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Total Synthesis of a Novel β-Glucosidase Inhibitor, Cyclophellitol Starting from D-Glucose

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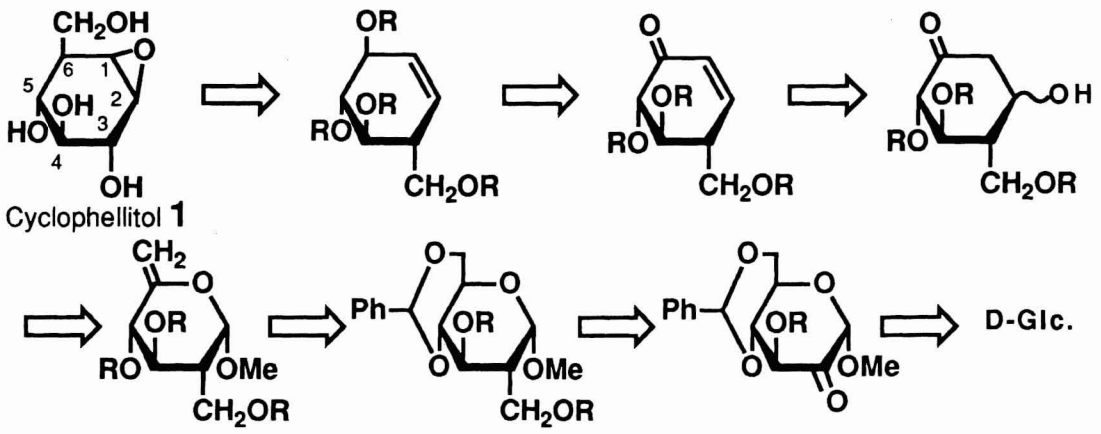
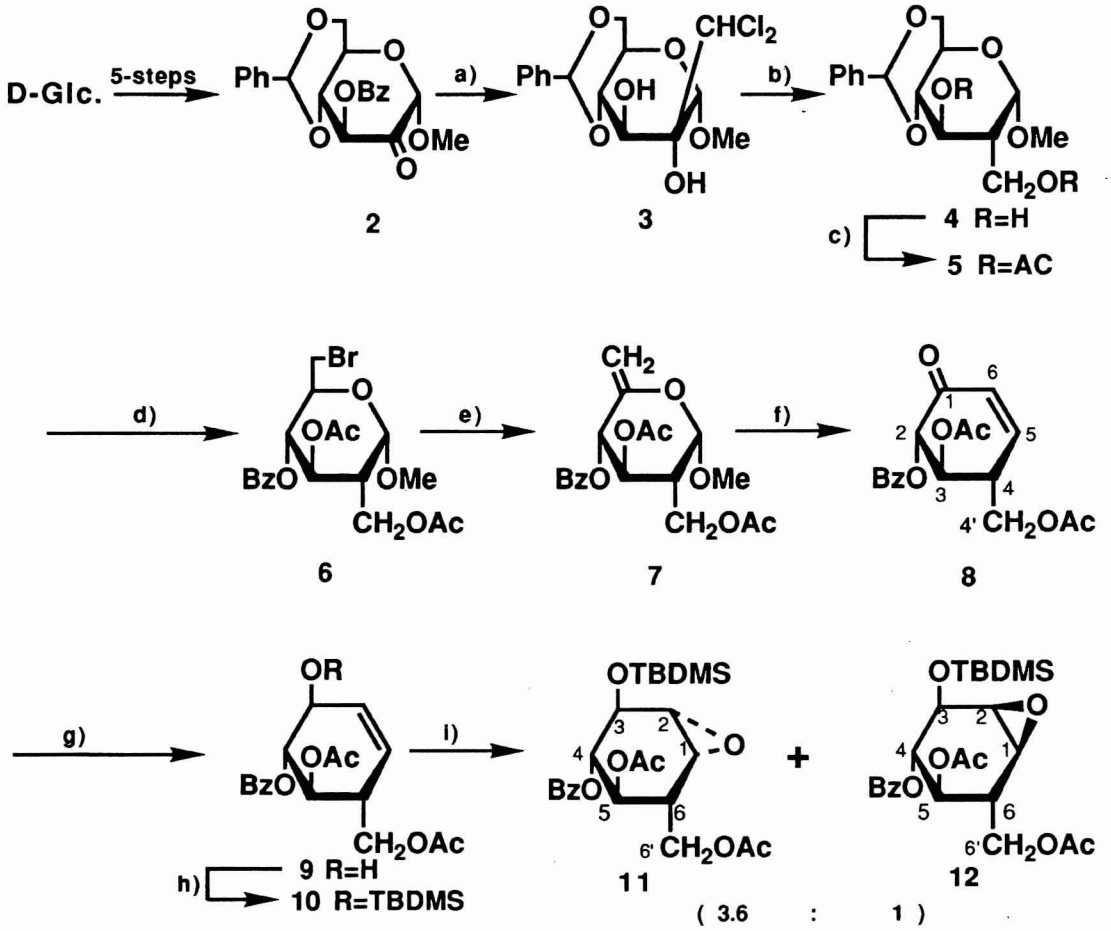
Cyclophellitol [1L-(1,2,4,6/3,5)-1,2-anhydro-6-(hydroxymethyl)-cyclohexane-1,2,3,4,5-pentol], a novel β-glucosidase inhibitor, has been synthesized from D-glucose via a branched-chain 6-deoxyhex-5-enopyranoside.

Cyclophellitol is a novel β-glucosidase inhibitor recently isolated from the culture filtrate of a mushroom, *phellinus sp.*, and also a potent inhibitor of infection of human immunodeficiency virus (HIV).[1] Total syntheses of cyclophellitol (**1**) from L-glucose,[2] L-quebrachitol,[3] and furan[4] were already reported. Recently, a new approach toward the methyl-branched cyclitols using palladium catalyst have been reported by Gero et al.[5] and also reported[6] by us the syntheses via the corresponding key intermediates, branched-chain 6-deoxyhex-5-enopyranosides, which were prepared from branched-chain hexopyranosides. Moreover, authors established a new approach for the syntheses of various functionalized branched-chain hexopyranosides by the use of dichloromethyllithium.[7] On the basis of above knowledge, we report here a new approach for the synthesis of **1** starting from D-glucose.

Our synthetic strategy of **1** from D-glucose is showed in scheme 1. The synthesis began with the preparation of methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosid-2-ulose (**2**).[8] (Scheme 2) Stereoselective introduction of dichloromethyl function[7] to compound **2** gave methyl 4,6-*O*-benzylidene-2-*C*-dichloromethyl-α-D-glucopyranoside (**3**), of which structure was confirmed by derivatization to the corresponding known 2-*C*-methyl derivative[8] by radical reduction. Hydride reduction of **3** with $NaBH_4$ in

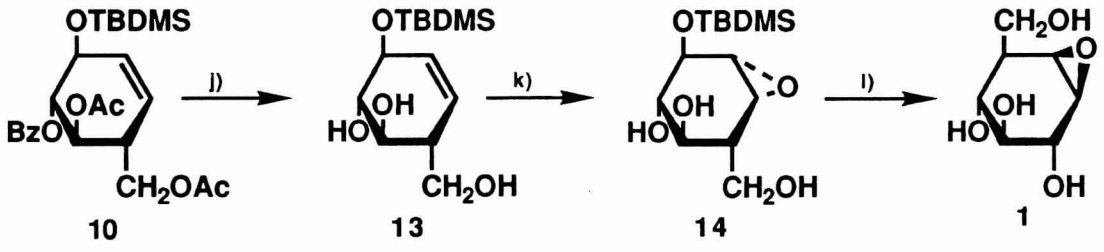


Scheme 1.



a) LDA, CH_2Cl_2 / THF, -78 °C, 82%. b) $NaBH_4$ / DMSO, 80 °C, 82%. c) Ac_2O / Py, r.t., quant.
d) NBS, $BaCO_3$ / CCl_4, reflux. e) NaI / Acetone, reflux, then DBU, MS4A / DMSO, 80 °C, 56% (from **5**).
f) $HgCl_2$ / Acetone-H_2O (5:2), reflux, then MsCl, Et_3N / CH_2Cl_2, 0 °C, 86%.
g) $NaBH_4$, $CeCl_3 \cdot 7H_2O$ / EtOH-CH_2Cl_2 (2:1), -78 °C, 67%. h) TBDMSCl, Imidazole / DMF, 40 °C, 94%.
i) m-CPBA / 1,2-Dichloroethane, 40 °C, **11**=50%, **12**=14%.

Scheme 2.



j) KOH / EtOH, r.t., 80%. k) m-CPBA / 1,2-Dichloroethane, 40 °C, 84%. l) 70%AcOH, r.t., quant.

Scheme 3.

DMSO at 80 °C, gave methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-hydroxymethyl-α-D-glucopyranoside (**4**) in 82% yield. Acetylation of **4** with Ac_2O in pyridine gave the corresponding acetyl derivative (**5**) in a quantitative yield. Oxidative ring opening of the benzylidene acetal of **5** with NBS and $BaCO_3$ in CCl_4, followed by displacement of bromine with iodine by treatment with NaI in acetone, then treatment with DBU in DMSO in the presence of MS 4A at 80 °C for 1 h, and usual work up and purification on a column of silica gel (TLC, hexane-ethyl acetate=2:1, *Rf* 0.55), gave syrupy methyl 2-*C*-acetoxymethyl-3-*O*-acetyl-4-*O*-benzoyl-2-deoxy-α-D-*xylo*-hex-5-enopyranoside (**7**) in 56% yield (3 steps from **5**). Ferrier reaction of **7** with $HgCl_2$ in acetone- H_2O (5:2) at 80 °C for 1h, then treatment of the product with methanesulfonyl chloride and Et_3N in CH_2Cl_2 at 0 °C, purification of the produced enone derivative on a column of silica gel (TLC, hexane-ethyl acetate=2:1, *Rf* 0.16), gave 2 L-(2,4 / 3)-4-acetoxymethyl-3-*O*-acetyl-2-*O*-benzoyl-5-cyclohexen-1-one (**8**) in 86% yield. Stereoselective reduction of **8** with $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in EtOH-CH_2Cl_2 (2:1) at -78 °C, and purification of the reaction mixture on a silica gel column (TLC, hexane-ethyl acetate=1:1, *Rf* 0.40), gave 1D-(1,3/2,4)-4-acetoxymethyl-3-*O*-acetyl-2-*O*-benzoyl-5-cyclohexene-1,2,3-triol (**9**) in 67% yield. To achieve its stereoselective epoxidation, the hydroxyl group of compound **9** was protected with a bulky TBDMS group by the use of TBDMSCl and imidazole in DMF to give 1D-(1,3/2,4)-4-acetoxymethyl-3-*O*-acetyl-2-*O*-benzoyl-1-*O*-*t*-butyldimethylsilyl-5-cyclohexene-1,2,3-triol (**10**), which was purified on a column of silica gel (TLC, hexane-ethyl acetate=2:1, *Rf* 0.58), in 94% yield. Epoxidation of **10** with *m*-CPBA in 1,2-dichloroethane at 40 °C for 24 h, washing with 1 mol dm^{-3} aq. NaOH, and purification on a column of silica gel (TLC, hexane-ethyl acetate=2:1, *Rf* 0.45), gave both 1L-(1,2,4,6/3,5)- and 1D-(1,2,3,5/4,6)-6-actoxymethyl-5-*O*-acetyl-1,2-anhydro-4-*O*-benzoyl-3-*O*-*t*-butyldimethylsilyl-cyclohexane-1,2,3,4,5-pentol (**11** and **12**) in 50 and 14% yields, respectively. For the improvement of the stereoselectivity of epoxidation (Scheme 3), **10** was treated with KOH in EtOH (pH 10) at r.t. for 20 min and purification on a column of silica gel (TLC, hexane-ethyl acetate=1:1, *Rf* 0.17) to give 1D-(1,3/2,4)-1-*O*-*t*-butyldimethylsilyl-4-hydroxymethyl-5-cyclohexene-1,2,3-triol (**13**) in 80% yield. Then, **13** was treated in a manner similar to that mentioned above to give the required single product (**14:** TLC, $CHCl_3$-MeOH=10:1, *Rf* 0.32) in 84% yield. From these results, the stereoselectivity of epoxidation should be controlled by an interaction between *m*-CPBA and the allylic hydroxyl group rather than steric effects of the acyl groups.[9] Acid hydrolysis of compound **14** with 70% acetic acid at r.t. for 1h gave the desired product **1** in a quantitative yield. The structure of **1** was confirmed by reported nmr data of its peracetyl derivative. As described in this paper, the above method might be useful for the synthesis of other methyl-branched cyclitol derivatives.

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10) ^{1}H NMR data (200 or 500 MHz) of key compounds: [**8**: δ=8.08-7.44 (m, 5H, Ph), 6.90 (dd, 1H, $J_{6,4}$=2.1Hz, $J_{6,5}$=10.0Hz, H-6), 6.27 (dd, 1H, $J_{5,4}$=2.7Hz, H-5), 5.72 (d, 1H, $J_{2,3}$=11.3Hz, H-2), 5.67 (dd, 1H, $J_{3,4}$=9.5Hz, H-3), 4.35 (dd, 1H, $J_{4'a,4}$=3.7Hz, $J_{4'a,4'b}$=11.6Hz, H-4'a), 4.20 (dd, 1H, $J_{4'b,4}$=5.2Hz, H-4'b), 3.15 (m, 1H, H-4), 2.10, 2.00 (each s, 3Hx2, OAcx2). **9**: δ=8.04-7.45 (m, 5H, Ph), 5.81 (ddd, 1H, $J_{5,1}$=$J_{5,4}$=2.4Hz, $J_{5,6}$=10.1Hz, H-5), 5.67 (ddd, 1H, $J_{6,1}$=$J_{6,4}$=2.2Hz, H-6), 5.40 (dd, 1H, $J_{3,2}$=10.7Hz, $J_{3,4}$=9.8Hz, H-3), 5.24 (dd, 1H, $J_{2,1}$=7.6Hz, H-2), 4.55 (m, 1H, H-1), 4.18 (dd, 1H, $J_{4'a,4}$=4.3Hz, $J_{4'a,4'b}$=11.3Hz, H-4'a), 4.06 (dd, 1H, $J_{4'b,4}$=5.2Hz, H-4'b), 2.89 (d, 1H, $J_{OH,1}$=5.2Hz, OH), 2.84 (m, 1H, H-4), 2.08, 1.93 (each s, 3Hx2, OAcx2). **10**: δ=8.03-7.42 (m, 5H, Ph), 5.67 (ddd, 1H, $J_{5,1}$=$J_{5,4}$=2.4Hz, $J_{5,6}$=10.4Hz, H-5), 5.59 (ddd, 1H, $J_{6,1}$=$J_{6,4}$=2.1Hz, H-6), 5.46 (dd, 1H, $J_{2,1}$=8.0Hz, $J_{2,3}$=10.7Hz, H-2), 5.31, (dd, 1H, $J_{3,4}$=9.6Hz, H-3), 4.57 (dddd, 1H, $J_{1,4}$=3.4Hz, H-1), 4.15 (dd, 1H, $J_{4'a,4}$=4.0Hz, $J_{4'a,4'b}$=11.3Hz, H-4'a), 4.03 (dd, 1H, $J_{4'b,4}$=5.2Hz, H-4'b), 2.85 (m, 1H, H-4), 2.07, 1.83 (each s, 3Hx2, OAcx2), 0.79 (s, 9H, *t*-butyl-Si), 0.03, -0.11 (each s, 3Hx2, Me_2-Si). **11**: δ=8.10-7.50 (m, 5H, Ph), 5.37 (dd, 1H, $J_{4,3}$=8.3Hz, $J_{4,5}$=10.7Hz, H-4), 5.18 (dd, 1H, $J_{5,6}$=10.0Hz, H-5), 4.43 (dd, 1H, J $_{6'a,6}$=4.2Hz, $J_{6'a,6'b}$=11.2Hz, H-6'a), 4.26 (dd, 1H, $J_{6'b,6}$=5.1Hz, H-6'b), 4.26 (d, 1H, H-3), 3.54 (dd, 1H, H-1), 3.26 (d, 1H, $J_{2,1}$=3.7Hz, H-2), 2.67 (m, 1H, H-6), 2.20, 1.90 (each s, 3Hx2, OAcx2), 0.91 (s, 9H, *t*-butyl-Si), 0.18, 0.10 (each s, 3Hx2, Me_2-Si). **12**: δ=8.09-7.46 (m, 5H, Ph), 5.52 (dd, 1H, $J_{4,5}$=10.8Hz, $J_{4,3}$=8.8Hz, H-4), 5.18 (dd, 1H, $J_{5,6}$=10.5Hz, H-5), 4.40-4.18 (m, 3H, H-3, H-6'a, and H-6'b), 3.45 (m, 1H, H-1), 3.27 (dd, 1H, $J_{2,3}$=6.5Hz, $J_{2,1}$=3.5Hz, H-2), 2.67 (m, 1H, H-6), 2.22, 1.89 (each s, 3Hx2, OAcx2), 0.90 (s, 9H, *t*-butyl-Si), 0.10, 0.06 (each s, 3Hx2, Me_2-Si). **13**: δ=5.57 (ddd, 1H, $J_{5,6}$=10.0Hz, $J_{5,4}$=2.7Hz, $J_{5,1}$=2.1Hz, H-5), 5.40 (ddd, 1H, $J_{6,1}$=$J_{6,4}$=2.1Hz, H-6), 4.18 (dddd, 1H, $J_{1,2}$=7.7Hz, $J_{1,4}$=3.6Hz, H-1), 3.83 (dd, 1H, $J_{4'a,4'b}$=10.7Hz, $J_{4'a,4}$=4.0Hz, H-4'a), 3.71 (dd, 1H, $J_{4'b,4}$=7.3Hz, H-4'b)3.70 (dd, 1H, $J_{3,2}$=$J_{3,4}$=9.7Hz, H-3), 3.60 (dd, 1H, H-2), 3.30 (bs, 1H, OH), 2.72 (bs, 1H, OH), 2.52-2.46 (m, 2H, H-4 and OH), 0.92 (s, 9H, *t*-butyl-Si), 0.13, 0.12 (each s, 3Hx2, Me_2-Si). **14**: δ=4.05 (dd, 1H, $J_{6'a,6'b}$=10.7Hz, $J_{6'a,6}$=7.0Hz, H-6'a), 3.99 (dd, 1H, $J_{6'b,6}$=5.2Hz, H-6'b), 3.77 (d, 1H, $J_{3,4}$=8.3Hz, H-3), 3.48 (dd, 1H, $J_{5,6}$=9.7Hz, $J_{5,4}$=10.1Hz, H-5), 3.38 (dd, 1H, $J_{4,3}$=8.3Hz, H-4), 3.24 (dd, 1H, $J_{1,6}$=2.1Hz, H-1), 3.02 (d, 1H, $J_{2,1}$=3.7Hz, H-2), 2.18 (m, 1H, H-6), 0.94 (s, 9H, *t*-butyl-Si), 0.18, 0.17 (each s, 3Hx2, Me_2-Si). Acetyl derivative of **1**: δ=5.12 (dd, 1H, $J_{4,3}$=8.5Hz, $J_{4,5}$=10.4Hz, H-4), 5.08 (d, 1H, H-3), 5.02 (dd, 1H, $J_{5,6}$=10.4Hz, H-5), 4.31 (dd, 1H, $J_{6'a,6}$=4.2Hz, $J_{6'a,6'b}$=11.3Hz, H-6'a), 4.16 (dd, 1H, $J_{6'b,6}$=7.3Hz, H-6'b), 3.43 (dd, 1H, $J_{1,2}$=3.7Hz, $J_{1,6}$=1.7Hz, H-1), 3.14 (d, 1H, H-2), 2.51 (dddd, 1H, H-6), 2.09, 2.05, 2.04, 2.00 (each s, 3Hx4, OAcx4). lit.[4]: δ=5.12 (dd, 1H, $J_{4,3}$=8.5Hz, $J_{4,5}$=10Hz, H-4), 5.07 (d, 1H, H-3), 5.00 (dd, 1H, $J_{5,6}$=10Hz, H-5), 4.28 (dd, 1H, $J_{6'a,6}$=4Hz, $J_{6'a,6'b}$=10Hz, H-6'a), 4.11 (dd, 1H, $J_{6'b,6}$=7.5Hz, H-6'b), 3.41 (dd, 1H, $J_{1,2}$=3.5Hz, $J_{1,6}$=1.5Hz, H-1), 3.11 (d, 1H, H-2), 2.49 (dddd, 1H, H-6), 2.07, 2.06, 2.04, 2.00 (each s, 3Hx4, OAcx4).

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