Total Synthesis of Cyclophellitol and (1*R*,2*S*)-Cyclophellitol from D-Mannose[1]

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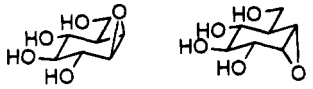
Received March 13, 1995

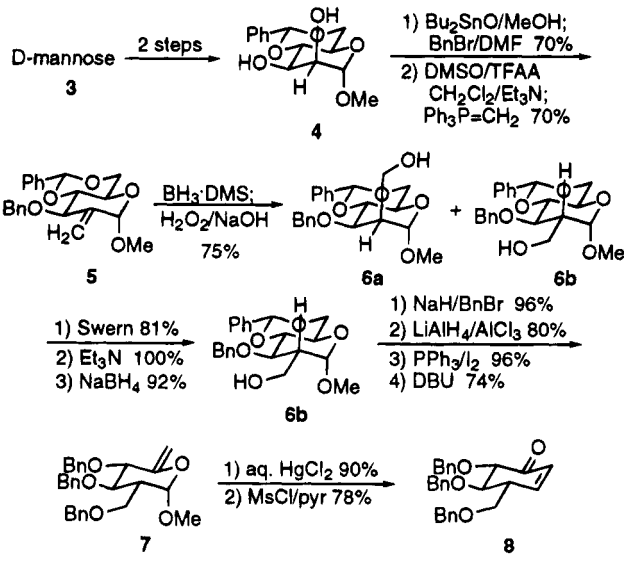
Several naturally occurring glycosidase inhibitors have recently been shown to possess various interesting biological activities, e.g., some have been reported to alter the infection of the causative agent of AIDS, the human immunodeficiency virus (HIV), possibly by perturbing the gp120 linked glycan structure.[4] The potential of these glucosidase inhibitors as anti-HIV therapeutic agents warrants further investigation especially since these glucosidase inhibitors show little toxicity *in vitro* and *in vivo*.[5] The natural product cyclophellitol (**1**), isolated by Tatsuta from the culture filtrate of a mushroom, *Phellinus* sp., has a unique structure as the fully oxygenated carbacyclic analogue of D-glucopyranose with an epoxide ring on the β-face of the molecule.[6] It exhibited extremely potent inhibitory activity against almond β-glucosidase with an IC_{50} of 0.8 μg/mL, stronger than the well known β-glucosidase inhibitors castanospermine, 1-deoxynojirimycin, and nojirimicin which have IC_{50}'s of 12 μg/mL, 43 μg/mL, 2.5 μg/mL, respectively.[6] For this reason, several syntheses of cyclophellitol (**1**) and its epoxide epimer, (1*R*,2*S*)-cyclophellitol (**2**),[7] have been reported recently.[8] Herein we report a new synthesis of cyclophellitol and (1*R*,2*S*)-cyclophellitol from the readily available sugar D-mannose **3**.



1 **2**

Although several syntheses of cyclophellitol are known, few utilize a readily available inexpensive carbohydrate precursor such as D-mannose or D-glucose. The conceptual breakthrough in planning our synthesis was to recognize that a rotation of the key intermediate **8** (Scheme 2) about the horizontal axis showed its overlap to the readily available D-hexopyranoses. All that would be required would be to prepare a 2α-hydroxymethyl sugar and then carry out a Ferrier rearrangement process to prepare the desired intermediate **8**. This was done as follows (Scheme 1). The known methyl benzylidenemannoside (**4**), available in two steps from D-mannose,[9] was converted into the alkene **5** by benzylation of the equatorial alcohol,[10] oxidation, and Wittig reaction.[11] Hydroboration–oxidation of this alkene was expected to occur preferentially from the axial direction, anti to the sterically hindering axial methoxy group.[12] However, the reaction furnished a 1:1 mixture of the two isomeric hydroxymethyl compounds **6a** and **6b**. Even with various sterically bulky borane reagents like 9-BBN, we observed at best only a 1:2 mixture favoring **6b**. The problem of the production of exclusively the equatorial isomer was solved by Swern oxidation of the mixture, quantitative equilibration to only the β-aldehyde in mild base,[13] and reduction to give only the equatorial hydroxymethyl compound **6b**.[14] Thus both the 2α-hydroxymethyl and the corresponding 2α-formyl compounds

Scheme 1



(1) Presented at the 33rd GECO Conference, Corsica, France, September 1992.

(2) American Chemical Society Arthur C. Cope Scholar, 1995.

(3) UCLA Mentorship Awardee, 1991–92.

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(7) (1*R*,2*S*)-cyclophellitol (**2**) has shown inhibitory activity against the baker yeast α-glucosidase with an IC_{50} of 10 μg/mL. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *J. Antibiot.* **1991**, *44*, 456, 912.

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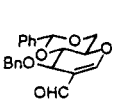
(11) This Wittig reaction was very sensitive to conditions. Our best results involved using the ketone without purification and removing all residual water by azeotropic distillation with benzene and allowing the intermediate ample time to complete the reaction (16 h). For another example of problems with Wittig reactions in similar systems, see: Jendrzejewski, S.; Ermann, D. *Tetrahedron Lett.* **1993**, *34*, 615.

(12) Miljkovic, M.; Gligorijevic, M.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 2118. This direction of attack is also favored electronically since the electron movement of the alkene electrons to the borane is opposite to the C–OMe dipole. (a) Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 1379. (b) Lane, C. *J. Org. Chem.* **1974**, *39*, 1437.

(13) Attempts to epimerize the aldehyde with sodium methoxide gave only traces of the desired compound **6b** and the interesting β-elimination product, the enal **i**, in quantitative yield. For a similar epimerization, see: Schmidt, R. R.; Preuss, R. *Tetrahedron Lett.* **1989**, *30*, 3409.



i

(14) For another method of preparing 2α-formyl pyranosides, see: Jung, M. E.; Choe, S. W. T. *Tetrahedron Lett.* **1993**, *34*, 6247.

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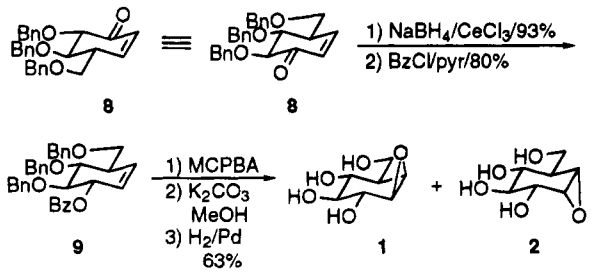
Scheme 2

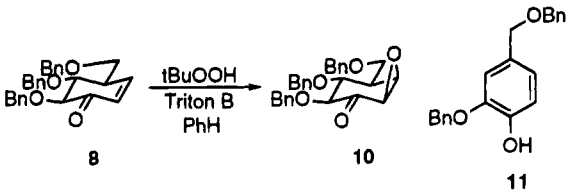


8 8 9 1 2

are now available. Benzylation, reductive opening of the benzylidene acetal,[15] iodide formation, and elimination furnished the alkene **7** in good yield. Ferrier rearrangement and elimination[16] gave the desired enone **8** in 70% yield.

The remainder of the synthesis was straightforward (Scheme 2). Reduction of the enone to the allylic alcohol and benzoylation gave **9** which was epoxidized with MCPBA to give a mixture of epoxides. Removal of the protecting groups then produced cyclophellitol (**1**) and its epimer (1*R*,2*S*)-cyclophellitol (**2**).[17] Although somewhat long, this synthesis is very efficient, producing the cyclophellitols in an overall yield of 5%.

Other routes to **1** were also investigated. For example, base-catalyzed epoxidation of the enone **8** was attempted using the mild base Triton B and *tert*-butyl hydroperoxide[18] which was expected to give mainly the β-epoxide **10** due to antiparallel attack of the peroxide ion on the enone. Reduction and removal of the protecting groups would then have given cyclophellitol (**1**). However, only the product of β-elimination, the phenol **11**, was obtained in 73% yield under the mildly basic conditions.



8 10 11

In conclusion, we have developed a new approach to the synthesis of the glycosidase inhibitors, cyclophellitol (**1**) and (1*R*,2*S*)-cyclophellitol (**2**), from a derivative **4** of D-mannose that proceeds in 5% overall yield. Further work on syntheses of similar compounds is underway in our laboratory.

Acknowledgment. We thank the National Institutes of Health (GM 47228) for generous financial support.

Supplementary Material Available: Experimental procedures and characterization data (22 pages).

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(17) These last three steps are those developed by Shing in his synthesis of cyclophellitol and its epimer.[8d] We thank Professor Shing for kindly providing both spectral data and a sample of the tribenzyl benzoate **9** which was identical in all respects to our synthetic **9**.

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