Total Synthesis of Simmondsin

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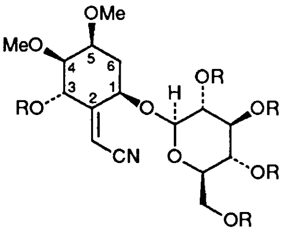
The first total synthesis of the naturally occurring cyanoglucoside, simmondsin **1**, starting from L-quebrachitol and D-glucose, is described, revealing the absolute configuration of this compound.

Simmondsin **1**, first isolated by Elliger *et al.* in 1973 from seeds of the jojoba plant, *Simmondsia californica*, shows activity in the inhibition of feeding for animals.[1] The structural study of **1** by spectral analysis and degradation methods revealed that **1** consists of D-glucose and a substituted cyclohexane derivative bearing an α,β-unsaturated nitrile group, connected by a β-glycosidic linkage.[1,2] Although a number of similar cyanoglucosides possessing interesting biological activities have been found in nature after the discovery of simmondsin,[3] the absolute configurations of **1** and other compounds in this class

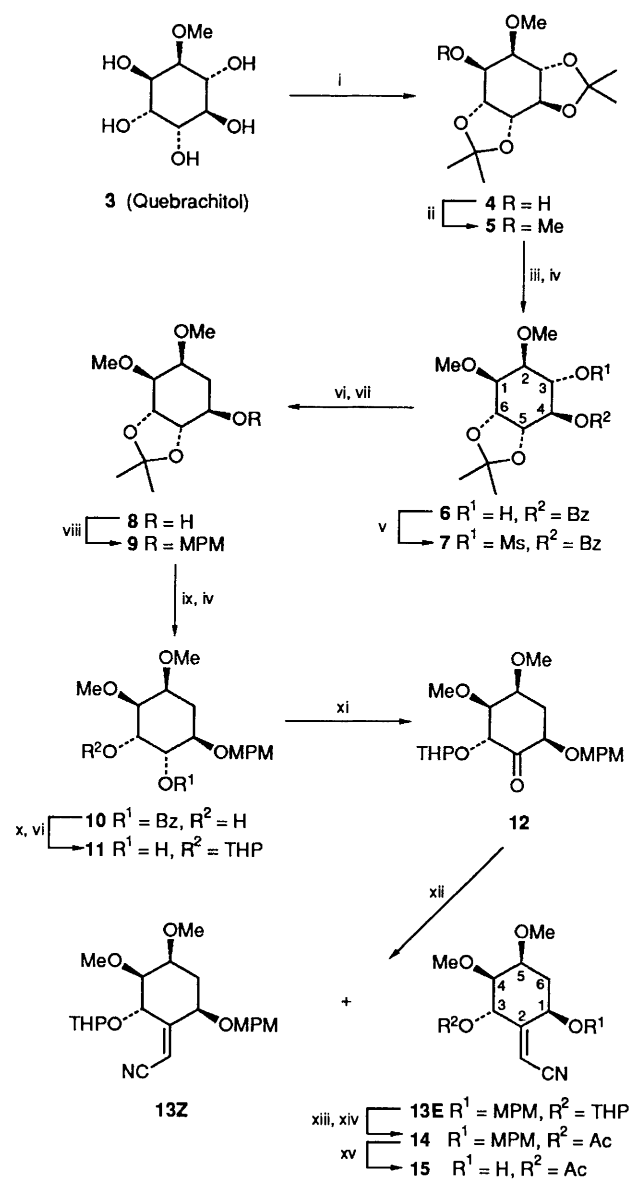


1 R = H : Simmondsin
2 R = Ac

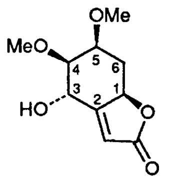
Fig. 1

have not yet been elucidated. We report herein the total synthesis of **1**, and so determined the absolute structure of the natural product.

We chose quebrachitol **3** as the homochiral starting material[4] for a synthesis of the aglycone (Scheme 1). The hydroxy group in the known **4**,[5] prepared in one step from **3**, was methylated to give **5** in 87% yield. Mild acid hydrolysis and subsequent treatment with an equimolar quantity of benzoyl chloride in pyridine mainly afforded **6**,† which was then mesylated (methanesulphonyl chloride, pyridine) to give **7** in 40% overall yield from **5**. Base treatment of **7**, followed by reduction of the resulting epoxide with lithium aluminium hydride ($LiAlH_4$), gave **8**, whose hydroxy group was protected as the *p*-methoxybenzyl (MPM) ether to provide **9** in 56% yield from **7**. The acetonide group in **9** was removed (toluene-*p*-sulphonic acid, methanol, room temp.), and the equatorial hydroxy group in the resulting diol was selectively benzoylated to give **10**† in 64% yield. Tetrahydropyranylation of **10** and subsequent deacylation (MeONa, MeOH) afforded **11** in 45% yield, whose hydroxy group was oxidised with pyridinium chlorochromate (PCC) to give ketone **12** in 80% yield. The crucial cyanomethylenation of **12** was achieved by Horner–Emmons alkenation using diethyl cyanomethylphosphonate and Bu^{t}OK in toluene, and the desired **13E** and its *Z*-isomer **13Z** were obtained in 43 and 37% yields, respectively. The geometry of the double bonds in **13E** and **13Z** were established chemically as follows: treatment of **13Z** with pyridinium toluene-*p*-sulphonate (PPTS)[6] in ethanol, followed by removal of the *O*-MPM group [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), wet CH_2Cl_2][7] gave the corresponding diol, which was treated with 1 mol dm^{-3} HCl–tetrahydrofuran (THF) (1 : 3, 50 °C) to give the butenolide **17**.† On the other hand, DDQ treatment and subsequent acid hydrolysis of **13E** [1 mol dm^{-3} HCl–THF (1 : 3), 50 °C] afforded another butenolide **16**†. From these results, the geometries of the double bonds were unambiguously determined.



Scheme 1 Bz = COPh, Ms = $MeSO_2$, MPM = *p*-$MeOC_6H_4CH_2$, THP = tetrahydropyranyl, Ts = *p*-$MeC_6H_4SO_2$. *Reagents and conditions:* i, see ref. 5; ii, NaH, MeI, *N,N*-dimethylformamide (DMF), room temp.; iii, TsOH (0.01 equiv.), MeOH, 0 °C; iv, BzCl, pyridine; v, MsCl, pyridine, 50 °C; vi, MeONa, MeOH; vii, $LiAlH_4$, THF, room temp.; viii, NaH, MPMCl, DMF, room temp.; ix, TsOH (0.1 equiv.), MeOH, room temp.; x, dihydropyran, TsOH, CH_2Cl_2; xi, PCC,CH_2Cl_2; xii, $NCCH_2P(O)(OEt)_2$, Bu^{t}OK, toluene; xiii, PPTS, EtOH; xiv, Ac_2O, pyridine; xv, DDQ, CH_2Cl_2–H_2O (10 : 1), room temp.



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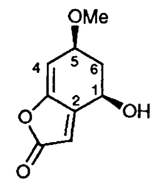

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Removal of the *O*-THP group in **13E** (PPTS, EtOH) and acetylation gave **14** in 82% yield. The *O*-MPM group was then deprotected (DDQ, wet CH_2Cl_2)[7] to provide the aglycone **15**,† suitable for condensation, in 50% yield. Glucosidation of **15** was achieved by condensation of **15** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate[8] (1,2-di-

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† All new compounds were characterised by 270 MHz ^1H NMR, IR and mass spectrometric and/or elemental analyses. Selected ^1H NMR (270 MHz) data for **6**: ($CDCl_3$–D_2O) δ 1.39, 1.53 (each s, 6H, isopropylidene), 3.50, 3.56 (each s, 6H, OMe × 2), 3.62 (dd, 1H, $J_{1,2}$ 2.4, $J_{2,3}$ 4.9 Hz, 2-H), 3.83 (dd, 1H, $J_{1,6}$ 4.9 Hz, 1-H), 3.95 (dd, 1H, $J_{3,4}$ 7.3 Hz, 3-H), 4.45 (dd, 1H, $J_{5,6}$ 6.4 Hz, 6-H), 4.51 (dd, 1H, $J_{4,5}$ 8.3 Hz, 5-H), 4.95 (dd, 1H, 4-H) and 7.45–8.13 (m, 5H, phenyl). For **15**: ($CDCl_3$) δ 1.60 (ddd, 1H, $J_{5,6}$ $J_{1,6}$ 2.9, $J_{6,6}$ 15.1 Hz, 6-H), 2.19 (s, 3H, OAc), 2.48 (ddd, 1H, $J_{5,6}$ 3.4, $J_{1,6}$ 3.4 Hz, 6′-H), 3.17 (dd, 1H, $J_{3,4}$ 9.8, $J_{4,5}$ 2.7 Hz, 4-H), 3.46, 3.59 (each s, 6H, OMe × 2), 4.01 (m, 1H, 5-H), 4.23 (d, 1H, $J_{1,OH}$ 9.8 Hz, OH), 4.92 (m, 1H, 1-H), 5.32 (d, 1H, $J_{3,vinyl}$ 2.0 Hz, vinyl) and 6.15 (dd, 1H, 3-H). For **16**: ($CDCl_3$) δ 1.74 (ddd, 1H, $J_{5,6}$ $J_{1,6}$ $J_{6,6'}$ 11.2 Hz, 6-H), 2.16 (d, 1H, $J_{3,OH}$ 2.9 Hz, OH), 2.62 (m, 1H, 6′-H), 3.44, 3.49 (each s, 6H, OMe × 2), 3.82 (m, 2H, 4,5-H) 4.91 (dd, 1H, $J_{3,4}$ 2.9 Hz, 3-H), 5.09 (ddd, 1H, $J_{1,6'}$ 6.3, $J_{1,vinyl}$ 1.5 Hz, 1-H) and 5.98 (d, 1H, vinyl). For **17**: ($CDCl_3$) δ 2.12 (ddd, 1H, $J_{1.6}$ 7.8, $J_{5.6}$ 6.8, $J_{6.6'}$ 13.2 Hz, 6-H), 2.32 (ddd, 1H, $J_{1,6'}$ δ $J_{5.6'}$ 3.9 Hz, 6′-H), 3.46 (s, 3H, OMe), 4.26 (ddd, 1H, $J_{4,5}$ 3.9 Hz, 5-H), 4.74 (m, 1H, 1-H), 6.03 (dd, 1H, $J_{4,vinyl}$ 2.0 Hz, 4-H) and 6.12 (dd, 1H, $J_{1,vinyl}$ < 1Hz, vinyl).

chloroethane, $BF_3\cdot OEt_2$, molecular sieves 4 Å, 0 °C, 30 min)[8,9] to give the β-glucoside **2** in 27% yield.‡ Finally, the *O*-acetyl groups in **2** were removed (MeONa, MeOH, 0 °C) to give simmondsin **1**, quantitatively. The spectral (^{1}H, ^{13}C NMR and IR) and physical properties of synthetic **1** {m.p. 94–95 °C, $[\alpha]_D^{25}$ − 69° (*c* 0.57, MeOH)} were in good accordance with those of the natural simmondsin {m.p. 98–99 °C, $[\alpha]_D^{25}$ − 73° (*c* 0.86, MeOH)}. From this synthesis, therefore, the absolute configuration of simmondsin was determined to be (2*E*)-(1*R*,3*S*,4*R*,5*S*)-2-(cyanomethylene)-3-hydroxy-4,5-dimethoxycyclohexyl β-D-glucopyranoside as depicted in Fig. 1.

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‡ The low yield of the glucosidation step might be attributed to the instability of **15** towards acidic reaction conditions.

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