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The synthesis and resolution of (±)-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol *

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Abstract

An improved procedure for the preparation of 1,2-*O*-isopropylidene-*myo*-inositol is described. Racemic 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol was prepared by tin-mediated benzylation of 1,2-*O*-isopropylidene-*myo*-inositol and resolved readily by crystallisation of the ω-camphanates. The use of the chiral 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositols as intermediates for the preparation of other chiral derivatives of *myo*-inositol was investigated.

1. Introduction

One of the major problems in the preparation of intermediates for the synthesis of the many chiral inositol phosphates of the phosphatidylinositol cycle (for reviews, see ref 2) concerns the optical resolution of these intermediates. We have described [3] several *myo*-inositol derivatives which can be resolved readily by crystallisation of the (−)- and (+)-ω-camphanates, and we describe here the resolution of the title compound by this procedure.

2. Results and discussion

We have described [4,5] preparations of 1,2-*O*-isopropylidene-*myo*-inositol (**2**) by the reaction of *myo*-inositol (**1**) with 2,2-dimethoxypropane and an acid catalyst

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* For a preliminary communication, see ref 1.

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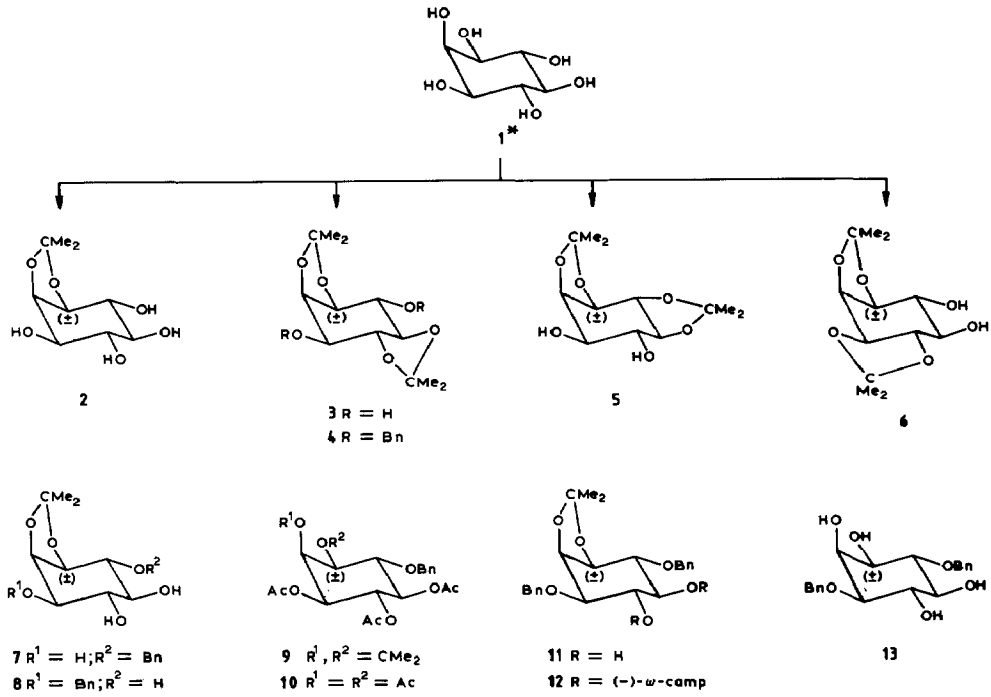
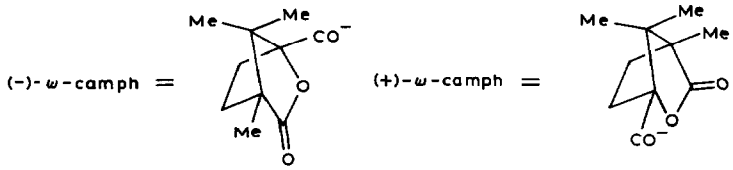
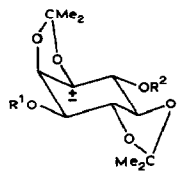


in hot methyl sulfoxide. Our first preparation [4] involved removal of the methyl sulfoxide by distillation, but subsequently we found conditions [5] where **2** was persuaded to crystallise directly from the solution (after neutralisation of the acid catalyst) in a yield of ca. 30%, leaving in solution the di-*O*-isopropylidene derivatives **3**, **5**, and **6** which were also formed in the reaction [5,6].

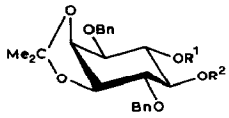
We have now improved the yield in this preparation by allowing **2** to crystallise from the acidic solution; in this way, compounds **3**, **5**, and **6** are also partially



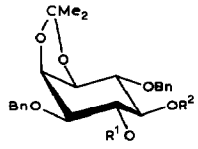
* In the formulae, racemic inositol derivatives are indicated (±) in the ring; chiral inositol derivatives, represented in their correct absolute configurations, are shown with the thickened lines in the ring, and *meso*-compounds are shown with neither of these modifications. Bn, CH_2Ph; Crot, CH_2-CH=CH-Me.



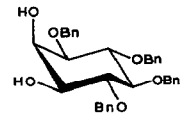
14 R^1 = H; R^2 = Bn
15 R^1 = Ac; R^2 = Bn
16 R^1 = Bn; R^2 = H
17 R^1 = Bn; R^2 = Ac
18 R^1 = $SiMe_2Bu^t$; R^2 = H



19 R^1 = R^2 = (−)-ω-camph
20 R^1 = R^2 = H
21 R^1 = R^2 = Ac
22 R^1 = R^2 = Bn
23 R^1, R^2 = CMe_2



24 R^1 = R^2 = (−)-ω-camph
25 R^1 = R^2 = (+)-ω-camph
26 R^1 = R^2 = H
27 R^1 = R^2 = Ac



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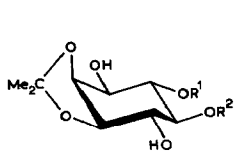
hydrolysed to give **2** which is obtained in ca. 75% yield. The product is contaminated with a small amount of **1** which is removed by crystallisation.

We recently found [7] that tin-mediated benzylation of **2** in the presence of two equivalents of dibutyltin oxide allows the isolation of the highly crystalline 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (**11**) in reasonable yield and this preparation is now described in detail. Previously [8], **11** was prepared by a more elaborate procedure involving partial hydrolysis of 1,4-di-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (**4**), and this route required a chromatographic separation of **11** from **4** and the tetraol **13** also formed in the reaction.

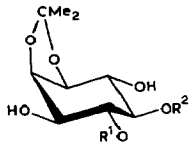
The diol **11** was converted into the diastereoisomeric mixture of bis-(−)-ω-camphanates **12** and crystallisation of the product gave the pure diastereoisomer **19** in ca. 70% yield. The absolute configuration was established by basic hydrolysis to the diol **20** followed by benzylation to **22**. Acid hydrolysis of the *O*-isopropylidene group from **22** gave the known [9] 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**28**). A small amount of the pure bis-(−)-ω-camphanate **24** could also be obtained by further crystallisation from the mother liquors remaining after **19** had been removed, but this was not a practical preparation. The contents of the mother liquors remaining after the removal of **19** were therefore saponified and the crude diol so obtained was converted into the bis-(+)-ω-camphanates. Crystallisation of these gave the pure bis-(+)-ω-camphanate **25** (the enantiomer of **19**) in high yield and this was saponified to give the diol **26**. The chiral diol **26** is suitable [10] for the preparation of intermediates for the synthesis of 1D-*myo*-inositol 1,4,5- and 2,4,5-trisphosphates.

Treatment of the chiral diol **20** with 2,2-dimethoxypropane and an acid catalyst gave the di-*O*-benzyl-di-*O*-isopropylidene derivative **23**, and catalytic hydrogenolysis of **23** in the presence of sodium hydrogen carbonate gave the chiral di-*O*-isopropylidene-*myo*-inositol **29**. The chiral compounds **29** and **31** have been obtained previously [11] by resolution of the *tert*-butyldimethylsilyl ether **18** involving chromatographic separation of diastereoisomeric esters with chiral acids.

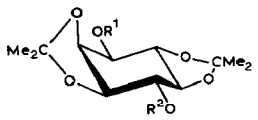
We have also found that tin-mediated benzylation of **2** with one equivalent of dibutyltin oxide gives **7** as the only isolable monobenzyl derivative (ca. 25% yield)



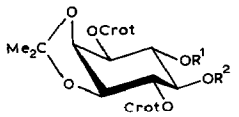
29 R^1, R^2 = CMe_2
30 R^1 = R^2 = H



31 R^1, R^2 = CMe_2
32 R^1 = R^2 = H



33 R^1 = H; R^2 = Bn
34 R^1 = R^2 = Ac
35 R^1 = Ac; R^2 = Bn



36 R^1, R^2 = CMe_2
37 R^1 = R^2 = H

and that **7** can also be obtained by catalytic hydrogenolysis of **11** in ethanol containing a small amount of triethylamine. The inhibitory effect of non-aromatic amines on the hydrogenolysis of alkyl benzyl ethers has been described [12]. In each case, **7** was isolated as the crystalline triacetate **9**, and the structure of **7** was established by hydrolysis of the *O*-isopropylidene group from **9** and acetylation of the product to give the known [8] 1,2,3,5,6-penta-*O*-acetyl-4-*O*-benzyl-*myo*-inositol (**10**). Catalytic hydrogenolysis of the dibenzyl ether **23** in the presence of base allowed the isolation of the monobenzyl ether **33** as an intermediate in this reaction. Previously [8], it was shown that partial benzylation of the diol **3** gave predominantly the monobenzyl ether **16** with **14** as a minor product, and that these two isomers could be distinguished readily [9] by TLC of the acetates **17** and **15**, respectively.

Catalytic hydrogenolysis of the racemic diol **11** under pressure in the presence of sodium hydrogen carbonate (to avoid migration of the isopropylidene group) gave 1,2-*O*-isopropylidene-*myo*-inositol (**2**) which was isolated as its tetraacetate [4]. Application of this procedure to the chiral diols **20** and **26** will provide the chiral tetraols **30** and **32**, respectively, and these should be suitable intermediates for the synthesis of 1D- and 1L-*myo*-inositol 1,4,5,6-tetrakisphosphate, both of which are components of the phosphatidylinositol cycle [13]. The synthesis of chiral **30** by a chemo-enzymatic method has been reported very recently [14].

Crotylation of the chiral diol **29** gave crystalline **36**, and partial hydrolysis of **36** gave the crystalline diol **37** which will be used as an intermediate in future synthetic work.

3. Experimental

General.—The general methods were as described [9].

*(±)-1,2-O-Isopropylidene-*myo*-inositol* (**2**).—A mixture of *myo*-inositol (**1**; 50 g, 277 mmol), 2,2-dimethoxypropane (85 mL), toluene-*p*-sulfonic acid (500 mg), and methyl sulfoxide (160 mL) was stirred at 90°C until a clear solution was obtained (ca. 30 min). The solution was cooled to 20°C, EtOH (200 mL) and ether (1 L) were added, and stirring was continued for 2 h when Et_3N (10 mL) was added. The mixture was stirred for 4 h and then left at room temperature overnight. The

product (48.2 g, 79%) was filtered, washed with 1:5 MeOH–ether (210 mL) and ether, and dried. The crude solid was recrystallised from EtOH in 10-g batches to give **2** (mp 182–184°C) identical with the material described previously [4,5].

*(±)-3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol[≡(±)-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol]* (**11**).—A mixture of (±)-1,2-*O*-isopropylidene-*myo*-inositol (**2**; 20 g, 90.8 mmol), dibutyltin oxide (46 g, 185 mmol), tetrabutylammonium bromide (59.2 g, 183 mmol), benzyl bromide (36 mL, 300 mmol), and MeCN (500 mL) was stirred and heated under reflux with a Soxhlet apparatus containing 3A molecular sieve for 8 h. TLC (ether) of the clear solution showed complete conversion of **2** (R_f 0) into major (R_f 0.5) and minor (R_f 0.75 and 0.85) products. The molecular sieve was removed, Et_3N (80 mL) was added, and refluxing was continued for 1 h to destroy the excess of benzyl bromide. The solution was cooled, the solvent was evaporated, the residue was distributed between ether (200 mL) and water (200 mL), and the title product then crystallised out. The mixture was stirred for 20 min (to be sure crystallisation was completed), and the product was filtered off and then washed with water and ether to give **11** (22.6 g, 62%); mp 161–163°C; identical with the material described previously [8].

*Bis-(−)-ω-camphanates (**24** and **19**) of 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol*.—A solution of the racemic diol **11** (6.5 g, 16 mmol) and (−)-ω-camphanic acid chloride (10 g, 46 mmol) in dry pyridine was kept at 20°C for 18 h. The solution was cooled in ice–water, water (2 mL) was added, the solution was kept at 20°C for 30 min and then diluted with water (200 mL), and the products were extracted with ether. The extract was washed successively with M HCl, satd aq KCl, and satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the mixed diastereoisomers **19** and **24**. ^{1}H NMR data: δ 0.84 (3 H), 0.87 (3 H), 0.89 (3 H), 0.91 (3 H), 0.99 (12 H), 1.08 (6 H), 1.09 (6 H) (7 s, 12 CMe of the camphanates portion), 1.33 (6 H) and 1.58 (6 H) (2 s, 2 CMe_2).

Crystallisation from 2:1 ether–light petroleum gave the pure diastereoisomer **19** (4.34 g, 70%); mp 148–150°C; $[\alpha]_D^{25}$ −9.1° (*c* 1, $CHCl_3$); ^{1}H NMR data: δ 0.87 (3 H), 0.91 (3 H), 0.99 (6 H), 1.08 (3 H), 1.09 (3 H) (5 s, 6 CMe of the camphanate portion), 1.32 (3 H), 1.57 (3 H) (2 s, CMe_2), 3.90 (m, 2 H, ring protons), 4.37 (m, 2 H, ring protons), 4.70, 4.73 (2 s, 4 H, 2 CH_2Ph), 5.25 (t, 1 H, *J* 6.7 Hz, H-5), 5.61 (dd, 1 H, *J* 6.7 and 8.6 Hz, H-6), 7.29 and 7.34 (2 s, 10 H, aromatic). Anal. Calcd for $C_{43}H_{52}O_{12}$: C, 67.88; H, 6.98%. Found: C, 67.98; H, 6.96%.

*1D-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol* (**20**).—The bis-(−)-ω-camphanate **19** (6.55 g, 8.5 mmol) was heated under reflux with NaOH (2 g) in MeOH (190 mL) for 1 h Solid carbon dioxide was added, the solvent was evaporated, the residue was extracted with CH_2Cl_2, and the extract was washed with water, dried (K_2CO_3), and concentrated to give the chiral alcohol **20** (3.09 g, 90%); mp 80–83°C (from light petroleum–EtOAc); $[\alpha]_D^{25}$ −4.0° (*c* 1, $CHCl_3$). ^{1}H NMR data: δ 1.34 (3 H), 1.48 (3 H) (2 s, CMe_2), 2.83 (broad signal, 2 OH), 3.23–3.62 (m, 3 H, ring protons), 3.84–4.34 (m, 3 H, ring protons), 4.59–4.99 (m, 4 H, 2 CH_2Ph; with major peaks at 4.59, 4.72, 4.77, 4.87, and 4.99), 7.33 (m, 10 H, aromatic). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05%. Found: C, 68.64; H, 7.17%.

The diacetate 1D-5,6-di-*O*-acetyl-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (**21**) from **20** had mp 84–86°C (from light petroleum); $[\alpha]_D^{25}$ −24.3° (*c* 1, $CHCl_3$). ^1H NMR data: δ 1.35 (3 H), 1.53 (3 H) (2 s, CMe_2), 2.00 (s, 6 H, 2 Ac), 3.75 (m, 2 H, ring protons), 4.30 (m, 2 H, ring protons), 4.70, 4.73 (2 s, 4 H, 2 CH_2Ph), 4.99 (t, 1 H, *J* 8.5 Hz, H-5), 5.41 (t, 1 H, *J* 8.5 Hz, H-6), 7.28 and 7.32 (2 s, 10 H aromatic). Anal. Calcd for $C_{27}H_{32}O_{10}$: C, 66.93; H, 6.66%. Found: C, 66.67; H, 6.74%.

1D-1,4,5,6-Tetra-O-*benzyl*-myo-*inositol* [9] (**28**) *from the diol* **20**.—The diol **20** was treated with NaH and benzyl bromide in DMF in the usual way until TLC (1:1 ether–light petroleum) showed complete conversion of **20** (R_f 0.25) into a product **22** (R_f 0.75). This was isolated in the usual way and treated with 9:1 MeOH–M HCl at reflux for 30 min when TLC (as above) showed conversion of **22** into **28** (R_f 0). Silica gel chromatography (9:1 CH_2Cl_2–ether) removed some contaminants from the benzylation reaction and gave the pure diol **28**; mp 148–149°C (from EtOAc–light petroleum); $[\alpha]_D^{25}$ +19.8° (*c* 1, $CHCl_3$) {lit. [9] mp 148–149°C, $[\alpha]_D^{25}$ +21° (*c* 1, $CHCl_3$); also see ref 9 for other literature values for this diol}. ^1H NMR data: δ 2.45 (d, *J* 4.3 Hz, OH), 2.54 (OH), 3.38–4.19 (m, 6 H, ring protons), 4.67–5.02 (m, 8 H, 4 CH_2Ph; with major peaks at 4.71, 4.79, and 4.88), 7.30 (s, 20 H, aromatic) were identical with those of the material prepared previously [9].

1D-3,6-Di-O-*benzyl-4,5-di*-O-*[(+)-ω-camphanoyl]-1,2*-O-*isopropylidene*-myo-*inositol* (**25**).—The contents of the mother liquors after the crystallisation of **19** were saponified and the product was converted into the (+)-ω-camphanates as described. Crystallisation of the product from ether–light petroleum gave **25**; mp 148–150°C (from 4:1:1 ether–EtOAc–light petroleum); $[\alpha]_D^{25}$ +10.0° (*c* 1, $CHCl_3$); with a ^1H NMR spectrum identical with that of its enantiomer **19**. Anal. Calcd for $C_{43}H_{52}O_{12}$: C, 67.88; H, 6.98%. Found: C, 67.58; H, 7.17%.

1D-3,6-Di-O-*benzyl-1,2*-O-*isopropylidene*-myo-*inositol* (**26**).—The bis-(+)-ω-camphanate **25** was saponified as described above for the bis-(−)-ω-camphanate **19**, to give the chiral diol **26**, with a ^1H NMR spectrum identical with that of the enantiomer **20**; mp 85–87°C; $[\alpha]_D^{25}$ +3.0° (*c* 1.53, $CHCl_3$). This gave a diacetate **27**; mp 83–85°C; $[\alpha]_D^{25}$ +22.1° (*c* 1.5, $CHCl_3$); with a ^1H NMR spectrum identical with that of its enantiomer **21**.

1D-1,4-Di-O-*benzyl-2,3:5,6-di*-O-*isopropylidene*-myo-*inositol* (**23**).—A mixture of the diol **20** (1 g, 2.5 mmol), toluene-*p*-sulfonic acid (50 mg), 2,2-dimethoxypropane (20 mL), and acetone (10 mL) was stirred at 20°C for 1 h, after which time most of **20** had reacted and TLC (3:1 ether–light petroleum) showed the presence of major (R_f 0.9) and minor (R_f 0.2) products. Triethylamine (1 mL) and solid $NaHCO_3$ (0.5 g) were added, the solvent was evaporated, and the residue was extracted with CH_2Cl_2. The filtrate was concentrated and the product was purified by column chromatography (3:1 ether–light petroleum followed by ether), yielding a crystalline compound (1.04 g, 81%); mp 159–161°C (from light petroleum); $[\alpha]_D^{25}$ +85.0° (*c* 1, $CHCl_3$). ^1H NMR data: δ 1.32 (3 H), 1.38 (3 H), 1.46 (3 H), 1.48 (3 H) (4 s, 2 CMe_2), 3.22–4.35 (m, 6 H, ring protons), 4.81, 4.85 (2 s, 4 H, 2 CH_2Ph), 7.35

(m, 10 H, aromatic). Anal. Calcd for $C_{23}H_{32}O_6$: C, 70.89; H, 7.32%. Found: C, 71.02; H, 7.35%.

1D-2,3:5,6-di-O-isopropylidene-myo-inositol (**29**) *and 1D-4-O-benzyl-2,3:5,6-di-O-isopropylidene-myo-inositol* (**33**).—A mixture of the di-*O*-benzyl-di-*O*-isopropylidene derivative **23** (1 g, 2.27 mmol), Pd–C (10%, Fluka, 500 mg), $NaHCO_3$ (100 mg), and EtOH (25 mL) was hydrogenated at room temperature and pressure. After 4 days, TLC (ether) showed that all the starting material had reacted, giving a mixture of **29** and 1D-4-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (**33**). The catalyst was filtered off through Celite and washed with EtOH. The filtrate was evaporated, and the residue was extracted with CH_2Cl_2 and chromatographed on silica gel (ether) to separate the minor (R_f 0.6, 0.237 g, 0.68 mmol, 30%) and the major (R_f 0.2, 0.359 g, 1.37 mmol, 60%) products. Recrystallisation of the major product from light petroleum–$CHCl_3$ gave **29**; mp 175–177°C; $[\alpha]_D^{25}$ +23.3° (*c* 1, MeCN) {lit. [11b] mp 159–161°C, $[\alpha]_D^{25}$ +22° (*c* 1.08, MeCN)}. ^{1}H NMR data: δ 1.38 (3 H), 1.46 (3 H), 1.48 (3 H), 1.54 (3 H) (4 s, 2 CMe_2), 2.61 (d, *J* 7.9 Hz, OH), 2.90 (br, OH), 3.31 (m, 2 H, ring protons), 3.93 (m, 3 H, ring protons), 4.48 (t, 1 H, *J* 4.3 Hz, ring proton). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75%. Found: C, 55.13; H, 7.55%.

The diacetate **34** from **29** had mp 206–207°C (from light petroleum–EtOAc); $[\alpha]_D^{25}$ −17.2° (*c* 1, $CHCl_3$). ^{1}H NMR data: δ 1.32 (3 H), 1.43 (3 H), 1.47 (3 H), 1.58 (3 H) (4 s, 2 CMe_2), 2.13 (3 H), 2.18 (3 H) (2 s, 2Ac), 3.47 (t, *J* 10.9 Hz, H-5), 4.13 (m, 2 H, H-3,6), 4.60 (t, *J* 4.3 Hz, H-2), 5.11 (dd, *J* 10.4 and 4.3 Hz, H-1), 5.28 (dd, *J* 10.9 and 6.7 Hz, H-4). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.03%. Found: C, 55.51; H, 6.94%.

Recrystallisation of the minor product from EtOAc–light petroleum gave **33**; mp 132–134°C; $[\alpha]_D^{25}$ +66.5° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}O_6 \cdot 0.25\ H_2O$: C, 64.30; H, 7.52%. Found: C, 64.55; H, 7.42%.

The acetate 1-*O*-acetyl-4-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (**35**) from **33** had mp 150–151°C (from light petroleum); $[\alpha]_D^{25}$ +5.2° (*c* 1, $CHCl_3$); and cochromatographed with the racemic acetate **15** described previously [9]. ^{1}H NMR data: δ 1.31 (3 H), 1.38 (3 H), 1.45 (3 H), 1.48 (3 H) (4 s, 2 CMe_2), 2.17 (s, 3 H, Ac), 3.58 (m, 2 H, ring protons), 4.13 (m, 2 H, ring protons), 4.60 (t, *J* 4.3 Hz, H-2), 4.88 (s, 2 H, CH_2Ph), 5.09 (dd, *J* 4.3 and 10.4 Hz, H-1), 7.34 and 7.36 (2 s, 5 H, aromatic). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19%. Found: C, 63.80; H, 7.19%.

(±)-3,4,5-Tri-O-acetyl-6-O-benzyl-1,2-O-isopropylidene-myo-inositol (**9**).—(*a*) A mixture of (±)-1,2-*O*-isopropylidene-*myo*-inositol (**2**; 2 g, 9.08 mmol), dibutyltin oxide (2.26 g, 9.08 mmol), tetrabutylammonium bromide (2.92 g, 9.08 mmol), benzyl bromide (5 mL, 42 mmol), and MeCN (50 mL) was stirred and heated under reflux with a Soxhlet apparatus containing 3A molecular sieves for 4 h. TLC (8:1 EtOAc–MeOH) of the clear solution showed a major product (R_f 0.5) together with starting material (R_f 0.2) and **11** (R_f 0.9). The molecular sieves were removed, Et_3N (10 mL) was added, and refluxing was continued for 1 h to destroy the excess of benzyl bromide. The solution was cooled, the solvent was evaporated, and the residue was distributed between ether (20 mL) and water (20 mL). A

product which crystallised out was filtered off, and washed with water and ether to give (±)-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol (**11**; 0.4 g, 11%); mp 161–163°C; identical with the material described previously [8].

The organic and aqueous layers were separated, the aqueous phase was concentrated, and the product was acetylated in the usual way. TLC (3:1 ether–light petroleum) of the product after usual work-up showed two components (R_f 0.5 and 0.6) which were separated by chromatography on silica gel (3:1 ether–light petroleum) to give 1.094 g (27%) of the faster product and 0.975 g (27%) of the slower product.

Recrystallisation of the faster product from light petroleum gave **9**; mp 90–91°C. ^{1}H NMR data: δ 1.34 (3 H), 1.53 (3 H) (2 s, CMe_2), 2.02 (6 H), 2.10 (3 H) (2 s, 3Ac), 3.72 (dd, 1 H, *J* 4.9 and 6.7 Hz, H-6), 4.32 (t, 1 H, *J* 5.5 Hz, H-2), 4.55 (dd, 1 H, *J* 3.7 and 6.1 Hz, H-1), 4.74 (s, 2 H, CH_2Ph), 5.10 (t, 1 H, *J* 6.7 Hz, H-5), 5.38 (m, 2 H, H-3,4), 7.31 (s, 5 H, aromatic). Anal. Calcd for $C_{22}H_{28}O_9$: C, 60.54; H, 6.47%. Found: C, 60.51; H, 6.49%.

The slower product was identical with (±)-3,4,5,6-tetra-*O*-acetyl-1,2-*O*-isopropylidene-*myo*-inositol previously prepared [4]. ^{1}H NMR data: δ 1.35 (3 H), 1.60 (3 H) (2 s, CMe_2), 2.02 (6 H), 2.08 (3 H), 2.13 (3 H) (3 s, 4Ac), 4.24 (t, 1 H *J* 5.8 Hz), 4.53 (dd, 1 H, *J* 3.7 and 5.5 Hz), 4.93–5.62 (m, 4 H).

(*b*) A mixture of **11** (0.5 g, 1.25 mmol), Pd–C (10%, Fluka, 0.5 g), Et_3N (0.5 mL), and EtOH (25 mL) was treated with H_2 at room temperature and pressure. After 4 days, TLC (8:1 EtOAc–MeOH) showed that all the starting material had reacted to give a mixture of two products (R_f 0.5 and 0.2). The catalyst was filtered off through Celite and washed with EtOH. The filtrate was evaporated and the residue was acetylated in the usual way. TLC (3:1 ether–light petroleum) of the ether layer after usual work-up showed a mixture of two products (R_f 0.5 and 0.6) identical with those described in (*a*). Column chromatography (3:1 ether–light petroleum) on silica gel gave **9** (60 mg, 11%) identical with the product described above and (±)-3,4,5,6-tetra-*O*-acetyl-1,2-*O*-isopropylidene-*myo*-inositol (0.182 g, 38%).

Compound **9** was treated with 9:1 MeOH–M HCl at reflux for 1 h when TLC (3:1 ether–light petroleum) showed conversion of **9** into a product (R_f 0) which was acetylated to give 1,2,3,5,6-penta-*O*-acetyl-4-*O*-benzyl-*myo*-inositol (**10**); mp 162–164°C (from light petroleum); identical with the material described previously [8]. ^{1}H NMR data: δ 1.95 (3 H), 1.98 (6 H), 2.00 (3 H), 2.18 (3 H) (4 s, 5Ac), 3.98 (t, *J* 9.2 Hz, 1 H, H-4), 4.64 (s, 2 H, CH_2Ph), 5.07 (m, 2 H, H-1,3), 5.17 (t, 1 H, *J* 9.2 Hz, H-5), 5.32 (t, 1 H, *J* 9.7 Hz, H-6), 5.57 (t, 1 H, *J* 2.7 Hz, H-2).

*Hydrogenolysis of (±)-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol* (**11**) *to give 1,2-*O*-isopropylidene-*myo*-inositol* (**2**).—A mixture of **11** (500 mg), $NaHCO_3$ (100 mg), Pd–C (500 mg, 10% Fluka), and EtOH (25 mL) was shaken under H_2 at 60 psi for 20 h. Water (50 mL) was added, the mixture was filtered through Celite, and the filtrate was concentrated. TLC (8:1 EtOAc–MeOH) of the product showed **2** (R_f 0.2) and the absence of **11** (R_f 0.9) and **7** (R_f 0.5). The crude product was acetylated with Ac_2O–pyridine to give 1,4,5,6-tetra-*O*-acetyl-2,3-*O*-isopropylidene-*myo*-inositol (250 mg, mp 123–125°C) identical with the material

described previously [4]. Under identical conditions but with Et_3N (100 mg) in place of $NaHCO_3$, the benzyl ethers were cleaved in 5 days.

1D-1,4-Di-O-crotyl-2,3:5,6-di-O-isopropylidene-myo-inositol (**36**).—A mixture of 1D-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (**29**; 0.3 g, 1.15 mmol), NaH (0.250 g, 10 mmol), and crotyl bromide (0.5 mL) in dry DMF (15 mL) was stirred at room temperature for 2 h. TLC (1:1 ether–light petroleum) showed conversion of **29** (R_f 0.1) into a product (R_f 0.85). This was isolated in the usual way and chromatographed on silica gel (1:2, ether–light petroleum) to give **36**; mp 87–89°C (from light petroleum and drops of Et_3N); $[\alpha]_D^{25}$ +31.9° (*c* 1, $CHCl_3$), ^1H NMR data: δ 1.37 (3 H), 1.44 (6 H), 1.54 (3 H) (3 s, 2 CMe_2), 1.60 (3 H), 1.73 (3 H) (2 broad signals =CHMe), 3.20–4.49 (m, 10 H, 6 ring protons and 2 OCH_2 of the crotyl groups), 5.70 (m, 2 CH=CH of the crotyl groups). Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75%. Found: C, 65.22; H, 8.72%.

1D-1,4-Di-O-crotyl-2,3-O-isopropylidene-myo-inositol (**37**).—A solution of **36** (0.355 g, 0.96 mmol) and toluene-*p*-sulfonic acid monohydrate (5 mg) in MeOH (10 mL) was kept at 20°C for 10 h after which time TLC (2:1 EtOAc–light petroleum) showed a major product (R_f 0.5) together with starting material (R_f 0.9) and 1,4-di-*O*-crotyl-*myo*-inositol (R_f 0.1). Triethylamine (1 mL) and $NaHCO_3$ (0.2 g) were added and the solvent was evaporated. The residue was extracted with CH_2Cl_2 and chromatographed on silica gel (2:1 EtOAc–light petroleum) to give 0.135 g (0.37 mmol) of **36**, 0.165 g (0.50 mmol) of **37**, and 0.02 g of 1,4-di-*O*-crotyl-*myo*-inositol.

Recrystallisation of the major product from EtOAc–light petroleum gave **37**; mp 108–110°C; $[\alpha]_D^{25}$ −21.7° (*c* 1, $CHCl_3$). ^1H NMR data: δ 1.38 (3 H), 1.53 (3 H) (2 s, CMe_2), 1.69 (3 H), 1.74 (3 H) (2 =CHMe), 2.78 (2 OH), 3.32–4.43 (m, 10 H, 6 ring protons and 2 OCH_2 of the crotyl groups), 5.60–5.73 (m, 2 CH=CH of the crotyl groups). Anal. Calcd for $C_{17}H_{28}O_6 \cdot 0.25\ H_2O$: C, 61.33; H, 8.63%. Found: C, 61.42; H, 8.54%.

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References

[1] T. Desai, J. Gigg, R. Gigg, and E. Martin-Zamora, *Abstr. Int. Carbohydr. Symp., XVIth, Paris, France, 1992*, A-150.

[2] M.J. Berridge, *Nature (London)*, 361 (1993) 315–325; D.C. Billington, *The Inositol Phosphates: Chemical Synthesis and Biological Significance*, VCH, Weinheim, 1993.

[3] T. Desai, J. Gigg, R. Gigg, S. Payne, and S. Penades, *Carbohydr. Res.*, 234 (1992) 1–21, and preceding papers.
[4] R. Gigg and C.D. Warren, *J. Chem. Soc., C*, (1969) 2367–2371.
[5] J. Gigg, R. Gigg, S. Payne, and R. Conant, *Carbohydr. Res.*, 142 (1985) 132–134.
[6] J. Gigg, R. Gigg, S. Payne, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, (1987) 2411–2414; (1988) 981.
[7] J. Gigg, R. Gigg, and E. Martin-Zamora, *Tetrahedron Lett.*, 34 (1993) 2827–2830.
[8] J. Gigg, R. Gigg, S. Payne, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, (1987) 423–429.
[9] T. Desai, A. Fernandez-Mayoralas, J. Gigg, R. Gigg, and S. Payne, *Carbohydr. Res.*, 205 (1990) 105–123.
[10] T. Desai, J. Gigg, R. Gigg, and E. Martin-Zamora, *Abstr. Int. Carbohydr. Symp. XVIth, Paris, France, 1992*, A-151.
[11] (a) J.G. Ward and R.C. Young, *Tetrahedron Lett.*, 29 (1988) 6013–6016; (b) M. Jones, K.K. Rana, and J.G. Ward, *ibid.*, 30 (1989) 5353–5356; (c) J.G. Ward and R.C. Young, *ACS Symp. Ser.*, 463 (1991) 214–228.
[12] B.P. Czech and R.A. Bartsch, *J. Org. Chem.*, 49 (1984) 4076–4078.
[13] T. Balla, L. Hunyady, A.J. Baukal, and K.J. Catt, *J. Biol. Chem.*, 264 (1989) 9386–9390; R.R. Mattingly, L.R. Stephens, R.F. Irvine, and J.C. Garrison, *ibid.*, 266 (1991) 15144–15153.
[14] P. Andersch and M.P. Schneider, *Tetrahedron: Asymm.*, 4 (1993) 2135–2138.