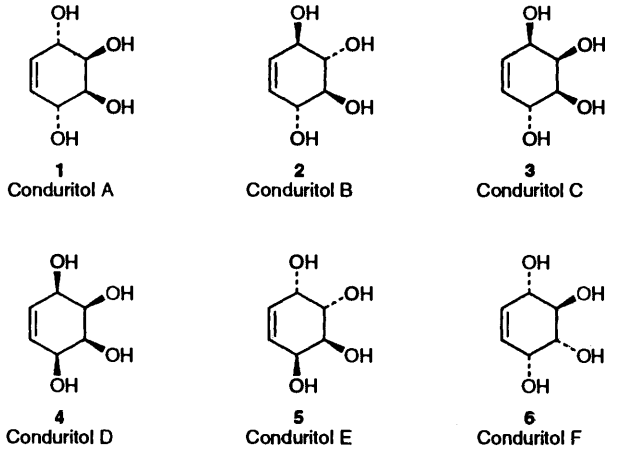
Synthesis of Conduritols A, (+)-C and (−)-C from D-Galactose

Hari Babu Mereyala* and Bapu Reddy Gaddam
Bio-Organic Laboratory, Indian Institute of Chemical Technology, Hyderabad-500007, India

A general approach for the stereoselective synthesis of conduritols A **1**, (+)-C **3** and (−)-C **3** starting from D-galactose is described. The utility of the key cyclohexenone intermediate **11** leading to the synthesis of conduritols **1**, (+)-**3** and (−)-**3** by straightforward synthetic manipulations is described.

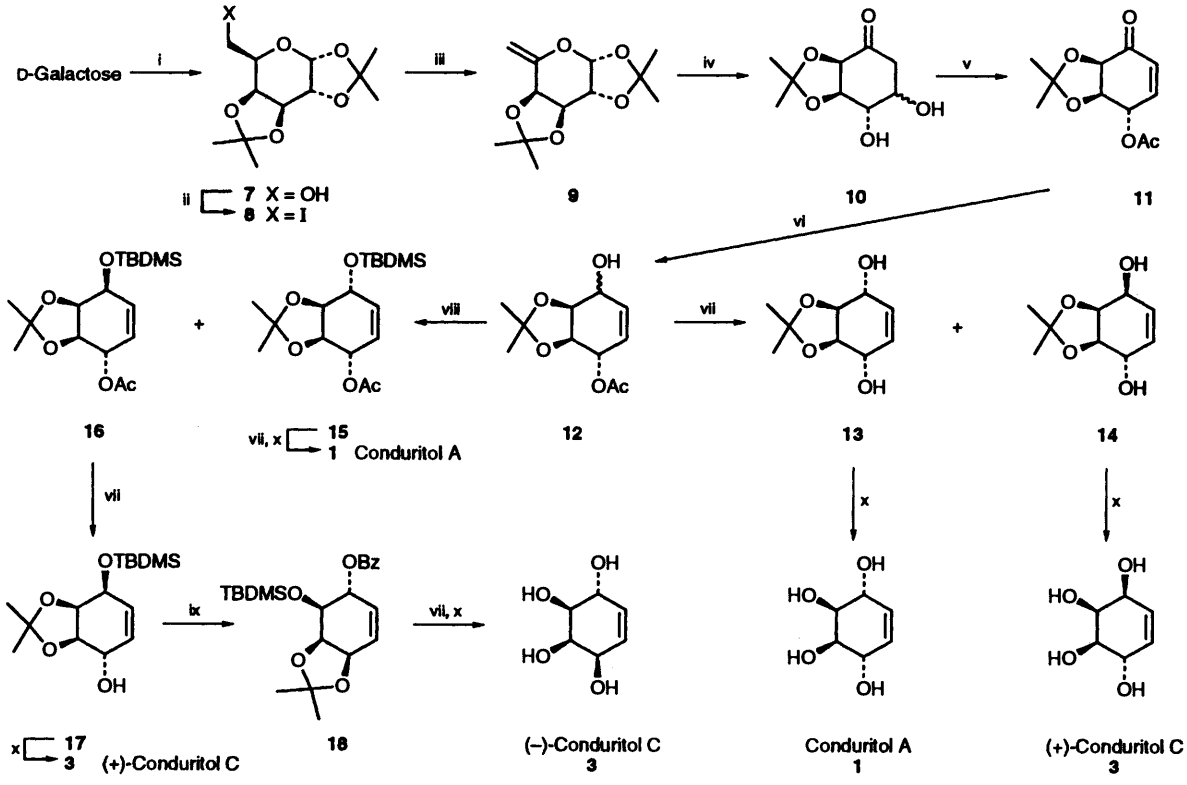
Conduritol was first isolated in 1908 by Kubler from the bark of the vine *Marsdenia condurango*,[1] and its constitution and configuration were later established by Dangschat and Fischer.[2] Conduritols are cyclohex-5-ene-1,2,3,4-tetraols, and exist in ten possible isomeric forms (two *meso* and four DL-pairs) and have been labelled A, B, C, D, E and F. All possible conduritol isomers have already been synthesized and their biological importance studied. Conduritol derivatives and aminoconduritols act as inhibitors of D-glycosidases.[3] Carless[4] has elegantly utilised chloro- and fluoro-benzenes for the synthesis of conduritols (−)-C and (+)-C by a microbial oxidation procedure. The shortest stereoselective synthesis of conduritol



(−)-C was the result of microbial oxidation of chlorobenzene to chlorobenzenediol followed by stereoselective oxidation with *m*-chloroperbenzoic acid and reductive dehalogenation. An enantiodivergent route for the synthesis of conduritol (−)-C has been reported by Takano *et al.*,[5] involving lipase-mediated asymmetric esterification of the *meso*-diol of the Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone. Vanderwalle and co-workers[6] have reported enantiotoposelective hydrolysis of *meso*-cyclohexene-1,4-diols to obtain conduritols (−)-C, (−)-E and (−)-F. They have also been synthesized either from the inositol quebrachitol[7] or by the 'naked sugar' approach of Vogel[8] or from carbohydrate sources such as D-glucose[9] and L-arabinose.[10] Preparation of conduritols and related compounds has been reviewed.[11] We describe here a general and stereospecific approach to the synthesis of several conduritols from D-galactose (Scheme 1).

D-Galactose was transformed into 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **7**[12] and subsequently into the 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **8**[13] in 82% yield on reaction with Ph_3P–I_2–imidazole in toluene at reflux for 15 min. Treatment of iodide **8** with NaH in hexamethylphosphoric triamide (HMPA) at room temperature for 2 h resulted in the isolation of the 5,6-enopyranose **9** in 91% yield as a crystalline compound, m.p. 141–142 °C. Compound **9** was efficiently transformed into the cyclohexanone derivative **10** in 83% yield on reaction with a catalytic amount of $Hg(OAc)_2$ in acetone–water (2:1)[14] at 0 °C for 15 min. Compound **10** was characterised from the appearance of its carbonyl absorption at 1710 cm^{-1} in the IR spectrum and also from the ^1H NMR spectrum where 6-H^{ax} and 6-H^{eq} appeared as multiplets between δ 2.53 and δ 2.73. Reaction of diol **10** with Ac_2O–pyridine at room temperature[15] for 4 h resulted in the formation of the αβ-unsaturated enone **11** in 73% yield. Enone **11** was characterised from the appearance of signals for 3-H and 2-H at δ 6.75 and δ 6.15, respectively, as doublets ($J_{2,3}$ 9.8 Hz). Appearance of the αβ-unsaturated carbonyl absorption at 1695 cm^{-1} in the IR spectrum also confirmed the formation of enone **11**. Reduction[4,16] of the enone **11** with $CeCl_3 \cdot 7H_2O$–$NaBH_4$ at −78 °C gave the alcohol **12** as an isomeric mixture (1/3 α-alcohol/β-alcohol). Deacetylation of compound **12** with a catalytic amount of NaOMe in methanol at room temperature gave an isomeric mixture of diols, which were subjected to column chromatographic separation to obtain the crystalline diol acetonide **13** in 21% yield (m.p. 102–104 °C) and crystalline acetonide **14** in 64% yield (m.p. 112–114 °C). Diol **13** is a *meso* compound and had a comparable ^1H NMR spectrum with that reported for a conduritol A derivative.[4] Diol **14** was characterised from its ^1H NMR spectral data and optical-rotation value of $[\alpha]_D$ 66.1 × 10^{-1} deg cm^2 g^{-1} (*c* 1.0, $CHCl_3$). Treatment of diol **13** with a catalytic amount of mineral acid gave conduritol A **1**, that had identical ^1H NMR spectra data and m.p. as reported in the literature for compound **1**.[17] Likewise, treatment of diol **14** with a catalytic amount of mineral acid gave (+)-conduritol C **3** in 77% yield that had identical ^1H NMR spectra and $[\alpha]_D$-value with the data reported in the literature.[18] For the synthesis of (−)-conduritol C **3**, acetate **12** was silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl)–pyridine and the product was separated by column chromatography to obtain the silyl derivatives **15** and **16** in 20% and 62% yield respectively, and were characterised from their ^1H NMR spectra.

Deacetylation of **16** with a catalytic amount of NaOMe gave the alcohol **17** in 93% yield. Mitsunobu[19] reaction of compound **17** with diethyl azodicarboxylate (DEAD)–Ph_3P–benzoic acid in toluene at 0 °C resulted in the isolation of the rearrangement product **18** in 63% yield due to bimolecular nucleophilic substitution (S_N2).[20] Formation of compound **18** was evident from its ^1H NMR spectrum and was further confirmed by deprotection of all the protecting groups to obtain (−)-conduritol C **3** that had identical $[\alpha]_D$ and ^1H NMR data with literature values.[8,18] If there was no migration of the double bond, compound **17** would lead to the formation of the *meso* compound conduritol D **4**[4] after removal of all protecting groups. Silyl derivatives **15** and **16** sere also deprotected to



Scheme 1 *Reagents and conditions:* i, acetone, conc. H_2SO_4;[10] ii, Ph_3P, I_2, imidazole, toluene, reflux, 15 min (82%); iii, NaH, HMPA, 2 h (91%); iv, $Hg(OAc)_2$, acetone–water (2:1), 0 °C, 15 min (83%); v, Ac_2O, pyridine, cat. DMAP, room temp., 4 h (73%); vi, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH −78 °C, 25 min (95%); vii, NaOMe, MeOH, room temp., 15 min; viii, TBDMSCl, pyridine, room temp., 6 h (82%); ix, Ph_3P, $PhCO_2H$, DEAD, toluene, 0 °C (63%); x, dil. HCl in MeOH, room temp., 15 min

obtain the corresponding tetraols conduritol A **1** and (+)-conduritol C **3**.

Experimental

^1H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform; coupling constants (J) are given in Hz. Optical rotations were measured with a JASCO DIP-370 instrument, and $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a Perkin-Elmer spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C on rotary evaporator.

6-Deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galacto-pyranose **8**.—To a solution of compound **7**[12] (5.0 g, 19.23 mmol) in toluene (100 cm^3) were added triphenylphosphine (7.56 g, 28.25 mmol), imidazole (3.92 g, 57.69 mmol) and iodine (7.33 g, 28.85 mmol) and the mixture was refluxed for 15 min. After completion of the reaction the mixture was cooled to room temperature and diluted with ethyl acetate (100 cm^3). The organic phase was washed successively with water, 5% aq. sodium thiosulfate and water, dried, and concentrated to obtain a solid residue, which was filtered on a bed of silica gel (40 g) (eluted with 10% ethyl acetate in hexane) to obtain the title compound **8** (5.97g, 82%) as a crystalline solid; m.p. 69–71 °C; $[\alpha]_D$ 47.5 (*c* 1.0, $CHCl_3$) {lit.,[13] m.p. 71–72 °C; $[\alpha]_D$ 49 (*c* 1.5, $CHCl_3$)}; δ_H 1.33, 1.35, 1.45 and 1.54 (12 H, 4 s, CMe_2), 3.21 (1 H, dd, $J_{6,6'}$ 9.9, $J_{5,6}$ 7.2, 6-H), 3.33 (1 H, dd, $J_{5,6'}$ 6.8, 6-H'), 3.94 (1 H, ddd, $J_{4,5}$ 1.5, 5-H), 4.30 (1 H, dd, $J_{1,2}$ 4.97, $J_{2,3}$ 2.4, 2-H), 4.40 (1 H, dd, $J_{3,4}$ 7.9, 4-H), 4.62 (1 H, dd, 3-H) and 5.54 (1 H, d, 1-H).

6-Deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-eno-pyranose **9**.—To hexane-washed NaH (0.56 g, 23.26 mmol) in HMPA (20 cm^3) was added a solution of compound **8** (5.89 g, 15.51 mmol) in HMPA (30 cm^3). The reaction mixture was stirred at room temperature for 2 h and quenched with methanol (1 cm^3), diluted with water, and extracted into dichloromethane (50 cm^3). The organic phase was washed with water, dried, and concentrated to obtain a solid residue, which was filtered on a bed of silica gel (30 g) (eluted with 10% ethyl acetate in hexane) to obtain crystalline *title compound* **9** (3.4 g, 91%); m.p. 141–142 °C (Found: C, 59.4; H, 7.4. $C_{12}H_{18}O_5$ requires C, 59.49; H, 7.49%); $[\alpha]_D$ −131.4 (*c* 3.0, $CHCl_3$); δ_H 1.33, 1.35 and 1.44 (12 H, 3 s, CMe_2), 4.22 (1 H, d, $J_{1,2}$ 3.4, 2-H), 4.53 (× 2), 4.62 and 4.73 (4 H, 3 s, 3- and 4-H and 6-H_2) and 5.55 (1 H, d, 1-H).

(2R,3R,4S,5S)- and (2R,3R,4S,5R)-4,5-Dihydroxy-2,3-(isopropylidenedioxy)cyclohexanone **10**.—The enol ether **9** (3.3 g, 13.64 mmol) was dissolved in acetone–water (90 cm^3; 2:1) at 0 °C, mercury(II) acetate (2.08 g, 6.55 mmol) was added, and the mixture was stirred for 15 min. After completion of the reaction, the mixture was neutralised with solid $NaHCO_3$ (4.0 g), then filtered, and the residue was washed with acetone (10 cm^3). The filtrate was concentrated to remove acetone and was then extracted into dichloromethane (30 cm^3 × 4). The organic phase was washed with water, dried, and concentrated to obtain a solid residue, which was filtered on a bed of silica gel (20 g) (eluted with 25% hexane in ethyl acetate) to obtain *title compound* **10** (2.28 g, 83%) as a syrup (Found: C, 53.4; H, 6.9. $C_9H_{14}O_5$ requires C, 53.46; H, 6.98%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (carbonyl); δ_H 1.35 and 1.40 (6 H, 2 s, CMe_2), 2.53–2.73 (2 H, m, 6-H_2), 4.10 (1 H, br s, 2-H), 4.22 (1 H, br t, $J_{3,4} = J_{4,5} = 5.9$, 4-H) and 4.45–4.55 (2 H, m, 3- and 5-H).

(4S,5R,6R)-4-Acetoxy-5,6-(isopropylidenedioxy)cyclohex-2-enone **11**.—The cyclohexanone derivative **10** (2.2 g, 10.38 mmol)

was dissolved in pyridine (5 cm^3), the solution was cooled to 0 °C, and Ac_2O (2.5 cm^3) was added dropwise, followed by a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction mixture was stirred at room temperature for 4 h, then was diluted with water (50 cm^3), and extracted into diethyl ether (50 cm^3 × 3). The combined ethereal layers were washed successively with saturated aq. copper(II) sulfate and water. The organic phase was dried and concentrated to a thick syrup, which was filtered on a bed of silica gel (20 g) (eluted with 25% ethyl acetate in hexane) to obtain *title compound* **11** (1.79 g, 73%) as a syrup (Found: C, 58.3; H, 6.2. $C_{11}H_{14}O_5$ requires C, 58.29; H, 6.24%); $[\alpha]_D$ 94.2 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1695 (carbonyl); δ_H 1.38 (6 H, s, CMe_2), 2.11 (3 H, s, OAc), 4.38 (1 H, d, $J_{5,6}$ 5.8, 6-H), 4.47 (1 H, ddd, 5-H), 5.55 (1 H, t, $J_{5,4}$ = $J_{4,3}$ = 3.6, 4-H), 6.15 (1 H, d, $J_{2,3}$ 9.8, 2-H) and 6.75 (1 H, ddd, $J_{3,5}$ 1.4, 3-H).

(1S,4S,5S,6R)- *and* (1S,4R,5S,6R)-4-*Hydroxy*-5,6-(*isopropylidenedioxy*)*cyclohex*-2-*enyl Acetate* **12**.—The enone **11** (1.7 g, 7.52 mmol) was dissolved in methanol (150 cm^3) and the solution was cooled to −78 °C. $CeCl_3 \cdot 7H_2O$ (2.95 g, 7.92 mmol) was added and the mixture was stirred for 25 min. $NaBH_4$ (1.70 g, 50.42 mmol) was added and 15 min later the reaction mixture was quenched by addition of acetic acid (1.5 cm^3), concentrated to a syrup, and filtered on a bed of silica gel (10 g) (eluted with 33% ethyl acetate in hexane) to obtain an isomeric mixture of *title compound* **12** (1.63 g, 95%) as a syrup (Found: C, 57.8; H, 6.9. $C_{11}H_{16}O_5$ requires C, 57.88; H, 7.07%); δ_H 1.46, 1.50 and 1.55 (6 H, 3 s, CMe_2), 2.0 and 2.1 (3 H, 2 s, OAc), 4.05–4.60 (3 H, m, 4-, 5- and 6-H), 5.15–5.30 (1 H, m, 1-H) and 5.55–6.10 (2 H, m, 2- and 3-H).

(1R,4S,5R,6S)- **13** *and* (1S,4S,5R,6S)-5,6-(*Isopropylidenedioxy*)*cyclohex*-2-ene-1,4-*diol* **14**.—Compound **12** (0.5 g, 2.19 mmol) was dissolved in methanol (10 cm^3) and a catalytic amount of sodium was added at 0 °C. The reaction mixture was stirred at room temperature for 15 min. After completion of the reaction the reaction mixture was neutralised with carbon dioxide and concentrated to yield a thick syrup, which was subjected to flash column chromatography [SiO_2, finer than 200 mesh; hexane–ethyl acetate (1:1)]; first eluted was *meso* compound **13** (85 mg, 21%) as a crystalline solid; m.p. 102–104 °C (lit.,[6] 101–102 °C); and next eluted was *isomer* **14** (260 mg, 64%) as a crystalline solid; m.p. 112–114 °C (Found: C, 58.0; H, 7.5. $C_9H_{14}O_4$ requires C, 58.05; H, 7.58%); $[\alpha]_D$ 66.1 (*c* 1.0, $CHCl_3$); δ_H 1.36 and 1.47 (6 H, 2 s, CMe_2), 4.25–4.58 (4 H, m, 1-, 4-, 5- and 6-H) and 5.8–6.8 (2 H, m, 2- and 3-H).

(1S,4R,5S,6R)- **15** *and* (1S,4S,5S,6R)-4-(tert-*Butyldimethylsiloxy*)-5,6-(*isopropylidenedioxy*)*cyclohex*-2-*enyl Acetate* **16**.—Compound **12** (1.0 g, 4.39 mmol) was dissolved in pyridine (2.5 cm^3), and TBDMSCl (0.69 g, 4.62 mmol) was slowly added at 0 °C during *ca.* 20 min along with a catalytic amount of DMAP. The mixture was stirred at room temperature for 6 h, diluted with water (30 cm^3), and extracted into diethyl ether (30 cm^3 × 3). The organic phase was washed with water, dried, and concentrated to a syrup, which was subjected to flash column chromatography [SiO_2, finer than 200 mesh; hexane–ethyl acetate (50:1)]; first eluted was the *title compound* **15** (0.3 g, 20%) as a syrup (Found: C, 59.6; H, 8.8. $C_{17}H_{30}O_5Si$ requires C, 59.61; H, 8.83%); δ_H 0.12 and 0.14 (6 H, 2 s, $SiMe_2$), 0.93 (9 H, s, Bu^t), 1.37 and 1.48 (6 H, 2 s, CMe_2), 2.15 (3 H, s, OAc), 4.06 (1 H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 5.3, 5-H), 4.18 (2 H, m, 4-H and 6-H), 5.15 (1 H, m, 1-H), 5.54 (1 H, dd, $J_{1,2}$ 2.1, $J_{2,3}$ 12.2, 2-H) and 5.71 (1 H, dd, $J_{3,4}$ 2.3, 3-H); and next eluted was the *title compound* **16** (0.93 g, 62%) as a syrup (Found: C, 59.55; H, 8.82%); $[\alpha]_D$ 152.6 (*c* 1.0, $CHCl_3$); δ_H 0.13 (6 H, s, $SiMe_2$), 0.94 (9 H, s, Bu^t) 1.35 and 1.43 (6 H, 2 s, CMe_2), 2.06 (3 H, s, OAc), 4.41 (2 H, m, 4-H and 6-H), 4.55 (1 H, br s, 5-H), 5.23 (1 H, t, $J_{1,6}$ = $J_{1,2}$ = 3.7, 1-H), 5.90 (1 H, dd, $J_{2,3}$ 9.6, 2-H) and 6.0 (1 H, dd, $J_{3,4}$ 4.5, 3-H).

(1S,4S,5S,6R)-4-(tert-*Butyldimethylsiloxy*)-5,6-(*isopropylidenedioxy*)*cyclohex*-2-*en*-1-*ol* **17**.—Compound **16** (0.85 g, 2.49 mmol) was dissolved in methanol (5 cm^3) cooled to 0 °C and a catalytic amount of sodium was added. The mixture was stirred at room temperature for 10 min. After completion of the reaction, the mixture was neutralised with carbon dioxide and concentrated to obtain a thick syrup, which was filtered on a bed of silica gel (10 g) (eluted with 20% ethyl acetate in hexane) to obtain the *title compound* **17** (0.69 g, 93%) as a syrup (Found: C, 60.0; H, 9.35. $C_{15}H_{28}O_4Si$ requires C, 59.96; H, 9.39%); $[\alpha]_D$ 67.8 (*c* 3.0, $CHCl_3$); δ_H 0.09 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 1.36 and 1.46 (6 H, 2 s, CMe_2), 4.30 (2 H, m, 5- and 6-H), 4.51 (2 H, br s, 1-H and 4-H) and 5.97 (2 H, s, 2- and 3-H).

(1R,4R,5R,6S)-6-(tert-*Butyldimethylsiloxy*)-4,5-(*isopropylidenedioxy*)*cyclohex*-2-*enyl Benzoate* **18**.—Compound **17** (0.4 g, 1.33 mmol) and triphenylphosphine (0.7 g, 2.67 mmol) were dissolved in toluene (2 cm^3), cooled to 0 °C under nitrogen, and DEAD (0.46 cm^3, 2.67 mmol) was added. The mixture was stirred for 10 min, a mixture of benzoic acid (0.24 g, 2.0 mmol) in toluene (1 cm^3) was added at 0 °C, and the mixture was stirred for an additional 20 min. The reaction mixture was directly subjected to column chromatography [SiO_2, 60–120 mesh; hexane–ethyl acetate (30:1)] to obtain the *title compound* **18** (0.34 g, 63%) as a syrup (Found: C, 65.3; H, 8.0. $C_{22}H_{32}O_5Si$ requires C, 65.31; H, 7.97%); $[\alpha]_D$ −147.44 (*c* 1.0, $CHCl_3$); δ_H 0.03 and 0.12 (6 H, 2 s, $SiMe_2$), 0.83 (9 H, s, Bu^t), 1.37 and 1.43 (6 H, 2 s, CMe_2), 4.09 (1 H, dd, $J_{1,6}$ 8.5, $J_{5,6}$ 2.4, 6-H), 4.42–4.56 (1 H, dd, $J_{4,5}$ 4.3, 5-H), 4.61–4.63 (1 H, m, 4-H), 5.8 (2 H, br s, 2- and 3-H), 5.84 (1 H, dd, *J* 2.0, 1-H) and 7.43–8.14 (5 H, ArH).

Conduritol A **1**.—Compound **15** (150 mg, 0.44 mmol) was dissolved in methanol (2 cm^3), cooled to 0 °C, and a catalytic amount of sodium was added. The mixture was stirred at room temperature for 15 min and was then acidified with methanolic HCl [0.5 cm^3; conc. HCl (1 cm^3) in methanol (10 cm^3)]. After completion of the reaction, the mixture was neutralised with $NaHCO_3$, filtered and washed with methanol. The filtrate was concentrated to yield a solid residue, which was filtered off on a bed of silica gel (5 g) (eluted with 20% methanol in ethyl acetate) to obtain conduritol A **1** (50 mg, 78%) as a crystalline solid; m.p. 145 °C (lit.,[17] 145.5–145.7 °C). Likewise, treatment of compound **13** (50 mg, 0.27 mmol) with dil. HCl gave conduritol A **1** (25 mg, 67%) as a crystalline solid.

(+)-*Conduritol C* **3**.—Compound **17** (150 mg, 0.5 mmol) was dissolved in methanol (2 cm^3), cooled to 0 °C. and one drop of methanolic HCl [conc. HCl (1 cm^3) in methanol (10 cm^3)] was added. The reaction mixture was stirred at room temperature for 1 h, then was neutralised with $NaHCO_3$, filtered, and washed with methanol. The filtrate was concentrated to yield a solid residue, which was filtered off on a bed of silica gel (5 g) (eluted with 20% methanol in ethyl acetate) to obtain (+)-conduritol C **3** (56 mg, 77%) as a crystalline solid, m.p. 126–128 °C; $[\alpha]_D$ 215 (*c* 0.5, water) {lit.,[18] m.p. 128–129 °C; $[\alpha]_D$ 213 (*c* 0.4, water)}; likewise, treatment of compound **14** (100 mg, 0.54 mmol) gave (+)-conduritol C **3** (61 mg, 77%) as a crystalline solid.

(−)-*Conduritol C* **3**.—Compound **18** (250 mg, 0.62 mmol) was dissolved in methanol (2 cm^3), cooled to 0 °C, a catalytic amount of sodium was added, and the mixture was stirred at room temperature for 2 h before being acidified with methanolic HCl [0.5 cm^3; conc. HCl (1 cm^3) in methanol (10 cm^3)] and was then stirred at room temperature for 15 min. After

completion of the reaction, the mixture was neutralised with $NaHCO_3$, filtered, and washed with methanol (2 cm^3). The filtrate was concentrated to yield a solid residue, which was filtered off on a bed of silica gel (5 g) (eluted with 20% methanol in ethyl acetate) to obtain (−)-conduritol C **3** (54 mg, 60%) as a crystalline solid, m.p. 126–127 °C; $[\alpha]_D$ −212 (*c* 0.5, water) {lit.,[8] m.p. 129–130 °C; $[\alpha]_D$ −209 (*c* 2.0, water)}.

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