Synthesis and Absolute Configuration of the Naturally Occurring Cyano Glucoside Simmondsin

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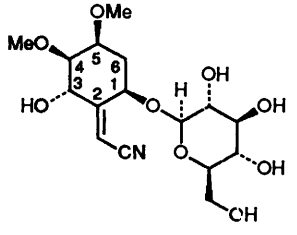
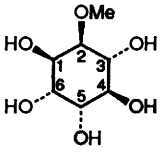
The synthesis of the naturally occurring cyano glucoside simmondsin, **1**, is reported. An optically active cyclitol, L-quebrachitol **2**, was stereoselectively converted into the aglycone **19**, which was condensed with D-glucose, followed by deprotection to provide simmondsin **1**. This synthesis successfully determined the absolute configuration of the natural product.

Simmondsin **1** was first isolated by Elliger *et al.* in 1973 from seeds of the jojoba plant, *Simmondsia californica*, and was reported to exhibit feeding inhibitory activity in animals.[1] The structural study of simmondsin **1**, with spectral analysis and degradation studies, by Elliger's group showed that simmondsin **1** consists of D-glucose bonded to a substituted cyclohexane derivative bearing an α,β-unsaturated nitrile group *via* a β-glycosidic linkage.[1,2] After the discovery of simmondsin, a number of similar cyano glucosides possessing interesting biological activities, *viz.* griffonin,[3] menisdaurin,[4] lithospermoside[5] and its epimer,[6] were isolated from plants. However, in spite of its intriguing structure as well as its unique biological activity, there has been no report of the total synthesis of simmondsin **1**, and the absolute configurations of simmondsin **1** and of other natural products in this class have not been elucidated. In this article we document a total synthesis and absolute structure of simmondsin **1** with full experimental details.[7]



1 Simmondsin



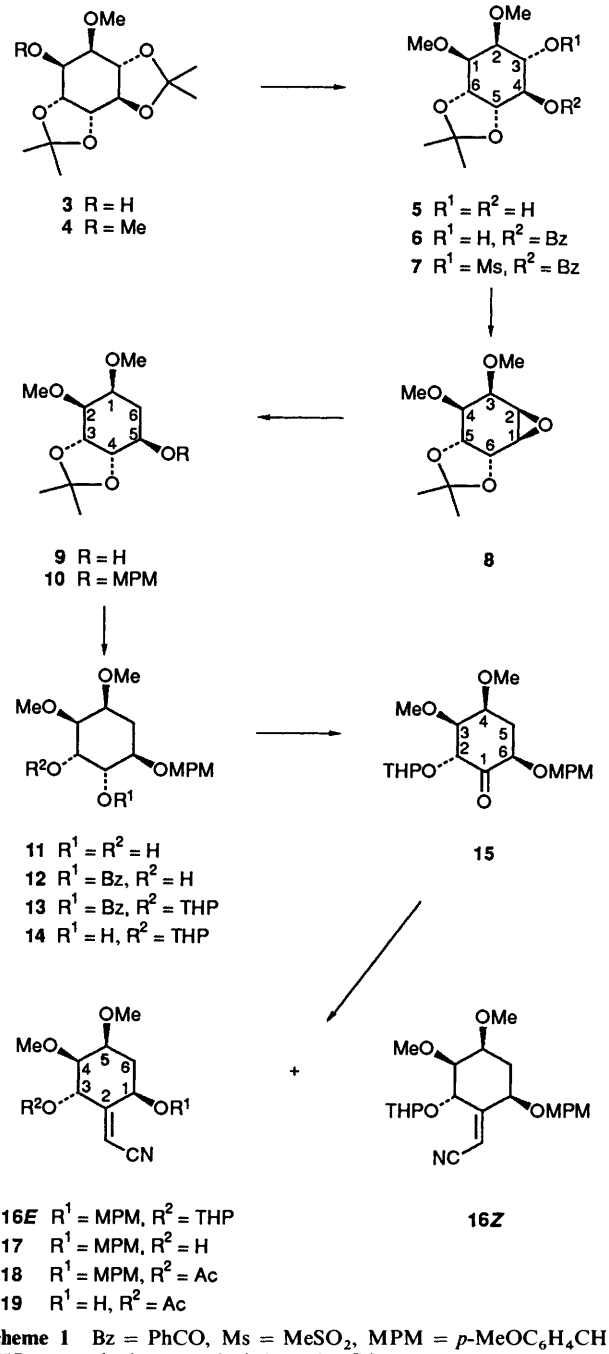
2 L-Quebrachitol

Although the absolute configuration of the aglycone moiety of simmondsin was not clear, the relative structural similarity of the aglycone to the naturally occurring optically active cyclitol L-quebrachitol, compound **2**,[8,9] led us to choose compound **2** as the starting material for the synthesis of the aglycone moiety. Thus, four asymmetric centres (C-1, -2, -4 and -6) of compound **2** were envisaged to correlate with C-4, -5, -1 and -3 of the aglycone, respectively. The hydroxy group in the known di-*O*-isopropylidene derivative **3**,[9b] prepared in one step from L-quebrachitol **2**, was *O*-methylated to give the fully protected derivative **4** in 96% yield. The *trans* *O*-isopropylidene group in compound **4** was selectively cleaved by mild acid hydrolysis to afford the diol **5**, which was treated with an equimolar quantity of benzoyl chloride in pyridine to give two mono-*O*-benzoyl derivatives in a ratio of ~5:1 in 60% yield from compound **4** (Scheme 1).

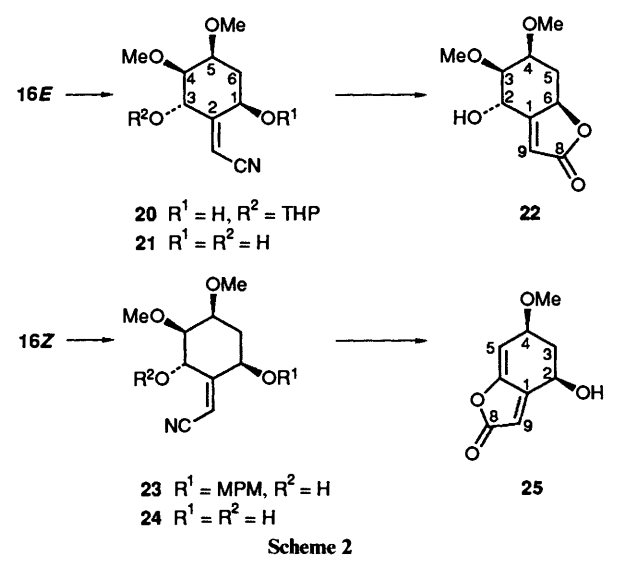
^{1}H NMR analysis of the major benzoate with spin–spin decoupling revealed that the proton attached to the carbon bearing the benzoyloxy group (δ 4.95) was coupled with 5-H (δ 4.51, $J_{4,5}$ 5.3 Hz) and there was observed no coupling between the proton at δ 4.95 and 2-H (δ 3.62), indicating that the major benzoate should be 4-*O*-benzoate **6**. Reaction of compound **6** with methanesulfonyl chloride provided mesylate **7** in 83% yield, which was then treated with sodium methoxide to afford the epoxide **8**. Lithium aluminium hydride reduction of epoxide **8** afforded the single alcohol **9** in 91% yield. In the ^{1}H NMR spectrum of the alcohol **9**, there was observed no coupling between the signal at δ 4.03 (5-H) and 1-H (δ 3.80), and the signal at δ 4.03 was coupled with 4-H (δ 4.29) and the C-6 methylene, supporting the assigned structure of compound **9**. The predominant formation of compound **9** might be rationalized by the presence of a *cis*-*O*-isopropylidene group at C-5 and -6 in compound **8**, which would not have allowed the approach of the reagent to C-1, due to stereoelectronic effects. The hydroxy group in compound **9** was protected as its *p*-methoxybenzyl ether to afford compound **10**, whose *O*-isopropylidene group was removed by acid hydrolysis to provide diol **11** in 75% yield from the alcohol **9**. An equatorial hydroxy group in diol **11** was selectively acylated with benzoyl chloride to give monoester **12** (87%). After tetrahydropyranylation of the remaining hydroxy function to give the tetraether **13**, the 4-OH group was regenerated by basic hydrolysis to afford the alcohol **14** in 87% yield from compound **12**. Oxidation of the alcohol **14** with pyridinium chlorochromate (PCC) gave ketone **15** in 87% yield. The crucial cyanomethylenation of ketone **15** was achieved by Horner–Emmons alkenation using diethyl cyanomethylphosphonate and Bu^{t}OK in toluene, and the desired acylonitrile **16E** and its *Z*-isomer **16Z** were isolated in 43 and 37% yield, respectively.

To establish the geometry of the double bonds in products **16E** and **16Z**, they were converted into butenolides **22** and **25**, respectively (Scheme 2). Hence, treatment of isomer **16E** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in wet dichloromethane[10] afforded compound **20**, whose THP group was removed under acidic conditions to give diol **21**. Treatment of diol **21** with aq. acid provided the known butenolide[2] **22**, previously obtained from natural simmondsin by acid hydrolysis, in 11% overall yield from **16E**. The physical (m.p. 138–139 °C; lit.,[2] 138–140 °C) and spectral properties of the butenolide **22** were in good accord with those of an authentic sample[2] reported by Elliger. On the other hand, removal of THP group in compound **16Z** gave the alcohol **23**, which was then treated with DDQ to afford diol **24**. Acid treatment of diol **24** generated another butenolide, **25**, in 9% overall yield from **16Z**. The ^{1}H NMR data as well as the mass spectrum (see Experimental section) supported the assigned structure. From these results, the geometries of the double bonds in compounds **16E** and **16Z** were unambiguously determined.

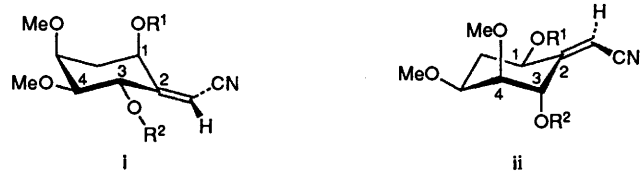
The ^{1}H NMR analysis of compounds having an α,β-unsaturated nitrile function suggested that the conformations of these compounds are strongly influenced by the geometry of the



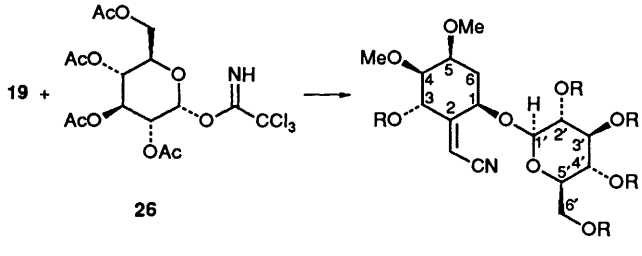
Scheme 1 Bz = PhCO, Ms = $MeSO_2$, MPM = *p*-$MeOC_6H_4CH_2$, THP = tetrahydropyran-2-yl, Ac = MeCO



Scheme 2



16Z, **23** and **24**), large coupling constants (~11 Hz) between 1-H and 6-H, and long-range couplings (~2 Hz) between 1-H and the vinyl proton, were observed. These results, as well as the small coupling constants $J_{3,4}$ < 5.2 Hz, and lack of coupling between 3-H and the vinyl protons, suggested the structure ii for these compounds. This significant conformational change between *trans*- and *cis*-olefins should probably be ascribed to steric factors. The severe allylic 1,3 strain[12] between the hydroxy and cyano groups would make conformation i and ii preferable for *trans*- and *cis*-olefins, respectively. It is noteworthy that conformation i is stable for *trans*-olefin compounds in spite of the presence of a 1,3-diaxial interaction of hydroxy functions. It has been reported by Elliger[1,2] that natural simmondsin also adopts conformation i.



Scheme 3

Removal of the *O*-THP group in compound **16E** to give the alcohol **17**, and acetylation gave compound **18** in 97% yield. The MPM protecting group was then removed to provide the aglycone **19**, suitable for condensation, in 72% yield. β-Glucosidation of aglycone **19** was successfully achieved by Schmidt's protocol.[13] Thus, treatment of compound **19** with trichloroacetimidate derivative **26**[14] in the presence of BF_3·OEt_2 and molecular sieves (1,2-dichloroethane) afforded the β-glucoside **27** in 27% yield (Scheme 3). The Koenigs–Knorr condensation of compound **19** with glucopyranosyl bromides or chlorides with various metal salts as catalysts gave less satisfactory

double bond. Compounds with a *trans* (to the C-2–C-3 bond) olefin always adopt conformation i whereas those having a *cis* (to C-2–C-3 bond) olefin adopt conformation ii. In the ^{1}H NMR spectrum of compound **18**, for example, 3-H was observed at δ 5.96 as dd ($J_{3,4}$ 8.8 and $J_{3,vinyl}$ 1.8 Hz). The large coupling constant between 3-H and 4-H revealed that the acetoxy group at C-3 has an equatorial orientation, and the relatively large long-range coupling between 3-H and the vinyl proton suggested that the C-3–H bond is parallel to the π orbital.[11] The signal of 1-H in compound **18** appeared at δ 4.56 with $J_{1,6}$ 4.8 and $J_{1,6'}$ 3.7 Hz, indicating that 1-H is equatorially oriented, and the lack of coupling between the vinyl proton suggested that the C-1–H bond is orthogonal to the π orbital,[11] supporting our hypothesis that compound **18** adopts conformation i. On the other hand, in the ^{1}H NMR of the compounds having a *cis*-olefin to C-2–C-3 bond (compounds

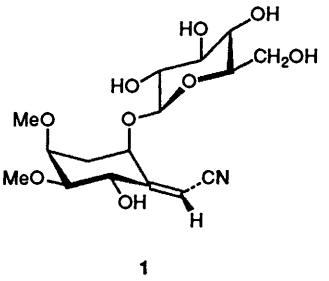


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Fig. 1 Absolute configuration of simmondsin 1

results, and the low yield of the condensation might be attributable to the relative instability of substrate **19** towards acidic reaction conditions. The ^{1}H NMR spectrum, as well as the m.p., of product **27** were in good accord with those of an authentic sample, reported by Elliger[1] [m.p. 164–165 °C (lit.,[1] 165–166 °C)], and the β-glucosidic linkage was confirmed from the ^{1}H NMR data (*J* 7.8 Hz at the anomeric centre). Finally, *O*-acetyl groups were removed by treatment of compound **27** with sodium methoxide in methanol to provide simmondsin **1**, quantitatively. The spectral (^{1}H, ^{13}C NMR and IR) and physical properties {m.p. 94–95 °C; $[\alpha]_D^{24}$ −69* (MeOH)} were in good accord with those of natural simmondsin {m.p. 98–99 °C; $[\alpha]_D^{25}$ −73 (MeOH)}. From this synthesis, therefore, the absolute configuration of simmondsin was determined to be (2*Z*)-(1*R*,3*S*,4*R*,5*S*)-2-cyanomethylene-3-hydroxy-4,5-dimethoxycyclohexyl β-D-glucopyranoside as depicted in Fig. 1.

Experimental

M.p.s were determined on a Mitamura-riken micro hot stage and are uncorrected. ^{1}H NMR spectra were measured with a JEOL JNM EX-90 (90 MHz) and a JEOL JNM-GSX 270 (270 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform, unless otherwise noted; *J*-values are given in Hz. ^{13}C NMR spectra were taken on a JEOL JNM-GSX 270 (67 MHz) spectrometer with $^{13}CDCl_3$ as internal standard (δ_C 77.0 ppm) for solutions in deuteriochloroform. High-resolution mass spectra were measured by a JEOL JMS-DX-302 spectrometer with EI mode (70 eV). Optical rotations were measured with a JASCO DIP-370 instrument. IR spectra were taken with a JASCO IR-810 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. pH Values were measured using pH paper.

1L-3,4:5,6-*Di*-O-*isopropylidene*-1,2-*di*-O-*methyl*-chiro-*inositol*† **4**.—To a stirred solution of 1L-3,4:5,6-di-*O*-isopropylidene-2-*O*-methyl-*chiro*-inositol‡ **3** (35 mg, 0.13 mmol) in *N*,*N*-dimethylformamide (DMF) (0.6 cm^3) at 0 °C was added 60% sodium hydride (6.1 mg, 0.15 mmol). After the mixture had been stirred at 0 °C for 40 min, iodomethane (0.016 cm^3, 0.26 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. After addition of methanol at 0 °C, the mixture was concentrated, and then diluted with EtOAc. The organic layer was washed with brine, then dried. Evaporation of the solvent left an oil which was chromatographed on a column of silica gel (1 g) with EtOAc–toluene (1:10, v/v) as eluent to give *compound* **4** (35 mg, 96%) as a syrup (Found: C, 58.0; H, 8.1. $C_{14}H_{24}O_6$ requires C, 58.3; H, 8.4%); $[\alpha]_D^{28}$ −16 (*c* 1.0, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.37, 1.43, 1.44 and 1.51 (each 3 H, 4 s, 2 × CMe_2), 3.44 (1 H, m, 2-H), 3.53 and 3.54 (each 3 H, 2 s, 2 × OMe), 3.61–3.78 (2 H, m, 3- and 4-H), 3.84 (1 H, m, 1-H) and 4.29–4.40 (2 H, m, 5- and 6-H).

1L-5,6-O-*Isopropylidene*-1,2-*di*-O-*methyl*-chiro-*inositol*§ **5**.—To a stirred solution of compound **4** (26 mg, 0.088 mmol) in methanol (0.5 cm^3) at 0 °C, was added toluene-*p*-sulfonic acid monohydrate (PTSA) (0.2 mg), and the mixture was stirred at 0 °C for 7 h. The reaction mixture was then neutralized by addition of triethylamine (pH 7 ~ 8), and was then concentrated to give a residue, which was chromatographed on a column of silica gel (1 g) with methanol–chloroform (1:20) as eluent to give *compound* **5** (18 mg, 81%) as a syrup (Found: C, 52.9; H, 7.9. $C_{11}H_{20}O_6$ requires C, 53.2; H, 8.1%); $[\alpha]_D^{28}$ −68 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 (OH); δ_H(270 MHz; $CDCl_3$) 1.37 and 1.49 (each 3 H, 2 s, CMe_2), 3.31 (1 H br s, OH), 3.33–3.68 (3 H, m, 2-, 3-, 4-H), 3.53 and 3.57 (each 3 H, 2 s, 2 × OMe), 3.73 (1 H, br s, OH), 3.82 (1 H, dd, $J_{1,2}$ 2.8, $J_{1,6}$ 3.9, 1-H), 4.15 (1 H, dd, $J_{4,5}$ 6.1, $J_{5,6}$ 6.1, 5-H) and 4.34 (1 H, dd, 6-H).

1L-4-O-*Benzoyl*-5,6-O-*isopropylidene*-1,2-*di*-O-*methyl*-chiro-*inositol*¶ **6**.—To a stirred solution of the diol **5** (40 mg, 0.16 mmol) in pyridine (0.6 cm^3) at 0 °C was added benzoyl chloride (0.026 cm^3, 0.23 mmol). After the mixture had been stirred at 0 °C for 27 h, methanol was added and the mixture was concentrated to give a residue, which was dissolved in EtOAc. The organic solution was washed successively with 0.5 mol dm^{-3} aq. HCl, saturated aq. sodium hydrogen carbonate, and brine, then dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (1 g) with EtOAc–toluene (1:10) as eluent to give a 5:1 mixture of compound **6** and its regioisomer (34 mg, 60%) as a syrup. This compound was used in the next step without further purification. A part of this *syrup* was further purified with silica gel chromatography and used as an analytical sample (Found: C, 61.15; H, 6.7. $C_{18}H_{24}O_7$ requires C, 61.4; H, 6.9%); $[\alpha]_D^{27}$ −94 (*c* 0.9, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3470 (OH) and 1730 (ester); δ_H(270 MHz; $CDCl_3$) 1.39 and 1.53 (each 3 H, 2 s, CMe_2), 3.50 and 3.56 (each 3 H, 2 s, 2 × OMe), 3.62 (1 H, dd, $J_{1,2}$ 2.4, $J_{2,3}$ 4.9, 2-H), 3.83 (1 H, dd, $J_{1,6}$ 4.9, 1-H), 3.95 (1 H, m, 3-H), 4.45 (1 H, dd, $J_{5,6}$ 6.4, 5-H), 4.51 (1 H, dd, $J_{4,5}$ 8.3, 5-H), 4.95 (1 H, dd, $J_{3,4}$ 7.3, 4-H) and 7.45–8.13 (5 H, m, Ph).

1L-4-O-*Benzoyl*-5,6-O-*isopropylidene*-1,2-*di*-O-*methyl*-3-O-*methylsulfonyl*-chiro-*inositol*‖ **7**.—To a solution of a 5:1 mixture of compound **6** and its regioisomer (29 mg, 0.083 mmol) in pyridine (0.5 cm^3) at 0 °C was added methanesulfonyl chloride (0.013 cm^3, 0.17 mmol). After being stirred at room temperature for 6 h, the mixture was treated with methanol and the resulting mixture was concentrated to give a residue. This was diluted with EtOAc and then washed successively with 0.5 mol dm^{-3} aq. HCl, saturated aq. sodium hydrogen carbonate, and brine, and dried. Evaporation of the solvent left a crystalline residue, which was purified on preparative TLC (PLC) with ethyl acetate–toluene (1:4) to give pure *compound* **7** (30 mg, 83%) as needles, m.p. 140.5–141.5 °C (from EtOH) (Found: C, 52.7; H, 6.05. $C_{19}H_{26}O_9S$ requires C, 53.0; H, 6.1%); $[\alpha]_D^{27}$ −46 (*c* 0.98, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1730 (ester); δ_H(270 MHz; $CDCl_3$) 1.36 and 1.59 (each 3 H, 2 s, CMe_2), 2.94 (3 H, s, SO_2Me), 3.56 and 3.58 (each 3 H, 2 s, 2 × OMe), 3.77 (1 H, dd, $J_{1,2}$ 2.4, $J_{2,3}$ 6.8, 2-H), 3.94 (1 H, dd, $J_{1,6}$ 3.4, 1-H), 4.37–4.44 (2 H, m, 5- and 6-H),

* Units for $[\alpha]_D$ are now 10^{-1} deg cm^2 g^{-1}.

† Systematically: 1L-1,2:3,4-di-*O*-isopropylidene-5,6-di-*O*-methyl-*chiro*-inositol.

‡ Systematically: 1L-1,2:3,4-di-*O*-isopropylidene-5-*O*-methyl-*chiro*-inositol.

§ Systematically: 1L-1,2-*O*-isopropylidene-5,6-di-*O*-methyl-*chiro*-inositol.

¶ Systematically: 1L-3-*O*-benzoyl-1,2-di-*O*-isopropylidene-5,6-di-*O*-methyl-*chiro*-inositol.

‖ Systematically: 1L-3-*O*-benzoyl-1,2-*O*-isopropylidene-5,6-di-*O*-methyl-4-*O*-methylsulfonyl-*chiro*-inositol.

4.98 (1 H, dd, $J_{3,4}$ 8.8, 3-H), 5.48 (1 H, dd, $J_{4,5}$ 7.8, 4-H) and 7.44–8.11 (5 H, m, Ph).

1D-1,2-*Anhydro*-5,6-O-*isopropylidene*-3,4-*di*-O-*methyl*-allo-*inositol* **8**.—To a stirred solution of the mesyl ester **7** (85 mg, 0.20 mmol) in methanol (1.5 cm^3) at 0 °C was added 1 mol dm^{-3} sodium methoxide in methanol (0.30 cm^3; 0.30 mmol) and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized by addition of IR-120B resin (H^+-form) and insoluble materials were removed by filtration. The filtrate was concentrated to give a residue, which was diluted with EtOAc. The organic solution was washed successively with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent gave a syrup, which was chromatographed on a silica gel column (2 g) with EtOAc–toluene (1:5) as eluent to afford *compound* **8** (38 mg, 84%) as a crystalline residue, m.p. 63–64 °C (from EtOH) (Found: C, 57.3; H, 7.6. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); $[\alpha]_D^{27}$ +30 (*c* 1.0, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.37 and 1.45 (each 3 H, 2 s, CMe_2), 3.24 (1 H, dd, $J_{1,2}$ 2.9, $J_{1,5}$ 1.0, 1-H), 3.42 (1 H, ddd, $J_{2,3}$ 2.0, $J_{2,4}$ 1.0, 2-H), 3.52 and 3.54 (each 3 H, 2 s, 2 × OMe), 3.72 (1 H, ddd, $J_{3,4}$ 4.4, $J_{4,5}$ 4.4, 4-H), 3.94 (1 H, dd, 3-H), 4.41 (1 H, ddd, $J_{5,6}$ 5.9, 5-H) and 4.55 (1 H, d, 6-H).

1D-(1,2,5/3,4)-3,4-O-*Isopropylidene*-1,2-*di*-O-*methylcyclohexanepentaol* **9**.—To a stirred suspension of lithium aluminium hydride (31 mg, 0.83 mmol) in tetrahydrofuran (THF) (1 cm^3) at 0 °C was added a solution of the epoxide **8** (38 mg, 0.17 mmol) in THF (1 cm^3) dropwise. After the mixture had been stirred at room temperature for 3 h, water was added and the product was extracted with EtOAc. The organic layer was washed with brine and dried. Removal of the solvent left a syrup, which was chromatographed on a silica gel column (1 g), with EtOAc–toluene (1:2) as eluent, to give *compound* **9** (35 mg, 91%) as a syrup (Found: C, 56.6; H, 8.6. $C_{12}H_{18}O_6$ requires C, 56.9; H, 8.7%); $[\alpha]_D^{27}$ +48 (*c* 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480 (OH); δ_H(270 MHz; $CDCl_3$) 1.38 and 1.49 (each 3 H, 2 s, CMe_2), 1.91 (1 H, ddd, $J_{1,6}$ 3.4, $J_{5,6}$ 4.9, $J_{6,6'}$ 14.7, 6-H), 2.09 (1 H, ddd, $J_{1,6'}$ 4.4, $J_{5,6'}$ 4.4, 6-H′), 3.35 (1 H, dd, $J_{1,2}$ 2.9, $J_{2,3}$ 6.4, 2-H), 3.47 and 3.53 (each 3 H, 2 s, 2 × OMe), 3.80 (1 H, m, 1-H), 4.03 (1 H, m, 5-H), 4.29 (1 H, dd, $J_{3,4}$ 5.9, $J_{4,5}$ 4.4, 4-H) and 4.36 (1 H, dd, 3-H).

1D-(1,2,5/3,4)-3,4-O-*Isopropylidene*-5-O-(p-*methoxybenzyl*)-1,2-*di*-O-*methylcyclohexanepentaol* **10**.—To a stirred solution of compound **9** (18 mg, 0.066 mmol) in DMF (0.5 cm^3) at 0 °C was added 60% sodium hydride (12 mg, 0.31 mmol). After the mixture had been stirred at 0 °C for 45 min, *p*-methoxybenzyl chloride (0.042 cm^3, 0.31 mmol) was added, and the resulting mixture was stirred at room temperature for 12 h before being poured into ice–water and stirred for 1 h, and the product was extracted with EtOAc. The extract was washed successively with saturated aq. sodium hydrogen carbonate and brine, then dried over anhydrous sodium carbonate and sodium sulfate. Removal of the solvent afforded a syrup, which was purified by PLC with acetone–toluene (1:5) to give *compound* **10** (22 mg, 81%) as a syrup (Found: C, 64.5; H, 7.7. $C_{19}H_{28}O_6$ requires C, 64.75; H, 8.0%); ν_{max}(neat)/cm^{-1} 1610 (*para*-substituted phenyl); δ_H(90 MHz; $CDCl_3$) 1.37 and 1.43 (each 3 H, 2 s, CMe_2), 1.69–2.18 (2 H, m, 6-H_2), 3.38 (3 H, s, OMe), 3.42–3.68 (3 H, m, 1-, 2- and 5-H), 3.51 and 3.80 (each 3 H, 2 s, 2 × OMe), 4.19 (1 H, dd, $J_{3,4}$ 6.3, $J_{4,5}$ 6.3, 4-H), 4.33 (1 H, dd, $J_{2,3}$ 3.8, 3-H), 4.54 and 4.72 (each 1 H, 2 d, *J* 11.0, ArCH_2) and 6.79–7.38 (4 H, m, ArH).

1D-(1,2,5/3,4)-5-O-(p-*Methoxybenzyl*)-1,2-*di*-O-*methylcyclohexanepentaol* **11**.—A solution of compound **10** (89 mg, 0.25 mmol) and PTSA (10 mg, 0.053 mmol) in methanol (2 cm^3) was stirred at room temperature for 4 h. The reaction mixture was neutralized by addition of triethylamine (pH 7~8), and was then concentrated to give a residue, which was chromatographed on a silica gel column (3 g), with EtOAc–hexane (2:3) as eluent, to give *compound* **11** (72 mg, 92%) as a syrup (Found: C, 61.1; H, 7.7. $C_{16}H_{24}O_6$ requires C, 61.5; H, 7.7%); $[\alpha]_D^{27}$ −65 (*c* 0.87, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 (OH) and 1610 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.71 (1 H, ddd, $J_{1,6}$ 11.7, $J_{5,6}$ 11.7, $J_{6,6'}$ 11.7, 6-H), 2.21 (1 H, ddd, $J_{1,6'}$ 3.9, $J_{5,6'}$ 3.9, 6-H′), 3.41 and 3.48 (each 3 H, 2 s, 2 × OMe), 3.52–3.61 (2 H, m, 1- and 5-H), 3.71 (1 H, dd, $J_{1,2}$ 3.4, $J_{2,3}$ 3.4, 2-H), 3.80 (1 H, m, 4-H), 3.81 (3 H, s, OMe), 4.21 (1 H, dd, $J_{3,4}$ 3.4, 3-H), 4.38 and 4.64 (each 1 H, 2 d, *J* 10.7, ArCH_2) and 6.87–7.30 (4 H, m, ArH).

1D-(1,2,5/3,4)-4-O-*Benzoyl*-5-O-(p-*methoxybenzyl*)-1,2-*di*-O-*methylcyclohexanepentaol* **12**.—To a stirred solution of the diol **11** (241 mg, 0.772 mmol) in pyridine (4 cm^3) was added benzoyl chloride (0.099 cm^3, 0.85 mmol) and the resulting mixture was stirred at 70 °C for 13 h. After addition of methanol at 0 °C, the reaction mixture was concentrated to give a residue, which was dissolved in EtOAc and washed successively with 1 mol dm^{-3} aq. HCl, saturated aq. sodium hydrogen carbonate, and brine, then dried. Removal of the solvent left a syrup, which was chromatographed on a silica gel column (10 g) with EtOAc–toluene (1:7) as eluent, to give *benzoate* **12** (281 mg, 87%) as a crystalline residue, m.p. 77–78 °C (from EtOH) (Found: C, 66.4; H, 6.7. $C_{23}H_{28}O_7$ requires C, 66.3; H, 6.8%); $[\alpha]_D^{27}$ −47 (*c* 1.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3440 (OH), 1710 (ester) and 1605 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.58 (1 H, br s, OH), 1.94 (1 H, ddd, $J_{1,6}$ 11.2, $J_{5,6}$ 11.2, $J_{6,6'}$ 11.2, 6-H), 2.21 (1 H, m, 6-H′), 3.42 and 3.53 (each 3 H, 2 s, 2 × OMe), 3.67 (1 H, ddd, $J_{1,2}$ 3.4, $J_{1,6'}$ 3.4, 1-H), 3.74 (1 H, dd, $J_{2,3}$ 3.4, 2-H), 3.76 (3 H, s, OMe), 3.90 (1 H, ddd, $J_{4,5}$ 9.3, $J_{5,6}$ 4.4, 5-H), 4.42 (1 H, dd, $J_{3,4}$ 2.9, 3-H), 4.49 and 4.60 (each 1 H, 2 d, *J* 11.7, ArCH_2), 5.38 (1 H, dd, 4-H) and 6.74–8.04 (9 H, m, ArH).

1D-(1,2,5/3,4)-4-O-*Benzoyl*-5-O-(p-*methoxybenzyl*)-1,2-*di*-O-*methyl*-3-O-(*tetrahydropyran*-2-*yl*)*cyclohexanepentaol* **13**.—A mixture of compound **12** (1.59 g, 3.82 mmol), 3,4-dihydro-2*H*-pyran (1.05 cm^3, 11.5 mmol) and PTSA (15 mg, 0.079 mmol) in dichloromethane (20 cm^3) was stirred at room temperature for 30 min. After neutralization with triethylamine (pH 7~8), the reaction mixture was concentrated, and then diluted with EtOAc. The organic solution was washed successively with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (60 g) with EtOAc–toluene (1:8) to give *compound* **13** (1.87 g, 98%) as a syrup (Found: C, 66.8; H, 7.2. $C_{28}H_{36}O_8$ requires C, 67.2; H, 7.25%); $[\alpha]_D^{26}$ −53 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1720 (ester) and 1610 (*para*-substituted phenyl); δ_H(90 MHz; $CDCl_3$) 1.33–1.71 (4 H, m, 2 methylenes of THP), 1.73–2.42 (4 H, m, methylene of THP and 6-H_2), 3.30–4.08 (5 H, m, 1-, 2- and 5-H, and OCH_2 of THP), 3.41, 3.54 and 3.77 (each 3 H, 3 s, 3 × OMe), 4.40 (1 H, dd, $J_{2,3}$ 4.3, $J_{3,4}$ 3.3, 3-H), 4.50–4.66 (3 H, m, ArCH_2 and –OCHO– of THP), 5.36 (1 H, dd, $J_{4,5}$ 9.8, 4-H) and 6.67–8.13 (9 H, m, ArH).

1D-(1,2,5/3,4)-5-O-(p-*Methoxybenzyl*)-1,2-*di*-O-*methyl*-3-O-(*tetrahydropyran*-2-*yl*)*cyclohexanepentaol* **14**.—To a stirred solution of compound **13** (1.61 g, 3.22 mmol) in methanol (25 cm^3) at room temperature was added 1 mol dm^{-3} sodium methoxide in methanol (6.44 cm^3, 6.44 mmol). After being stirred at 50 °C for 9 h, the reaction mixture was neutralized with resin (pH 7; IR 120B, H^+-form) and the insoluble materials were removed by filtration. The filtrate was concentrated to give a residue, which was chromatographed on a silica gel column (40 g) with EtOAc–toluene (1:3) as eluent, to give *compound* **14** (1.13 g, 89%) as a syrup (Found: C, 63.7; H, 7.85. $C_{21}H_{32}O_7$ requires C, 63.6; H, 8.1%); $[\alpha]_D^{27}$ −20 (*c* 1.9, $CHCl_3$);

ν_{max}(neat)/cm^{-1} 3450 (OH) and 1610 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.48–1.58 (4 H, m, 2 methylenes of THP), 1.63–1.82 (3 H, m, methylene of THP and 6-H), 2.22 (1 H, m, 6-H′), 3.40 and 3.48 (each 3 H, 2 s, 2 × OMe), 3.51–3.84 (5 H, m, 1-, 2-, 5-H, and OCH_2 of THP), 3.80 (3 H, s, OMe), 4.18–4.66 (4 H, m, ArCH_2 and 3- and 4-H), 4.82 (1 H, m, –OCHO– of THP) and 6.85–7.34 (4 H, m, ArH).

2D-(2/3,4,6)-6-O-(p-*Methoxybenzyl*)-3,4-*di*-O-*methyl*-2-O-(*tetrahydropyran*-2-*yl*)-2,3,4,6-*tetrahydroxycyclohexanone* **15**.—To a stirred suspension of PCC (3.07 g, 14.3 mmol) and molecular sieves 4 Å (powder; 3.0 g) in dichloromethane (30 cm^3) at 0 °C was added a solution of compound **14** (1.13 g, 2.85 mmol) in dichloromethane (10 cm^3) dropwise. After being stirred at room temperature for 6 h, the reaction mixture was partially concentrated and chromatographed on a silica gel column (60 g), with diethyl ether as eluent, to give the *ketone* **15** (973 mg, 87%) as a syrup (Found: C, 63.9; H, 7.4. $C_{21}H_{30}O_7$ requires C, 63.9; H, 7.7%); $[\alpha]_D^{26}$ +68 (*c* 0.58, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1740 (C=O) and 1610 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.45–1.82 (6 H, m, 3 methylenes of THP), 2.04–2.37 (2 H, m, 5-H_2), 3.38–4.78 (9 H, m, 2-, 3-, 4-, 6-H, ArCH_2, and OCH_2 and –OCHO– of THP), 3.43, 3.47 and 3.80 (each 3 H, 3 s, 3 × OMe) and 6.82–7.38 (4 H, m, ArH).

(2E)-(1R,3S,4S,5S)-2-*Cyanomethylene*-4,5-*dimethoxy*-1-(p-*methoxybenzyloxy*)-3-(*tetrahydropyran*-2-*yloxy*)*cyclohexane* **16E** *and its* 2Z-*Isomer* **16Z**.—To a stirred solution of ketone **15** (992 mg, 2.51 mmol) and diethyl cyanomethylphosphonate (2.03 cm^3, 12.5 mmol) in toluene (15 cm^3) under Ar was added potassium *tert*-butoxide (704 mg, 6.28 mmol), and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with EtOAc, washed with brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (25 g) with EtOAc–toluene (1:12) as eluent to give, first, *compound* **16Z** (388 mg, 37%) as a syrup (Found: C, 66.0; H, 7.4; N, 3.5. $C_{23}H_{31}NO_6$ requires C, 66.2; H, 7.5; N, 3.35%); $[\alpha]_D^{27}$ −36 (*c* 0.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2210 (CN) and 1610 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.45–1.63 (5 H, m, 2 methylenes of THP and 6-H), 1.66–1.80 (2 H, m, methylene of THP), 2.33 (1 H, ddd, $J_{1.6'}$ 5.2, $J_{5.6'}$ 4.8, $J_{6.6'}$ 11.4, 6-H′), 3.41 and 3.52 (each 3 H, 2 s, 2 × OMe), 3.53 (1 H, m, 4-H), 3.54 (1 H, m, OCH of THP), 3.68 (1 H, ddd, $J_{4.5}$ 3.3, $J_{5.6}$ 12.1, 5-H), 3.81 (3 H, s, OMe), 3.91 (1 H, m, OCH of THP), 4.10 (1 H, ddd, $J_{1.6}$ 11.9, $J_{1.vinyl}$ 2.4, 1-H), 4.40 1 H, m, –OCHO– of THP), 4.46 and 4.59 (each 1 H, 2 d, *J* 11.7, ArCH_2), 5.11 (1 H, d, $J_{3.4}$ 3.4, 3-H), 5.82 (1 H, d, vinyl) and 6.86–7.25 (4 H, m, ArH).

The second fraction gave *regioisomer* **16E** (451 mg, 43%) as a syrup (Found: C, 66.0; H, 7.45; N, 3.3%); $[\alpha]_D^{23}$ −28 (*c* 0.92, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2180 (CN) and 1630 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.44–1.64 (5 H, m, 2 methylenes of THP and 6-H), 1.73–1.84 (2 H, m, methylene of THP), 2.50 (1 H, ddd, $J_{1.6'}$ 3.4, $J_{5.6'}$ 3.4, $J_{6.6'}$ 15.6, 6-H′), 3.13 (1 H, dd, $J_{3.4}$ 9.3, $J_{4.5}$ 3.4, 4-H), 3.41 (3 H, s, OMe), 3.44 (1 H, m, OCH of THP), 3.48 (3 H, s, OMe), 3.74 (1 H, m, 5-H), 3.80 (3 H, s, OMe), 3.83 (1 H, m, OCH of THP), 4.33 and 4.52 (each 1 H, 2 d, *J* 11.7, ArCH_2), 4.64 (1 H, dd, $J_{1.6}$ 3.4, 1-H), 4.82 (1 H, m, –OCHO– of THP), 4.83 (1 H, m, 3-H), 5.88 (1 H, d, $J_{3.vinyl}$ 1.5, vinyl) and 6.83–7.30 (4 H, m, ArH).

(2Z)-(1R,3S,4R,5S)-2-*Cyanomethylene*-3-*hydroxy*-4,5-*dimethoxy*-1-(p-*methoxybenzyloxy*)*cyclohexane* **17**.—A mixture of compound **16E** (46 mg, 0.11 mmol) and pyridinium toluene-*p*-sulfonate (PPTS) (3 mg) in ethanol (1 cm^3) was stirred at 50 °C for 4 h. After addition of triethylamine, the mixture was concentrated to give a residue, which was chromatographed on a silica gel column (1 g) with EtOAc–toluene (1:3) as eluent to give *compound* **17** (36 mg, 97%) as a syrup (Found: M^+, 333.1560. $C_{18}H_{23}NO_5$ requires *M*, 333.1576); $[\alpha]_D^{26}$ −12 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3380 (OH), 2180 (CN), and 1630 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.46 (1 H, m, 6-H), 1.65 (1 H, br s, OH), 2.64 (1 H, ddd, $J_{1.6'}$ 2.6, $J_{5.6'}$ 2.9, $J_{6.6'}$ 16.1, 6-H′), 2.99 (1 H, dd, $J_{3.4}$ 10.3, $J_{4.5}$ 2.9, 4-H), 3.44, 3.48 and 3.80 (each 3 H, 3 s, 3 × OMe), 3.93 (1 H, ddd, $J_{5.6}$ 2.9, 5-H), 4.36 and 4.50 (each 1 H, 2 d, *J* 11.4, ArCH_2), 4.67 (1 H, dd, $J_{1.6}$ 3.7, 1-H), 4.87 (1 H, dd, $J_{3.vinyl}$ 2.2, 3-H), 5.84 (1 H, d, vinyl) and 6.84–7.29 (4 H, m, ArH).

(2E)-(1R,3S,4S,5S)-3-*Acetoxy*-2-*cyanomethylene*-4,5-*dimethoxy*-1-(p-*methoxybenzyloxy*)*cyclohexane* **18**.—A mixture of compound **17** (8.9 mg, 0.027 mmol) and acetic anhydride (0.5 cm^3) in pyridine (0.5 cm^3) was stirred at room temperature for 2 h. After addition of methanol, the mixture was concentrated to give a residue, which was chromatographed on a silica gel column (1 g) with EtOAc–toluene (1:3) as eluent to give *acetate* **18** (10.8 mg, 100%) as a crystalline residue, m.p. 70–73 °C (from EtOH) (Found: C, 63.6; H, 6.65; N, 3.85. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%); $[\alpha]_D^{22}$ −2 (*c* 0.54, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2150 (CN), 1780 (C=O) and 1650 (*para*-substituted phenyl); δ_H(270 MHz; $CDCl_3$) 1.63 (1 H, ddd, $J_{1.6}$ 3.7, $J_{5.6}$ 3.7, $J_{6.6'}$ 15.0, 6-H), 2.15 (3 H, s, OAc), 2.46 (1 H, ddd, $J_{1.6'}$ 4.8, $J_{5.6'}$ 4.8, 6-H′), 3.28 (1 H, dd, $J_{3.4}$ 8.8, $J_{4.5}$ 2.9, 4-H), 3.42, 3.47 and 3.80 (each 3 H, 3 s, 3 × OMe), 3.82 (1 H, m, 5-H), 4.35 (1 H, d, *J* 11.4, ArCHH), 4.56 (1 H, m, 1-H), 4.60 (1 H, d, *J* 11.4, ArCHH), 5.47 (1 H, d, $J_{3.vinyl}$ 1.8, vinyl), 5.96 (1 H, dd, 3-H) and 6.88–7.32 (4 H, m, ArH).

(2E)-(1R,3S,4S,5S)-3-*Acetoxy*-2-*cyanomethylene*-1-*hydroxy*-4,5-*dimethoxycyclohexane* **19**.—To a stirred mixture of compound **18** (164 mg, 0.438 mmol) in dichloromethane (12 cm^3)–water (1.5 cm^3) was added DDQ (149 mg, 0.657 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2, washed with water, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (5 g) with EtOAc–toluene (1:6) as eluent to afford *compound* **19** (80. 2 mg, 72%) as a syrup (Found: C, 56.2; H, 6.6; N, 5.4. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5%); $[\alpha]_D^{18}$ −9 (*c* 0.35, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH), 2160 (CN) and 1780 (C=O); δ_H(270 MHz; $CDCl_3$) 1.60 (1 H, ddd, $J_{1.6}$ 2.9, $J_{5.6}$ 2.9, $J_{6.6'}$ 15.1, 6-H), 2.19 (3 H, s, OAc), 2.48 (1 H, ddd, $J_{1.6'}$ 3.4, $J_{5.6'}$ 3.4, 6-H′), 3.17 (1 H, dd, $J_{3.4}$ 9.8, $J_{4.5}$ 2.7, 4-H), 3.46 and 3.59 (each 3 H, 2 s, 2 × OMe), 4.01 (1 H, m, 5-H), 4.23 (1 H, d, $J_{1.OH}$ 9.8, OH), 4.92 (1 H, m, 1-H), 5.32 (1 H, d, $J_{3,vinyl}$ 2.0, vinyl) and 6.15 (1 H, dd, $J_{3.4}$ 9.8, 3-H); δ_C(67 MHz; $CDCl_3$) 20.7, 32.9, 58.7, 59.8, 69.2, 70.2, 77.4, 84.7, 93.7, 115.1, 161.5 and 169.0

(2E)-(1R,3S,4S,5S)-2-*Cyanomethylene*-1-*hydroxy*-4,5-*dimethoxy*-3-(*tetrahydropyran*-2-*yloxy*)*cyclohexane* **20**.—To a stirred mixture of compound **16E** (5.5 mg, 0.013 mmol) in dichloromethane (0.9 cm^3)–water (0.05 cm^3) was added DDQ (6.0 mg, 0.026 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc and washed successively with saturated aq. sodium thiosulfate, saturated aq. sodium hydrogen carbonate, and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (0.5 g) with EtOAc–toluene (1:6) as eluent to afford *compound* **20** (2.9 mg, 74%) as a syrup (Found: M^+, 297.1570. $C_{12}H_{17}NO_5$ requires *M*, 297.1576); $[\alpha]_D^{18}$ −22 (*c* 1.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480 (OH) and 2160 (CN); δ_H(270 MHz; $CDCl_3$) 1.49–1.65 (5 H, m, 2 methylenes of THP and 6-H), 1.79–1.85 (2 H, m, methylene of THP), 2.47 (1 H, ddd, $J_{1.6'}$ 3.3, $J_{5.6'}$ 3.3, $J_{6.6'}$ 15.4, 6-H′), 3.08 (1 H, dd, $J_{3.4}$ 9.9, $J_{4.5}$ 2.9, 4-H), 3.49 (3 H, s, OMe), 3.52 (1 H, m, OCH of THP), 3.56 (3 H, s, OMe), 3.81 (1 H, m, OCH of THP), 3.95 (1 H, m, 5-H),

4.19 (1 H, d, $J_{1.OH}$ 9.9, OH), 4.86 (1 H, dd, $J_{3,vinyl}$ 2.2, 3-H), 4.91 (1 H, m, –OCHO– of THP), 4.95 (1 H, m, 1-H) and 5.78 (1 H, d, vinyl).

(2E)-(1R,3S,4R,5S)-2-*Cyanomethylene*-1,3-*dihydroxy*-4,5-*dimethoxycyclohexane* **21**.—A mixture of compound **20** (18 mg, 0.061 mmol) and PPTS (2 mg) in ethanol (1 cm^3) was stirred at 55 °C for 6 h. After addition of triethylamine, the mixture was concentrated to give a residue, which was chromatographed on a silica gel column (1 g) with EtOAc–toluene (1:4) as eluent to give *diol* **21** (8.1 mg, 62%) as a syrup (Found: M^+, 213.1012. $C_{18}H_{23}NO_5$ requires *M*, 213.1001); $[\alpha]_D^{23}$ +13 (*c* 0.55, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3380 (OH) and 2180 (CN); δ_H(270 MHz; $CDCl_3$) 1.55 (1 H, ddd, $J_{1.6}$ 2.9, $J_{5.6}$ 2.9, $J_{6.6'}$ 15.6, 6-H), 2.51 (1 H, ddd, $J_{1.6'}$ 2.9, $J_{5.6'}$ 2.9, 6-H'), 2.83 (1 H, d, $J_{3.OH}$ 2.0, 3-OH), 2.99 (1 H, dd, $J_{3.4}$ 9.8, $J_{4.5}$ 2.9, 4-H), 3.52 and 3.57 (each 3 H, 3 s, 2 × OMe), 4.03 (1 H, m, 5-H), 4.08 (1 H, d, $J_{1.OH}$ 9.8, 1-OH), 4.84 (1 H, ddd, $J_{3,vinyl}$ 2.0, 3-H), 4.91 (1 H, ddd, 1-H) and 5.67 (1 H, d, vinyl).

(2S,3R,4S,6R)-2-*Hydroxy*-3,4-*dimethoxy*-7-*oxabicyclo*-[4.3.0]*non*-1(9)-*en*-8-*one* **22**.—A mixture of the diol **21** (19.5 mg, 0.092 mmol) in THF (1.5 cm^3)–aq. 1 mol dm^{-3} HCl (0.5 cm^3) was heated at 55 °C for 5 h. The mixture was then poured into ice–water and then extracted three times with EtOAc. The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (1 g) with acetone–toluene (1:5) as eluent to afford lactone **22** (4.6 mg, 24%) as a crystalline residue, m.p. 138–139 °C (from benzene) (lit.,[2] 138–140 °C) (Found: C, 56.1; H, 6.6. Calc. for $C_{10}H_{14}O_5$: C, 56.1; H, 6.6%); $[\alpha]_D^{22}$ −168 (*c* 0.1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3410 (OH) and 1750 (C=O); δ_H(270 MHz; $CDCl_3$) 1.74 (1 H, ddd, $J_{4.5}$ 11.2, $J_{5.6}$ 11.2, $J_{5.5'}$ 11.2, 5-H), 2.16 (1 H, d, $J_{2.OH}$ 2.9, OH), 2.62 (1 H, m, 5-H'), 3.44 and 3.49 (each 3 H, 2 s, 2 × OMe), 3.77–3.87 (2 H, m, 3- and 4-H), 4.91 (1 H, dd, $J_{2.3}$ 2.9, 2-H), 5.09 (1 H, ddd, $J_{5'.6}$ 6.3, $J_{6.9}$ 1.5, 6-H) and 5.98 (1 H, d, 9-H).

(2E)-(1R,3S,4R,5S)-2-*Cyanomethylene*-3-*hydroxy*-4,5-*dimethoxy*-1-(p-*methoxybenzyloxy*)*cyclohexane* **23**.—A mixture of compound **16Z** (115 mg, 0.275 mmol) and PPTS (10 mg) in ethanol (2 cm^3) was stirred at 50 °C for 25 h. After addition of triethylamine, the mixture was concentrated to give a residue, which was chromatographed on a silica gel column (1 g) with EtOAc–toluene (1:5) as eluent to give *compound* **23** (66 mg, 71%) as a syrup (Found: C, 64.6; H, 6.9; N, 4.1. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.2%); $[\alpha]_D^{27}$ −13 (*c* 0.78, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440 (OH), 2220 (CN) and 1610 (*para*-substituted phenyl); δ_H(90 MHz; $CDCl_3$) 1.84 (1 H, m, 6-H), 2.31 (1 H, m, 6-H'), 3.41 and 3.52 (each 3 H, 2 s, 2 × OMe), 3.61–3.88 (2 H, m, 4- and 5-H), 3.82 (3 H, s, OMe), 4.30 (1 H, ddd, $J_{1.6}$ 11.0, $J_{1.6'}$ 5.1, $J_{1,vinyl}$ 2.1, 1-H), 4.45 and 4.61 (each 1 H, 2 d, *J* 10.4, ArCH_2), 5.08 (1 H, d, $J_{3.4}$ 3.6, 3-H), 5.72 (1 H, d, vinyl) and 6.78–7.32 (4 H, m, ArH).

(2Z)-(1R,3S,4R,5S)-2-*Cyanomethylene*-1,3-*dihydroxy*-4,5-*dimethoxycyclohexane* **24**.—To a stirred mixture of compound **23** (132.5 mg, 0.397 mmol) in dichloromethane (9 cm^3)–water (1 cm^3) was added DDQ (90.2 mg, 0.397 mmol), and the mixture was stirred at room temperature for 32 h. The reaction mixture was diluted with EtOAc and washed successively with saturated aq. sodium thiosulfate, saturated aq. sodium hydrogen carbonate, and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (3 g) with acetone–toluene (1:3) as eluent to afford *diol* **24** (68 mg, 80%) as a syrup (Found: C, 56.05; H, 6.9; N, 6.5. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%); $[\alpha]_D^{27}$ −55 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3410 (OH) and 2220 (CN); δ_H(90 MHz; $CDCl_3$) 1.82–2.58 (2 H, m, 6-H_2), 3.46 and 3.53 (each 3 H, 2 s, 2 × OMe), 3.63 (1 H, dd, $J_{3.4}$ 5.2, $J_{4.5}$ 2.7, 4-H), 3.86 (1 H, ddd, $J_{5.6}$ 4.5, $J_{5.6'}$ 9.2, 5-H), 4.54 (1 H, m, 1-H), 5.08 (1 H, d, 3-H) and 5.69 (1 H, d, $J_{1,vinyl}$ 2.0, vinyl).

(2R,4S)-2-*Hydroxy*-4-*methoxy*-7-*oxabicyclo*[4.3.0]*nona*-1(9),5-*dien*-8-*one* **25**.—A mixture of the diol **24** (25 mg, 0.12 mmol) in THF (1.5 cm^3)–aq. 1 mol dm^{-3} HCl (0.5 cm^3) was heated at 55 °C for 10 h. The mixture was poured into ice–water and then extracted three times with EtOAc. The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a residue, which was chromatographed on a silica gel column (1 g) with acetone–toluene (1:6) as eluent to afford *lactone* **25** (3.4 mg, 16%) as a syrup (Found: M^+, 182.0586. $C_9H_{10}O_4$ requires *M*, 182.0579); $[\alpha]_D^{26}$ −117 (*c* 0.27, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH) and 1770 (C=O); δ_H(270 MHz; $CDCl_3$) 2.12 (1 H, ddd, $J_{2.3}$ 7.8, $J_{3.4}$ 6.8, $J_{3.3'}$ 13.2, 3-H), 2.32 (1 H, ddd, $J_{2.3'}$ 3.9, $J_{3'.4}$ 3.9, 3-H'), 3.46 (3 H, s, OMe), 4.26 (1 H, ddd, $J_{4.5}$ 3.9, 4-H), 4.74 (1 H, m, 2-H), 6.03 (1 H, dd, $J_{5.9}$ 2.0, 5-H) and 6.12 (1 H, m, 9-H).

(2E)-(1R,3S,4S,5S)-3-*Acetoxy*-2-*cyanomethylene*-4,5-*dimethoxycyclohexyl* 2′,3′,4′,6′-*Tetra*-O-*acetyl*-β-D-*glucopyranoside* (*Simmondsin Penta*-O-*acetate*) **27**.—To a stirred mixture of compound **19** (11.8 mg, 0.0462 mmol), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate[14] **26** (31.9 mg, 0.0647 mmol), and molecular sieves 4 Å (20 mg) in 1,2-dichloroethane (0.5 cm^3) at 0 °C under Ar was added BF_3•OEt_2 (0.006 cm^3, 0.023 mmol). After being stirred at 0 °C for 20 min, the reaction mixture was quenched by addition of saturated aq. sodium hydrogen carbonate. The product was extracted with dichloromethane, washed with brine, and dried. Removal of the solvent afforded a residue, which was chromatographed on a silica gel column (1 g) with acetone–hexane (1:4) as eluent to give the glycoside **27** (7.2 mg, 27%) as a crystalline residue, m.p. 164–165 °C [from ethyl acetate–hexane (1:1)] (lit.,[1] 165–166 °C) (Found: C, 53.3; H, 5.9; N, 2.4. Calc. for $C_{26}H_{35}NO_{14}$: C, 53.3; H, 6.0; N, 2.4%); $[\alpha]_D^{22}$ −24 (*c* 0.39, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2220 (CN) and 1760 (C=O); δ_H(270 MHz; $CDCl_3$) 1.62 (1 H, ddd, $J_{1.6a}$ 4.4, $J_{5.6a}$ 4.4, $J_{6a.6b}$ 15.1, 6-H[a]), 2.00, 2.02, 2.04, 2.08 and 2.14 (each 3 H, 5 s, 5 × OAc), 2.44 (1 H, ddd, $J_{1.6b}$ 4.4, $J_{5.6b}$ 4.4, 6-H[b]), 3.20 (1 H, dd, $J_{3.4}$ 9.3, $J_{4.5}$ 3.4, 4-H), 3.35 and 3.42 (each 3 H, 2 s, 2 × OMe), 3.66 (1 H, ddd, $J_{4'.5'}$ 9.8, $J_{5'.6'a}$ 2.4, $J_{5'.6'b}$ 3.9, 5′-H), 3.81 (1 H, m, 5-H), 4.03 (1 H, dd, $J_{6'a.6'b}$ 12.2, 6′-H[b]), 4.25 (1 H, dd, 6′-H[a]), 4.70 (1 H, d, $J_{1'.2'}$ 7.8, 1′-H), 4.79 (1 H, dd, 1-H), 5.04–5.23 (3 H, m, 2′-, 3′- and 4′-H), 5.43 (1 H, d, $J_{3,vinyl}$ 2.0, vinyl) and 6.03 (1 H, dd, 3-H); δ_C(67 MHz; $CDCl_3$) 20.6 (3 C), 20.7 (2 C), 30.7, 56.7, 58.4, 61.3, 68.2, 70.8, 71.0, 72.1, 72.9, 74.3, 75.8, 82.7, 95.9, 101.0, 115.6, 159.5, 168.4, 168.9, 169.3, 170.3 and 170.7.

(2Z)-(1R,3S,4R,5S)-2-(*Cyanomethylene*)-3-*hydroxy*-4,5-*dimethoxycyclohexyl* β-D-*Glucopyranoside* (*Simmondsin*) **1**.—To a stirred solution of simmondsin penta-*O*-acetate **27** (4.5 mg, 0.0077 mmol) in methanol (0.5 cm^3) at 0 °C was added 1 mol dm^{-3} sodium methoxide in methanol (0.0077 cm^3, 0.0077 mmol), and the resulting solution was stirred at 0 °C for 2 h. The reaction mixture was neutralized by addition of resin (ph 7; IR-120B, H^+-form), and the resin was removed by filtration. Removal of the solvent left a syrup, which was chromatographed on a silica gel column (1 g) with methanol–EtOAc (1:10) as eluent to provide compound **1** (3.2 mg, quantitatively) as a crystalline residue, m.p. 94–95 °C [from methanol–acetone (1:1)] (natural product 98–99 °C; lit.,[1] 95–100 °C) (Found: C, 49.9; H, 6.6; N, 3.5. Calc. for $C_{16}H_{25}NO_9$•$0.5H_2O$: C, 50.0; H, 6.8; N, 3.6%); $[\alpha]_D^{24}$ −69 (*c* 0.57, MeOH) [natural product, $[\alpha]_D^{25}$ −73 (*c* 0.86, MeOH)]; ν_{max}(KBr)/cm^{-1} 3410 (OH) and 2220 (CN);

δ_H(270 MHz; [$^2H_4$]MeOH) 1.69 (1 H, ddd, $J_{1.6a}$ 3.9, $J_{5.6a}$ 3.9, $J_{6a.6b}$ 15.1, 6-H^a), 2.51 (1 H, ddd, $J_{1.6b}$ 3.9, $J_{5.6b}$ 3.9, 6-H^b), 3.14 (1 H, dd, $J_{3.4}$ 9.3, $J_{4.5}$ 2.9, 4-H), 3.20–3.39 (4 H, m, 2′-, 3′-, 4′- and 5′-H), 3.45 and 3.47 (each 3 H, 2 s, 2 × OMe), 3.65 (1 H, dd, $J_{5'.6'a}$ 6.1, $J_{6'a.6'b}$ 12.2, 6′-H^a), 3.83 (1 H, dd, $J_{5'.6'b}$ 2.0, 6′-H^b), 3.91 (1 H, m, 5-H), 4.38 (1 H, d, $J_{1'.2'}$ 7.3, 1′-H), 4.73 (1 H, dd, $J_{3,vinyl}$ 2.0, 3-H), 4.88 (1 H, m, 1-H) and 5.70 (1 H, d, vinyl); δ_C(67 MHz; [$^2H_4$]MeOH) 32.0, 58.1, 58.5, 62.7, 70.2, 71.3, 74.7, 76.4, 76.7, 78.1, 86.3, 95.2, 104.0, 117.5 and 166.4.

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