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Synthesis of Cyclophellitol Utilizing a Palladium Chloride Mediated-Ferrier-II Rearrangement

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Dedicated to Professor K. K. Balasubramanian on the occasion of his sixty fifth birthday.

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Abstract: Cyclophellitol and its C3-epimer have been synthesized from 5-enoglucopyranoside and 5-enomannopyranoside, respectively. The carbocyclic skeleton was constructed through a Ferrier-II reaction meditated by $PdCl_2$.

Keywords: Glycosidase inhibitor, Ferrier-II reaction, palladium chloride.

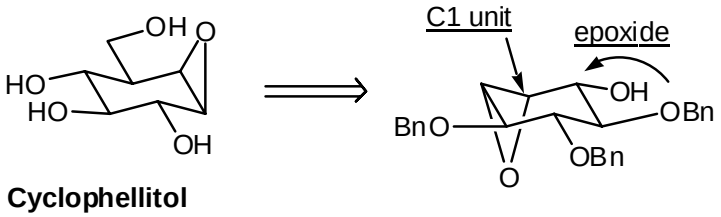
Introduction

Since Ferrier developed a cyclization of saccharides using mercurate [Ferrier-II reaction] in 1979 [1], the ring conversion of 6-membered rings using saccharides has been intensively studied [2, 3]. Because naturally occurring and biologically active compounds often contain a ring structure with multi-functional groups, stereochemical control of chiral centers on these rings becomes crucial in the total synthesis of these compounds. The Ferrier-II reaction is remarkably useful for the total synthesis of compounds with a complicated conformation such as cyclitols. Cyclophellitol is a β-D-glucosidase inhibitor first isolated by Umezawa in 1990 [4]. It is known to have high activity, and its application has been expected to range from an anti-virus and anti-HIV agent to an inhibitor of cancer metastasis. The structure of cyclophellitol, an epoxy ring in the β-position on a multi-substituted cyclitol in the glucose-conformation, resembles that of β-D-glucoside. We investigated synthetic methods of not only cyclophellitol but also its epimers, ultimately aiming at the study of structure activity relationship [5].

Results and Discussion

Figure 1 shows the strategy for the synthesis of cyclophellitol. Commercially available D-glucoside is converted into a cyclohexane ring through Ferrier-II reaction, and then an epoxy ring is formed stereoselectively.

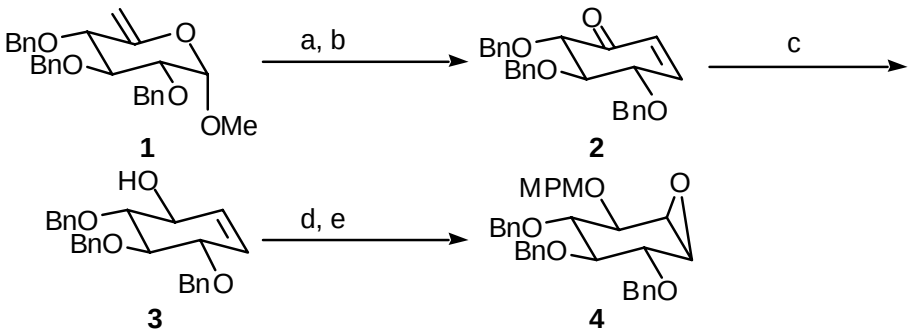
Figure 1



Cyclophellitol
β-D-glucosidase inhibitor
IC_{50} < 0.8 μg / mL

For the introduction of a hydroxymethyl group as a C1 unit, regio- and stereoselective nucleophilic addition to the epoxy ring is examined. Finally, an elimination reaction forms a β-epoxy ring to complete the total synthesis of cyclophellitol.

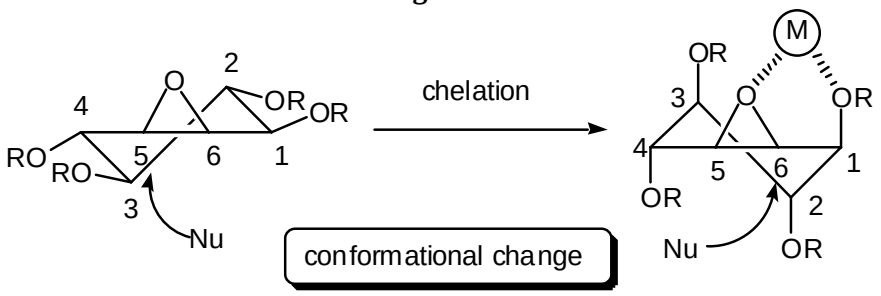
Figure 2



Reagents and Conditions: a)$PdCl_2$, dioxane - H_2O, 60 °C, 3 h, 81%; b) MsCl, Et_3N, CH_2Cl_2, r.t., 9 h, 74%; c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 15 min, 87%; d) *m*CPBA, Na_2HPO_4, CH_2Cl_2, r.t., 4 days, quant.; e) NaH, MPMCl, DMF - THF, r.t., 2 h, 93%.

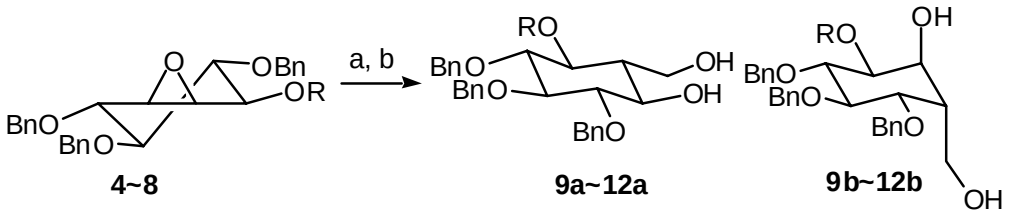
In the beginning, 5-enoglucopyranoside **1** [6] was used in Ferrier-II reaction mediated by a catalytic amount of palladium chloride. We have recently reported on the Ferrier-II reaction using palladium chloride instead of mercury salt [7]. This reaction is more advantageous than the conventional methods because it proceeds under very mild conditions, which especially suit the reaction of multi-substituted carbohydrates [8]. In this case, the ring conversion was completed by using 0.05 equivalent of palladium chloride and the obtained cyclohexanone was converted to an enone **2** [6] *via* an elimination reaction. The enone **2** was reduced under Luche's conditions [9] to provide a β-alcohol **3** [10]. Then β-form epoxide was formed stereoselectively on the cyclohexane ring, and the hydroxyl group was protected by an MPM group to provide an intermediate, the epoxide **4** (Figure 2).

Figure 3



The key reaction in this total synthetic pathway is the regioselective and nucleophilic attack of hydroxymethyl group to the epoxide **4**. Generally, a nucleophile predominantly attacks at the axial position of epoxide in the ring opening reaction of cyclohexane. Therefore, we expected that the nucleophilic substitution to this epoxide would occur at the axial position C5, and would not show the desired regioselectivity (Figure 3) We then thought that if the conformation of the epoxide could be changed, we would be able to introduce a hydroxymehyl group from the desired C6 position. As shown in Figure 3, chelation between metals and oxygen atoms of the epoxide and an ether oxygen may drastically change the conformation of the cyclohexane ring, resulting in the axial nucleophilic attack at the C6 position. For induce such chelation, we used a boron reagent Mes_2BCH_2Li [11] and studied the regio-selectivity of ring opening of the epoxide using substrates that are protected at the C1, a coordinative position of chelation, with variation of the protecting groups (Table 1).

Table 1



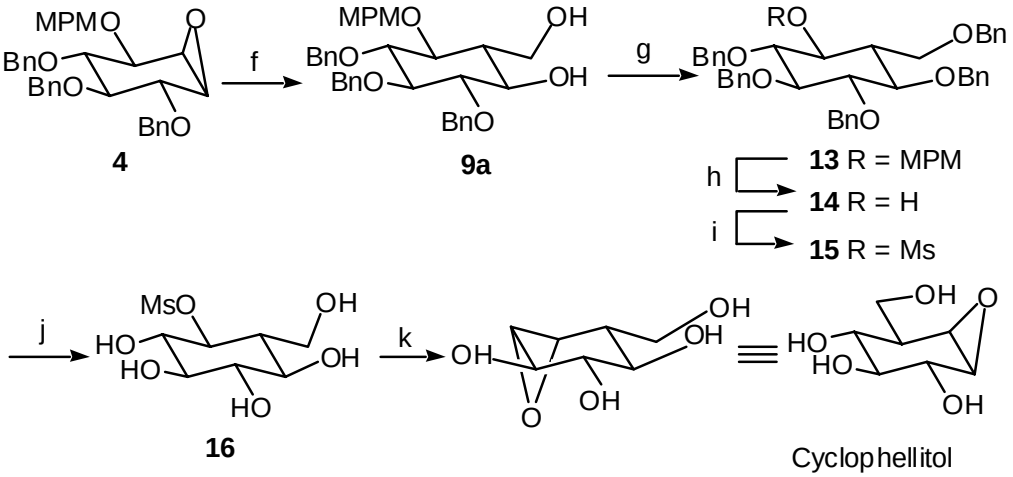
Entry	R	Epoxide	Yield (%)	Regioselectivity
1	MPM [c]	**4**	78	**9a** : **9b** > **99 : 1**
2	Bn	**5** [12]	60	**10a** : **10b** > **99 : 1**
3	BOM	**6**	65	**11a** : **11b** = **94 : 6**
4	TBDMS [c]	**7**	83	**12a** : **12b** < **1 : 99**
5	Ac	**8**	0	–

Reagents and Conditions: a) Mes_2BCH_2Li (10.0 eq), THF, rt, 6h; b) NaOH, H_2O_2, THF-MeOH, rt; c) oxidation conditions: mCPBA (9.0 eq), Na_2HPO_4 (10.0 eq), rt, 30h.

Unfortunately, because acyl protective groups react with the boron reagent, we did not obtain the hydroxymethylated products (entry 5). Hydroxymethyl addition, however, occurred smoothly in the substrate with an ether protective group. Interestingly, the substrate protected with MPM, benzyl, and BOM groups produced the hydroxymethyl products **9a**~**11a** in which the nucleophile attacked at the

opposite C6 position due to the chelation, but protection by a TBDMS groups resulted in only **12b** in which nucloephile attacked at the originally axial C5 position. Thus, a significant difference in the selectivity was observed depending on the nature of the protecting group. Presumably, this change in selectivity originated from differences in the coordinative power by the oxygen of the protected OH group. As shown in Figure 3, chelation of the metal to the oxygens of both the oxirane and C1 alkoxy group might change the conformation of the substrates to cause unusual regioselectivity. On the other hand, the oxygen of the siloxy group might not coordinate to the metal because of bulkiness of the silyl group. In this case, the usual selectivity was observed. Based on these results, we selected the MPM group as the most appropriate protective group, and carried out the synthesis illustrated in Figure 4.

Figure 4



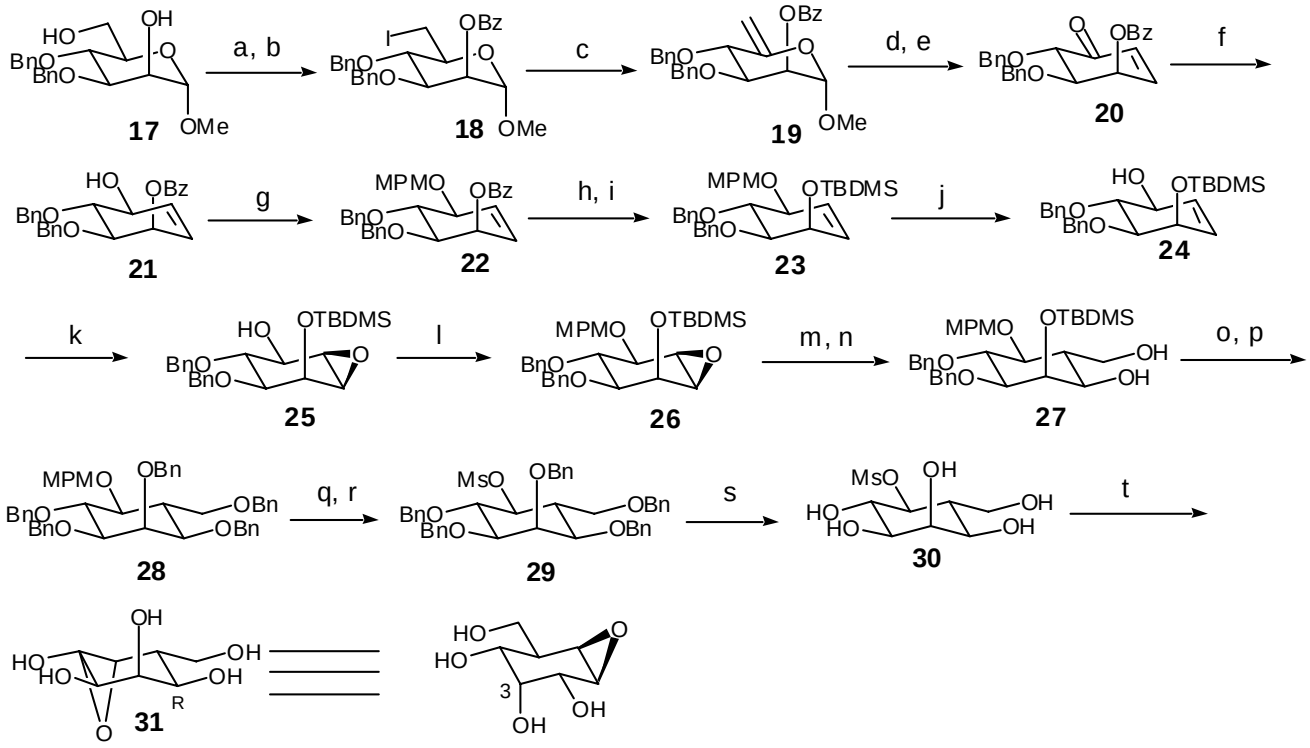
Reagents and Conditions: f) Mes_2BCH_2Li, THF, r.t., 6 h; NaOH, H_2O_2, THF – MeOH, r.t., 1 day, 78%; g) NaH BnBr, DMF-THF, r.t., 4 days, 93%; h) DDQ, CH_2Cl_2 – H_2O, 0ºC, 1.5 h, 96%; 1) MsCl, Et_3N, CH_2Cl_2, r.t., 12 h, 91%; j) $Pd(OH)_2$/C, MeOH, r.t., 1 day, 77%; k) 1.0M NaOH, 1 h, 82%.

Two hydroxy groups of the diol **9a** obtained through the hydroxymethylation process were protected by benzyl groups and the MPM group was converted to a mesyl group. Then, all the benzyl groups were simultaneously deprotected by catalytic hydrogenation to obtain the pentaol **16**. The pentaol readily underwent epoxide cyclization under alkaline conditions, and cyclophellitol was thus synthesized from **1** in 14% total yield.

In this synthetic method, the initial D-glycosides readily give rise to various epimers depending on the conformation of glycosides and types of protective groups. The same method could be successfully applied to the synthesis of the epimer of cyclophellitol with a different configuration at C3 (Figure 5).

The Ferrier-II reaction of the 5-enomannoside **19** promoted by a catalytic amount of $PdCl_2$ provided the corresponding cyclohexanone, which was subjected to a dehydration with MsCl-pyridine to give enone **20**. Stereoselective reduction under Luche's conditions afforded the β-alcohol **21**. After protection of the hydroxy group, debenzoylation and subsequent protection with TBDMSOTf-lutidine afforded **23**.

Figure 5



Reagents and Conditions: a) PPH_3, imidazole, I_2, toluene, 80ºC, 30 min., 80%; b) BzCl, Et_3N, DMAP, r.t., 21 h., 99%; c) AgF, Py, r.t., 20 h., 99%; d) $PdCl_2$, dioxane – H_2O, 60ºC, 3 h., 86%; e) MsCl, Et_3N, CH_2Cl_2, 0ºC, 5 min., 95%; f) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0ºC, 30 min., 97% (α:β = 1:5); g) $CCl_3C(=NH)OMPM$, TfOH. Et_2O, r.t., 10 min., 95%; h) 2N NaOH, MeOH, r.t., 12 h., 82%; i) TBDMSOTf, lutidine, CH_2Cl_2, r.t., 10 min., 95%; j) DDQ, CH_2Cl_2 - H_2O, 0ºC, 3 h., 95%; k) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, r.t., 14 h., 86%; l) MPMCl, NaH, DMF – THF, 0ºC, 2.5 h., 66%; m) Mes_2BCH_2Li, THF, r.t., 1 h.; n) 5N NaOH, H_2O_2, r.t., 30 min., 76% (2 steps); o) TBAF, THF, r.t., 2 days; p) NaH, BnCl, DMF – THF, 60ºC, 4 h., 89% (2 steps); q) DDQ, CH_2Cl_2 – H_2O, r.t., 3 h., quant.; r) MsCl, Et_3N, $ClCH_2CH_2Cl$, 60ºC, 5 h., 61%; s) H_2, $Pd(OH)_2$/C, MeOH, r.t., 20 h., 73%; t) 1.0M NaOH, r.t., 20 h., quant.

Deprotection of the MPM ether of **23** provided the β-alcohol **24**, which was oxidized with *m*-CPBA to yield the epoxide **25** efficiently in a highly diastereoselective manner. The remaining hydroxy group was protected as an MPM ether to give **26**. The subsequent introduction of a hydroxymethyl group by nucleophilic opening of the epoxide afforded the diol **27** in good yield. Deprotection of **27** and successive benzylation afforded **28**, which was deprotected with DDQ and then mesylation provided the mesylate **29**. The fully-benzylated mesylate **29** was subjected to hydrogenolysis using 1 atm of H_2 and $Pd(OH)_2$ in MeOH to generate the deprotected mesylate **30**. Finally, treatment of **30** with aqueous NaOH afforded the cyclophellitol C3- epimer.

Conclusions

We have presented a facile synthesis of cyclophellitol and its C3-epimer utilizing Ferrier-II reaction mediated by $PdCl_2$. This method enables not only the synthesis of various diastereomers of cyclophellitol but also application of the new strategy for the regioselective hydroxymethylation reaction of highly oxygenated cyclohexanes.

Acknowledgements

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Experimental

General

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a JASCO FT/IR-8000 spectrometer. HRFAB-MS were recorded with a JEOL SX-102A. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 600 MHz with a JEOL GSX-600 spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in ppm downfield from TMS. Optical rotations were measured with a JASCO DIP-370 in a 1-dm cell. Analytical and preparative TLC was conducted on precoated TLC plates (silica gel 60 F_{254}, Merck). Column chromatography was performed using Merck silica gel 60 N (100–210 μm). All anhydrous solvents were purified according to standard methods.

Spectral Data

(1S,2R,3S,4S,5R,6R)-2,3,4-Tris(benzyloxy)-5-[(4-methoxybenzyl)oxy]-7-oxabicyclo[4.1.0]heptane (**4**): ^{1}H-NMR ($CDCl_3$) δ: 7.50-7.24 (m, 17H), 6.90-6.85 (m, 2H), 4.90-4.60 (m, 8H), 3.88 (m, 2H), 3.79 (s, 3H), 3.60 (dd, 1H, J=10.4, 8.5), 3.46 (dd, 1H, J=10.4, 7.9), 3.27 (m, 1H), 3.18 (d, 1H, J=3.7); ^{13}C-NMR ($CDCl_3$) δ: 159.3, 138.6, 137.6, 130.32, 129.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 113.83, 79.0, 76.7, 75.9, 75.5, 73.3, 72.7, 55.2, 53.9; HRMS (EI) for $C_{35}H_{36}O_6$ (M^+): Calcd 552.2512; Found 552.2512.; Mp.110°C

(*1S,2R,3R,4S,5R,6S)-2,3,4-Tris(benzyloxy)-5-[(benzyloxy)methoxy]-7-oxabicyclo[4.1.0]heptane* (**6**): ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.27 (m, 20H), 5.00 (d, 1H, J=7.0), 4.94 (d, 1H, J=7.0), 4.89-4.59 (m, 6H), 4.07 (1H, dd, J=10.4, 1.8), 3.89 (d, 1H, J=7.9), 3.56 (dd, 1H, J=10.4, 8.5), 3.49 (dd, 1H, J=10.4, 7.9), 3.43 (m, 1H), 3.22 (d, 1H, J=3.7); HRMS (CI) for $C_{35}H_{36}O_2$ (M^+): Calcd 552.2512; Found 552.2514.

tert-Butyl(dimethyl)[[(1S,2R,3S,4R,5R,6S)-3,4,5-tris(benzyloxy)-7-oxabicyclo[4.1.0]hept-2-yl]oxy]-silane (**7**): ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.19 (m, 15H), 4.85-4.64 (m, 6H), 4.09 (m, 1H), 3.90 (m, 1H), 3.46

(m, 2H), 3.25 (m, 1H), 3.18 (d, 1H, J = 4.0), 0.93 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 138.8, 138.6, 137.7, 128.5, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 83.4, 79.7, 79.4, 75.7, 75.5, 73.3, 57.6, 54.0, 25.8, 18.1, -4.5, -4.6; HRMS (EI) for $C_{33}H_{42}O_5Si$ (MH^+): Calcd 546.2802; Found 546.2802.

(1S,2R,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-7-oxabicyclo[4.1.0]hept-2-yl acetate (**8**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.21 (m, 15H), 5.28 (d, 1H, J=8.2), 4.78-4.70 (m, 5H), 4.60 (d, 1H, J=11.6), 3.90 (d, 1H, J=7.3), 3.66-3.56 (m, 2H), 3.40 (m, 1H), 3.23 (d, 1H, J=3.7), 2.02 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 170.5, 138.3, 137.4, 128.5, 128.3, 128.0, 127.8, 127.6, 83.2, 78.9, 75.6, 75.5, 73.6, 73.2, 54.6, 54.0, 20.9l; HRMS (EI) for $C_{29}H_{30}O_6$ (M^+): Calcd 474.2043; Found 474.2044.

(1R,2S,3R,4R,5S,6R)-2,3,4-Tris(benzyloxy)-6-(hydroxymethyl)-5-[(4-methoxybenzyl)oxy]cyclohexanol (**9a**): ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.26 (m, 15H), 7.21 (m, 2H), 6.85 (m, 2H), 4.98 (d, 1H, J=11.6), 4.93-4.81 (m, 5H), 4.68 (d, 1H, J=11.3), 4.56 (d, 1H, J=10.7), 3.89 (dd, 1H, J=10.7, 3.1), 3.77 (s, 3H), 3.74 (dd, 1H, J=10.7, 4.7), 3.63 (dd, 1H, J=9.2, 9.2), 3.49 (m, 2H), 3.39 (m, 2H), 1.65 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ:152.6, 138.7, 138.6, 138.5, 130.4, 130.1, 129.9, 128.9, 128.7, 128.2, 128.1, 128.0, 127.9, 127.8, 114.2, 80.9, 79.3, 77.6, 77.5, 76.0, 75.9, 75.7, 75.2, 61.0, 47.5, 40.9; HRMS (EI) for $C_{36}H_{40}O_7$ (M^+): Calcd 584.2774; Found 584.2771; Mp. 131°C

(1R,2S,3R,4R,5S,6R)-2,3,4,5-Tetrakis(benzyloxy)-6-(hydroxymethyl)cyclohexanol (**10a**): ^{1}H-NMR ($CDCl_3$) δ: 7.36-7.26 (m, 20H), 5.01-4.84 (m, 6H), 4.70-4.62 (m, 2H), 3.91 (m, 1H), 3.75 (m, 1H), 3.66 (dd, 1H, J=9.5, 9.5), 3.51 (m, 2H), 3.40 (m, 2H), 1.68 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 138.4, 138.3, 138.1, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 86.3, 85.1, 83.2, 77.5, 77.2, 75.7, 75.5, 75.3, 70.6, 60.5, 46.1; MS (EI) for $C_{35}H_{38}O_6$ (M^+) : Calcd 554.2668; Found 554.2654

(1R,2R,3R,4R,5S,6R)-2,3,4-Tris(benzyloxy)-5-[(benzyloxy)methoxy]-6-(hydroxymethyl)cyclohexanol (**11a**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.22 (m, 20H), 5.20-4.70 (m, 9H), 4.53 (d, 1H, J=11.9), 3.94 (m, 1H), 3.85 (m, 1H), 3.60-3.36 (m, 5H), 1.57 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 138.5, 138.3, 137.0, 128.6, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 97.1, 85.8, 85.5, 83.1, 76.5, 75.7, 75.6, 75.4, 70.7, 69.1, 58.0, 46.0; HRMS (EI) for $C_{29}H_{33}O_7$: Calcd 493.2226; Found 493.2226.

(1S,2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-2-[(benzyloxy)methoxy]-6-(hydroxymethyl)cyclohexanol (**11b**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.22 (m, 20H), 5.05-4.55 (m, 10H), 4.18 (m, 1H), 4.00-3.50 (m, 6H), 2.58 (m, 1H); HRMS (EI) for $C_{29}H_{33}O_7$: Calcd 493.2226; Found 493.2226.

(1S,2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-2-{[tert-butyl(dimethyl)silyl]oxy}-6-(hydroxymethyl)cyclohexanol (**12b**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.21 (m, 15H), 4.86-4.64 (m, 6H), 4.11 (dd, 1H, J=8.8, 5.9), 3.87 (m, 2H), 3.80 (dd, 1H, J=8.8, 8.8), 3.75 (dd, 1H, J=8.8, 2.9), 3.69 (dd, 1H, J=8.8, 8.8), 3.60 (dd, 1H, J=11.0, 4.8), 2.59 (dddd, 1H, J=8.1, 4.8, 5.9, 2.9), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 138.8, 138.7, 138.0, 131.4, 128.5, 128.3, 128.2, 127.9, 127.8, 127.5, 127.4, 125.8, 82.4, 82.3, 80.1, 76.7, 75.6, 73.9, 73.8, 72.9, 61.4, 43.0, 25.8, 15.6, -4.5, -4.8; HRMS (EI) for $C_{34}H_{46}O_6Si$: Calcd 578.3064; Found 578.3063.

(1S,2R,3S,4S,5R,6S)-2,3,4,5-Tetrakis(benzyloxy)-6-[(benzyloxy)methyl]cyclohexanol (**14**): ^{1}H-NMR ($CDCl_3$+D_2O) δ: 7.33-7.26 (m, 25H), 5.00-4.44 (m, 10H), 3.82 (dd, 1H, J=8.8, 2.2), 3.70 (m, 2H), 3.62 (m, 2H), 3.53 (m, 1H), 3.40 (dd, 1H, J=9.2, 9.2), 1.69 (m, 1H); HRMS (EI) for $C_{42}H_{44}O_6$ (M^+): Calcd 644.3138; Found 644.3130.

(1S,2S,3R,4S,5R,6R)-2,3,4,5-Tetrakis(benzyloxy)-6-[(benzyloxy)methyl]cyclohexylmethanesulfonate (**15**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.10 (m, 25H), 5.10-4.35 (m, 11H), 3.87 (m, 1H), 3.75 (m, 1H), 3.67 (m, 1H), 3.65-3.56 (m, 3H), 2.80 (s, 3H), 1.85 (m, 1H); HRMS (EI) for $C_{36}H_{39}O_8S$ (M^+): Calcd 631.2366; Found 631.2365.

(1S,2S,3R,4S,5R,6R)-2,3,4,5-Tetrahydroxy-6-(hydroxymethyl)cyclohexylmethanesulfonate (**16**): ^{1}H-NMR (D_2O) δ: 4.70 (dd, 1H, J=9.9, 9.9), 3.98 (d, 1H, J=12.0), 3.79 (d, 1H, J=12.0), 3.67 (dd, 1H, J=9.2, 9.2), 1H), 3.34 (m, 4H), 1.82 (dd, 1H, J=11.0, 11.0); HRMS (CI) for $C_{13}H_{24}NO_6$ (MH^+): Calcd 290.160363; Found 290.160300.

Cyclophellitol: ^{1}H-NMR (D_2O) δ: 4.01 (dd, 1H, J=11.0, 4.0), .83 (dd, 1H, J=11.0, 7.3), 3.79 (d, 1H, J=8.4), 3.56 (dd, 1H, J=4.0, 1.8), 1H), 3.38 (dd, 1H, J=10.3, 8.4), 3.27 (m, 2H), 2.13 (m, 1H); ^{13}C-NMR (D_2O) δ: 77.0, 71.6, 67.5, 61.2, 57.0, 56.7l; MS (EI) for $C_7H_{12}O_5$ (M^+): 176, (M^+-H_2O): 158.

Methyl 2-O-benzoyl-3,4-di-O-benzyl-6-deoxy-6-iodo-α-D-mannopyranoside (**18**): ^{1}H-NMR ($CDCl_3$) δ: 8.18-8.14 (m, 2H), 7.70-7.23 (m, 13H), 5.62 (m, 1H), 4.96 (d, 1H, J=10.7), 4.83 (d, 1H, J=1.8), 4.77 (d, 1H, J=11.3), 4.69 (d, 1H, J=10.7), 4.55 (d, 1H, J=11.3), 4.11 (dd, 1H, J=9.5, 1.3), 3.82 (dd, 1H, J=9.5, 9.5), 3.59-3.46 (m, 3H), 3.42 (s, 3H); IR (thin film) cm^{-1}: 2954 (broad), 1736, 1611, 1524, 1439, 1323, 1204; HRMS (EI) for $C_{28}H_{29}O_6I$ (M^+): Calcd 588.1009; Found 588.1022.

Methyl 2-O-benzoyl-3,4-di-O-benzyl-6-deoxy -α-D-lyxo-hex-5-enopyranoside (**19**): ^{1}H-NMR ($CDCl_3$) δ: 8.08-8.04 (m, 2H), 7.61-7.22 (m, 13H), 5.62 (dd, 1H, J=5.5, 3.0), 4.94 (brs, 1H), 4.88 (brs, 1H), 4.84-4.61 (m, 5H, J=11.3), 4.36 (d, 1H, J=9.5), 4.05 (dd, 1H, J=9.5, 3.0); ^{13}C-NMR ($CDCl_3$) δ: 170.4, 166.0, 130.2, 130.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 106.3, 84.8, 81.2, 77.4, 77.2, 72.4, 60.4; HRMS (EI) for $C_{28}H_{28}O_6$ (M^+) : Calcd 460.1886; Found 460.1876.

(1R,5S,6R)-5,6-Bis(benzyloxy)-4-oxocyclohex-2-en-yl benzoate (**20**): ^{1}H-NMR ($CDCl_3$) δ: 8.02-8.00 (m, 2H), 7.65-7.21 (m, 13H), 6.90 (dd, 1H, J=10.4, 4.0), 6.17 (d, 1H, J=10.4),6.07 (dd, 1H, J=3.7, 3.7), 4.88 (d, 1H, J=11.9), 4.70 (m, 3H), 4.24 (d, 1H, J=7.6), 4.19 (dd, 1H, J=7.6, 3.4); ^{13}C-NMR ($CDCl_3$) δ: 165.7, 143.6, 138.6, 136.8, 133.2, 128.3, 127.7, 126.5, 125.6, 86.6, 77.0, 76.9, 71.4, 69.5; HRMS (EI) for $C_{27}H_{24}O_5$ (M^+): Calcd 428.1624; Found 428.1639.

(1R,4S,5R,6R)-5,6-Bis(benzyloxy)-4-hydroxycyclohex-2-en-1-yl benzoate (**21**): ^{1}H-NMR (CD_3OD) δ: 7.95 (m, 2H), 7.56-7.11 (m, 13H), 5.89-5.80 (m, 3H), 4.78-4.50 (m, 4H), 4.15 (d, 1H, J=7.3), 3.84 (dd, 1H, J=10.3, 7.3), 3.69 (dd, 1H, J=10.3, 3.7); HRMS (CI) for $C_{13}H_{24}NO_6$ (MH^+): Calcd 290.160363; Found 290.160300.

(1R,4S,5R,6R)-5,6-Bis(benzyloxy)-4-[(4-methoxybenzyl)oxy]cyclohex-2-en-1-yl benzoate (**22**): ^{1}H-NMR ($CDCl_3$) δ: 7.95 (m, 2H), 7.40-7.10 (m, 12H), 6.85 (m, 2H), 5.86 (m, 1H), 5.80 (m, 2H), 4.90 (1H, d, J=11.0), 4.76 (1H, d, J=11.0), 4.70 (1H, d, J=11.6), 4.63 (1H, d, J=11.0), 4.56 (2H,m), 4.39 (3H, s), 4.05 (1H,m), 3.70 (2H,m); ^{13}C-NMR ($CDCl_3$) δ: 166.0, 159.2, 138.8, 138.4, 131.4, 130.1, 129.8, 129.7, 129.5, 128.5, 128.3, 127.7, 114.1, 114.0, 79.2, 78.7, 75.4, 68.7, 67.2, 64.6, 62.9, 55.5; HRMS (CI) for $C_{13}H_{24}NO_6$ (MH^+): Calcd 290.160363; Found 290.160300.

[[(1R,4S,5R,6S)-5,6-Bis(benzyloxy)-4-[(4-methoxybenzyl)oxy]cyclohex-2-en-1-yl]oxy](tert-butyl)-dimethylsilane (**23**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.20 (m, 12H), 6.85 (m, 2H), 5.77-5.67 (m, 2H), 4.92 (d, 1H, J=11.0), 4.79 (d, 1H, J=11.0), 4.73 (s, 2H), 4.59 (d, 1H, J=11.3), 4.54 (d, 1H, J=11.3), 4.32 (dd, 1H, J=8.2, 4.9), 4.22-4.02 (m, 2H), 3.80 (s, 3H), 3.40 (dd, 1H, J=9.8, 4.4), 0.88 (s, 9H), 0.08 (3H,s), 0.05 (3H, s); MS (EI) for $C_{34}H_{44}O_5Si$ (M^+) 560, (M^+-tBu) 503.

(1S,4R,5S,6R)-5,6-Bis(benzyloxy)-4-[[tert-butyl(dimethyl)silyl]oxy]cyclohex-2-en-1-ol (**24**): ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.26 (m, 10H), 5.78 (dd, 1H, J=10.4, 3.4), 5.70 (dd, 1H, J=10.4, 3.1), 4.82 (d, 1H, J=11.9), 4.74-4.61 (m, 3H), 4.52 (m, 1H), 4.01 (m, 1H), 3.86 (dd, 1H, J=6.7, 4.3), 3.64 (dd, 1H, J=6.7, 3.5), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 159.3, 143.0, 138.5, 129.9, 128.9, 128.7, 128.6, 128.1, 128.0, 127.9, 123.7, 121.8, 79.2, 79.0, 78.1, 77.4, 73.5, 72.6, 69.4, 54.3, 26.1, 22.3, -4.3; HRMS (EI) for $C_{26}H_{36}O_4Si$ (M^+): Calcd 440.2383; Found 440.2383.

(1R,2R,3S,4S,5S,6R)-3,4-Bis(benzyloxy)-5-[[tert-butyl(dimethyl)silyl]oxy]-7-oxabicyclo[4.1.0]heptan-2-ol (**25**): ^{1}H-NMR ($CDCl_3$) δ: 7.38-7.18 (m, 10H), 4.78 (d, 1H, J=11.9), 4.54 (m, 3H), 4.36 (dd, 1H, J=4.0, 3.1), 3.96 (m, 1H), 3.65 (dd, 1H, J=4.0, 3.1), 3.56 (dd, 1H, J=4.0, 4.0), 3.48 (dd, 1H, J=4.0, 4.0), 2.86 (d, 1H, J=10.1), 0.96 (s, 9H), 0.15 (s, 3H), 0.13 (3H, s); ^{13}C-NMR ($CDCl_3$) δ:137.8, 128.6, 128.3, 128.1, 127.7, 127.5, 80.8, 76.8, 76.6, 73.6, 72.8, 67.8, 55.7, 54.3, 25.7, 19.6, -4.8; HRMS (EI) for $C_{26}H_{36}O_5Si$(M^+): Calcd 456.2332; Found 456.2327.

[[(1R,2S,3S,4R,5R,6R)-3,4-Bis(benzyloxy)-5-[(4-methoxybenzyl)oxy]-7-oxabicyclo[4.1.0]hept-2-yl]-oxy](tert-butyl)dimethylsilane (**26**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.20 (m, 12H), 6.92-6.82 (m, 2H), 4.88-4.62 (m, 6H), 4.31 (dd, 1H, J=4.6, 4.6), 3.89 (dd, 1H, J=10.1, 8.2), 3.80 (s, 3H), 3.74 (dd, 1H, J=8.2, 2.1), 3.22 (dd, 1H, J=4.5, 2.1), 3.19 (dd, 1H, J=4.5, 4.5), 3.14 (dd, 1H, , J=10.1, 4.6), 0.94 (s, 9H), 0.13 (3H, s), 0.11 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 157.7, 137.9, 131.0, 129.5, 1283.2, 127.6, 127.4, 127.3, 125.9, 122.7, 122.3, 76.9, 76.8, 76.7, 76.6, 70.0, 65.9, 58.8, 57.5, 50.4, 25.8, 19.7, -4.5; HRMS (EI) for $C_{34}H_{44}O_6Si$ (M^+): Calcd 576.2907; Found 576.2907.

(1R,2R,3S,4R,5S,6R)-3,4-Bis(benzyloxy)-2-[[tert-butyl(dimethyl)silyl]oxy]-6-(hydroxymethyl)-5-[(4-methoxybenzyl)oxy]cyclohexanol (**27**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.20 (m, 12H), 6.90-6.83 (m, 2H), 4.98 (d, 1H, J=11.0), 4.84 (m, 2H), 4.70 (s, 2H), 4.55 (d, 1H, J=11.0), 4.15 (dd, 1H, J=2.1, 2.1), 3.94 (dd, 1H, J=9.8, 9.8), 3.87 (dd, 1H, J=10.7, 3.7), 3.81 (m, 4H), 3.43 (m, 1H), 3.31 (dd, 1H, J=11.0, 9.8), 3.25 (dd, 1H, J=9.8, 2.1), 2.05 (2H, brs), 1.96 (1H, m); ^{13}C=NMR ($CDCl_3$) δ: 159.6, 138.6, 133.2, 129.2, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 114.2, 111.2, 78.6, 78.1, 77.0, 75.6, 75.1, 73.6, 72.1, 69.9, 61.4, 44.7, 26.3, 18.7, -4.8; HRMS (EI) for $C_{35}H_{48}O_7Si$(M^+): Calcd 608.3169; Found 608.3169.

1-Methoxy-4-[[(1S,2R,3R,4R,5R,6R)-2,3,4,5-tetrakis(benzyloxy)-6-[(benzyloxy)methyl]-2-cyclohexyl]-oxymethyl]benzene (**28**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.20 (m, 27H), 7.12 (d, 1H, J=8.5), 6.80 (d, 1H, J=8.5), 4.96 (d, 1H, J=10.7), 4.82 (m, 4H), 4.64 (m, 2H), 4.49 (m, 2H), 4.38 (m, 2H), 4.07 (m, 2H), 3.76 (s, 3H), 3.63 (dd, 1H, J=9.2, 9.2), 3.47 (dd, 1H, J=11.6, 1.8), 3.32 (dd, 1H, J=9.8, 1.8), 2.31 (1H, m); HRMS (EI) for $C_{43}H_{45}O_7$ (M^+): Calcd 673.3166; Found 673.3165.

(1S,2S,3R,4R,5R,6R)-2,3,4,5-Tetrakis(benzyloxy)-6-[(benzyloxy)methyl]cyclohexylmethanesulfonate (**29**): ^{1}H-NMR ($CDCl_3$) δ: 7.40-7.16 (m, 25H), 5.09 (dd, 1H, J=11.3), 4.82 (dd, 1H, J=11.0, 11.0), 4.69-4.35 (m, 9H), 4.12 (dd, 1H, J=9.5, 9.5), 4.03 (brs, 1H), 3.88 (dd, 1H, J=9.5, 2.5), 3.65 (dd, 1H, J=9.5, 1.5), 3.50 (dd, 1H, J=11.3, 2.1), 3.36 (dd, 1H, J=11.3, 2.1), 2.81 (s, 3H), 2.45 (m, 1H); HRMS (EI) for $C_{43}H_{46}O_8S$ (M^+): Calcd 722.2914; Found 722.2916.

(1S,2S,3R,4R,5R,6R)-2,3,4,5-Tetrahydroxy-6-(hydroxymethyl)cyclohexylmethanesulfonate (**30**): HRMS (CI) for $C_{13}H_{24}NO_6$ (MH^+): Calcd 290.160363; Found 290.160300.

(1S,2R,3R,4R,5R,6R)-5-(Hydroxymethyl)-7-oxabicyclo[4.1.0]heptane-2,3,4-triol (**31**): ^{1}H-NMR (D_2O) δ: 3.85 (m, 1H), 3.82 (m, 2H), 3.65 (m, 1H), 3.43 (bs, 1H), 3.28 (d, 1H, J=9.5), 3.07 (m, 1H), 2.14 (m, 1H); ^{13}C-NMR (D_2O) δ: 71.0, 67.4, 66.2, 60.5, 56.3, 55.4, 38.5; HRMS (CI) for $C_{13}H_{24}NO_6$ (MH^+): Calcd 290.160363; Found 290.160300.

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