,4-tri-O-benzyl-β-D-idopyranoside (**4**) *and α-L-glucopyranoside.* — To a stirred suspension of dicyclohexylborane in THF [prepared from cyclohexene (8.7 mL, 85.6 mmol) and 10M borane-methyl sulfide (4.3 mL, 42.8 mmol) in dry THF (42.8 mL)] was added at 0° a solution of **3** (ref. 8, 3.19 g, 7.13 mmol) in dry THF (31.9 mL). After being stirred for 1.5 h at 25°, the mixture was cooled to 0° and water (70 mL), 3M aqueous NaOH (14.3 mL), and 30% H_2O_2 (14.6 mL) were successively added. After being stirred for 20 min at 50°, the mixture was separated and the aqueous layer was extracted with EtOAc (70 mL × 2). The combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The contaminated cyclohexanol was evaporated at 50° and the residue chromatographed on silica gel (250 g) with 4:1 benzene–EtOAc to afford the β-D-idopyranoside **4** (2.80 g, 85%) and α-L-glucopyranoside (0.39 g, 12%) as colorless syrups.

Compound **4** had $[\alpha]_D$ −28° (*c* 0.50); R_F 0.27 (3:1 benzene–EtOAc); ^{1}H-n.m.r. (400 MHz): δ 7.35–7.25 (m, 15 H, 3 × Ph), 4.80 and 4.73 (ABq, each 1 H, J 11.2 Hz, OCH_2Ph), 4.75 and 4.69 (ABq, each 1 H, J 11.2 Hz, OCH_2Ph), 4.77 and 4.56 (ABq, each 1 H, J 11.2 Hz, OCH_2Ph), 4.53 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.04 (dd, 1 H, $J_{2,3} = J_{3,4} = 8.0$ Hz, H-3), 3.97 (ddd, 1 H, $J_{4,5} = J_{5,6} = J_{5,6'} = 5.6$ Hz, H-5), 3.89 (ddd, 1 H, J_{gem} 12.8, $J_{6',OH}$ 4.8 Hz, H-6'), 3.82 (ddd, 1 H, $J_{6,OH}$ 8.0 Hz, H-6), 3.63 (dd, 1 H, H-4), 3.48 (s, 3 H, OMe), 3.47 (dd, 1 H, H-2), and 2.71 (dd, 1 H, OH).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.40; H, 6.94. Found: C, 72.05; H, 6.65.

The compound having R_F = 0.44 (3:1 benzene–EtOAc) was identical with methyl 2,3,4-tri-*O*-benzyl-α-L-glucopyranoside, the intermediate isolated during the preparation[8] of **3**, in R_F value and ^{1}H-n.m.r. spectrum.

*Methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-β-*D*-ido-hept-6-enopyranoside* (**5**). — To a stirred solution of oxalyl chloride (0.083 ml, 0.966 mmol) in dry CH_2Cl_2 (1.24 mL) was added at −78° a solution of Me_2SO (0.137 mL, 1.93 mmol) in dry CH_2Cl_2 (0.83 mL). After 10 min stirring, a solution of **4** (224 mg, 0.483 mmol) in dry CH_2Cl_2 (2.2 mL) was added and the mixture was stirred for 15 min at −78°. Triethylamine (0.404 ml, 2.92 mmol) was added and the mixture was stirred for 15 min at −78° and warmed to −40°. Saturated aqueous NH_4Cl (6.3 mL) was added and the mixture was separated. The aqueous layer was extracted with EtOAc (5 mL × 2) and the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residual aldehyde (223 mg, 100%) was dissolved in dry benzene (6.6 mL) and to this was added methylidenetriphenylphosphorane (534 mg, 1.93 mmol). After being stirred for 15 min at 25°, the mixture was concentrated and the residue was dissolved in ether and washed with water. The aqueous layer was extracted with ether (6 mL × 2) and the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (2 g) with 7:1 hexane–EtOAc to afford **5** (167 mg, 75%) as a pale-yellow syrup: $[\alpha]_D$ −6.5° (*c* 0.50); R_F 0.30 (8:1 hexane–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.40–7.25 (m, 15 H, 3 × Ph), 6.29 (ddd, 1 H, $J_{5,6}$ 9.8, $J_{6,7E}$ 16.0, $J_{6,7Z}$ 9.8 Hz, H-6), 5.35–5.25 (m, 2 H, 2 × H-7), 4.82 and 4.79 (ABq, each 1 H, *J* 12.0 Hz, OCH_2Ph), 4.78 and 4.69 (ABq, each 1 H, *J* 12.0 Hz, OCH_2Ph), 4.62 and 4.59 (ABq, each 1 H, *J* 12.0 Hz, OCH_2Ph), 4.58 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.29 (dd, 1 H, $J_{4,5}$ 5.8, $J_{5,6}$ 9.8 Hz, H-5), 4.02 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 8.2 Hz, H-3), 3.62 (dd, 1 H, H-4), 3.48 (dd, 1 H, H-2), and 3.37 (s, 3 H, OMe).

Anal. Calc. for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00. Found: C, 75.55; H, 7.03.

*(1*R*,2*R*,3*S*,4*S*,5*R*)-3,4,5-Tribenzyloxy-2-hydroxy-8-oxa-7-azabicyclo[4.3.0]non-6-ene* (**7**). — A solution of **5** (641 mg, 1.39 mmol) in 1:2 (v/v) 1.2M aqueous HCl–1,4-dioxane (18 mL) was heated for 12 h at 80°. Upon cooling to room temperature, the mixture was extracted with EtOAc (18 mL × 1, 6 mL × 2) and the extracts were washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on silica gel (60 g) with 4:1 hexane–EtOAc to give the idopyranose (513 mg, 83%) as colorless crystals. This was dissolved in dry pyridine (10.3 mL) and to this was added hydroxylamine hydrochloride (0.40 g, 5.75 mmol) at 25°. After being stirred for 2 h at 25°, the mixture was concentrated and the residue was dissolved in EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$, dried, and concentrated to afford the oxime **6** (509 mg, 96%). [A small sample of this syrup was purified by silica gel column chromatography with 2:1 hexane–EtOAc for measurement of the ^{1}H-n.m.r. spectrum: R_F 0.35 (2:1 hexane–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.48 (d, 0.75 H, $J_{1,2}$ 8.0 Hz, *E*-H-1), 7.45 (s, 0.75 H, *E*-NOH), 7.35–7.25 (m, 15 H, 3 × Ph), 6.98 (d, 0.25 H, $J_{1,2}$ 6.0 Hz, *Z*-H-1), 5.81 (ddd, 1 H, $J_{5,6}$ 5.0, $J_{6,7Z}$ 10.2, $J_{6,7E}$ 17.0 Hz, H-6), 5.23 (ddd, 1 H, $J_{5,7E} = J_{gem}$ = 1.6 Hz, *E*-H-7), 5.14 (ddd, 1H, $J_{5,7Z}$ 1.6 Hz, Z–H–7), 4.94(dd, 0.25 H, $J_{1,2}$ 6.0, $J_{2,3}$ 3.0 Hz, *Z*-H-2), 4.80–4.35 (m, 6 H, 3 × OCH_2Ph), 4.25 (dd, 0.75 H, $J_{1,2}$ 8.0, $J_{2,3}$ 4.0 Hz, *E*-H-2), 4.05–3.95 (m, 1 H, H-5), 3.80 (dd, 0.75 H, $J_{2,3}$ 4.0, $J_{3,4}$ 6.0 Hz, *E*-H-3), 3.78 (dd, 0.25 H, $J_{2,3}$ 3.0, $J_{3,4}$ 6.0 Hz, *Z*-H-3), 3.73 (dd, 1 H, $J_{3,4}$ 6.0, $J_{4,5}$ 3.0 Hz, H-4), 2.53 (d, 0.25 H, *J* 7.2 Hz, *Z*-5-OH), and 2.51 (d, 0.75 H, *J* 7.2 Hz, *E*-5-OH).] This oxime **6** was dissolved

in dry CH_2Cl_2 (16.4 mL) and to this was added 5% aqueous NaOCl (4.0 mL) at 0°. After being stirred for 1.5 h at 25°, the mixture was concentrated and the residue was dissolved in EtOAc (16 mL) and washed with saturated aqueous NH_4Cl, NaCl, dried, and concentrated. The residue was chromatographed on silica gel (40 g) with 3:2 hexane–EtOAc to afford **7** (355 mg, 70%) as colorless crystals: m.p. 144–147° (EtOAc–hexane) $[\alpha]_D$ −125° (*c* 0.50); R_F 0.34 (3:2 hexane–EtOAc; ^{1}H-n.m.r. (270 MHz): δ 7.45–7.25 (m, 15 H, 3 × Ph), 5.06, 5.02, 5.01, 4.81, 4.69, and 4.63 (each 1 H, *J* 11.2 Hz, 3 × OCH_2Ph), 4.53 (dd, 1 H, $J_{1,9'}$ 10.0, J_{gem} 8.0 Hz, H-9'), 4.38 (dd, 1 H, $J_{4,5}$ 9.2, $J_{1,5}$ 1.0 Hz, H-5), 4.25 (dd, 1 H, $J_{1,9}$ 8.0 Hz, H-9), 3.69 (dd-like, 1 H, $J_{3,4}$ 9.2 Hz, H-4), 3.50–3.35 (m, 2 H, H-2,3), 3.23 (dddd, 1 H, $J_{1,2}$ 8.4 Hz, H-1), and 2.44 (d, 1 H, *J* 2.0 Hz, 2-OH).

Anal. Calc. for $C_{28}H_{29}NO_5$: C, 73.19; H, 6.36; N, 3.05. Found: C, 73.26; H, 6.17; N, 3.15.

(2S,3R,4S,5R,6R)-2,3,4-Tribenzyloxy-5-hydroxy-6-hydroxymethylcyclohexanone (**8**). — A mixture of **7** (197 mg, 0.429 mmol), AcOH (0.15 mL, 2.57 mmol), Raney Ni-W4, and 5:1 (v/v) 1,4-dioxane–water (5.7 mL) was vigorously stirred under 1 atm of H_2 for 1.5 h at 25°. The mixture was filtered with Celite and the filter cake washed with 1,4-dioxane. The filtrate and washings were concentrated and the residue was chromatographed on silica gel (15 g) with 1:1 hexane–EtOAc to afford **8** (159 mg, 80%) as colorless crystals: m.p. 132–135° (EtOAc–hexane), $[\alpha]_D$ −55° (*c* 0.50); R_F 0.30 (1:1 hexane–EtOAc); i.r. (KBr) 1720 cm^{-1}; ^{1}H-n.m.r. (270 MHz): δ 7.425–7.25 (m, 15 H, 3 × Ph), 5.03, 4.95, 4.90, 4.78, 4.74, and 4.55 (each 1 H, *J* 11.0 Hz, 3 × OCH_2Ph), 4.19 (dd, 1 H, $J_{2,3}$ 9.0, $J_{2,6}$ 1.2 Hz, H-2), 4.01 (ddd, 1 H, J_{6,CH_2} 4.0, J_{gem} 12.0, $J_{CH_2,OH}$ 6.0 Hz, one of CH_2OH), 3.94 (ddd, 1 H, J_{6,CH_2} 5.0, $J_{CH_2,OH}$ 8.2 Hz, one of CH_2OH), 3.77 (dd-like, 1 H, $J_{3,4} = J_{4,5}$ = 9.0 Hz, H-4), 3.64 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 11.8, $J_{5,OH}$ 2.2 Hz, H-5), 3.63 (dd, 1 H, H-3), 2.68 (d, 1 H, 5-OH), 2.61 (dddd, 1 H, H-6), and 2.46 (dd, 1 H, CH_2OH).

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.61; H, 6.31.

(1S,2R,3S,4R,5R,6S)-2,3,4-Tribenzyloxy-5-[(1-methylethyl)diethylsilyl]oxy-6-[[(1-methylethyl)diethylsilyl]oxymethyl]cyclohexanol (**9**) *and its C-1 epimer.* — To a stirred solution of **8** (163 mg, 0.352 mmol) in dry CH_2Cl_2 (4.9 mL) was added at 0° 2,6-luthidine (0.164 mL, 1.41 mmol) and diethylisopropylsilyl triflate (0.219 mL, 1.06 mmol). After being stirred for 0.5 h at 0°, the mixture was diluted with water (5 mL) and EtOAc (5 mL) and separated. The aqueous layer was extracted with EtOAc (5 mL × 2) and the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (13 g) with 20:1 hexane–EtOAc to afford the disilylated ketone (240 mg, 95%) as a colorless syrup. A portion of this syrup (94.5 mg, 0.131 mmol) was dissolved in dry THF (1.9 mL) and to this was added at 0° $BH_3 \cdot Me_2S$ (10M, 0.13 mL, 1.3 mmol). After being stirred for 12 h at 25°, the mixture was poured into saturated aqueous $NaHCO_3$ (2 mL), and extracted with EtOAc (2 mL × 2). The organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (9.5 g) with 15:1 hexane–EtOAc to afford **9** (56.7 mg, 60%) and its C-1 epimer (18.9 mg, 20%) as colorless syrups.

Compound **9** had $[\alpha]_D$ +24° (*c* 0.50); R_F 0.30 (15:1 hexane–EtOAc); ^{1}H-n.m.r. (400

MHz): δ 7.375–7.075 (m, 15 H, 3 × Ph), 4.92 and 4.84 (ABq, each 1 H, J 11.3 Hz, OCH_2Ph), 4.83 and 4.73 (ABq, each 1 H, J 10.4 Hz, OCH_2Ph), 5.08 and 4.74 (ABq, each 1 H, J 12.0 Hz, OCH_2Ph), 4.07 (dd, 1 H, J_{6,CH_2} 3.0, J_{gem} 10.1 Hz, one of CH_2OH), 3.78 (dd, 1 H, J_{6,CH_2} 5.9 Hz, one of CH_2OH), 3.675–3.575 (m, 2 H, H-1, 5), 3.50–3.35 (m, 3 H, H-2, 3, 4), 3.37 (d, 1 H, J 0.9 Hz, 1-OH), 1.59 (m, 1 H, H-6), 1.05–0.875 (m, 26 H, 2 × Si(CH$_2$*Me*)$_2$, 2 × SiPr^i), and 0.70–0.55 [m, 8 H, 2 × Si(CH_2Me)$_2$].

Anal. Calc. for $C_{42}H_{64}O_6Si_2$: C, 69.96; H, 8.95. Found: C, 69.71; H, 8.68.

The C-1 epimer of **9** had R_F 0.38 (15:1 hexane–EtOAc); ^{1}H-n.m.r. (400 MHz): δ 7.375–7.125 (m, 15 H, 3 × Ph), 5.10–4.675 (m, 6 H, 3 × OCH_2Ph), 4.29 (br dd, 1 H, $J_{1,2} = J_{1,6} = 3.0$ Hz, H-1), 3.975–3.825 (m, 4 H, H-3, 5, CH_2OH), 3.44 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 3.29 (dd, 1 H, $J_{3,4} = J_{4,5} = 9.2$ Hz, H-4), 2.57 (s, 1 H, 1-OH), 1.575–1.475 (m, 1 H, H-6), 1.05–0.85 (m, 26 H, 2 × Si(CH$_2$*Me*)$_2$, 2 × SiPr^i), and 0.70–0.50 [m, 8 H, 2 × Si(CH_2Me)$_2$].

Swern oxidation of the C-1 epimer of **9**. — The C-1 epimer of **9** (160 mg, 0.222 mmol) was oxidized by the same procedure described in the preparation of **5** to afford the disilylated ketone of **8** (128 mg, 80%) after silica gel column chromatography (20:1 hexane–EtOAc).

(1S,2R,3R,4R,5R,6S)-1,2,3-Tribenzyloxy-6-methanesulfonyloxy-4-[(1-methylethyl)diethylsilyl]oxy-5-[[(1-methylethyl)diethylsilyl]oxy]methylcyclohexane (**10**). — To a stirred, ice-cooled solution of **9** (31.8 mg, 44.1 mmol) in dry pyridine (0.48 mL) was added mesyl chloride (25.6 μL, 0.331 mmol). After being stirred for 12 h at 25°, EtOH (38.5 μL, 0.662 mmol) was added to the mixture and the resultant mixture was stirred for 0.5 h at 25°. The mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, NaCl, dried, and concentrated. The residue was chromatographed on silica gel (3.5 g) with 12:1 hexane–EtOAc to afford the labile mesylate **10** (28.1 mg, 80%) as colorless crystals: R_F 0.36 (10:1 hexane–EtOAc); ^{1}H-n.m.r. (400 MHz): δ 7.35–7.10 (m, 15 H, 3 × Ph), 4.98 and 4.73 (ABq, each 1 H, J 11.2 Hz, OCH_2Ph), 4.65 (s, 2 H, OCH_2Ph), 4.83 and 4.64 (ABq, each 1 H, J 12.6 Hz, OCH_2Ph), 4.64 (dd, 1 H, $J_{1,6}$ 9.0, $J_{5,6}$ 8.6 Hz, H-6), 4.14 (dd, 1 H, $J_{3,4} = J_{4,5} = 6.0$ Hz, H-4), 4.05 (dd, 1 H, $J_{1,2}$ 9.0 Hz, H-1), 3.94 (dd, 1 H, J_{5,CH_2} 3.9, J_{gem} 10.0 Hz, one of OCH_2Si), 3.79 (dd, 1 H, J_{5,CH_2} 6.6 Hz, one of OCH_2Si), 3.65–3.55 (m, 2 H, H-2, 3), 2.84 (s, 3 H, OMs), 2.06 (m, 1 H, H-5), 1.05–0.90 (m, 26 H, 2 × Si(CH$_2$*Me*)$_2$, 2 × SiPr^i), and 0.725–0.575 [m, 8 H, 2 × Si(CH_2Me)$_2$].

Cyclophellitol (**1**). — (a) A mixture of **10** (19.5 mg, 0.0244 mmol), $Pd(OH)_2$ (9.8 mg), and MeOH (0.59 mL) was vigorously stirred under 1 atm of H_2 for 0.5 h at 25°. The mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (1.3 g) with 1:2 hexane–EtOAc as fast as possible to afford the labile triol (9.0 mg), which was immediately dissolved in dry $CHCl_3$ (0.9 mL) and to this was added at 0° 28% NaOMe in MeOH (4 μL). After 10 min, the mixture was made neutral with Amberlite IRC-50 (CG-50) and filtered. The filtrate was concentrated and the residue chromatographed on silica gel (0.9 g) with 25:1 CH_2Cl_2–acetone to afford the labile epoxide **11** (5.5 mg) [R_F 0.36 (25:1 CH_2Cl_2–acetone); ^{1}H-n.m.r. (270 MHz, CD_3OD): δ 4.12 (dd, 1 H, $J_{5,8'}$ 4.0, J_{gem} 9.8 Hz, H-8'), 3.70 (dd, 1 H, $J_{5,8}$ 9.8 Hz, H-8), 3.61

(d, 1 H, $J_{1,2}$ 0, $J_{2,3}$ 7.8 Hz, H-2), 3.46 (br dd, 1 H, $J_{1,6}$ 3.8, $J_{5,6}$ 2.0 Hz, H-6), 3.24 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 8.6 Hz, H-4), 3.17 (dd, 1 H, H-3), 3.08(d, 1 H, H-1), 2.00 (dddd, 1 H, H-5), 1.05–0.95 (m, 26 H, 2 × $Si(CH_2Me)_2$, 2 × $SiPr^i$), and 0.75–0.60 (m, 8 H, 2 × $Si(CH_2Me)_2$)]. This epoxide **11** (5.5 mg) was immediately dissolved in dry THF (0.55 mL) and to this solution was added at 0° M Bu_4NF in THF (25.4 μL, 25.4 μmol). After 10 min at 25°, water was added to the mixture and the resultant mixture was concentrated. The residue was chromatographed on silica gel (0.5 g) with 10:3:1 EtOAc–2-propanol–water to afford cyclophellitol (**1**, 1.7 mg, 40% from **10**) as colorless crystals: m.p. 149–151° (from H_2O) [lit.[1] m.p. 149–151° (H_2O)], $[\alpha]_D$ +103° (*c* 0.50, H_2O) [lit.[1] $[\alpha]_D$ +103° (*c* 0.50, H_2O)]; ^{1}H-n.m.r. (400 MHz, D_2O, DOH = 4.80): δ 4.00 (dd, 1 H, $J_{8a,8b}$ 11.3, $J_{5,8a}$ 4.0 Hz, H-8a), 3.82 (dd, 1 H, $J_{5,8b}$ 7.5 Hz, H-8b), 3.78 (br d, $J_{1,2} < 0.2$ Hz, H-2), 3.55 (br dd, 1 H, $J_{5,6}$ 1.8 Hz, H-6), 3.37 (dd, 1 H, $J_{2,3}$ 8.4 Hz, H-3), 3.26 (d, 1 H, $J_{1,6}$ 3.8 Hz, H-1), 3.25 (t, 1 H, $J_{3,4}$ 10.2 Hz, H-4), and 2.12 (m, 1 H, $J_{4,5}$ 10.0 Hz, H-5).

(b) A mixture of **10** (22.5 mg, 28.2 μmol), $Pd(OH)_2$, and MeOH (0.6 mL) was vigorously stirred under 1 atm of H_2 for 12 h at 25°. The mixture was filtered and concentrated. The residue was chromatographed on silica gel (0.8 g) with 10:3:1 EtOAc–2-propanol–water to afford the deprotected mesylate **12** (6.1 mg, 80%) as a colorless syrup [R_F 0.35 (10:3:1 EtOAc–2-propanol–water); ^{1}H-n.m.r. (270 MHz, D_2O, DOH = 4.80): δ 4.64 (dd, 1 H, $J_{5,6}$ 10.0, $J_{1,6}$ 9.0 Hz, H-6), 3.97 (dd, 1 H, J_{5,CH_2} 2.4, J_{gem} 11.6 Hz, one of CH_2OH), 3.79 (dd, 1 H, J_{5,CH_2} 2.4 Hz, one of CH_2OH), 3.67 (dd, 1 H, *J* 9.0, *J* 9.0 Hz), 3.52 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, H-4), 3.42 (dd, 1 H, *J* 9.0, 9.0 Hz), 3.33 (dd, 1 H, *J* 9.0, *J* 9.0 Hz), 3.32 (s, 3 H, OMs), and 1.82 (dddd, 1 H, $J_{5,6}$ 10.0 Hz, H-5)]. This sample (6.1 mg, 22.4 μmol) was dissolved in water (0.46 mL) and to this was added at 0° M aqueous NaOH (0.0169 mL, 16.9 μmol). After being stirred for 1 h at 0°, the mixture was made neutral with CG-50 (H^+) and the resin was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel (0.5 g) with 10:3:1 EtOAc–2-propanol–water to afford cyclophellitol (**1**, 3.0 mg, 75%) as colorless crystals.

*Methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-*α*-*D*-galacto-hept-6-enopyranoside* (**14**). — To a stirred solution of oxalyl chloride (1.85 mL, 21.6 mmol) in dry CH_2Cl_2 (27.8 mL) was added at −78° a solution of Me_2SO (3.07 mL, 43.2 mmol) in dry CH_2Cl_2 (18.5 mL). After 10 min stirring, a solution of **13** (5.03 g, 10.8 mmol) in dry CH_2Cl_2 (50 mL) was added and the mixture was stirred for 15 min at −78°. Triethylamine (9.03 mL, 64.8 mmol) was added and the mixture was stirred for 15 min at −78° and warmed to −40°. The saturated aqueous NH_4Cl solution (144 mL) was added and the mixture was separated. The aqueous layer was extracted with EtOAc (120 mL × 2) and the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residual aldehyde (5.01 g, 100%) was dissolved in dry benzene (150 mL) and to this was added methylidenetriphenylphosphorane (7.50 g, 27.0 mmol). After being stirred for 10 min at 25°, the mixture was concentrated and the residue was dissolved in ether (120 mL) and washed with water (120 mL). The aqueous layer was extracted with ether (120 mL × 2) and the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed

on silica gel (250 g) with 6:1 hexane–EtOAc to afford **14** (4.50 g, 91%) as a pale-yellow syrup: $[\alpha]_D$ +30° (*c* 0.50); R_F 0.37 (6:1 hexane–EtOAc); ^{1}H-n.m.r. (270 MHz); δ 7.40–7.20 (m, 15 H, 3 × Ph), 5.84 (ddd, 1 H, $J_{5,6}$ 6.0, $J_{6,7Z}$ 10.2, $J_{6,7E}$ 17.0 Hz, H-6), 5.29 (ddd, 1 H, $J_{gem} = J_{5,7E} = 1.2$ Hz, *E*-H-7), 5.15 (ddd, 1 H, $J_{5,7Z}$ 1.2 Hz, *Z*-H-7), 4.91, 4.85, 4.84, 4.71, 4.69, and 4.64 (each 1 H, *J* 11.6 Hz, 3 × OCH_2Ph), 4.73 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 4.16 (br dd, 1 H, H-5), 4.07 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 3.95 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.79 (dd, 1 H, $J_{4,5}$ 1.6 Hz, H-4), and 3.36 (s, 3 H, OMe).

Anal. Calc. for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00. Found: C, 75.67; H, 6.84.

*2,3,4-Tri-*O*-benzyl-6,7-dideoxy-*D-galacto-*hept-6-enose* (E,Z)-*oxime* (**15**). — To a stirred, ice-cooled solution of **14** (2.00 g, 4.33 mmol) in Ac_2O (40 mL) was added a solution of concd. H_2SO_4 (0.06 mL) in Ac_2O (20 mL) and the mixture was stirred for 10 min at 0°. The saturated aqueous $NaHCO_3$ solution (50 mL) was added and the mixture was extracted with EtOAc (50 mL × 2). The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue (2.12 g) was dissolved in dry MeOH (42 mL) and to this stirred, ice-cooled solution was added NaOMe (234 mg, 4.33 mmol). After being stirred for 10 min at 0° and for 0.5 h at 25°, the mixture was made neutral with CG-50 (H^+) in MeOH and the resin was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel (57 g) with 3:1 hexane–EtOAc to afford the free sugar (1.80 g, 92%) as a colorless syrup. To an ice-cooled, stirred solution of this free sugar (1.78 g, 3.98 mmol) in dry pyridine (36 mL) was added hydroxylamine hydrochloride (1.40 g, 20.1 mmol). After being stirred for 3 h at 25°, the mixture was evaporated and the residue was dissolved in EtOAc (20 mL) and washed with saturated, aqueous $NaHCO_3$, NaCl, dried, and concentrated to afford the crude **15** (1.83 g, 100%) as a colorless syrup. A portion of this sample was chromatographed on silica gel with 6:1 benzene–EtOAc to afford an analytical sample of **15**: $[\alpha]_D$ +51° (*c* 0.53); R_F 0.60 (5:1 benzene–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.60 (br, 0.3 H, *Z*-NOH), 7.44 (d, 0.7 H, $J_{1,2}$ 8.0 Hz, *E*-H-1), 7.39–7.15 (m, 15 H, 3 × Ph), 6.96 (d, 0.3 H, $J_{1,2}$ 6.2 Hz, *Z*-H-1), 6.03 (ddd, 1 H, $J_{5,6}$ 4.0, $J_{6,7E}$ 17.0, $J_{6,7Z}$ 10.4 Hz, H-6), 5.40 (ddd, 1 H, $J_{5,7E}$ 2.0, J_{gem} 2.0 Hz, *E*-H-7), 5.23 (ddd, 1 H, $J_{5,7Z}$ 2.0 Hz, *Z*-H-7), 5.08–3.70 (m, 10 H, H-2,3,4,5,3 × OCH_2Ph), 2.66 (d, 0.7 H, *J* 9.0 Hz, *E*-5-OH), and 2.61 (d, 0.3 H, *J* 9.0 Hz, *Z*-5-OH).

Anal. Calc. for $C_{28}H_{31}NO_5$: C, 72.87; H, 6.77; N, 3.04. Found: C, 72.84; H, 6.73; N, 3.02.

(1S,2R,3S,4R,5S)-3,4,5-Tribenzyloxy-2-hydroxy-8-oxa-7-azabicyclo[4.3.0]non-6-ene (**16**) *and its C-1 epimer* **17**. — To a solution of the crude sample of **15** (1.55 g) in dry toluene (47 mL) was added 5% aqueous NaOCl (11.5 mL, 8.06 mmol) and the mixture was heated for 0.5 h at 100°. Upon cooling to room temperature, saturated aqueous NH_4Cl (47 mL) was added and the mixture was separated. The aqueous layer was extracted with EtOAc (40 mL × 2) and the combined organic extracts were washed with saturated, aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (60 g) with 4:1 benzene–EtOAc to afford **16** (0.231 g, 15%) as colorless crystals and **17** (1.16 g, 75%) as a colorless syrup.

Compound **16** had m.p. 142–144° (EtOAc–hexane), $[\alpha]_D$ +133° (*c* 0.50); R_F 0.17

(5:1 benzene–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.50–7.20 (m, 15 H, 3 × Ph), 5.05, 4.87, 4.86, 4.71, 4.65, and 4.60 (each 1 H, J 11.4 Hz, 3 × OCH_2Ph), 4.74 (dd, 1 H, $J_{4,5}$ 9.2, $J_{1,5}$ 1.0 Hz, H-5), 4.38 (dd, 1 H, $J_{1,9'}$ 12.0, J_{gem} 8.2 Hz, H-9'), 4.30 (dd, 1 H, $J_{1,9}$ 8.2 Hz, H-9), 3.99 (dd, 1 H, $J_{3,4}$ 2.0 Hz, H-4), 3.94–3.875 (m, 2 H, H-2,3), 3.77 (m, 1 H, H-1), and 2.14 (d, 1 H, J 5.0 Hz, 2-OH).

Anal. Calc. for $C_{28}H_{29}NO_5$: C, 73.19; H, 6.36; N, 3.05. Found: C, 72.89; H, 6.54; N, 2.99.

Compound **17** had $[\alpha]_D$ −54° (*c* 0.50); R_F 0.54 (5:1 benzene–EtOAc); ^{1}H-n.m.r. (270 MHz) δ 7.40–7.20 (m, 15 H, 3 × Ph), 4.69–4.35 (m, 8 H, H-5, 9', 3 × OCH_2Ph), 4.21 (dd, 1 H, J 10.0, J 8.8 Hz, H-9), 4.05–3.94 (m, 2 H), 3.78 (dd, 1 H, $J_{2,2}$ 9.4 Hz), 3.43 (ddd, 1 H, $J_{1,2} = J_{1,9} = J_{1,9'}$ = 10.0 Hz, H-1), and 2.57 (d, 1 H, J 1.4 Hz, 2-OH).

Anal. Calc. for $C_{28}H_{29}NO_5$: C, 73.19; H, 6.36; N, 3.05. Found: C, 72.89; H, 6.29; N, 3.08.

(2R,3S,4S,5R,6S)-2,3,4-Tribenzyloxy-5-hydroxy-6-hydroxymethylcyclohexanone (**18**). — A mixture of **16** (132 mg, 0.288 mmol), 5:1 (v/v) 1,4-dioxane–water (3.9 mL), AcOH (0.100 mL, 1.70 mmol), and Raney Ni-W4 was vigorously stirred under 1 atm of H_2 for 12 h at 25°. The mixture was filtered with Celite and the filter cake washed with 1,4-dioxane. The filtrates and washings were concentrated and the residue was chromatographed on silica gel (9.8 g) with 3:2 benzene–EtOAc to afford **18** (99.6 mg, 75%) as a colorless syrup: $[\alpha]_D$ +88° (*c* 0.50); R_F 0.38 (1.5:1 benzene–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.50–7.20 (m, 15 H, 3 × Ph), 4.97, 4.89, 4.87, 4.70, 4.67, and 4.63 (each 1 H, J 11.6 Hz, 3 × OCH_2Ph), 4.95–4.87 (m, 2 H, H-5, one of CH_2OH), 4.06 (d, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 4.13 (dd, 1 H, $J_{3,4}$ 3.8 Hz, H-3), 4.05 (s, 1 H, 5-OH), 4.03 (dd, 1 H, $J_{4,5}$ 3.8 Hz, H-4), 3.79 (ddd, 1 H, J_{6,CH_2} 2.4, J_{gem} 12.0, $J_{CH_2,OH}$ 10.2 Hz, one of CH_2OH), 2.89 (m, 1 H, H-6), and 2.76 (dd, 1 H, $J_{CH_2,OH}$ 4.2 Hz, CH_2OH).

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.21: H, 6.54. Found: C, 72.49; H, 6.43.

Isoxazoline opening of **17**. — A mixture of **17** (980 mg, 2.13 mmol), 5:1 (v/v) 1,4-dioxane–water (29 mL), AcOH (0.730 mL, 12.8 mmol), and Raney Ni-W4 was vigorously stirred under 1 atm of H_2 for 4 h at 25°. The mixture was filtered with Celite and the filter cake washed with 1,4-dioxane. The combined filtrate and washings were concentrated and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, NaCl, dried, and concentrated. The residue was chromatographed on silica gel (10 g) with 1:1 hexane–EtOAc to afford **18** (690 mg, 70%) and **19** (276 mg, 28%) as colorless syrups.

Compound **19** had $[\alpha]_D$ +5.6° (*c* 0.50); ^{1}H-n.m.r. (270 MHz): δ 7.47–7.10 (m, 15 H, 3 × Ph), 4.60–4.35 (m, 6 H, 3 × OCH_2Ph), 4.16 (ddd, 1 H, $J_{5,OH}$ 2.0, $J_{4,5} = J_{5,6}$ = 9.0 Hz, H-5), 4.06 (dd, 1 H, $J_{3,4}$ 2.2 Hz, H-4), 4.00–3.93 (m, 3 H, H-3, CH_2OH), 3.80 (d, 1 H, $J_{2,3}$ 4.4 Hz, H-2), 2.98 (ddd, 1 H, $J_{6,CH_2} = J_{6,CH_2}$ = 4.2 Hz, H-6), 2.66 (d, 1 H, J 2.0 Hz, 5-OH), and 2.52 (dd, 1 H, $J_{CH_2,OH} = J_{CH_2,OH}$ = 6.4 Hz, CH_2OH).

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 73.07; H, 6.54.

Epimerization of **19** *to* **18**. — A mixture of **19** (23.6 mg, 51.0 μmol), Et_3N (14.2 μL, 0.102 mmol), and dry CH_2Cl_2 (0.7 mL) was kept for 2 days at 25° and then 1% aqueous HCl was added and the mixture was extracted with EtOAc. The organic extracts were

washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (2.4 g) with 1:1 hexane–EtOAc to afford **18** (15.3 mg, 65%) and **19** (6.1 mg, 26%).

*1D-4,5,6-Tri-O-benzyl-2-deoxy-2-hydroxymethyl-*chiro*-inositol* (**20**). — To a solution of **18** (292 mg, 0.631 mmol) in dry THF (9.0 mL) was added at 0° $BH_3 \cdot Me_2S$ (10M, 0.190 mL, 1.90 mmol). After being stirred for 0.5 h at 0°, the mixture was poured into saturated aqueous $NaHCO_3$ (9 mL) and extracted with EtOAc (9 mL × 2). The organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (15 g) with 2:3 benzene–EtOAc to afford **20** (235 mg, 80%) as a colorless syrup: $[\alpha]_D$ +11° (*c* 0.50); ^{1}H-n.m.r. (270 MHz): δ 7.40–7.20 (m, 15 H, 3 × Ph), 5.06, 4.82, 4.68, and 4.63 (each 1 H, *J* 12.0 Hz, 2 × OCH_2Ph), 4.67 (s, 2 H, OCH_2Ph), 4.18–4.10 (m, 2 H, H-1, one of CH_2OH), 3.97–3.77 (m, 5 H, H-3, 4, 5, 6, one of CH_2OH), 3.30, 2.53, and 2.26 (each br, each 1 H, 3 × OH), and 1.97 (m, 1 H, H-2).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.40; H, 6.94. Found: C, 72.64; H, 6.84.

(1R,2S,3S,4R,5R,6S)-2,3,4-Tribenzyloxy-5-[(1-methylethyl)diethylsilyl]oxy-6-[[(1-methylethyl)diethylsilyl]oxy]methylcyclohexanol (**21**) *and 1D-4,5,6-tri-O-benzyl-2-deoxy-2-[[(1-methylethyl)diethylsilyl]oxy]methyl-*chiro*-inositol* (**22**). — To an ice-cooled, stirred solution of **20** (262 mg, 0.564 mmol) in dry DMF (8 mL) was added imidazole (76.7 mg, 1.13 mmol) and diethylisopropylsilyl chloride (0.119 mL, 0.676 mmol). After being stirred for 1 h at 0°, imidazole (76.7 mg, 1.13 mmol) and diethylisopropylsilyl chloride (0.119 mL, 0.676 mmol) was added and the stirring was continued for an additional 3 h. Water (8 mL) and hexane (8 mL) were successively added and the mixture was separated. The aqueous layer was extracted with hexane (8 mL × 2) and the combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (30 g) with 15:1 hexane–EtOAc and then 8:1 hexane–EtOAc to afford **21** (244 mg, 60%) as colorless crystals and **22** (131 mg, 39%) as a colorless syrup.

Compound **21** had $[\alpha]_D$ +34° (*c* 0.50); R_F 0.57 (10:1 hexane–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.45–7.20 (m, 15 H, 3 × Ph), 5.16 and 4.68 (ABq, each 1 H, *J* 11.6 Hz, OCH_2Ph), 4.80 and 4.60 (ABq, each 1 H, *J* 11.6 Hz, OCH_2Ph), 4.58 and 4.53 (ABq, each 1 H, *J* 11.0 Hz, OCH_2Ph), 4.17 (dd contaminated with H-1, 2 H, J_{6,CH_2} 3.8, J_{gem} 10.2 Hz, one of CH_2OH), 4.06 (dd, 1 H, $J_{4,5}$ 8.4, $J_{5,6}$ 10.6 Hz, H-5), 3.96 (br s, 1 H, 1-OH), 3.95 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 10.0 Hz, H-3), 3.87 (dd, 1 H, J_{6,CH_2} 3.8 Hz, one of CH_2OH), 3.85 (dd, 1 H, $J_{1,2}$ 3.2 Hz, H-2), 3.73 (dd, 1 H, H-4), 1.93 (m, 1 H, H-6), 1.07–0.85 [m, 26 H, 2 × Si(CH_2Me)$_2$, 2 × SiPr^i)], and 0.75–0.55 [m, 8 H, 2 × Si(CH_2Me)$_2$].

Anal. Calc. for $C_{42}H_{64}O_6Si_2$: C, 69.96; H, 8.95. Found: C, 70.05; H, 8.68.

Compound **22** had R_F 0.25 (10:1 hexane–EtOAc); ^{1}H-n.m.r. (270 MHz): δ 7.40–7.20 (m, 15 H, 3 × Ph), 5.07 and 4.69 (ABq, each 1 H, *J* 11.0 Hz, OCH_2Ph), 4.83 and 4.63 (ABq, each 1 H, *J* 12.0 Hz, OCH_2Ph), 4.67 (s, 2 H, OCH_2Ph), 4.47 (s, 1 H, OH), 4.31 (dd, 1 H, *J* 2.4, J_{gem} 10.0 Hz, one of CH_2OH), 4.21 (br dd, 1 H, *J* 3.2, *J* 3.2 Hz), 4.03–3.76 (m, 5 H), 2.37 (d, 1 H, *J* 2.0 Hz, OH), 1.87 (m, 1 H, H-2), 1.05–0.90 [m, 13 H, Si(CH_2Me)$_2$, SiPr^i], and 0.75–0.55 [m, 4 H, Si(CH_2Me)$_2$].

(1R,2R,3S,4R,5R,6R-5-Hydroxymethyl-6-methanesulfonyloxycyclohexane-1,2,-3,4-tetraol (**24**). — To a stirred, ice-cooled solution of **21** (47.2 mg, 66.5 μmol) in dry pyridine (0.9 mL) was added methanesulfonyl chloride (30.4 μL, 0.393 mmol). After being stirred for 12 h at 25°, EtOH (60μL) was added to the mixture and the resultant mixture was stirred for 0.5 h at 25°. The mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, NaCl, dried, and concentrated. The residue was chromatographed on silica gel (2.5 g) with 1:3 hexane–benzene to afford **23** (49.7 mg, 95%) as a pale-yellow syrup. A mixture of this **23** (49.7 mg, 62.2 μmol), Pd-C (25.0 mg), and MeOH (5.0 mL) was vigorously stirred under 1 atm of H_2 for 6 h at 25°. The mixture was filtered through Celite and the filter cake washed with MeOH. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (1.7 g) with 10:3:1 EtOAc–2-propanol–water to afford **24** (16.1 mg, 95%) as a colorless syrup: $[\alpha]_D$ +89° (*c* 1.00, H_2O); ^{1}H-n.m.r. (270 MHz ,D_2O, DOH = 4.80): δ 4.98 (dd, 1 H, $J_{5,6}$ 4.0, $J_{1,6}$ 3.4 Hz, H-6), 4.21 (dd, 1 H, $J_{1,2}$ = 3.4 Hz, H-1), 3.98 (dd, 1 H, J_{gem} 11.0, J_{5,CH_2} 4.2 Hz, one of CH_2OH), 3.73 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2), 3.61 (dd, 1 H, J_{5,CH_2} 11.0 Hz, one of CH_2OH), 3.59 (dd, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 3.39 (dd, 1 H, $J_{4,5}$ 11.0 Hz, H-4), 3.25 (s, 3 H, OMs), and 2.22 (m, 1 H, H-5).

Anal. Calc. for $C_8H_{16}O_8S \cdot 0.5H_2O$: C, 34.17; H, 6.09. Found: C, 34.29; H, 6.29.

1,6-Epicyclophellitol (**2**). — To an ice-cooled, stirred solution of **24** (13.1 mg, 0.0481 mmol) in dry MeOH (1.3 mL) was added 5M NaOMe in MeOH (10.9 μL, 54.5 μmol). After being stirred for 2 h at 0°, the mixture was made neutral with CG-50 (H^+) and the resin was filtered off. The filtrate was concentrated and the residue chromatographed on silica gel (0.7 g) with 10:3:1 EtOAc–2-propanol–water to afford **2** (7.4 mg, 87%) as colorless crystals: m.p. 150–152° (MeOH, needles); $[\alpha]_D$ +80° (*c* 0.36, H_2O); R_F 0.28 (10:3:1 EtOAc–2-propanol–water); ^{1}H-n.m.r. (270 MHz, D_2O, DOH = 4.80): δ 3.91 (dd, 1 H, $J_{5,8'}$ 3.4, J_{gem} 11.2 Hz, H-8'), 3.90 (dd, 1 H, $J_{1,2}$ 2.3, $J_{2,3}$ 8.4 Hz, H-2), 3.78 (dd, 1 H, $J_{5,8}$ 5.8 Hz, H-8), 3.46 (dd, 1 H, $J_{1,6}$ 3.9 Hz, H-1), 3.42 (dd, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 3.34 (dd, 1 H, $J_{4,5}$ 8.8 Hz, H-4), 3.33 (d, 1 H, $J_{1,6}$ 3.9, $J_{5,6}$ 0 Hz, H-6), and 2.04 (ddd, 1 H, H-5).

Anal. Calc. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.42; H, 6.45.

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