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Enantiospecific Total Synthesis of a β-Glucosidase Inhibitor, Cyclophellitol

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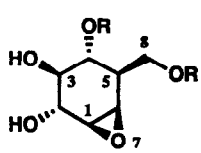
Summary: Cyclophellitol has been synthesized from L-glucose through an intramolecular cycloaddition of a nitrile oxide derived from an oxime.

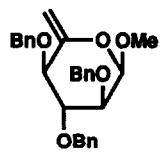
Cyclophellitol (**1**)[1] is a novel β-glucosidase inhibitor isolated from a culture filtrate of a mushroom, *Phellinus sp.* and is expected to inhibit infection of human immunodeficiency virus. The absolute structure **1** was established by X-ray crystallographic analysis to disclose the fully oxygenated skeleton.

We report herein the enantiospecific synthesis of cyclophellitol (**1**) and record a general method of entry into the highly oxygenated cyclohexanes (*e.g.*, pseudo-sugars[2]). The key step in this approach is an intramolecular cycloaddition of a nitrile oxide to an olefin. Very recently, the synthesis of five- and six-membered carbocycles has been independently reported by using an intramolecular nitron cycloaddition.[3]

Our synthesis began with the preparation of the *xylo*-hex-5-enopyranoside **2** from L-glucose according to the Sepulchre's procedure.[4] Stereoselective hydroboration of **2** with dicyclohexylborane (THF, 25°C, 1.5h, then H_2O_2/NaOH, 50°C, 20 min) gave the D-idopyranoside **3**[5] (85%; $[\alpha]_D$ -28°), which was oxidized [$(COCl)_2$/DMSO/TEA/CH_2Cl_2, -78°C, 15 min] to an aldehyde, followed by a Wittig reaction ($Ph_3P{=}CH_2$/PhH, 25°C, 15 min) to afford the olefin **4**[5] (75%; $[\alpha]_D$ -6.5°). This was hydrolyzed (HCl/aq. dioxane, 80°C, 12h) to an idopyranose, which was treated with $NH_2OH{\bullet}HCl$ (pyridine, 25°C, 1h) to give the oxime **5**[5] (80%). Intramolecular cycloaddition of **5** in question was realized by using NaOCl (CH_2Cl_2, 25°C, 1.5h) *via* the intermediary nitrile oxide[6] to afford the isoxazoline **6**[5] as a single product (70%; $[\alpha]_D$ -125°). The stereochemistry was confirmed by the ^1H NMR analyses of compounds **6** - **10** and , finally the completion of the synthesis presented below. The diastereoselectivity is rationalized by a *syn* periplanar steric interaction between the nitrile oxide and α-benzyloxy group in its transition state.[7] This isoxazoline could be a key intermediate for syntheses of highly functionalized cyclohexanes. Hydrogenolysis (H_2/Raney Ni-W4/AcOH/aq. dioxane, 25°C, 1.5h) of **6** gave the



1: R = H
10: R = DEIPS



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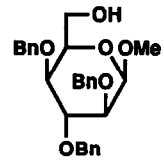

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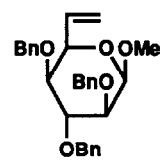

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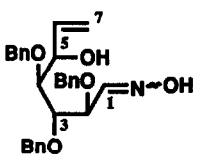

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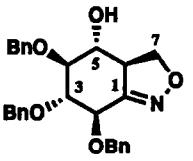

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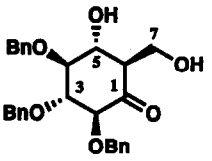

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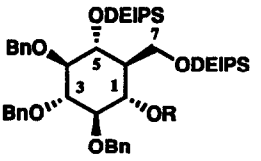

8: R = H
9: R = Ms

keto-diol 7[5] (80%, $[\alpha]_D$ -55°). After silylation (90%; DEIPS-OTf[8]/2,6-lutidine/CH_2Cl_2, 0°C, 0.5h), the resulting ketone was reduced (BH_3•Me_2S/THF, 25°C, 12h) to yield the desired α-alcohol 8[5] (60%; $[\alpha]_D$ +24°). The undesired β-alcohol was obtained in 20% yield, and then recycled to the ketone 7 by oxidation [$(COCl)_2$/DMSO/TEA]. Mesylation (MsCl/Py, 25°C, 12h) of 8 provided the labile mesylate 9[5] (75%), which was de-O-benzylated (H_2/$Pd(OH)_2$/MeOH) followed by epoxidation (MeONa/$CHCl_3$, 0°C, 10 min) to give the labile epoxide 10[5] [$[\alpha]_D$ +49° (c 0.14, MeOH)]. Deprotection (*n*-Bu_4NF/THF, 25°C, 10 min) completed the synthesis, giving cyclophellitol (**1**) [40% from 9; plates (H_2O), mp 149-151°C, $[\alpha]_D$ +103° (c 0.5, H_2O)] identical with that obtained from natural sources by IR, ^1H NMR and biological activity (inhibition against almond-derived β-glucosidase with IC_{50} of 0.8 μg/ml).[1]

The application of this synthetic strategy using other carbohydrates for the construction of other related substances is an exciting prospect.

References and notes

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5. All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were measured using a 0.5 dm tube, for solutions (c 0.5) in $CHCl_3$ at 25°C. Significant ^1H NMR (270MHz, 400 MHz) spectral data [δ ($CDCl_3$, TMS), J (Hz)] are the following. **3**: 2.71 (1H, dd, OH, J=8.0, 4.8), 3.63 (1H, dd, H-4, J=8.0, 5.6), 3.97 (1H, ddd, H-5, J=5.6, 5.6, 5.6). **4**: 3.62 (1H, dd, H-4, J=8.2, 5.8), 4.29 (1H, dd, H-5, J=5.8, 9.8), 5.25-5.35 (2H, m, 2XH-7), 6.29 (1H, ddd, H-6, J=9.8, 9.8, 16.0). **5**: 5.14 (1H, ddd, H-7Z, J=1.6, 1.6, 10.2), 5.23 (1H, ddd, H-7E, J=1.6, 1.6, 17.0), 5.81 (1H, ddd, H-6, J=5.0, 10.2, 17.0), 6.98 (0.25H, d, H-1Z, J=6.0), 7.48 (0.75H, d, H-1E, J=8.0). **6**: 3.23 (1H, dddd, H-6, J=1.0, 8.4, 8.0, 10.0), 4.38 (1H, dd, H-2, J=1.0, 9.2). **7**: 2.61 (1H, dddd, H-6, J=1.2, 11.8, 4.0, 5.0), 3.64 (1H, ddd, H-5, J=2.2, 9.0, 11.8), 4.19 (1H, dd, H-2, J=1.2, 9.0). **8**: 0.55-0.70 [8H, m, 2XSi($C\underline{H}_2Me)_2$], 0.87-1.05 [26H, m, 2XSi($CH_2\underline{Me})_2$, 2XSi^{i}Pr], 3.37 (1H, d, OH, J=0.9). **9**: 2.84 (3H, s, OMs), 4.05 (1H, dd, H-2, J=9.0, 9.0), 4.64 (1H, dd, H-1, J=9.0, 8.6). **10** (CD_3OD): 0.60-0.75 [8H, m, 2XSi($C\underline{H}_2Me)_2$], 0.95-1.05 [26H, m, 2XSi($CH_2\underline{Me})_2$, 2XSi^{i}Pr], 2.00 (1H, m, H-5), 3.08 (1H, d, H-1, J=0, 3.8), 3.17 (1H, dd, H-3, J=7.8, 8.6), 3.24 (1H, dd, H-4, J=8.6, 8.6), 3.46 (1H, br dd, H-6, J=3.8, 2.0), 3.61 (1H, d, H-2, J=0, 7.8), 3.70 (1H, dd, H-8, J=9.8, 9.8), 4.12 (1H, dd, H-8', J=4.0, 9.8).
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