

Facile Syntheses of Cyclophellitol and its (1*R*,6*S*)-, (1*R*,2*S*,6*S*)-, (2*S*)-Diastereoisomers from (–)-Quinic acid

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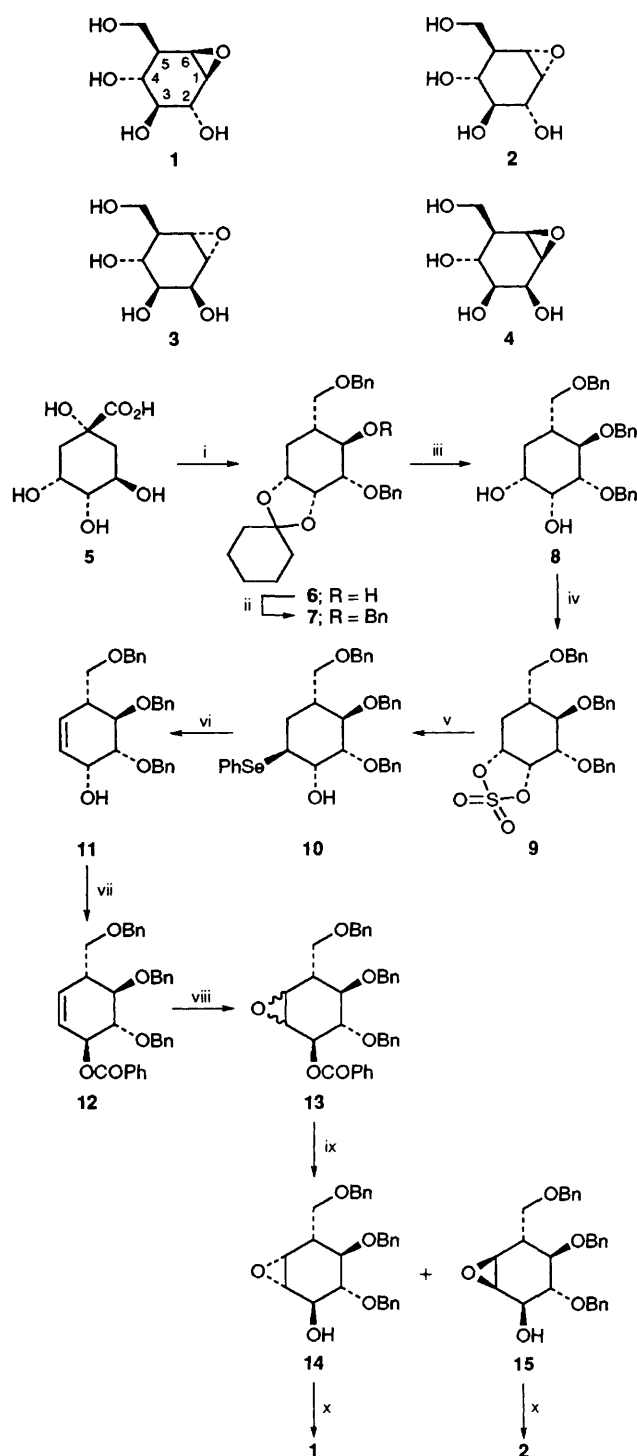
Cyclophellitol and its (1*R*,6*S*)-, (1*R*,2*S*,6*S*)-, (2*S*)-diastereoisomers are constructed from quinic acid involving a regioselective cyclic sulfate ring opening reaction, a regiospecific oxidative elimination, and an epoxidation reaction.

Cyclophellitol {(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0.]heptane-2,3,4-triol} **1**, isolated from the culture filtrates of mushroom *Phellinus* *sp.*, has been shown to be a potent inhibitor of β-D-glucosidase.¹ Interests in cyclophellitol have yielded three syntheses starting from L-glucose,^{2,3} from L-quebrachitol⁴ and from a Diels–Alder adduct.⁵ The structure of cyclophellitol **1** corresponds to a pseudo-β-D-glucopyranose whereas its (1*R*,6*S*)-diastereoisomer **2**,[†] a

pseudo-α-D-glucopyranose, has been synthesised from D-galactose and demonstrated to be a specific α-D-glucosidase inhibitor.³ Along the same vein of reasoning, (1*R*,2*S*,6*S*)- and (2*S*)-diastereoisomers of cyclophellitol, *i.e.* **3** and **4** (pseudo-α- and -β-D-mannopyranose), would be expected to be an α- and a β-D-mannosidase inhibitor, respectively. Indeed, **3** has recently been constructed from D-galactose and displayed α-D-mannosidase inhibitory activity.⁶ As part of our programme on the use of quinic acid as a homochiral precursor in organic synthesis, we have already described enantiospecific syntheses of 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC),⁷ pseudo-β-D-mannopyran-

[†] It is inappropriate to name this compound as 1,6-*epi*-cyclophellitol because *epi* implies difference in configuration at only one atom.

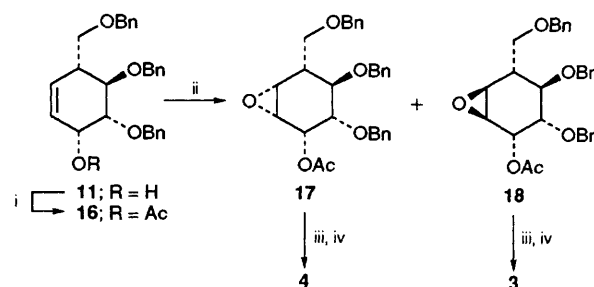
ose, pseudo- β -D-fructopyranose,⁸ pseudo- α -D-glucopyranose and pseudo- α -D-mannopyranose.⁹ This communication demonstrates further the versatility of this approach in the facile syntheses of **1**, **2**, **3** and **4**.



Scheme 1 Reagents and conditions: i, 6 steps (41.6%), see Ref. 9; ii, NaH, tetrahydrofuran, 0 °C then benzyl (Bn) bromide, Buⁿ₄NI (cat.), reflux, overnight (82%); iii, CF₃CO₂H, CH₂Cl₂, room temp., 24 h (90%); iv, triethylamine, thionyl chloride, CH₂Cl₂, 0 °C, 5 min then NaIO₄, RuCl₃, CCl₄, MeCN, H₂O, 0 °C–room temp., 1 h, (89%); v, diphenyl diselenide, sodium borohydride, EtOH, 0 °C then H₂SO₄, H₂O, (80%); vi, MCPBA, CH₂Cl₂, –40 °C then Pr₂NEt, toluene, 80 °C, (72%); vii, benzoic acid, triphenyl phosphine, diethylazodicarboxylate, toluene, 0 °C, 30 min, (93%); viii, MCPBA, CH₂Cl₂, reflux, 48 h, (66%); ix, potassium carbonate (cat.), MeOH, room temp., (95%), (**14** : **15** = 1 : 2.7); x, H₂, 5% Pd/C, EtOH, room temp., (for **1**, 98%; for **2**, 100%).

The route to cyclophellitol **1** and its (1*R*,6*S*)-diastereoisomer **2** is illustrated in Scheme 1. Our previous work has indicated that quinic acid **5** can be converted readily into the alcohol **6** in six stages with an overall yield of 41.6%.⁹ Blocking the free alcohol in **6** as the benzyl ether **7** followed by acid hydrolysis afforded the diol **8**, m.p. 110–112 °C; [α]_D²⁰ + 26.3 (c 1.2, CHCl₃).[‡] According to the Sharpless protocol,¹⁰ the diol **8** was transformed smoothly into the cyclic sulfate **9**, m.p. 106–108 °C; [α]_D²⁰ + 27.8 (c 0.9, CHCl₃). Regioselective opening of the cyclic sulfate **9** with selenide anion followed by acid hydrolysis formed the *trans*-diaxial seleno-alcohol **10** as the sole product. Oxidative elimination of **10** via the selenoxide occurred regioselectively¹¹ away from the hydroxy group, leading to the allylic alcohol **11** as a colourless oil, [α]_D²⁸ + 54.3 (c 1.3, CHCl₃). The configuration of the alcohol in **11** was inverted via the Mitsunobu reaction¹² to the β -benzoate **12**, m.p. 54.5–55.5 °C; [α]_D²⁸ + 216 (c 1.2, CHCl₃). Epoxidation of the alkene in **12** with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of inseparable oxiranes **13** which upon debenzoylation provided, after chromatography, the alcohols **14**, m.p. 76.5–78.5 °C; [α]_D²³ + 111 (c 0.4, CHCl₃) and **15**, m.p. 112–113 °C; [α]_D²⁸ + 86.4 (c 0.6, CHCl₃) in a ratio of 1 : 2.7.[§] Deprotection of **14** and **15** gave cyclophellitol **1**, m.p. 146–148 °C [lit.,¹ m.p. 149–151 °C]; [α]_D²³ + 100 (c 0.3, H₂O) {lit.,¹ [α]_D + 103 (c 0.5, H₂O)} and its (1*R*,6*S*)-diastereoisomer **2**, m.p. 155–157 °C [lit.,³ m.p. 150–152 °C]; [α]_D²³ + 83.3 (c 0.3, H₂O) {lit.,³ [α]_D + 80 (c 0.4, H₂O)}.[¶]

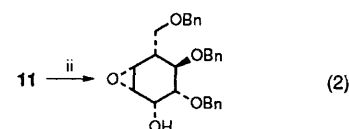
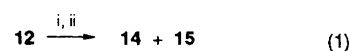
The formation of (1*R*,2*S*,6*S*)- and (2*S*)-diastereoisomers of cyclophellitol, **3** and **4**, is shown in Scheme 2. Acetylation of **11** afforded the acetate **16** in which the alkene moiety was epoxidised to give the readily separable oxiranes **17**, m.p. 59–61 °C; [α]_D²⁴ + 4.8 (c 2.7, CHCl₃), and **18**, [α]_D²⁴ + 14.3 (c



Scheme 2 Reagents and conditions: i, (MeCO)₂O (Ac₂O), pyridine, *N,N*-dimethylaminopyridine (cat.), CH₂Cl₂, room temp., 24 h (96%); ii, MCPBA, CH₂Cl₂, reflux, 42 h, (77%, **17** : **18** = 1 : 1.2); iii, potassium carbonate (cat.), MeOH, room temp., 24 h; iv, H₂, 5% Pd/C, EtOH, room temp., (two steps, for **3**, 86%; for **4**, 81%).

[‡] All new compounds gave satisfactory analytical and spectral data.

[§] Debenzoylation of **12** formed the corresponding allylic alcohol which was epoxidised to give **14** and **15** in a ratio of 5 : 95 [eqn. (1)]. Epoxidation of **11** gave **19** as the sole product [eqn. (2)].



Reagents and conditions: i, NaOMe (cat.), MeOH, room temp., 12 h, (94%); ii, MCPBA, CH₂Cl₂, room temp., 36 h, (for **14** and **15**, 70%; for **19**, 95%).

[¶] ¹³C NMR data (62.5 MHz, D₂O, dioxane was used as an internal reference at δ 67.4): for **1**, δ 44.3, 56.8, 56.9, 61.4, 67.8, 71.7, 77.1; for **2**, δ 45.0, 55.8, 58.2, 61.3, 70.4, 72.1, 74.0; for **3**, δ 45.3, 55.6, 56.6, 61.6, 66.7, 68.0, 71.2; for **4**, δ 44.8, 54.4, 56.9, 61.8, 66.4, 66.7, 73.2.

2.0, CHCl_3), in a ratio of 1 : 1.2. § Deprotection of **17** and **18** yielded **3**, m.p. 129–131 °C (lit.,⁶ oil); $[\alpha]_{\text{D}}^{23}$ –39.5 (c 0.9, H_2O) {lit.,⁶ $[\alpha]_{\text{D}}^{25}$ –76 (c 0.1, H_2O) } and 2-*epi*-cyclophellitol **4**, m.p. 148–150 °C; $[\alpha]_{\text{D}}^{24}$ + 7.0 (c 0.4, H_2O). ¶

The present approach to cyclophellitols from quinic acid is flexible and versatile and thus opens routes for facile syntheses of not only other diastereoisomeric pseudo-anhydropyranoses but also their aziridine analogues. Research in this direction is in progress.

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