Total Syntheses of (±)-Cyclophellitol and (1*R**,6*S**)-Cyclophellitol

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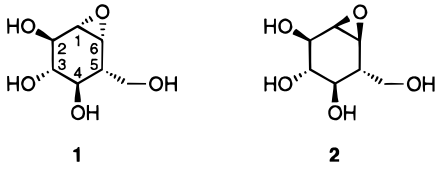
A stereodivergent synthesis of (±)-cyclophellitol (**1**) and its unnatural diastereoisomer (1*R**,6*S**)-cyclophellitol (**2**), starting from the Diels−Alder adduct of furan and acrylic acid, is reported. The stereochemistry of the key step, the epoxidation of alkene **7**, is controlled by the nature of the hydroxyl protecting groups.

Introduction

Glycosidase inhibitors have been recognized as potential therapeutic agents against HIV infection and metastasis.[1] In this way, some cyclohexene oxides[2] may act as specific inhibitors of glycosidases because of their resemblance to true sugars and by the irreversible formation of bonds at the active site of the enzyme.[3] In this context, the naturally occurring carbasugar derivative (+)-cyclophellitol (**1**) (Figure 1), isolated from a *Phellinus* sp. of mushroom inhibits almond β-glucosidase with higher potency ($IC_{50} = 0.8\ \mu g/mL$) than that of other well-known inhibitors such as castanospermine or nojirimycin.[4] The β-equatorial orientation of the C_1−O bond as in β-glucose and its half-chair conformation may be crucial for its strong activity.[3] Several analogues of cyclophellitol have been synthesized and biologically evaluated in order to establish a structure−inhibition relationship.[5] For instance, (1*R*,6*S*)-cyclophellitol (**2**) is a weaker inhibitor of α-glucosidase as well as β-glucosidase and inhibits experimental metastasis.[5a,6]

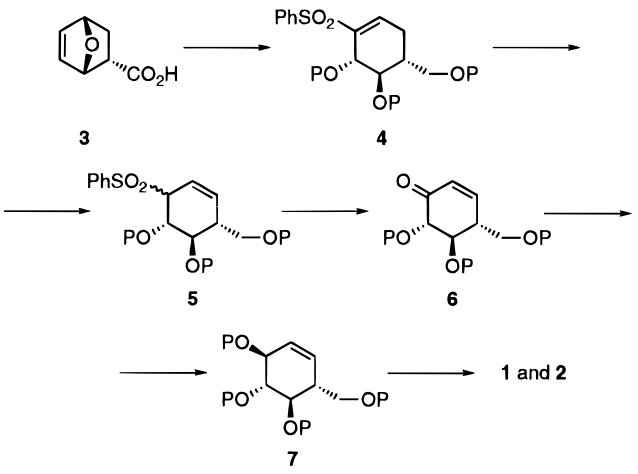
The synthetic approaches to cyclophellitol described thus far employ two different strategies for the construction of the oxirane ring: an intramolecular nucleophilic substitution[7] or the epoxidation of a suitable alkene precursor.[8] However, the latter is the only way for the divergent preparation of **1** and **2** without significant modifications in the common synthetic route. In this manner, the selective access to each diastereoisomer could be achieved from the same intermediate by choosing the appropriate protecting groups for the hydroxyl substituents in order to control the stereochemistry of the epoxidation process.



1 **2**

Figure 1.

Scheme 1



In recent years we have prepared some members of the carbasugar family such as 5a-carba-α-glucopyranose[9a] and validamine and three of its diastereoisomers[9b] using as a pivotal intermediate the cyclohexenyl sulfone **4**, available from the *endo*adduct of furan and acrylic acid **3**[10] (Scheme 1). Within this project, the next targets we selected were compounds **1** and **2** which we hoped to prepare through the isomerization of the double bond in **4** to the allylic position[11] and subsequent oxidative desulfonylation[12] of **5** to the enone **6**. Transformation of

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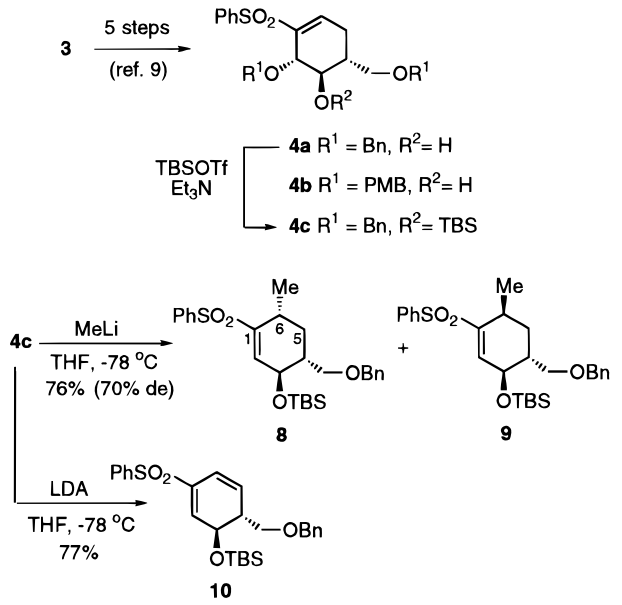
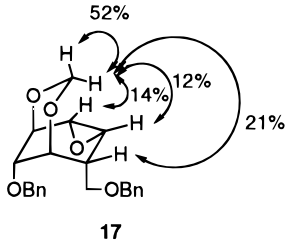
Scheme 2



6 into the related allylic alcohol **7** followed by epoxidation controlled by the free hydroxy groups could lead selectively to either cyclophellitol **1** or its unnatural diastereoisomer **2**.[13] Although the sequence reported here has been carried out using racemic compounds, it should be possible to obtain the final products in enantiomerically pure form since the optical resolution of **3** has been described.[10b]

Results and Discussion

Sulfones **4a**−**c** were prepared as previously reported[9] (Scheme 2). Starting from compounds **4**, none of the conditions tested to achieve the isomerization led us to the corresponding allyl sulfone. However, several products were obtained in synthetically useful yields. For instance, reaction of **4c** with MeLi at −78 °C afforded a 85:15 mixture of compounds **8** and **9**, arising from the S_N2' addition of the organolithium reagent. Both products were obtained in varying amounts depending on the conformation of the starting material as determined by the protecting groups.[14] Thus, when hydroxy sulfone **4a** was treated with MeLi, followed by silylation (TBSOTf, Et_3N) of the crude mixture, a 40:60 ratio of **8** and **9** was obtained.[15] The stereochemistry of the methyl group in **8** was deduced by observation of two axial−axial coupling constants (13.4 and 10.6 Hz) in the adjacent H-5 axial proton in its ^1H NMR spectra. On the other hand, the use of non-nucleophilic bases gave rise to the isomerization with concomitant elimination of the *β*′-benzyloxy group. Thus, the reaction of **4c** with LDA or *t*-BuOK yielded the diene **10**.[16] It should be noted that related dienyl systems have been previously prepared from dienes[17] or by SO_2 extrusion of (arylsulfonyl)sulfolenes[18] and used as synthetic intermediates on the basis of their dienic properties.[17a] Moreover, the double bonds are able to be differentiated in epoxidation or cyclopropanation reactions, depending on the conditions employed.[19] The synthetic exploitation of these processes is now under investigation in our laboratory.



17

Figure 2.

The failure of the isomerization reaction in our synthetic plan led us to design an alternative way to the enone **6**. Thus, the α-bromo ketone **12a** was prepared from sulfone **4a** by nucleophilic epoxidation followed by reaction with $MgBr_2{\cdot}OEt_2$[9b] (Scheme 3). The subsequent dehydrohalogenation reaction in the presence of $CaCO_3$ in DMF gave the desired enone **6a**. The stereoselective carbonyl reduction under Luche's conditions[20] yielded the related diol **7a**. Finally, the epoxidation of **7a** controlled by the free allylic hydroxy group[21] using *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by debenzylation by catalytic hydrogenation afforded (1*R**,6*S**)-cyclophellitol (**2**), which was isolated and characterized as its tetraacetyl derivative **14**.[8a]

In order to invert the selectivity of the epoxidation process, our initial attempts included changing the protecting groups in diol **7a** using a protection−debenzylation sequence. However, the preparation of diol **15** was unsuccessful using several debenzylation conditions (Na/NH_3, $BF_3{\cdot}OEt_2/EtSH$,[22] TMSCl/NaI,[23] $PhSSiMe_3/ZnI_2$/TBAI,[24] $BCl_3{\cdot}SMe_2$[25]) due to partial losses and migrations of the protecting groups employed (TBS and acetyl) (Scheme 4). In the search for suitable protecting groups, we found that treatment of **7a** with HNa and $MeOCH_2Cl$ in refluxing THF produced the bicyclic acetal **16** in good yield. Its epoxidation with *m*-CPBA gave **17** as a single diastereoisomer due to the steric hindrance of the *β*-face of the double bond by the methylene acetal moiety. The orientation of the oxirane ring was confirmed by NOE measurements (Figure 2). Unfortunately,

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(13) For a preliminary communication of this work, see: Aceña. J. L.; de Alba, E.; Arjona, O.; Plumet, J. *Tetrahedron Lett.* **1996**, *37*, 3043−3044.

(14) The change of conformation on sulfones **4** was also used for their selective nucleophilic epoxidation with LiOO-*t*-Bu; see ref 9b.

(15) For a mechanistic study of the related S_N2' addition of organometallic reagents to *β*′-aminocyclohexenyl sulfones or their quaternary ammonium salts, see: Pan, Y.; Hardinger, S. A.; Fuchs, P. L. *Synth. Commun.* **1989**, *19*, 403−416.

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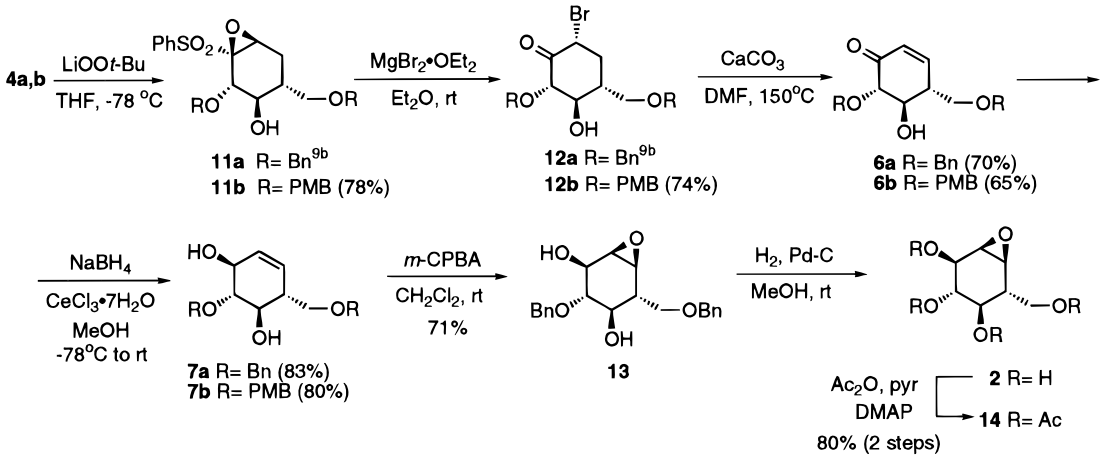
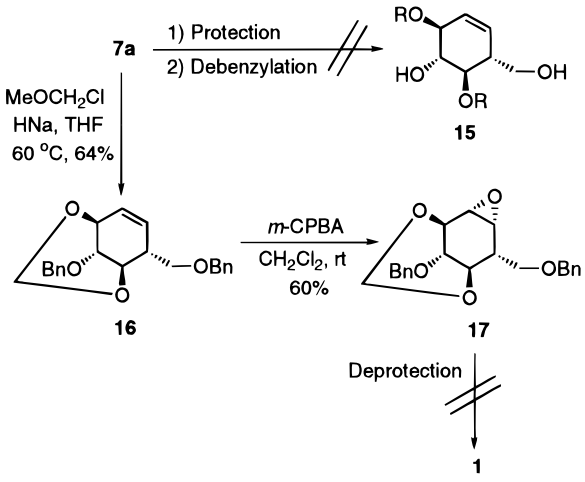
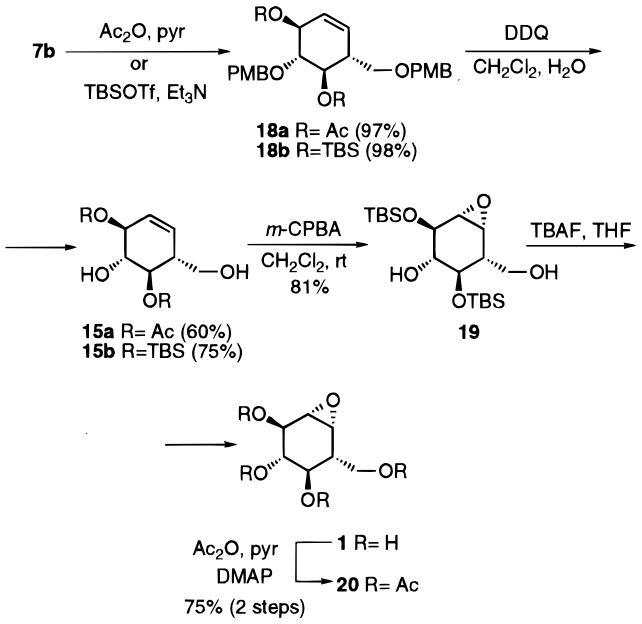
Scheme 3



Scheme 4



Scheme 5



the deprotection of **17** was not possible due to the lability of the epoxide under the harsh conditions required for the acetal cleavage.

In view of the problems encountered in the removal of the benzyl groups in **7a**, we decided to repeat the sequence with protecting groups that were easier to remove. Thus, diol **7b** was prepared in an identical manner as before, replacing the benzyl groups by PMB functionalities. Acetylation of this compound to **18a** or silylation to **18b** followed by clean deprotection with DDQ[26] produced diols **15a** and **15b**, respectively (Scheme 5). Epoxidation of the acetyl derivative **15a** with *m*-CPBA followed by acetylation afforded a mixture of tetraacetyl-(±)-cyclophellitol and its diastereoisomer in a 60:40 ratio. A totally stereoselective epoxidation could be achieved using a bulkier substituent at the allylic position. Thus, treatment of **15b** with *m*-CPBA gave **19** as a single product. Final desilylation with tetrabutylammonium fluoride (TBAF) yielded (±)-cyclophellitol (**1**) which was isolated as its tetraacetate **20**.[8a]

In summary, (±)-cyclophellitol has been prepared in 14 steps starting from furan. This synthesis constitutes the shortest route developed to date with the exception of Vogel's synthesis.[7c] Moreover, the unnatural isomer (1*R**,6*S**)-cyclophellitol is also accessible in 12 steps via the common intermediate **7**, providing the best way known to obtain both inhibitors through a divergent synthetic sequence.

(26) Treatment of **18a** with DDQ in CH_2Cl_2/H_2O caused migrations of the acetyl groups. The reaction was carried out in anhydrous conditions instead.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of dry argon using freshly distilled solvents under anhydrous conditions. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone; dichloromethane, toluene, triethylamine, diisopropylamine, *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA), pyridine, and *N*,*N*-dimethylformamide (DMF) were distilled from CaH_2. Lithium diisopropylamide (LDA) was purchased from Aldrich (2.0 M solution in heptane, THF and ethylbenzene). Commercial methyllithium (1.6 M, low halide solution in ether) and *n*-butyllithium (1.6 M solution in hexane) were purchased from Aldrich. *m*-Chloroperoxybenzoic acid (*m*-CPBA) was washed with a 5% aqueous solution of $NaHCO_3$ prior to use. Flash chromatography was performed using E. Merck 230−400 mesh silica gel. Analytical TLC was carried out on 0.20 mm Merck precoated silica gel plates (60F-254), with detection by UV light, acidic vanillin solution, and a 10% solution of phosphomolybdic acid in ethanol. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 250 or 300 MHz with $CDCl_3$ as solvent. The following abbreviations are used to describe peak patterns when appropriate: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Elemental analyses were performed at the Universidad Complutense de Madrid.

(3*R,4*R**,6*R**)-4-((Benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)-6-methyl-1-(phenylsulfonyl)cyclohex-1-ene, 8.** To a cold (−78 °C) solution of 39 mg (0.07 mmol) of

4c[9b] in 0.5 mL of THF was added 0.13 mL (0.21 mmol) of MeLi. After the mixture was stirred at −78 °C for 2 h, a saturated aqueous solution of NH_4Cl was added. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 25 mg of an inseparable mixture of **8** and **9** in an 85:15 ratio determined by integration of the methyl signals at 1.11 and 1.17 ppm, respectively, in the ^{1}H NMR spectra (76% overall yield). Data for **8**: $R_f = 0.26$ (hexane:EtOAc, 5:1). ^{1}H NMR (300 MHz): δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.86 (s, 9 H), 1.11 (d, 3 H, J = 6.8 Hz), 1.37 (td, 1 H, J = 13.4, 10.6 Hz), 1.67−1.77 (m, 1 H), 1.99 (ddd, 1 H, J = 13.7, 5.4, 2.6 Hz), 2.55−2.60 (m, 1 H), 3.50 (d, 2 H, J = 4.6 Hz), 4.31 (ddd, 1 H, J = 9.4, 3.2, 1.7 Hz), 4.42 (d, 1 H, J = 11.9 Hz), 4.52 (d, 1 H, J = 11.9 Hz), 6.62 (br s, 1 H), 7.29−7.35 (m, 5 H), 7.54 (t, 2 H, J = 7.7 Hz), 7.62 (t, 1 H, J = 7.2 Hz), 7.88 (d, 2 H, J = 7.0 Hz). ^{13}C NMR (75 MHz): δ −5.0, −4.5, 18.0, 20.3, 25.7, 30.6, 34.6, 42.3, 68.6, 70.3, 73.2, 89.2, 127.6, 128.0, 128.4, 129.0, 133.2, 138.3, 140.2, 142.5, 144.6. IR ($CHCl_3$): 2950, 1480 cm^{-1}. Anal. Calcd for $C_{27}H_{38}O_4SSi$: C, 66.76; H, 7.88. Found: C, 66.65; H, 7.72.

(5*R,6*R**)-5-((Benzyloxy)methyl)-6-((*tert*-butyldimethylsilyl)oxy)-2-(phenylsulfonyl)cyclohexa-1,3-diene, 10.** To a cold (−78 °C) solution of 107 mg (0.19 mmol) of **4c**[9b] in 1.6 mL of THF was added 0.28 mL (0.57 mmol) of LDA. After the mixture was stirred at −78 °C for 1 h, a saturated aqueous solution of NH_4Cl was added. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 5:1) to give 68 mg of **10** as a white solid (77% yield). Data for **10**: $R_f = 0.25$ (hexane:EtOAc, 5:1). Mp: 59−60 °C. ^{1}H NMR (300 MHz): δ 0.06 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9 H), 2.62−2.72 (m, 1 H), 3.39 (dd, 1 H, J = 9.1, 5.4 Hz), 3.45 (dd, 1 H, J = 9.1, 5.4 Hz), 4.43 (d, 1 H, J = 12.1 Hz), 4.53 (d, 1 H, J = 12.1 Hz), 4.70 (dd, 1 H, J = 11.4, 3.0 Hz), 5.98 (dd, 1 H, J = 10.1, 3.4 Hz), 6.08 (d, 1 H, J = 10.1 Hz), 6.75 (br s, 1 H), 7.25−7.28 (m, 5 H), 7.52 (t, 2 H, J = 7.7 Hz), 7.61 (t, 1 H, J = 7.4 Hz), 7.87 (d, 2 H, J = 7.7 Hz). ^{13}C NMR (75 MHz): δ −5.0, −4.3, 17.9, 25.7, 43.1, 67.6, 68.7, 73.1, 118.4, 127.6, 127.7, 127.9, 128.4, 129.2, 132.9, 133.4, 136.6, 137.8, 137.9, 139.3. IR ($CHCl_3$): 1160 cm^{-1}. Anal. Calcd for $C_{27}H_{38}O_4SSi$: C, 66.35; H, 7.28. Found: C, 66.08; H, 7.05.

(4*R,5*R**,6*S**)-6-(Benzyloxy)-4-((benzyloxy)methyl)-5-hydroxycyclohex-2-en-1-one, 6a.** To a solution of 310 mg (0.74 mmol) of **12a**[9b] in 3.7 mL of DMF was added 370 mg (3.7 mmol) of $CaCO_3$. After the mixture was stirred at 150 °C for 2.5 h, H_2O was added. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 175 mg of **6a** as a colorless oil (70% yield). Data for **6a**: $R_f = 0.23$ (hexane:EtOAc, 2:1). ^{1}H NMR (300 MHz): δ 2.74−2.80 (m, 1 H), 2.81 (br s, 1 H), 3.67 (dd, 1 H, J = 9.0, 6.0 Hz), 3.79 (dd, 1 H, J = 9.2, 4.3 Hz), 3.93−4.01 (m, 2 H), 4.55 (s, 2 H), 4.66 (d, 1 H, J = 11.4 Hz), 5.17 (d, 1 H, J = 11.4 Hz), 6.07 (dd, 1 H, J = 10.1, 3.0 Hz), 6.86 (dd, 1 H, J = 10.1, 2.0 Hz), 7.29−7.45 (m, 10 H). ^{13}C NMR (75 MHz): δ 44.9, 69.2, 71.4, 73.5, 74.2, 84.6, 127.6, 127.8, 128.1, 128.3, 128.5, 128.6, 128.9, 137.8, 137.9, 148.8, 197.5. IR ($CHCl_3$): 3600−3300, 1700 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.35; H, 6.49.

(4*R,5*R**,6*S**)-5-Hydroxy-6-((*p*-methoxybenzyl)oxy)-4-(((*p*-methoxybenzyl)oxy)methyl)cyclohex-2-en-1-one, 6b.** According to the procedure described for the synthesis of **6a**, from 276 mg (0.58 mmol) of **12b**, 134 mg of **6b** was obtained as a colorless oil (65% yield). Data for **6b**: $R_f = 0.27$ (hexane:EtOAc, 1:1). ^{1}H NMR (300 MHz): δ 2.71−2.78 (m, 1 H), 2.76 (s, 1 H), 3.62 (dd, 1 H, J = 8.9, 6.0 Hz), 3.75 (dd, 1 H, J = 9.0, 4.2 Hz), 3.81 (s, 6 H), 3.90−3.95 (m, 2 H), 4.47 (s, 2 H), 4.59 (d, 1 H, J = 10.9 Hz), 5.09 (d, 1 H, J = 10.9 Hz), 6.06 (dd, 1 H, J = 10.2, 3.0 Hz), 6.83 (d, 1 H, J = 10.2 Hz), 6.87 (d, 2 H, J = 8.1 Hz), 6.90 (d, 2 H, J = 7.7 Hz), 7.23 (d, 2 H, J = 8.6 Hz), 7.36 (d, 2 H, J = 8.4 Hz). ^{13}C NMR (75 MHz): δ 44.7, 55.3, 68.8, 71.2, 73.0, 73.7, 84.0, 113.8, 113.9, 128.9, 129.2, 130.1, 148.9, 159.5, 197.8. IR ($CHCl_3$): 3600−3200, 1700 cm^{-1}. Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.20; H, 6.39.

(1*R,2*R**,3*S**,6*R**)-2-(Benzyloxy)-6-((benzyloxy)methyl)cyclohex-4-ene-1,3-diol, 7a.** To a cold (−78 °C) solution of 373 mg (1.00 mmol) of $CeCl_3 \cdot 7H_2O$ in 2 mL of MeOH was added 23 mg (0.60 mmol) of $NaBH_4$. After the mixture was stirred for 30 min, a solution of 170 mg (0.50 mmol) of **6a** in 3 mL of MeOH was added. The mixture was slowly warmed up to room temperature and stirred for 2.5 h. A 0.5 N HCl solution was added, and the crude mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (CH_2Cl_2:hexane:EtOAc, 10:1:1) to give 141 mg of **7a** as a white solid (83% yield). Data for **7a**: R_f = 0.12 (hexane:EtOAc, 2:1). Mp: 156−157 °C. ^{1}H NMR (300 MHz): δ 1.97 (d, 1 H, J = 4.8 Hz), 2.55−2.65 (m, 1 H), 3.12 (d, 1 H, J = 1.3 Hz), 3.47 (dd, 1 H, J = 9.9, 7.7 Hz), 3.57 (dd, 1 H, J = 8.8, 6.6 Hz), 3.63 (dd, 1 H, J = 8.9, 5.4 Hz), 3.79 (td, 1 H, J = 10.1, 1.3 Hz), 4.27−4.32 (m, 1 H), 4.55 (s, 2 H), 4.87 (d, 1 H, J = 11.7 Hz), 4.96 (d, 1 H, J = 11.7 Hz), 5.51 (dt, 1 H, J = 10.1, 2.1 Hz), 5.61 (dt, 1 H, J = 10.1, 2.4 Hz), 7.31−7.40 (m, 10 H). ^{13}C NMR (75 MHz): δ 44.4, 71.9, 72.2, 72.4, 73.4, 74.8, 85.6, 126.9, 127.6, 127.7, 127.9, 128.0, 128.4, 128.6, 129.2, 137.8, 138.6. IR ($CHCl_3$): 3600−3200 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.99; H, 7.03.

(1*R,2*R**,3*S**,6*R**)-2-((*p*-Methoxybenzyl)oxy)-6-(((*p*-methoxybenzyl)oxy)methyl)cyclohex-4-ene-1,3-diol, 7b.** According to the procedure described for the synthesis of **7a**, from 740 mg (1.86 mmol) of **6b**, 595 mg of **7b** was obtained as a white solid (80% yield). Data for **7b**: $R_f = 0.17$ (hexane:EtOAc, 1:1). Mp: 124−125 °C. ^{1}H NMR (300 MHz): δ 2.12 (br s, 1 H), 2.49−2.61 (m, 1 H), 3.15 (br s, 1 H), 3.43 (dd, 1 H, J = 9.7, 7.9 Hz), 3.53 (t, 1 H, J = 8.9 Hz), 3.58 (dd, 1 H, J = 8.9, 5.5 Hz), 3.72 (t, 1 H, J = 9.5 Hz), 3.79 (s, 6 H), 4.20−4.27 (m, 1 H), 4.47 (s, 2 H), 4.78 (d, 1 H, J = 11.2 Hz), 4.86 (d, 1 H, J = 11.2 Hz), 5.47 (br d, 1 H, J = 10.1 Hz), 5.58 (br d, 1 H, J = 10.2 Hz), 6.87 (d, 2 H, J = 8.4 Hz), 6.89 (d, 2 H, J = 8.2 Hz), 7.21 (d, 2 H, J = 8.6 Hz), 7.32 (d, 2 H, J = 8.4 Hz). ^{13}C NMR (75 MHz): δ 44.3, 55.2, 71.7, 72.1, 72.5, 73.0, 74.5, 85.2, 113.8, 114.0, 126.9, 129.2, 129.2, 129.6, 129.9, 130.7, 159.2, 159.3. IR ($CHCl_3$): 3600−3300 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.75; H, 6.64.

(1*R,2*R**,3*S**,4*R**,5*R**,6*S**)-3-(Benzyloxy)-5-((benzyloxy)methyl)-7-oxabicyclo[4.1.0]heptane-2,4-diol, 13.** To a solution of 36 mg (0.11 mmol) of **7a** in 1.5 mL of CH_2Cl_2 was added 46 mg (0.26 mmol) of *m*-CPBA. The reaction was stirred for 36 h. A 5% aqueous solution of $NaHCO_3$ was added, and the crude mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 27 mg of **13** as a white solid (71% yield). Data for **13**: R_f = 0.27 (hexane:EtOAc, 1:1). Mp: 116−117 °C. ^{1}H NMR (300 MHz): δ 2.11 (d, 1 H, J = 6.7 Hz), 2.24 (dt, 1 H, J = 9.6, 4.9 Hz), 2.63 (d, 1 H, J = 2.0 Hz), 3.17 (d, 1 H, J = 4.0 Hz), 3.37 (dd, 1 H, J = 4.5, 2.1 Hz), 3.40 (dd, 1 H, J = 10.0, 8.1 Hz), 3.54 (td, 1 H, J = 9.9, 2.0 Hz), 3.70 (m, 2 H), 4.00 (ddd, 1 H, J = 8.4, 6.6, 2.1 Hz), 4.55 (s, 2 H), 4.78 (d, 1 H, J = 11.4 Hz), 4.90 (d, 1 H, J = 11.4 Hz), 7.29−7.38 (m, 10 H). ^{13}C NMR (75 MHz): δ 42.6, 54.7, 56.9, 69.4, 70.3, 72.7, 73.5, 75.4, 82.8, 127.6, 127.8, 128.0, 128.1, 128.5, 128.7, 137.9, 138.3. IR ($CHCl_3$): 3600−3200 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.68; H, 6.64.

(1*R,2*R**,3*S**,4*R**,5*R**,6*S**)-2,3,4-Triacetoxy-5-(acetoxymethyl)-7-oxabicyclo[4.1.0]heptane (Tetra-*O*-acetyl-(1*R**,6*S**)-cyclophellitol), 14.** To a solution of 17 mg (0.05 mmol) of **13** in 2 mL of MeOH was added 51 mg of 10% Pd−C. The mixture was stirred for 24 h in a Parr hydrogenator at 60 psi. The crude was filtered through a sort pad of silica gel with MeOH. The residue was acetylated with 1 mL of Ac_2O, 1 mL of pyridine and a catalytic amount of DMAP. After 12 h the crude mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:Et_2O, 1:2) to give 13 mg of **14** (80% yield). Its spectral features were identical to those reported in the literature.[8a]

(1*R,2*R**,3*S**,6*R**)-2-(Benzyloxy)-6-((benzyloxy)methyl)cyclohex-4-ene-1,3-diol 1,3-*O*-(Methylene acetal), 16.** To a solution of 75 mg (0.22 mmol) of **7a** in 2.2 mL of THF were added 26 mg (0.66 mmol) of HNa (60% in mineral oil) and 0.05 mL (0.66 mmol) of $MeOCH_2Cl$. After the mixture was stirred at 60 °C for 24 h, a 5% aqueous solution of $NaHCO_3$

was added. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 5:1) to give 50 mg of **16** as a colorless oil (64% yield). Data for **16**: $R_f = 0.34$ (hexane:EtOAc, 2:1). ^{1}H NMR (300 MHz): δ 2.73 (tt, 1 H, $J = 7.8$, 2.9 Hz), 3.52 (d, 2 H, $J = 7.7$ Hz), 3.97 (td, 1 H, $J = 3.7$, 0.9 Hz), 4.34 (d, 1 H, $J = 4.0$ Hz), 4.42−4.45 (m, 1 H), 4.46 (d, 1 H, $J = 12.1$ Hz), 4.47 (s, 2 H), 4.55 (d, 1 H, $J = 12.1$ Hz), 4.63 (d, 1 H, $J = 6.3$ Hz), 5.01 (d, 1 H, $J = 6.3$ Hz), 5.78 (ddd, 1 H, $J = 10.0$, 6.1, 3.1 Hz), 6.38 (ddd, 1 H, $J = 10.0$, 3.4, 1.2 Hz), 7.20−7.36 (m, 10 H). ^{13}C NMR (75 MHz): δ 41.1, 66.5, 68.7, 70.6, 70.9, 71.4, 72.8, 81.9, 120.2, 127.3, 127.5, 127.6, 128.3, 136.2, 137.8, 138.0. IR ($CHCl_3$): 1110 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.77; H, 6.75.

(1*S,2*R**,3*S**,4*R**,5*R**,6*R**)-3-(Benzyloxy)-5-((benzyloxy)-methyl)-7-oxabicyclo[4.1.0]heptane-2,4-diol 2,4-*O*-(Methylene acetal), 17.** According to the procedure described for the synthesis of **13**, from 56 mg (0.16 mmol) of **16**, 35 mg of **17** was obtained as a colorless oil (60%). Data for **17**: $R_f =$ 0.26 (hexane:EtOAc, 2:1). ^{1}H NMR (300 MHz): δ 2.73 (td, 1 H, $J = 7.6$, 4.5 Hz), 3.32 (t, 1 H, $J = 3.4$ Hz), 3.56 (t, 1 H, $J =$ 4.0 Hz), 3.60 (dd, 1 H, $J = 9.1$, 7.9 Hz), 3.83 (dd, 1 H, $J = 9.1$, 7.6 Hz), 3.90 (t, 1 H, $J = 3.5$ Hz), 3.99 (d, 1 H, $J = 3.9$ Hz), 4.42−4.52 (m, 4 H), 4.57 (d, 1 H, $J = 11.9$ Hz), 4.65 (d, 1 H, J = 6.4 Hz), 5.31 (d, 1 H, $J = 6.5$ Hz), 7.24−7.36 (m, 10 H). NOE between H-1 and H-acetal-ax, 14%; H-5 and H-acetal-ax, 21%; H-6 and H-acetal-ax, 12%; H-acetal-eq and H-acetal-ax, 52%. ^{13}C NMR (75 MHz): δ 39.3, 48.9, 51.7, 66.8, 68.1, 69.4, 71.5, 73.3, 73.6, 83.7, 127.5, 127.6, 127.7, 127.7, 128.4, 128.4, 137.9, 138.3. IR ($CHCl_3$): 1110 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.55; H, 6.38.

(3*S,4*R**,5*R**,6*R**)-3,5-Diacetoxy-4-((*p*-methoxybenzyl)-oxy)-6-(((*p*-methoxybenzyl)oxy)methyl)cyclohexene, 18a.** To a solution of 59 mg (0.15 mmol) of **7b** in 1.5 mL of CH_2Cl_2 were added 0.06 mL (0.59 mmol) of Ac_2O, 0.05 mL (0.59 mmol) of pyridine, and a catalytic amount of DMAP. After the mixture was stirred for 1 h at room temperature, the crude mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 2:1) to give 69 mg of **18a** as a white solid (97% yield). Data for **18a**: $R_f = 0.21$ (hexane:EtOAc, 2:1). Mp: 78−79 °C. ^{1}H NMR (300 MHz): δ 1.97 (s, 3 H), 2.00 (s, 3 H), 2.58−2.70 (m, 1 H), 3.31 (dd, 1 H, $J = 9.1$, 6.5 Hz), 3.46 (dd, 1 H, $J = 9.1$, 4.9 Hz), 3.77 (dd, 1 H, $J = 9.7$, 7.7 Hz), 3.79 (s, 6 H), 4.40 (s, 2 H), 4.59 (s, 2 H), 5.19 (t, 1 H, $J = 9.6$ Hz), 5.49 (br d, 1 H, $J = 7.6$ Hz), 5.56 (br d, 1 H, $J = 10.2$ Hz), 5.72 (br d, 1 H, $J = 10.1$ Hz), 6.85 (d, 2 H, $J = 8.6$ Hz), 6.86 (d, 2 H, $J = 8.7$ Hz), 7.19 (d, 2 H, $J = 8.6$ Hz), 7.24 (d, 2 H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz): δ 21.0, 21.1, 42.6, 55.2, 70.0, 71.3, 73.0, 73.8, 74.2, 79.4, 113.7, 125.5, 129.0, 129.1, 129.4, 130.0, 130.4, 159.1, 159.1, 170.2, 170.2. IR ($CHCl_3$): 1740, 1710, 1520 cm^{-1}. Anal. Calcd for $C_{27}H_{32}O_8$: C, 66.93; H, 6.66. Found: C, 66.77; H, 6.50.

(3*S,4*R**,5*R**,6*R**)-3,5-Bis(*tert*-butyldimethylsilyl)oxy)-4-((*p*-methoxybenzyl)oxy)-6-(((*p*-methoxybenzyl)oxy)-methyl)cyclohexene, 18b.** To a cold (−78 °C) solution of 168 mg (0.42 mmol) of **7b** in 4 mL of THF were added 0.23 mL (1.68 mmol) of Et_3N and 0.39 mL (1.68 mmol) of TBSOTf. After the mixture was stirred for 1 h at −78 °C, a saturated aqeuous solution of K_2CO_3 was added. The crude mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:EtOAc, 10:1) to give 264 mg of **18b** as a colorless oil (100% yield). Data of **18b**: $R_f = 0.41$ (hexane: EtOAc, 5:1). ^{1}H NMR (300 MHz): δ −0.09 (s, 3 H), 0.01 (s, 3 H), 0.03 (s, 3 H), 0.10 (s, 3 H), 0.85 (s, 9 H), 0.87 (s, 9 H), 2.42−2.51 (m, 1 H), 3.40−3.48 (m, 2 H), 3.56 (dd, 1 H, $J = 8.7$, 3.4 Hz), 3.73 (t, 1 H, $J = 9.4$ Hz), 3.81 (s, 6 H), 4.36 (d, 1 H, $J =$ 11.8 Hz), 4.36−4.42 (m, 1 H), 4.53 (d, 1 H, $J = 12.1$ Hz), 4.74 (d, 1 H, $J = 11.4$ Hz), 4.89 (d, 1 H, $J = 11.4$ Hz), 5.53 (br d, 1 H, $J = 10.4$ Hz), 5.60 (br d, 1 H, $J = 10.4$ Hz), 6.85 (d, 2 H, J = 8.7 Hz), 6.89 (d, 2 H, $J = 8.4$ Hz), 7.26 (d, 2 H, $J = 8.7$ Hz), 7.27 (d, 2 H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz): δ −5.0, −4.5, −4.3, −3.5, 18.0, 18.2, 25.9, 26.0, 46.1, 55.1, 55.2, 69.2, 71.1, 72.6, 74.3, 86.0, 113.1, 113.7, 127.9, 128.0, 129.2, 129.9, 130.4, 131.6, 158.3, 159.1. IR ($CHCl_3$): 1520, 1250 cm^{-1}. Anal. Calcd for $C_{35}H_{56}O_6Si_2$: C, 66.83; H, 8.97. Found: C, 66.65; H, 8.82.

(1*R,2*S**,5*R**,6*R**)-2,6-Diacetoxy-5-(hydroxymethyl)cyclohex-3-en-1-ol, 15a.** To a solution of 56 mg (0.12 mmol) of **18a** in 2.3 mL of CH_2Cl_2 was added 79 mg (0.35 mmol) of DDQ. After the mixture was stirred for 6 h at room temperature, brine was added. The crude mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane: EtOAc, 1:1) to give 15 mg of **15a** as a colorless oil (60% yield). Data for **15a**: $R_f = 0.13$ (hexane:EtOAc, 1:2). ^{1}H NMR (300 MHz): δ 2.14 (s, 3 H), 2.18 (s, 3 H), 2.44−2.51 (m, 1 H), 3.00−3.20 (m, 2 H), 3.59 (dd, 1 H, $J = 11.8$, 4.2 Hz), 3.68 (dd, 1 H, $J = 11.8$, 3.0 Hz), 3.96 (dd, 1 H, $J = 10.2$, 7.7 Hz), 5.06 (dd, 1 H, $J = 10.1$, 9.8 Hz), 5.42 (br d, 1 H, $J = 7.7$ Hz), 5.65 (br d, 1 H, $J = 9.9$ Hz), 5.75 (br d, 1 H, $J = 10.2$ Hz). ^{13}C NMR (75 MHz): δ 21.0, 21.1, 44.1, 61.7, 72.0, 73.1, 75.6, 126.4, 130.2, 171.6, 172.2. IR ($CHCl_3$): 3600−3300, 1740 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.95; H, 6.48.

(1*R,2*S**,5*R**,6*R**)-2,6-Bis((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)cyclohex-3-en-1-ol, 15b.** According to the procedure described for the synthesis of **15a**, from 150 mg (0.24 mmol) of **18b** in 4.5 mL of CH_2Cl_2 and 0.25 mL of H_2O, 70 mg of **15b** was obtained as a colorless oil (75% yield). Data for **15b**: $R_f = 0.22$ (hexane:EtOAc, 5:1). ^{1}H NMR (300 MHz): δ 0.10 (s, 3 H), 0.10 (s, 3 H), 0.12 (s, 3 H), 0.14 (s, 3 H), 0.89 (s, 18 H), 1.56 (s, 1 H), 2.19 (s, 1 H), 2.38−2.48 (m, 1 H), 3.52 (t, 1 H, $J = 8.9$ Hz), 3.68 (t, 1 H, $J = 9.4$ Hz), 3.72−3.78 (m, 2 H), 4.15 (br d, 1 H, $J = 8.7$ Hz), 5.49 (br d, 1 H, $J = 10.4$ Hz), 5.58 (br d, 1 H, $J = 10.1$ Hz). ^{13}C NMR (75 MHz): δ −4.8, −4.5, −4.4, −3.6, 18.2, 18.3, 25.9, 26.0, 47.2, 62.3, 71.5, 73.6, 77.9, 127.0, 131.6. IR ($CHCl_3$): 3600−3300 cm^{-1}. Anal. Calcd for $C_{19}H_{40}O_4Si_2$: C, 58.71; H, 10.37. Found: C, 58.55; H, 10.29.

(1*S,2*R**,3*S**,4*R**,5*R**,6*R**)-2,4-Bis((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-7-oxabicyclo[4.1.0]heptan-3-ol, 19.** According to the procedure described for the synthesis of **13**, from 45 mg (0.11 mmol) of **15b**, 38 mg of **19** was obtained as a white solid (81% yield). Data for **19**: $R_f = 0.36$ (hexane:EtOAc, 2:1). Mp: 79−80 °C. ^{1}H NMR (300 MHz): δ 0.09 (s, 6 H), 0.14 (s, 3 H), 0.15 (s, 3 H), 0.88 (s, 9 H), 0.91 (s, 9 H), 1.96−2.04 (m, 1 H), 3.02 (d, 1 H, $J = 4.0$ Hz), 3.30 (dd, 1 H, $J = 9.4$, 8.4 Hz), 3.37 (br d, 1 H, $J = 3.7$ Hz), 3.43 (t, 1 H, $J = 9.4$ Hz), 3.75 (d, 1 H, $J = 8.1$ Hz), 3.84 (dd, 1 H, $J = 10.7$, 6.4 Hz), 3.99 (dd, 1 H, $J = 10.7$, 3.4 Hz). ^{13}C NMR (75 MHz): δ −4.7, −4.7, −4.5, −3.7, 18.2, 18.3, 25.8, 26.0, 44.9, 55.8, 56.0, 62.1, 68.4, 72.6, 77.8. IR ($CHCl_3$): 3600−3300 cm^{-1}. Anal. Calcd for $C_{19}H_{40}O_5Si_2$: C, 56.39; H, 9.96. Found: C, 56.08; H, 9.40.

Tetra-*O*-acetyl-(±)-cyclophellitol, 20. To a solution of 14 mg (0.03 mmol) of **19** in 0.2 mL of THF was added 0.1 mL (0.10 mmol) of TBAF (1 M solution in THF). After the mixture was stirred for 30 min at room temperature, a few drops of H_2O were added and the crude mixture was concentrated under reduced pressure. The residue was acetylated with 1 mL of Ac_2O, 1 mL of pyridine, and a catalytic amount of DMAP. After 12 h the crude mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane:Et_2O, 1:2) to give 9 mg of **20** (75% yield). Its spectral features were identical to those reported in the literature.[8a]

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Supporting Information Available: Available characterization data and experimental procedures for the synthesis of **12b** and their synthetic precursors (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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