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An unexpected access to 5-*epi*-cyclophellitol: a new cyclitol member

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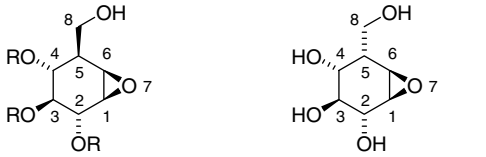
Abstract—A thorough reinvestigation of the hydroboration–oxidation of methylene epoxycyclohexane **3** has revealed the formation of a direct precursor of the hitherto unreported 5-*epi*-cyclophellitol. Hydroboration of the starting precursor **3** takes place with total and opposite stereocontrol to that previously described in the literature. The stereochemistry of this new cyclophellitol isomer has been unambiguously confirmed by comparison with reference compounds obtained by independent methods.

1. Introduction

(+)-Cyclophellitol **1a** (Fig. 1)[1] is a β-glucosidase inhibitor isolated from the mushroom *Phellinus* sp.,[2] which has also been postulated as an HIV inhibitor as well as a potential antimetastatic.[3] From a structural standpoint, **1a** can be considered a carbasugar analogue of D-glucopyranose with a characteristic β-epoxide ring. Several syntheses of **1a**, as well as those of analogues differing on the stereochemistry of one or several stereogenic centers, have been described in the literature.[4] Over the course of our current research on aminocyclitol derivatives as modulators of glicosphingolipid metabolism,[5–7] we required the synthesis of 2,3,4-tri-*O*-benzylcyclophellitol **1b** for a subsequent epoxide opening with nucleophiles.



1a: R=H; (+)-cyclophellitol
1b: R=Bn
1c: (+)-5-*epi*-cyclophellitol

Figure 1. Structures of (+)-cyclophellitol **1a**, the 2,3,4-tri-*O*-benzyl derivative **1b**, and (+)-5-*epi*-cyclophellitol **1c**.

2. Results and discussion

Among the different approaches to the cyclophellitol skeleton described in the literature, we followed the sequence described by Uzan et al.[8,9] for the synthesis of **1b** from enone **2**, obtained via a multi-step sequence from methyl-α-D-glucopyranoside.[10] The approach relied on the nucleophilic epoxidation of **2**, followed by Wittig olefination and stereoselective hydroboration–oxidation of intermediate methylene epoxycyclohexane **3** (Scheme 1). However, contrary to what was described by the above authors, the epimeric cyclophellitol derivative **4** was obtained instead.

Compound **4** was in agreement with the spectroscopic data described by Uzan et al. for this transformation.[9,11] However, a comparison of its ^{1}H NMR spectrum and physical data with those described for **1b** by other authors[12–14] shows significant and striking differences. The most noticeable ones were observed in the region between 2 and 4 ppm in the ^{1}H NMR spectrum, as well as an upfield shift of 4.2 ppm for C5 in compound **4** in the ^{13}C NMR spectrum ($CDCl_3$).[12,15] In addition, regio- and stereoselective lithium-promoted nucleophilic opening of perbenzylated epoxide **5** with NaN_3, following our previously described protocol,[16,17] afforded azido alcohol **6** (Scheme 2), whose stereochemistry was assigned by spectroscopic methods. Thus, the small J values observed for vicinal couplings C5(H)–C4(H) and C5(H)–C6(H) are in agreement with a C(5)H equatorial disposition in the presumably most stable conformation (see Scheme 2). In addition, the large J_{1-6}

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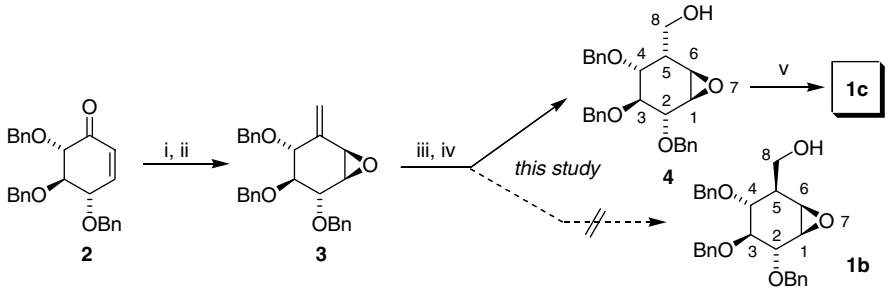
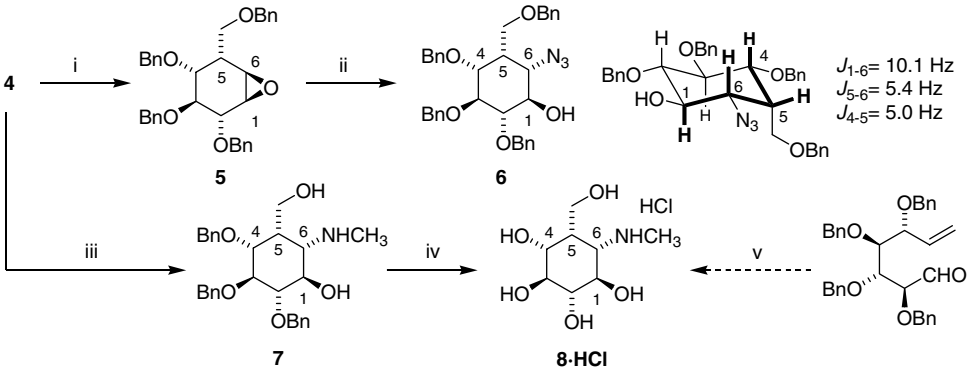


Scheme 1. Reagents and conditions: (i) *t*-BuOOH, Triton B, CH_2Cl_2; (ii) $Ph_3P{=}CHBr$, BuLi, THF; (iii) 1 M $BH_3{\cdot}THF$, THF; (iv) 30% H_2O_2, 2 N NaOH, THF–H_2O (1:1) (72%); (v) 1 M BCl_3, heptane–CH_2Cl_2 (−78 °C).



Scheme 2. Reagents and conditions: (i) BnBr, NaH, DMF; (ii) NaN_3, CH_3CN, $LiClO_4$; (iii) 2 M CH_3NH_2 (2 M in THF), CH_3CN, $LiClO_4$; (iv) BCl_3 (1 M in heptane), CH_2Cl_2, −78 °C; (v) Ref. 20.

coupling constant also observed is consistent with the expected *trans*-diaxial opening of the starting epoxide under the above conditions.[16,17] These data are clearly different from those described in the literature for the epimer of **6** at C(5),[18] the compound, which should be expected from **1b** under otherwise identical reaction conditions.[19]

In addition, the stereochemistry of **4** was unambiguously confirmed by its regio and stereoselective conversion into amino alcohol **8** (Scheme 2), and comparison of its spectroscopic data with those described in the literature for the same compound obtained by an alternative synthesis.[20,21]

3. Conclusion

In light of the above results, we can conclude that the stereochemical course of the borane reduction of **3** affords 2,3,4-tri-*O*-benzyl-5-*epi*-cyclophellitol **4** following an stereochemical course opposite to that described in the literature for this process.[8] The reaction outcome can be rationalized by assuming that the hydroboration of **3** takes place with strict stereocontrol from the face opposite to the bulky benzyloxy group at C4.[22] Debenzylation of **4** in the presence of BCl_3[23] afforded the hitherto unreported (+)-5-*epi*-cyclophellitol **1c** (Fig. 1), a new cyclophellitol isomer of the cyclitol family of natural products. In conclusion, a close investigation of a described protocol has shown the opportunity to gain access to a new isomeric cyclophellitol isomer. This finding represents a valuable addition to the current repertoire of cyclitol derivatives[4] and will allow a deeper insight into the influence of the stereochemistry of the hydroxymethyl group on the interaction of these types of systems with biological targets. Studies along this line, as well those addressed at the evaluation of amino cyclitol derivatives arising from the stereocontrolled epoxide opening of **1c**, are currently underway in our laboratory and will be reported in due course.

4. Experimental

4.1. General methods

Solvents were distilled prior to use and dried by standard methods. Melting points are uncorrected. FT-IR spectra are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions at 500 MHz or 300 MHz or 200 MHz (for ^1H) and 125 or 75 or 50 MHz (for ^{13}C), unless otherwise indicated. Chemical shifts were reported in delta (δ) units, parts per million (ppm) relative to the singlet at 7.24 ppm of $CDCl_3$ for ^1H and in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C. ESI/HRMS spectra were recorded on a Waters LCT Premier Mass spectrometer.

4.2. 2,3,4-Tri-*O*-benzyl-5-*epi*-cyclophellitol 4

A solution of 536 mg (1.25 mmol) of **3** in freshly distilled THF (5.5 mL) under Ar was treated with a $BH_3{\cdot}THF$

complex (3.8 mL of a 1 M solution in THF). The mixture was stirred for 15 min at rt, cooled to 5 °C in an ice bath and diluted with 5.5 mL of a 1:1 THF–H_2O mixture, after which it was treated with a solution of 2 M NaOH (4.0 mL) and 30% H_2O_2 (2.2 mL). After stirring for 30 min at rt, the reaction mixture was diluted with H_2O (20 mL) and extracted with Et_2O (4 × 50 mL). Usual work-up followed by flash chromatography (hexanes–EtOAc from 9:1 to 3:2) afforded 402 mg (72% yield) of **4**, as a colorless oil. IR (film, cm^{-1}): 3446, 3029, 2879, 1496, 1453, 1365; ^{13}C NMR (125 MHz, $CDCl_3$, assignments based on gHMQC): 39.8 (C5), 53.6 (C1), 55.5 (C6), 61.1 (C7), 73.0, 73.9, 74.9 (CH_2OPh), 77.2 (C4), 79.4 (C2), 80.1 (C3), 127.6–128.6 (CH_{Ar}), 137.7, 137.9, 138.6 (C_{Ar}); ^1H NMR (500 MHz, $CDCl_3$, assignments based on gCOSY and gHMQC): 2.83 (m, 1H, H5), 3.20 (d, 1H, $J_{1-6} = 3.6$ Hz, H1), 3.30 (m, 1H, H6), 3.65–3.85 (m, 3H, H3, H4, H7), 3.95 (m, 1H, H2), 4.10 (m, 1H, H7′), 4.60–4.90 (m, 6H, 3 × CH_2OPh), 7.20–7.30 (m, 15H, H_{Ar}). $[\alpha]_D = +3.7$ (*c* 1, $CHCl_3$); lit.:[1] $[\alpha]_D = +4.0$ (*c* 1, $CHCl_3$); mp: 89–91 °C; lit.:[1] mp: 44–47.5 °C.

4.3. 2,3,4,8-Tetra-*O*-benzyl-5-*epi*-cyclophellitol 5

Benzyl bromide (1.1 mL, 9.28 mmol) was added dropwise to a suspension of 95% NaH (0.54 g, 22.5 mmol) in DMF (25 mL) at rt. The resulting mixture was cooled to 5 °C (ice-water bath) and treated with a solution of **4** (3.6 g, 8.08 mmol) in DMF (20 mL). The cooling bath was removed and the reaction allowed to stir for 3 h, after which it was quenched with H_2O (15 mL) and extracted with Et_2O (3 × 50 mL). The usual work-up afforded a syrup, which was purified by flash chromatography (hexanes–EtOc 9:1) to afford 3.76 g (87% yield) of **5**.

IR (film): 3034, 3003, 2910, 1496. ^{13}CNMR ($CDCl_3$, 75 MHz): 38.3 (C6), 53.9 (C1), 56.7 (C6), 67.3 (C7), 72.9, 73.9, 75.0 (CH_2Ph), 75.9 (C2), 79.8 (C4), 80.7 (C3), 127–129 (aromatic), 138–149 (aromatic). ^1H NMR ($CDCl_3$, 300 MHz, assignments based on gHMQC): 2.88 (m, 1H, H5), 3.21(d, $J = 5.4$ Hz, 1H, H1), 3.45(m, 1H, H6), 3.65 (dd, $J = 8.1$ Hz, $J' = 5.4$ Hz, 1H, H4), 3.73–3.90 (m, 4H, H2, H3, H7, H7′), 4.55–4.88 (m, 8H), 7.2–7.4 (m, 15H). $[\alpha]_D = +31.5$ (*c* 2.8, $CHCl_3$). HRMS: *m*/*z* calcd for $C_{35}H_{36}NaO_5$ (M+23): 559.2460; found: 559.2468.

4.4. (1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-2-Azido-4,5,6-tris(benzyloxy)-3-(benzyloxymethyl)cyclohexanol 6

A solution of the starting epoxide **5** (500 mg, 1.2 mmol) in CH_3CN (10 mL) was slowly added dropwise under argon at rt over previously dried $LiClO_4$ (2.87 g, 27.0 mmol). A solution of 780 mg (12 mmol) of NaN_3 in CH_3CN (2.5 mL) was then added and the reaction mixture was stirred at 80 °C under argon. After 18 h, the reaction mixture was cooled to rt, quenched with H_2O (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation afforded the crude azido alcohol, which was purified by filtration through a plug of silica and elution with hexanes–EtOAc (9:1 to 8:2). IR (film): 3405, 3062, 3029, 2867, 2103, 1496, 1453, 1269. ^{13}C NMR ($CDCl_3$, 75 MHz): 40.8, 62.3, 63.5, 72.1, 72.7, 73.3, 75.1, 75.4, 79.9, 82.4, 84.1, 127.4, 127.7, 127.8, 127.9, 128.1, 128.3, 129.4, 138.2, 138.3, 1398.7. ^1H NMR ($CDCl_3$, 300 MHz): 2.45 (m, 1H, H5), 3.35 (t, $J = J' = 10.1$ Hz, 1H, H1), 3.52 (dd, $J = 10.1$, $J' = 5.4$ Hz, 1H, H6), 3.65 (dd, $J = 9.5$, $J' = 5.0$ Hz, 1H, H4), 3.71 (dd, $J = 14.5$, $J' = 5.5$ Hz, 1H, H7), 3.75 (dd, $J = 14.5$, $J' = 5.5$ Hz, 1H, H7′), 4.05–4.30 (m, 2H, H2, H3), 4.60–5.0 (m, 8H), 7.2–7.4 (m, 20H). HRMS: *m*/*z* calcd for $C_{35}H_{37}N_3NaO_5$ (M+23): 602.2631; found: 602.2643.

4.5. (1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-2,3,4-Tris(benzyloxy)-5-(hydroxymethyl)-6-(methylamino)cyclohexanol 7

Following the same protocol described for **6**, treatment of epoxide **4** (40 mg, 0.089 mmol) with $MeNH_2$ (0.5 mL of a 2 M solution in THF) afforded **7** (39 mg, 92% yield) after flash chromatography on 9:1 CH_2Cl_2–MeOH. ^{13}C NMR: 34.8, 47.7, 60.5, 60.9, 70.6, 72.7, 75.8, 77.1, 80.5, 82.2, 84.8, 127.9–128.9, 138.1–138.6. ^1H NMR: 2.54 (s, 3H, CH_3), 2.79 (m, 1H, H5), 3.36 (t, 1H, $J = J' = 9.7$ Hz, H1), 3.59 (dd, 1H, $J = 9.7$ Hz, $J' = 5.1$ Hz, H6), 3.68 (t, 1H, $J = J' = 9.7$ Hz, H2), 3.89–3.97 (m, 4H, H3, H4, H7, H7′), 4.56–5.00 (m, 6H, 3 × CH_2OPh), 7.27–7.34 (m, 15H, CHAr). HRMS: *m*/*z* calcd for $C_{29}H_{34}NNaO_5$ (M+23): 499.2335; found: 499.2346.

4.6. (1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-5-(Hydroxymethyl)-6-(methylamino)cyclohexane-1,2,3,4-tetraol hydrochloride 8·HCl

A solution of **7** (24 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) under nitrogen at −78 °C, was treated with 1 M BCl_3 solution in heptane (0.4 mL). After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to 0 °C and stirred for additional 24 h. The mixture was cooled to −78 °C, quenched with methanol (1 mL) and evaporated under reduced pressure. The resulting residue was taken up in a 1:1 MeOH–H_2O mixture, filtered through a small pad of charcoal, and lyophilized to afford **8·HCl** in 95% yield.

^{13}C NMR (125 MHz, DMSO-d_6, assignments based on gHSQC): 32.0 (CH_3), 40.4 (C5), 55.9 (C7), 60.6 (C6), 69.8 (C1), 70.4 (C4), 73.1 (C3), 76.4 (C2); lit.: see Ref. 2 ^{13}C NMR (125 MHz, D_2O): 32.2 (CH_3), 38.7 (C5), 57.2 (C7), 61.0 (C6), 69.5 (C1), 70.3 (C4), 72.8 (C3), 75.8 (C2). ^1H NMR (500 MHz, D_2O, assignments based on gCOSY): 2.65 (m, 1H, H5), 2.70 (s, 3H, CH_3), 3.05 (dd, $J = 11.2$, $J' = 5.5$ Hz, 1H, H6), 3.15 (app t, 1H, $J = J' = 11.2$ Hz, H2), 3.33 (app t, 1H, $J = J' = 11.2$ Hz, H3), 3.48–3.60 (m, 3H, H4, NH_2^+), 3.72 (app t, 1H, $J = J' = 11.0$ Hz, H7′), 3.78 (app t, 1H, $J = J' = 11.2$ Hz, H1), 3.85 (dd, $J = 11.0$, $J' = 5.5$ Hz, 1H, H7); lit (in DMSO-d_6, D_2O): see Ref. 20 HRMS: *m*/*z* calcd for $C_8H_{16}NNaO_5$ (M+23): 229.0926; found: 299.0915.

4.7. 5-*epi*-Cyclophellitol; (1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol 1c

Following the same protocol as described above for the synthesis of amino alcohol **8**, 22.5 mg of epoxide **4** (0.05 mmol) afforded 8.5 mg (98% yield) of 5-*epi*-cyclophellitol **1c**. ^1H NMR (500 MHz, D_2O): 2.50 (m, 1H), 3.10 (m, 1H), 3.35–3.45 (m, 2H), 3.50 (dd, 1H), 3.65 (m,

2H), 3.80 (dd, 1H). ^{13}C NMR (125 MHz, D_2O): 39.5, 55.2, 55.9, 56.8, 65.7, 69.9, 71.4. $[\alpha]_D = +65.9$ (*c* 0.4, H_2O) HRMS: *m/z* calcd for $C_7H_{12}O_5Na$ (M+23): 199.0582; found: 199.0581.

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1. The systematic nomenclature for (+)-cyclophellitol is (1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol. This numbering will be used through this work. However, (+)-cyclophellitol can also be named as the inositol derivative as 1,2-anhydro-3-deoxy-3-(hydroxymethyl)-D-*myo*-inositol. 5-*epi*-Cyclophellitol, [(1*S*,2*R*,3*S*,4*R*,5*S*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0]heptane-2,3,4-triol], can be also named as 3-*epi*-cyclophellitol, as the inositol derivative.
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