Enantioselective Synthesis of (+)-Cyclophellitol

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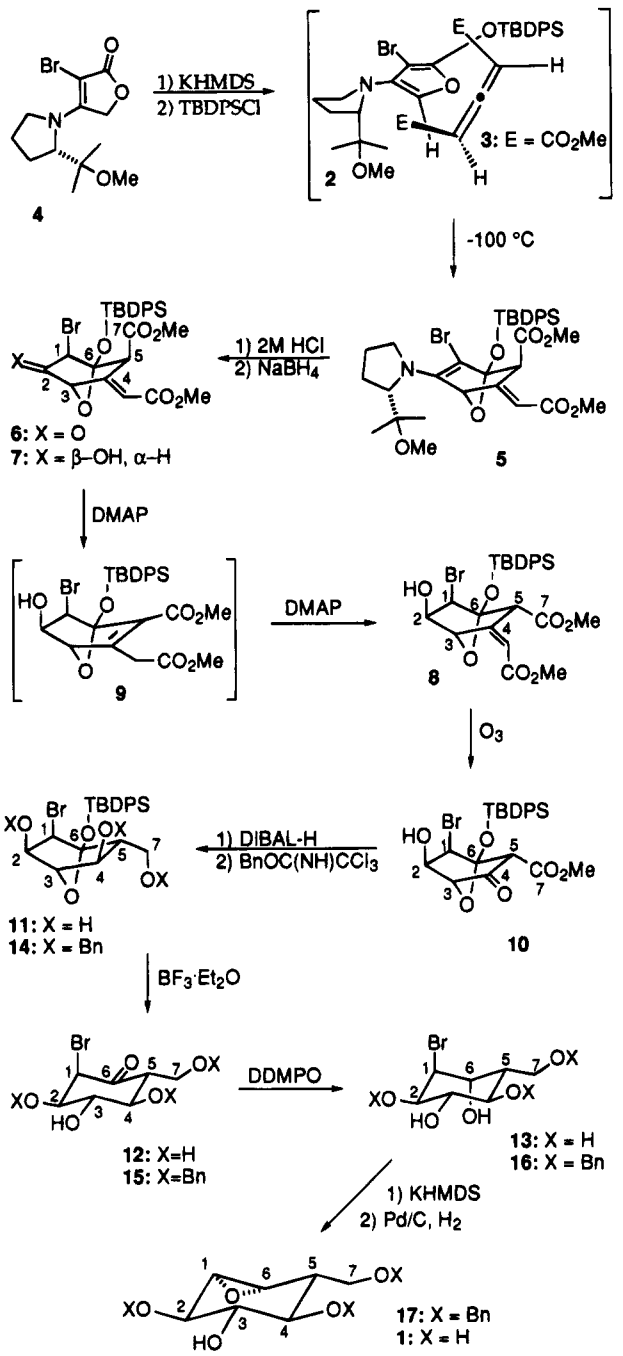
Cyclophellitol ((+)-**1**: (1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-(hydroxymethyl)-7-oxabicyclo[4.1.0]heptane-2,3,4-triol) has been isolated from the culture filtration of a mushroom, *Phellinus* sp.[1] Its structure and absolute configuration have been determined both by X-ray crystallography and total synthesis from L-glucose, respectively.[1,2] The natural product has attracted considerable subsequent synthetic attention in that it has been shown to be an inactivator of β-glucosidase[3] and potentially of use as an inhibitor of human immunodeficiency virus.[4] Our interest in the fabrication of densely functionalized nonracemic cyclohexane ring systems, *via* nonracemic Diels–Alder reactions,[5] prompted us to attempt a synthesis of **1**.[6]

To this end, the nonracemic furan **2** was prepared by deprotonation (KHMDS in THF (0 °C, 4 h)) of the vinylogous urethane lactone (VUL) **4** followed by treatment of the resulting potassium enolate with *tert*-butyldiphenylsilyl chloride (TBDPSCl, 0 °C, 1 h).[7] Racemic dimethyl 2,3-pentadienedioate (**3**, 4 equiv, 1 M THF) was added (−100 °C, Et_2O/CO_2).[8] After stirring (6 h), the marginally stable [2:2:1]oxabicyclic enamine adduct **5** (91% crude) was isolated by filtration through alumina.[9] Adduct **5** arises from a double diastereofacially selective reaction in which kinetic resolution of the allenic diester **3** occurs.[10] We felt that **5** contained the requisite seeds of structure and functionality to permit its conversion into the natural product **1** and set out to test this assumption.

Treatment of **5** (2 M HCl, CH_3CN, 0 °C) gave the axial bromo ketone **6** (93%).[11] Stereoselective reduction ($NaBH_4$/EtOH, −78 °C) of **6** afforded the *syn* bromohydrin **7** (94%). **7** possesses the correct functionality and stereochemistry at C_1 and C_2, respectively, as required by the structure **1**. We next faced the problem of reforming C_4 and C_5 of **7** to the correct stereochemistry, carbon content, and oxidation state without prematurely disrupting its oxabicyclic ketal structure.



Adjusting the stereochemistry of the axial ester residue at C_5 was first addressed. This was best carried out by treatment of **7** (DMAP, 0.2 equiv, THF, 22 °C, 48 h) to give the C_5 equatorial ester **8** (79%). Careful ^1H study of this reaction indicated that the transformation **7** to **8** proceeded through the intermediate **9** and that competing β-elimination of the bridge oxygen did not occur with alacrity under these conditions.[12] Ozonolysis of **8** (O_3, CH_2Cl_2, −78 °C, 4 h; DMS, −78 °C, 1 h, 22 °C, 1 h) afforded the unstable β-keto ester **10** (86%, crude).[13] Lastly, reduction of **10** (DIBALH, toluene, −78 °C, 30 min, −20 °C, 3.5 h; CH_3OH, 2 M HCl, 0 °C) correctly set the secondary alcohol center at C_4 of **11** (81%).

The stage was now set for cleavage of the oxabicyclic ketal residue of **11** into the cyclohexanone tetrol **12**, followed by reduction of the ketonic moiety into its C_6 axial alcohol analogue **13**. Admixture of **11** with $BF_3{\cdot}Et_2O$ (CH_2Cl_2, −20 °C) gave **12** (70%, crude) as a highly polar

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(6) To date, all of these syntheses commence from sugars except for the work of Vogel which results in racemic **1**.
(7) See ref 5 for the preparation of **4**.
(8) For the preparation of this allene see: Bryson, T. A.; Dolak, T. M. *Org. Synth.* **1977**, *57*, 62.
(9) On prolonged standing or on chromatography on silica gel, **5** suffers either hydrolysis of the enamine residue (minor) or ring opening of the bicyclic ketal (major).
(10) Optical activity is exhibited by the allenic diester, **3**, recovered from this reaction.

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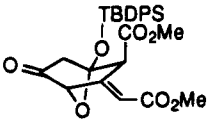
and water soluble compound. Reduction of **12** under a wide variety of conditions, unfortunately, gave only very low (<30%) yields of **13**. Thus, we protected **11** (Bundles' procedure)[14] as its tribenzyl ether **14** (84%). **14** smoothly cleaved with $BF_3{\cdot}Et_2O$ (CH_2Cl_2, −20 °C) to the tractable cyclohexanone **15** (85%).

(11) Compound **6**, and hence compound **5**, are formed with greater than 99% ee. This was demonstrated in the following fashion. Nonracemic **6** was dehalogenated (Bu_3SnH, AIBN, THF, 22 °C, 18 h) to give the ketone **i**.



i

Racemic **i** was prepared starting from the diisopropylamine analogue of the VUL **4**. Racemic **i** was chromatographed on a nonracemic HPLC column under conditions which allowed base line separation of racemic **i** into its racemates. Chiral stationary-phase HPLC analyses were performed with a Varian 3010 pump and LDC spectromonitor using chiralcel OJ columns supplied by J. T. Baker. The spectra were recorded with a LDC UV/vis recording spectrometer. UV−vis (EtOH) λ_s 250 nm; $HPLC_{ret}$ 71.68 (50% **i**), 78.63 (50% ent **i**), 98:2 hexane: ethanol, 0.07 mL/min. Under identical conditions, nonracemic **i** did not exhibit a detectable presence of its racemate.

(12) Prolonged exposure of **8** (1 week) to these reaction conditions did result in β-elimination of the bridge oxygen.

(13) In contrast to **8**, compound **10** suffered rapid β-elimination of the bridge oxygen to give a variety of products.

The last significant hurdle remaining in this construction of **1**, namely the reduction of **15** into its C_6 axial alcohol analogue **16**, was then addressed. Diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (DDMPO) (22 °C, toluene) treatment of **15** gave **16** (74%).[15] Epoxide **17** was readily obtained (92%) from **16** (KHMDS, THF, −78 °C, 2 h). Hydrogenolysis of **17** (Pd/C, CH_3OH, H_2, 22 °C, 10 h) afforded synthetic (+)-**1** (97%) demonstrated to be identical to that obtained from natural sources by all of the usual criteria.[16]

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Supplementary Material Available: General experimental procedures and characterization data are given (9 pages).

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(16) The synthetic (+)-cyclophellitol was identical to that obtained from natural sources by ^1H-NMR and ^{13}C-NMR spectra, IR spectra, optical rotation, and melting point; see ref 1.