Carbohydrate Research, 205 (1990) 105–123
Elsevier Science Publishers B.V., Amsterdam

The synthesis and resolution of (±)-1,5,6-tri-*O*-benzyl-*myo*-inositol*†

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(Received November 28th, 1989; accepted for publication, January 25th, 1990)

ABSTRACT

Racemic 1,5,6-tri-*O*-benzyl-*myo*-inositol was prepared by five routes and converted into 1,5,6-tri-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol, the camphanates of which were readily separated by chromatography. The absolute configurations of the chiral derivatives were established by their conversion into the known chiral 1,4,5,6-tetra-*O*-benzyl-*myo*-inositols. 1D-1,5,6-Tri-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol was converted into 1D-1,3,5,6-tetra-*O*-benzyl-*myo*-inositol and thence into 1D-2,4-di-*O*-methyl-*myo*-inositol. 1D-1,5,6-Tri-*O*-benzyl-*myo*-inositol was converted into 1D-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol, the diacetate of which is a chiral analogue of "thermosalient crystals". The potential of the above compounds for the synthesis of natural products is surveyed.

INTRODUCTION

Chiral *myo*-inositol 1,2,6-trisphosphates were required for comparison with a biologically active *myo*-inositol 1,2,6-trisphosphate obtained by the hydrolysis of *myo*-inositol hexakisphosphate ("phytic acid")[2§]. As intermediates for the synthesis of these trisphosphates, we chose the corresponding chiral 1,5,6-tri-*O*-benzyl-*myo*-inositols (**49** and **51**) and found that the latter are available by a comparatively easy optical resolution. Since the three free hydroxyl groups of **49** can be differentiated readily by standard manipulations (*e.g.*, the formation of the isopropylidene derivative and tin-mediated alkylations), it is also valuable as an intermediate for the synthesis of several other inositol derivatives of biological interest.

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* Dedicated to Professor Leslie Hough in the year of his 65th birthday.

† The Allyl Group for Protection in Carbohydrate Chemistry, Part 22. Presented in part at the XIVth International Carbohydrate Symposium, Stockholm, Sweden, August 14–19, 1988, at the joint Carbohydrate–Lipid Group meeting of the Royal Society of Chemistry, Sheffield, September 11–14, 1988, and at EUROCARB V, the Vth European Symposium on Carbohydrates, Prague, Czechoslovakia, August 21–25, 1989. For Part 21, see ref. 1.

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§ This isomer (PP56) is currently in preclinical development at Perstorp Pharma, Perstorp, Sweden. (M. J. Siren, A. K. Sim, A. P. McCraw, M. E. Cleland, and T. Gustafsson, 8th Int. Symp. on Atherosclerosis CIC, Rome, 1988; J. C. Ruf, M. Ciavatti, and S. Renaud, NATO Adv. Res. Workshop, Bendor, 1988).

0008-6215/90/$ 03.50

RESULTS AND DISCUSSION

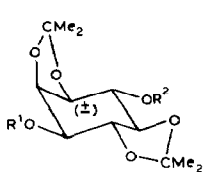
Five routes were investigated for the synthesis of the title compound. For the first route, racemic 3-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**1**) was prepared by partial benzylation of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol and isolation of the monobenzyl fraction by chromatography as described[3].

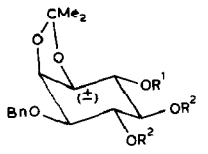
Although **1** was not separated by t.l.c. from its regioisomer, 6-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol[3] (**2**) (which is a minor product of the partial benzylation), the acetates (**3** and **4**) were well resolved and could be separated by column chromatography. The acetates (**5** and **6**) of the corresponding *p*-methoxybenzyl ethers[3] were also separated by chromatography. Hydrolysis of **6** gave the previously undescribed 1,2:4,5-di-*O*-isopropylidene-6-*O*-*p*-methoxybenzyl-*myo*-inositol (**7**). The acetates[3] of the corresponding monoallyl ethers were also separated by t.l.c. and each 3-acetate was less polar than the 6-acetate.

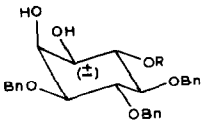
Allylation of **1** gave racemic 6-*O*-allyl-3-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**8**) which, on controlled partial acidic hydrolysis, gave **10** due to preferential hydrolysis of the *trans* (diequatorial) isopropylidene group. The diol **10** was converted into the tribenzyl ether **11** and removal of the isopropylidene group from the latter gave the diol **15**. The allyl group was removed from **15** by the action of Pd–C[4] or by isomerisation[5] to the prop-1-enyl ether **16** and subsequent acid hydrolysis to give the required racemic 1,5,6-tri-*O*-benzyl-*myo*-inositol (**17**).

For optical resolution studies, **17** was converted into the isopropylidene derivative **12** by the action of dimethoxypropane. Although the direct conversion of **11** into **12** by deallylation would be a more convenient route to the alcohol **12**, previous work[6] has shown that the action of potassium *tert*-butoxide in methyl sulphoxide on ethers of 1,2-*O*-isopropylidene-*myo*-inositol leads to elimination of the isopropylidene group and less economical methods of deallylation would be required for this transformation. In this first route, two stages, namely, the preparation of the monobenzyl ether **1** and the partial hydrolysis of the di-*O*-isopropylidene derivative **8**, were not high-yielding and, because of the potential use of this intermediate in several projected syntheses, other routes were investigated.

The second route to racemic 1,5,6-tri-*O*-benzyl-*myo*-inositol (**17**) started from racemic 1,6-di-*O*-allyl-*myo*-inositol[1] (**18**) that was prepared[1] by allylation of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**30**, obtained by hydrolysis of the dibenzoate[1] **32**), to give **25**, and subsequent acid hydrolysis. In the preparation of the dibenzoate **32** (which is the intermediate for three of the preparations described) from the mixture of di-*O*-isopropylidene-*myo*-inositol dibenzoates by solvent fractionation[1], an inspection of the methyl resonances of the isopropylidene groups in the n.m.r. spectrum is a useful guide to the purity of **32**. The chemical shift data for the dibenzoates of the three isomeric di-*O*-isopropylidene-*myo*-inositols, as well as those for the tetrabenzoate of 1,2-*O*-isopropylidene-*myo*-inositol, are recorded. Benzylation of the dibutylstannylene derivative of **18** in the presence of tetrabutylammonium bromide[7] gave mainly the benzyl ether **19** (characterised by deallylation and subsequent acetylation to give 1-*O*-benzyl-



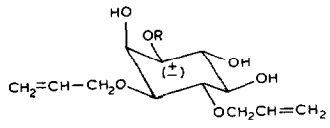


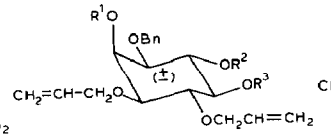


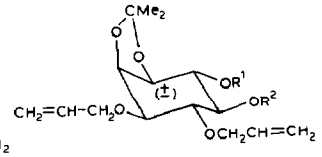
*1 R^1=Bn, R^2=H
2 R^1=H, R^2=Bn
3 R^1=Bn, R^2=Ac
4 R^1=Ac, R^2=Bn
5 R^1=Bn(*p*MeO), R^2=Ac
6 R^1=Ac, R^2=Bn(*p*MeO)
7 R^1=H, R^2=Bn(*p*MeO)
8 R^1=Bn, R^2=CH_2-CH=CH_2
9 R^1=Bn, R^2=Bn(*p*MeO)

10 R^1=CH_2-CH=CH_2, R^2=H
11 R^1=CH_2-CH=CH_2, R^2=Bn
12 R^1=H, R^2=Bn
13 R^1=camphanate, R^2=Bn
14 R^1=Bn(*p*MeO), R^2=H

15 R=CH_2-CH=CH_2
16 R=CH=CH-CH_3
17 R=H







18 R=H
19 R=Bn

20 R^1=H, R^2,R^3=CMe_2
21 R^1=CH_2-CH=CH_2, R^2,R^3=CMe_2
22 R^1=CH_2-CH=CH_2, R^2=R^3=H
23 R^1=CH_2-CH=CH_2, R^2=R^3=Ac
24 R^1=CH_2-CH=CH_2, R^2=R^3=Bn

25 R^1,R^2=CMe_2
26 R^1=R^2=H
27 R^1=R^2=Bn

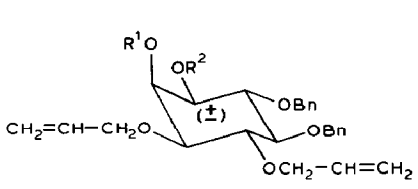
myo-inositol penta-acetate). Compound **19** was converted into the isopropylidene derivative **20** which was allylated to give racemic 1,2,6-tri-*O*-allyl-3-*O*-benzyl-4,5-*O*-isopropylidene-*myo*-inositol (**21**). Hydrolysis of the isopropylidene group from **21** and benzylation of the product **22** gave 1,2,6-tri-*O*-allyl-3,4,5-tri-*O*-benzyl-*myo*-inositol (**24**), which was deallylated[4] with Pd–C to give **17**.

In the third route, 1,6-di-*O*-allyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol[1] (**25**) was partially hydrolysed to give the mono-isopropylidene derivative **26** which was converted into 1,6-di-*O*-allyl-4,5-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (**27**). Hydrolysis of **27** gave crystalline 1,6-di-*O*-allyl-4,5-di-*O*-benzyl-*myo*-inositol (**28**), and benzylation of the dibutylstannylene derivative of **28** gave 1,6-di-*O*-allyl-3,4,5-tri-*O*-benzyl-*myo*-inositol (**29**) which on deallylation gave **17**.

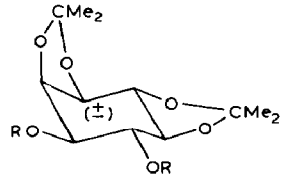
For the fourth route, racemic 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol[1] (**30**) was converted into **31** and this was partially hydrolysed to give 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol (**33**) which gave a crystalline acetate **34**. Alkylation of the dibutylstannylene derivative of **33** with benzyl bromide gave mainly 3,4,6-tri-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol (**35**) with a smaller amount of the required

*In the formulae, racemic inositol derivatives are indicated by (±) in the ring, and chiral inositol derivatives, represented in their correct absolute configuration, are shown with thickened lines in the ring.

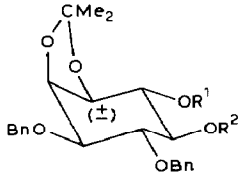
regioisomer **12**, and these products were well separated by t.l.c. Therefore, the alkylation of the dibutylstannylene derivative of **33** was repeated with allyl bromide and with *p*-methoxybenzyl chloride. In the reaction with allyl bromide, little regiospecificity was observed (although the products were well separated in t.l.c.) but, with *p*-methoxybenzyl chloride, the same regiospecificity was observed as with benzyl bromide. The major product (~65%) was **38** with a smaller amount of the regioisomer **36**, and these compounds were readily separated by chromatography. Benzylation of the *p*-methoxybenzyl ether **38** gave the tribenzyl ether **40** and removal of the *p*-methoxybenzyl group with dichlorodicyanoquinone[8] gave the alcohol **12**. Because this last route gave directly **12**, which was required for the optical resolution, it is probably the most useful of the four methods of preparation. For this reason, a fifth route was developed using similar intermediates. *p*-Methoxybenzylation of **1** gave **9** and this was partially hydrolysed to give 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-methoxybenzyl-*myo*-inositol (**14**).



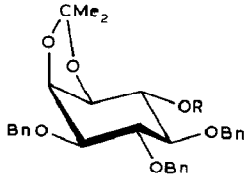
28 $R^1=R^2=H$
29 $R^1=H$, $R^2=Bn$



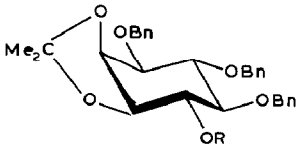
30 R = H
31 R = Bn
32 R = Bz



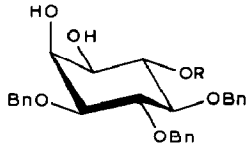
33 $R^1=R^2=H$
34 $R^1=R^2=Ac$
35 $R^1=Bn$, $R^2=H$
36 $R^1=H$, $R^2=Bn(p\text{MeO})$
37 $R^1=Ac$, $R^2=Bn(p\text{MeO})$
38 $R^1=Bn(p\text{MeO})$, $R^2=H$
39 $R^1=Bn(p\text{MeO})$, $R^2=Ac$
40 $R^1=Bn(p\text{MeO})$, $R^2=Bn$



41 R = camphanate
42 R = H
43 R = Bn

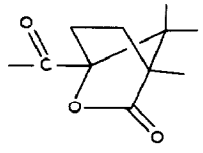


44 R = camphanate
45 R = H
46 R = Bn
47 $R=CH_2\text{-}CH=CH_2$



48 R = Bn
49 R = H

Camphanate =



Benzylation of **14** gave the tribenzyl ether **40** which was converted into **12** as described above.

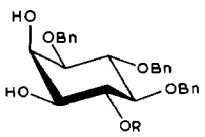
For the optical resolution, **12** was converted into the ω-camphanates (**13**). The diastereoisomers (**41** and **44**) were well resolved in t.l.c. and were readily separated by column chromatography on silica gel (or by preparative h.p.l.c.) To establish their absolute configurations, the camphanates (**41** and **44**) were individually hydrolysed to the alcohols **42** and **45** which were converted into the tetrabenzyl ethers (**43** and **46**). On hydrolysis, **43** and **46** gave the diols (**48** and **50**) whose absolute configurations have been established[9]. Thus, the less polar camphanate (in t.l.c.) has the absolute configuration shown in **41**. Acid hydrolysis of the isopropylidene derivatives (**42** and **45**) gave the chiral tri-*O*-benzyl-*myo*-inositols (**49** and **51**) which were required for phosphorylation studies.

The relative ease of separation of the diastereoisomeric camphanates (**41** and **44**) and consequent access to the chiral alcohols (**42** and **45**) suggested the use of these derivatives for the synthesis of other chiral *myo*-inositol intermediates for the preparation of inositol phosphates involved in the "phosphatidylinositol cycle" (for reviews, see refs. 10 and 11) and of other *myo*-inositol derivatives of biological interest.

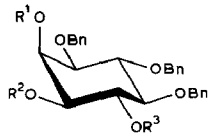
The allyl ether **47** was prepared from the chiral alcohol **45** and hydrolysed to give the diol **52**. Benzylation of the dibutylstannylene derivative of **52** gave the tetrabenzyl ether **53** and this, on deallylation, gave 1D-1,3,5,6-tetra-*O*-benzyl-*myo*-inositol (**55**). Compound **55** was also prepared by direct benzylation of the dibutylstannylene derivative of the chiral triol **51**. Similarly, **17** was converted into the racemic tetrabenzyl ether **63**. The camphanates (**67**) of **63** were prepared, and crystallisation of the mixture gave the pure bis-camphanate **62** identical with that prepared from 1D-1,3,5,6-tetra-*O*-benzyl-*myo*-inositol (**55**).

Methylation of the chiral diol **55** gave the dimethyl ether **56** which, on hydrogenolysis, gave 1D-2,4-di-*O*-methyl-*myo*-inositol (**68**) that gave a crystalline tetra-acetate (**69**) with a larger optical rotation. These derivatives were required as chiral reference compounds for optical resolution studies of intermediates prepared for the synthesis of 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate (**71**), which is a component of the "phosphatidylinositol cycle". The enantiomer of the diol **55** [which is similarly available from 1L-1,5,6-tri-*O*-benzyl-*myo*-inositol (**49**)] is also a potential intermediate for the synthesis of 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate (**71**) since it has benzyl protection on the four hydroxyl groups required to be phosphorylated.

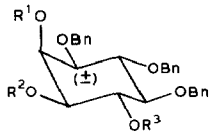
We have recorded[1] that crystals of racemic 3,4-di-*O*-acetyl-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol (**64**) show interesting "jumping" behaviour on heating to 70° and named them "thermosalient crystals". Subsequent investigations[12], using differential scanning calorimetry, have shown two "jumping" temperatures at 30 and 70° due to solid phase transitions. We were interested to see if the chiral analogue **61** of **64** behaved similarly. For this purpose, the dibutylstannylene derivative of 1D-4-*O*-allyl-1,5,6-tri-*O*-benzyl-*myo*-inositol (**52**) was allylated to give the diallyl ether **57**, which was benzylated to give 1D-3,4-di-*O*-allyl-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol (**58**). Deallylation of **58** gave 1D-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol (**60**) which was acetylated to give **61**. The



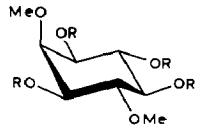
50 R = Bn
51 R = H



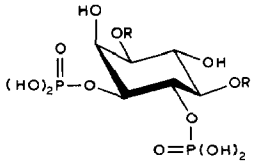
52 $R^1 = R^2 = H$, $R^3 = CH_2\text{-}CH = CH_2$
53 $R^1 = H$, $R^2 = Bn$, $R^3 = CH_2\text{-}CH = CH_2$
54 $R^1 = H$, $R^2 = Bn$, $R^3 = CH = CH\text{-}CH_3$
55 $R^1 = R^3 = H$, $R^2 = Bn$
56 $R^1 = R^3 = Me$, $R^2 = Bn$
57 $R^1 = H$, $R^2 = R^3 = CH_2\text{-}CH = CH_2$
58 $R^1 = Bn$, $R^2 = R^3 = CH_2\text{-}CH = CH_2$
59 $R^1 = Bn$, $R^2 = R^3 = CH = CH\text{-}CH_3$
60 $R^1 = Bn$, $R^2 = R^3 = H$
61 $R^1 = Bn$, $R^2 = R^3 = Ac$
62 $R^1 = R^3 =$ camphanate, $R^2 = Bn$



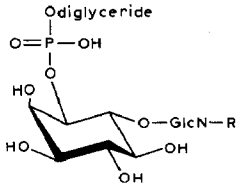
63 $R^1 = R^3 = H$, $R^2 = Bn$
64 $R^1 = Bn$, $R^2 = R^3 = Ac$
65 $R^1 = Bn$, $R^2 = R^3 = H$
66 $R^1 = Bn$, $R^2 = R^3 =$ camphanate
67 $R^1 = R^3 =$ camphanate, $R^2 = Bn$



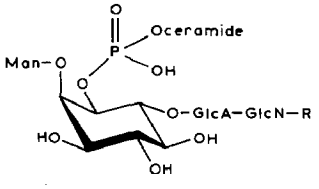
68 R = H
69 R = Ac



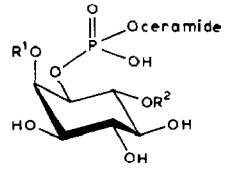
70 R = H
71 R = $P(OH)_2$ (=O)



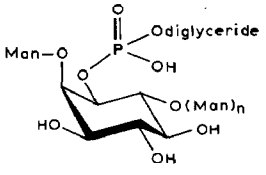
72 R = Oligosaccharide plus protein



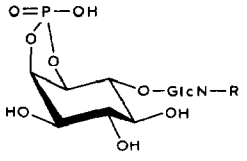
73 R = Oligosaccharide



74 R^1 or R^2 =
α-Man-(1→3)-α-Man
or
α-Man-(1→3)
α-Man
α-Gal*f*-(1→6)



75



76 R = oligosaccharide plus protein

chiral acetate **61** did not show the same "jumping" behaviour, on heating, as the racemate **64**. Subsequent X-ray crystallographic studies[13] showed that the unit cell of **64** contained two molecules of each enantiomer.

The chiral diol **60** is also a suitable intermediate for the synthesis of 1D-*myo*-inositol 3,4-bisphosphate (**70**), which is a component of the "phosphatidylinositol

cycle", and it was also required as a chiral reference compound for resolution studies of racemic 1,2,5,6-tetra-*O*-benzyl-*myo*-inositol[1] (**65**). The diastereoisomers of the bis-camphanate **66** were not resolved by t.l.c., but one of them crystallised from the mixture and gave **60** on basic hydrolysis.

The chiral alcohol **42** should also be a useful intermediate in the synthesis of other molecules of biological interest. (*a*) The "lipid anchor" of various cell surface enzymes and glycoproteins[10,14] that have[15] the basic structure **72**, which may be present also in the putative "insulin second messenger"[16]. Enzymic hydrolysis of the diglyceride from **72** releases the inositol phosphate-containing glycan as an immunologically active molecule ("cross-reacting determinant") which contains[14a,17] a *myo*-inositol 1,2-cyclic phosphate residue **76** in the epitope. This cyclic phosphate should also be available from **42**. (*b*) "Phytoglycolipid", a phytosphingosine-containing glycolipid from plant seeds[18], has the basic structure **73** and related compounds are present in tobacco leaves[19]. (*c*) The serologically active phosphatidylinositol mannosides (**75**) of *Mycobacterium tuberculosis*[20]. (*d*) The serologically active glycolipids (**74**) from *Histoplasma capsulatum*[19b,21].

EXPERIMENTAL

General. — The light petroleum used for t.l.c. had b.p. 40–60°; otherwise, the fraction used had b.p. 60–80°. T.l.c. was carried out on Silica Gel G (Merck). Extracts were concentrated under reduced pressure. Optical rotations were measured with a Bendix automatic polarimeter. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Jeol FX90Q Fourier-transform spectrometer.

*(±)-6-*O*-Acetyl-3-*O*-benzyl-* (**3**) *and (±)-3-*O*-acetyl-6-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol* (**4**). — The mixture of 3- and 6-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol was prepared by partial benzylation of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol; the 3-*O*-benzyl derivative crystallised[3] from the mixture. The products remaining in the mother liquor were acetylated with acetic anhydride–pyridine in the usual way and t.l.c. (ether–light petroleum, 1:1) showed two products (R_F 0.5 and 0.35). The acetates were separated by chromatography on silica gel (above solvent) and recrystallised from ethyl acetate–light petroleum (1:1). The acetate **4** of R_F 0.5 had m.p. 151–152°. ^{1}H-N.m.r. data: δ 1.31, 1.38, 1.45, 1.48 (4 s, 2 CMe_2), 2.17 (s, Ac), 4.60 (t, J 4.88 Hz, H-2), 4.82 (s, CH_2Ph), 5.09 (dd, J 4.2 and 10.38 Hz, H-3), 7.34, 7.36 (2 s, aromatic) (Found: C, 64.51; H, 7.29. $C_{21}H_{28}O_7$ calc.: C, 64.27; H, 7.19%).

Basic hydrolysis of this material gave known[3] 6-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol.

The acetate **3** of R_F 0.35 [which co-chromatographed with the acetate prepared from the pure 3-benzyl ether[3] **1**] had m.p. 183–185°. ^{1}H-N.m.r. data: δ 1.34, 1.44, 1.48, 1.60 (4 s, 2 CMe_2), 2.10 (s, Ac), 3.33 (dd, J 9.15 and 10.98 Hz), 3.77 (dd, J 4.27 and 10.37 Hz), 4.31 (t, J 4.27 Hz, H-2), 4.83, 4.87 (ABq, CH_2Ph), 7.36, 7.38 (2 s, aromatic) (Found: C, 64.28; H, 7.23%).

*(±)-6-*O*-Acetyl-1,2:4,5-di-*O*-isopropylidene-3-*O*-p-methoxybenzyl-*myo*-inositol*

(5), *(±)-3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-6-*O*-*p*-methoxybenzyl*-myo-*inositol* **(6)**, *and (±)-1,2:4,5-di-*O*-isopropylidene-6-*O*-*p*-methoxybenzyl*-myo-*inositol* **(7)**. — Partial *p*-methoxybenzylation of 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol and isolation of the mono-*p*-methoxybenzyl ethers followed by crystallisation gave[3] the 3-*p*-methoxybenzyl ether. Acetylation of the material in the mother liquor gave the acetates **5** and **6** [t.l.c. (ether–light petroleum, 1:1), R_F 0.5 and 0.4], which were separated by silica gel chromatography and recrystallised from ethyl acetate–light petroleum. The acetate **6** of R_F 0.5 had m.p. 148–150°. ^{1}H-N.m.r. data: δ 1.31, 1.39, 1.44, 1.48 (4 s, 2 CMe_2) 2.16 (s, Ac), 3.79 (s, OMe), 4.58 (t, *J* 4.27 Hz, H-2), 4.75 (s, CH_2Ph), 5.08 (dd, *J* 4.27 and 10.98 Hz, H-3), 6.81, 6.91, 7.28, 7.38 (4 s, aromatic) (Found: C, 62.81; H, 7.32. $C_{22}H_{30}O_8$ calc.: C, 62.54; H, 7.16%).

Basic hydrolysis of **6** gave (±)-1,2:4,5-di-*O*-isopropylidene-6-*O*-*p*-methoxybenzyl-*myo*-inositol (**7**), m.p. 145–147° (from ethyl acetate–light petroleum, 1:5). ^{1}H-N.m.r. data: δ 1.36, 1.39, 1.45, 1.46 (4 s, 2 CMe_2), 3.79 (s, OMe), 4.74 (s, CH_2Ph), 6.81, 6.91, 7.28, 7.38 (4 s, aromatic) (Found: C, 63.47; H, 7.43. $C_{20}H_{28}O_7$ calc.: C, 63.14; H, 7.42%).

The acetate **5** [R_F 0.4, which co-chromatographed with the acetate prepared from pure 1,2:4,5-di-*O*-isopropylidene-3-*O*-*p*-methoxybenzyl-*myo*-inositol[3]] had m.p. 189–191°. ^{1}H-N.m.r. data: δ 1.33, 1.44, 1.48, 1.59 (4 s, 2 CMe_2), 2.11 (s, Ac), 3.81 (s, OMe), 4.77, 4.80 (ABq, CH_2Ph), 6.84, 6.93, 7.30, 7.40 (4 s, aromatic) (Found: C, 62.33; H, 7.24%).

*(±)-6-*O*-Allyl-3-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene*-myo-*inositol* **(8)**. — Treatment of **1** with allyl bromide and sodium hydride in *N,N*-dimethylformamide, with isolation of the product in the usual way[3], gave **8**, m.p. 118–120° (from light petroleum) (Found: C, 67.71; H, 7.88. $C_{22}H_{30}O_6$ calc.: C, 67.67; H, 7.75%).

*(±)-6-*O*-Allyl-3-*O*-benzyl-1,2-*O*-isopropylidene*-myo-*inositol* (**10**). — A solution of **8** (6.1 g) and toluene-*p*-sulphonic acid monohydrate (500 mg) in acetone (110 mL) and water (2.8 mL) was kept for 45 min at 25°. Triethylamine (1 mL) was added, the solvents were evaporated, and toluene was evaporated from the residue. The residue was extracted with hot light petroleum (containing a little triethylamine), in order to remove **8**, and then with dichloromethane. The latter extract was washed with water, dried (K_2CO_3), and concentrated. Crystallisation of the crude product from ethyl acetate–light petroleum (1:2) gave **10** (2.67 g, 49%), m.p. 120–121° (Found: C, 64.95; H, 7.62. $C_{19}H_{26}O_6$ calc.: C, 65.12, H, 7.48%). The light petroleum extract was combined with the residue from the mother liquor and treatment of this with dimethoxypropane in acidic acetone gave **8** which was recycled.

*(±)-4-*O*-Allyl-1,5,6-tri-*O*-benzyl*-myo-*inositol* (**15**). — The diol **10** (3 g) was treated with an excess of benzyl bromide and sodium hydride in *N,N*-dimethylformamide, and the product was isolated in the usual way[3]. The crude product was heated for 45 min under reflux in methanol (180 mL) and M hydrochloric acid (20 mL). An excess of sodium hydrogen carbonate was added, the solvents were evaporated, and toluene was evaporated from the residue. The product was extracted from the residue with dichloromethane, the extract was dried (K_2CO_3), and the crystalline product was chromatographed on silica gel (ether) to give **15** (3.8 g, 90%), m.p. 99–101° (from ethyl

acetate–light petroleum, 1:10) (Found: C, 73.73; H, 7.18. $C_{30}H_{34}O_6$ calc.: C, 73.45; H, 6.99%).

(±)-1,5,6-Tri-O-*benzyl-4*-O-*(prop-1-enyl)*-myo-*inositol* (**16**). — The allyl ether **15** was treated with potassium *tert*-butoxide in methyl sulphoxide in the usual way[5] at 50° for 2 h, after which time t.l.c. (ether–light petroleum, 3:1) showed complete conversion of **15** (R_F 0.35) into a product (R_F 0.5). The solution was diluted with water, and the crystalline product was collected and recrystallised from ethyl acetate–light petroleum (1:10) to give **16**, m.p. 98–100° (Found: C, 73.07; H, 7.09. $C_{30}H_{34}O_6$ calc.: C, 73.45; H, 6.99%).

Chemical shifts for the resonances of the isopropylidene methyl groups of the dibenzoates of 1,2:4,5-, 1,2:5,6-, and 1,2:3,4-di-O-*isopropylidene*-myo-*inositol and of 3,4,5,6-tetra*-O-*benzoyl-1,2*-O-*isopropylidene*-myo-*inositol in the n.m.r. spectra.* — 1,2:4,5, δ 1.30, 1.44, 1.51, 1.64 (4 s, 2 CMe_2); 1,2:5,6, δ 1.34 (6 H), 1.48 (3 H), 1.51 (3 H) (3 s, 2 CMe_2); 1,2:3,4, δ 1.40 (3 H), 1.53 (6 H), 1.67 (3 H) (3 s, 2 CMe_2); 1,2, δ 1.38, 1.72 (2 s, CMe_2).

(±)-2,3,4,5-Tetra-O-*acetyl-1,6-di*-O-*allyl*-myo-*inositol.* — Acetylation of racemic 1,6-di-*O*-allyl-*myo*-inositol[1] (**18**) with acetic anhydride–pyridine in the usual way gave the title compound, m.p. 144–146° (from ethyl acetate–light petroleum). ^{1}H-N.m.r. data: δ 1.99 (6 H), 2.06 (3 H), 2.16 (3 H), (3 s, 4 Ac) (Found: C, 55.74; H, 6.62. $C_{20}H_{28}O_{10}$ calc.: C, 56.07; H, 6.59%).

(±)-1,6-Di-O-*allyl-3*-O-*benzyl*-myo-*inositol* (**19**). — A mixture of **18** (2 g), dibutyltin oxide (2 g), tetrabutylammonium bromide (2.7 g), and toluene (100 mL) was heated for 2 h under reflux with azeotropic removal of water. Benzyl bromide (1 mL) was added, and the mixture was heated for 21 h under reflux, after which time t.l.c. (ethyl acetate) showed a major product (R_F 0.5) and minor products (R_F 0.9, 0.8, and 0.4). The solution was cooled and concentrated, ether (50 mL) was added, and the precipitate was removed. The filtrate was extracted with water (3 × 50 mL) after which t.l.c. showed that most of the polar products (R_F 0.4 and 0.5) were in the aqueous layer. The aqueous layer was concentrated to dryness, and a solution of the residue in dichloromethane was dried (K_2CO_3) and concentrated. The crude product was chromatographed on silica gel (ethyl acetate) to separate the major (R_F 0.5, 700 mg) and the minor (R_F 0.4, 100 mg) products. Recrystallisation of the major product from ethyl acetate–light petroleum (1:7) gave **19**, m.p. 94–96° (Found: C, 65.03; H, 7.35. $C_{19}H_{26}O_6$ calc.: C, 65.12; H, 7.48%), which gave a triacetate, m.p. 113–114°. ^{1}H-N.m.r. data: δ 1.99, 2.04, 2.16 (3 s, 3 Ac), 4.47, 4.63 (ABq, CH_2Ph), 5.74 (t, H-2) (Found: C, 63.46; H, 6.82. $C_{25}H_{32}O_9$ calc.: C, 63.01; H, 6.77%).

The n.m.r. spectrum of the acetate of the minor polar product [R_F 0.4; δ 1.95, 1.98, 2.04 (3 s, 3 Ac)] indicated that it was the 2-benzyl ether, and the n.m.r. spectra of the acetates of the minor products (R_F 0.8 and 0.9) indicated that they were mixtures of dibenzyl ethers.

(±)-2,3,4,5,6-Penta-O-*acetyl-1*-O-*benzyl*-myo-*inositol*[22,23]. — (*a*) A mixture of **19** (200 mg), 10% Pd–C (20 mg), ethanol (9.5 mL), water (0.5 mL), and toluene-*p*-sulphonic acid (4 mg) was heated for 13 h under reflux. Sodium hydrogen carbonate (5 mg) was added, the hot solution was filtered, the residue was extracted with hot aqueous

95% ethanol (20 mL), and the extract was filtered. The combined filtrates were concentrated to dryness and the residue was acetylated with acetic anhydride–pyridine (1:2) at 50° for 5 h. The solution was diluted with water, and the crystalline precipitate was collected and recrystallised from ethyl acetate–light petroleum (1:5) to give the title compound (120 mg), m.p. 166–167°; lit.[22] m.p. 168–170°; lit.[23] m.p. 167–168°. The ^{1}H-n.m.r. spectrum was as described[23].

(*b*) 1-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol[3] (**1**) was heated under reflux in acetic acid–water (4:1) for 1 h and the solvents were then evaporated. The product was acetylated with acetic anhydride–pyridine (1:2) for 5 h at 50°. The mixture was worked-up as in (*a*) to give the title compound, m.p. 168–170°.

(±)-1,6-Di-O-*allyl-3*-O-*benzyl-4,5*-O-*isopropylidene*-myo-*inositol* (**20**). — A solution of **19** (17 g) in acetone (100 mL) and 2,2-dimethoxypropane (100 mL) containing toluene-*p*-sulphonic acid (500 mg) was kept for 6 h at 20°, after which time t.l.c. (ether–light petroleum, 1:1) showed a major product (R_F 0.5) and some **19** (R_F 0). Triethylamine (2 mL) and sodium hydrogen carbonate (500 mg) were added, the solvents were evaporated, and toluene was evaporated from the residue which was extracted with dichloromethane. The extract was dried (K_2CO_3) and concentrated, and the crude product was chromatographed on silica gel (ether–light petroleum, 1:1) to give **20** (13 g), m.p. 57–59° (from ethyl acetate–light petroleum, 1:10) (Found: C, 67.81; H, 7.82. $C_{22}H_{30}O_6$ calc.: C, 67.67; H, 7.75%), which gave a syrupy acetate. ^{1}H-N.m.r. data: δ 1.44, 1.46 (2 s, CMe_2), 2.13 (s Ac), 4.67 (s, CH_2Ph), 7.32 (s, aromatic).

(±)-5,6-Di-O-*acetyl-2,3,4-tri*-O-*allyl-1*-O-*benzyl*-myo-*inositol* (**23**). — Compound **20** was treated with allyl bromide and sodium hydride in *N,N*-dimethylformamide, and the product was isolated in the usual way to give the triallyl ether **21** as a syrup. The latter was treated with M hydrochloric acid–methanol (1:9) for 30 min at reflux, an excess of sodium hydrogen carbonate was added, and the solvents were evaporated. The diol **22** was extracted from the residue with dichloromethane and acetylated with acetic anhydride–pyridine to give **23**, m.p. 123–124° (from ethyl acetate–light petroleum, 1:4). ^{1}H-N.m.r. data: δ 1.98, 2.02 (2 s, 2 Ac), 4.56, 4.59 (ABq, CH_2Ph) (Found: C, 66.26; H, 7.34. $C_{26}H_{34}O_8$ calc.: C, 65.80; H, 7.22%).

(±)-2,3,4-Tri-O-*allyl-1,5,6-tri*-O-*benzyl*-myo-*inositol* (**24**). — The diol **22** (prepared by hydrolysis of **23** with sodium hydroxide in methanol) was treated with benzyl bromide and sodium hydride in *N,N*-dimethylformamide, and the product was isolated in the usual way to give **24**, m.p. 36° (Found: C, 75.64; H, 7.32. $C_{36}H_{42}O_6$ calc.: C, 75.76; H, 7.42%).

(±)-1,6-Di-O-*Allyl-4,5-di*-O-*benzyl*-myo-*inositol* (**28**). — A solution of 1,6-di-*O*-allyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol[1] (**25**, 8.7 g) and toluene-*p*-sulphonic acid (500 mg) in acetone (100 mL) and water (5 mL) was kept for 4 h at 20°. T.l.c. (ether) then showed a major product (R_F 0.2), some **25** (R_F 1.0), and some **18** (R_F 0). Triethylamine (1 mL) and sodium hydrogen carbonate (500 mg) were added and the solvents were evaporated. Water (25 mL) was added to the residue and the remaining **25** was extracted with light petroleum. Extraction of the aqueous layer with dichloromethane then gave the diol **26** (2.4 g) as a syrup. This compound was treated with benzyl bromide and

sodium hydride in *N,N*-dimethylformamide in the usual way, to give the dibenzyl ether **27** which was treated with M hydrochloric acid–methanol (1:10) for 30 min at reflux. Sodium hydrogen carbonate (2 g) was added, the solvents were evaporated, and the product was extracted from the residue with ether and chromatographed on silica gel to give **28** (2.4 g), m.p. 68–69° (from light petroleum) (Found: C, 71.02; H, 7.14. $C_{26}H_{32}O_6$ calc.: C, 70.89; H, 7.32%), which gave a syrupy diacetate. ^{1}H-N.m.r. data: δ 1.92, 2.08 (2 s, 2 Ac), 7.26, 7.31 (2 s, aromatic).

(±)-4,5-Di-O-*acetyl-1,6-di*-O-*benzyl-2,3*-O-*isopropylidene*-myo-*inositol* (**34**). — 1,2:5,6-Di-*O*-isopropylidene-*myo*-inositol[1] (**30**) was treated with benzyl bromide and sodium hydride in *N,N*-dimethylformamide and the product isolated in the usual way, to give the dibenzyl ether **31** as a syrup (R_F 0.5; ether–light petroleum, 1:2). A solution of the crude **31** (9.3 g) and toluene-*p*-sulphonic acid (690 mg) in acetone (140 mL) and water (3.5 mL) was kept for 50 min at 20°, when t.l.c. (chloroform–ethyl acetate, 1:1) showed some **31** (R_F 0.95), a major product (R_F 0.3), and some tetraol (R_F 0). Triethylamine (2.8 mL) and sodium hydrogen carbonate (780 mg) were added and the solvents were evaporated. The residue was extracted with dichloromethane, and the extract was dried (K_2CO_3) and concentrated to dryness. The residue was extracted with light petroleum to remove the residual **31**, and ether was added. The crystalline precipitate (tetraol) was removed and the filtrate was concentrated to give the crude diol **33** as a syrup. This compound was treated with acetic anhydride–pyridine for 5 h at 50°, and the product was isolated in the usual way and crystallised from light petroleum to give **34** (2.4 g, 23%), m.p. 127–128° ^{1}H-N.m.r. data: δ 1.34, 1.59 (2 s, CMe_2), 1.93, 2.03 (2 s, 2 Ac), 7.30, 7.34 (2 s, aromatic). (Found: C, 66.85; H, 6.62. $C_{27}H_{32}O_8$ calc.: C, 66.93; H, 6.67%).

Recovered **31** was recycled.

(±)-1,6-Di-O-*benzyl-2,3*-O-*isopropylidene-4*-O-p-*methoxybenzyl*-myo-*inositol* (**38**). — Compound **34** was hydrolysed with an excess of sodium hydroxide in methanol at 50°. Solid carbon dioxide was added, the solvent was evaporated, and the diol **33** was extracted from the residue with dichloromethane. A mixture of **33** (470 mg, 1.17 mmol), acetonitrile (50 mL), dibutyltin oxide (350 mg, 1.4 mmol), tetrabutylammonium bromide (380 mg, 1.17 mmol), and *p*-methoxybenzyl chloride (0.47 mL, 3.5 mmol) was heated under reflux in a Soxhlet apparatus containing molecular sieve 3 Å (2 g) until t.l.c. (ether–light petroleum, 3:2) indicated complete conversion of **33** (R_F 0) into major (R_F 0.6) and minor (R_F 0.3) products. The solvent was evaporated and the product was chromatographed on silica gel (ether–light petroleum, 1:2 in stages to 3:2) to give **38** (390 mg, 64%) and **36** (140 mg, 23%) as syrups.

Compound **38** gave a syrupy acetate **39**. ^{1}H-N.m.r. data: δ 1.29, 1.46 (2 s, CMe_2), 1.88 (s, Ac), 3.72 (s, OMe), 4.96 (t, *J* 7.9 Hz, H-5) (Found: C, 70.33; H, 6.71. $C_{33}H_{38}O_8$ calc.: C, 70.44; H, 6.81%).

Compound **36** gave an acetate (**37**), m.p. 112–113° (from ethyl acetate–light petroleum). ^{1}H-N.m.r. data: δ 1.32, 1.59 (2 s, CMe_2), 1.99 (s, Ac), 3.77 (s, OMe), 5.29 (dd, *J* 7.5 and 10 Hz, H-6) (Found: C, 70.37; H, 6.94%).

(±)-3-O-*Benzyl-1,2:4,5-di*-O-*isopropylidene-6*-O-p-*methoxybenzyl*-myo-*inosi-*

tol (**9**). — The benzyl ether **1** (ref. 3) was treated with an excess of *p*-methoxybenzyl chloride and sodium hydride in *N,N*-dimethylformamide. The product was isolated in the usual way[3] and crystallised from ethyl acetate–light petroleum (1:5) to give **9**, m.p. 132–133° (Found: C, 68.53; H, 7.13. $C_{27}H_{34}O_7$ calc.: C, 68.91; H, 7.28%).

*(±)-3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-methoxybenzyl*-myo*-inositol* (**14**). — A solution of **9** (1 g) and pyridinium toluene-*p*-sulphonate (50 mg) in methanol (50 mL) was kept for 9 h at 20°, when t.l.c. (ether–dichloromethane, 1:1) showed almost complete conversion of **9** (R_F 0.95) into major (R_F 0.5) and minor (R_F 0.2) products. Triethylamine (1 mL) and sodium hydrogen carbonate (100 mg) were added, the solvent was evaporated, and the major product was extracted from the residue with dichloromethane [most of the minor product (R_F 0.2, 1-*O*-benzyl-4-*O*-*p*-methoxybenzyl-*myo*-inositol) was insoluble in dichloromethane]. The crude product was chromatographed on silica gel (above solvent) to give **14** (690 mg), m.p. 148–149° (from ethyl acetate–light petroleum, 1:1) (Found: C, 67.17; H, 7.29. $C_{24}H_{30}O_7$ calc.: C, 66.96; H, 7.03%).

*(±)-1,5,6-Tri-*O*-benzyl-2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzyl*-myo*-inositol* (**40**). — (*a*) The alcohol **38** (370 mg) was treated with sodium hydride and benzyl bromide in *N,N*-dimethylformamide, and the product was isolated in the usual way and chromatographed on silica gel (ether–light petroleum, 1:2) to give **40** (390 mg, 90%), m.p. 76–77° (from ethyl acetate–light petroleum) (Found: C, 74.84; H, 6.99. $C_{38}H_{42}O_7$ calc.: C, 74.73; H, 6.93%).

(*b*) The diol **14** was treated with an excess of sodium hydride and benzyl bromide in *N,N*-dimethylformamide, and the product was isolated in the usual way and chromatographed on silica gel, as in (*a*), to give **40**, m.p. 76–77°.

*(±)-1,5,6-Tri-*O*-benzyl*-myo*-inositol* (**17**). — (*a*) The prop-1-enyl ether **16** (2.8 g) was heated for 30 min under reflux in methanol (45 mL) and M hydrochloric acid (5 mL). An excess of sodium hydrogen carbonate was added and the solvents were evaporated. The residue was extracted with chloroform, and the extract was dried (K_2CO_3) and concentrated to give **17** (2 g, 78%), m.p. 154–156° (from ethyl acetate–light petroleum, 2:1) (Found: C, 72.02; H, 6.70. $C_{27}H_{30}O_6$ calc.: C, 71.98; H, 6.71%).

The triacetate of **17** had m.p. 117–119° (from ethyl acetate–light petroleum, 1:5). ^{1}H-N.m.r. data: δ 1.90, 1.99, 2.16 (3 s, 3 Ac) (Found: C, 68.67; H, 6.38. $C_{33}H_{36}O_9$ calc.: C, 68.73; H, 6.38%).

(*b*) A mixture of the triallyl ether **24** (7.7 g), ethanol (75 mL), water (5 mL), 10% Pd–C (700 mg), and toluene-*p*-sulphonic acid (100 mg) was heated for 11 h under reflux, then filtered, and the insoluble material was washed well with hot chloroform–methanol (1:1). Sodium hydrogen carbonate (100 mg) was added to the filtrate which was concentrated to dryness. The residue was extracted with chloroform, the extract was dried (K_2CO_3), and the product was recrystallised as described in (*a*), to give **17** (5 g), m.p. 153–155°.

(*c*) A mixture of the diol **28** (2.2 g), dibutyltin oxide (1.28 g), and tetrabutylammonium bromide (1.6 g) in toluene (50 mL) was heated for 2 h under reflux in a Dean and Stark apparatus. Benzyl bromide (0.7 mL) was then added and the mixture heated for 2

h under reflux when t.l.c. (ether–light petroleum, 1:1) showed conversion of **28** (R_F 0.2) into a product (R_F 0.6). The solvent was evaporated, ether (100 mL) and saturated aqueous sodium hydrogen carbonate (50 mL) were added to the residue, and the mixture was stirred for 1 h and then filtered. The ether layer was separated, dried (K_2CO_3), and concentrated to give crude **29**. A mixture of the crude product, ethanol (50 mL), water (3.5 mL), Pd–C (10%, 500 mg), and toluene-*p*-sulphonic acid monohydrate (67 mg) was heated under reflux with stirring for 11 h, when t.l.c. (dichloromethane–ethyl acetate, 1:1) showed conversion of **29** (R_F 1) into a major product (R_F 0.2, co-chromatographing with the triol **17**), a trace of monoallyl derivative(s) (R_F 0.8), and another trace product (R_F 0.35). The mixture was filtered through Celite and the solids were washed with hot chloroform–methanol (1:1). Triethylamine was added to the filtrate, the solvents were evaporated, and the residue was recrystallised from ethyl acetate–light petroleum (1:1) to give 17 (735 mg), m.p. 153–154°. More **17** (650 mg) was obtained by chromatography of the material in the mother liquor on silica gel (ether–dichloromethane, 2:1, followed by the same mixture containing 5% of methanol). The n.m.r. spectrum of the acetate of the trace product (R_F 0.35, 137 mg) indicated that it was probably the triacetate of 2,4,5-tri-*O*-benzyl-*myo*-inositol.

(±)-1,5,6-Tri-O-*benzyl-2,3*-O-*isopropylidene*-myo-*inositol* (**12**). — (*a*) A solution of **17** (3 g) and toluene-*p*-sulphonic acid (100 mg) in acetone (60 mL) and 2,2-dimethoxypropane (10 mL) was kept for 8 h at 20°, when t.l.c. (ether–light petroleum 2:1) showed a major product (R_F 0.5) with trace products (R_F 0.6, 0.8, and 0.9). Triethylamine (1 mL) and sodium hydrogen carbonate (100 mg) were added, the solvents were evaporated, the residue was extracted with dichloromethane, and the product was chromatographed on silica gel [ether–light petroleum (1:1) followed by ether] to give the pure major product (3.1 g, 95%). Recrystallisation from ethyl acetate–light petroleum (1:1) gave **12**, m.p. 89–90° (Found: C, 73.32; H, 6.94. $C_{30}H_{34}O_6$ calc.: C, 73.45; H, 6.99%).

The acetate of **12** had m.p. 98–99° (from light petroleum). ^{1}H-N.m.r. data: δ 1.33, 1.59 (2 s, CMe_2), 1.96 (s, Ac) (Found: C, 72.44; H, 6.97. $C_{32}H_{36}O_7$ calc.: C, 72.16; H, 6.81%).

The ^{1}H-n.m.r. spectrum of the crystalline acetate of the minor product (R_F 0.6) indicated that it was probably 2-*O*-acetyl-1,5,6-tri-*O*-benzyl-3,4-*O*-isopropylidene-*myo*-inositol.

(*b*) Water (0.5 mL) and dichlorodicyanoquinone (125 mg, 0.55 mmol) were added to a solution of **40** (150 mg, 0.24 mmol) in dichloromethane (6 mL) and the mixture was stirred for 45 min at 20°, when t.l.c. (ether–light petroleum, 3:2) showed complete conversion of **40** (R_F 0.8) into a product (R_F 0.4). The mixture was diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried (K_2CO_3), and concentrated. The crude product was chromatographed on silica gel (above solvent) to give **12** (110 mg, 91%).

(−)-ω-Camphanates of D- (**44**) *and* L-*1,5,6-tri*-O-*benzyl-2,3*-O-*isopropylidene*-myo-*inositol* (**41**). — A solution of the racemic **12** (5 g, 10.2 mmol) and (−)-ω-camphanic acid chloride (2.64 g, 12.2 mmol) in dry pyridine (40 mL) was kept for 12 h at

20°, then cooled in ice. Water (2 mL) was added, and the solution was kept for 30 min at 20°, then diluted with water (200 mL). The crystalline product was collected, and a solution in dichloromethane was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to give the diastereoisomeric camphanates **13** (6.7 g, 98%). T.l.c. (ether–light petroleum, 2:1) showed two products (R_F 0.7 and 0.8) and the absence of **12** (R_F 0.6). The mixed camphanates **13** (3 g) were chromatographed on silica gel (250 g) in ether–light petroleum–dichloromethane (1:3:1) to give **41** (1.2 g), R_F 0.8, m.p. 177–179° (from ethyl acetate–light petroleum, 1:2), $[\alpha]_D^{26}$ −47° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.95, 0.99, 1.09 (3 s, 3 CMe), 1.31, 1.58 (2 s, CMe_2) (Found: C, 71.66; H, 6.84. $C_{40}H_{46}O_9$ calc.: C, 71.62; H, 6.91%).

Eluted next was a mixed fraction (0.5 g) and then **44** (1.2 g), R_F 0.7, m.p. 190–191° (from ethyl acetate–light petroleum, 1:1), $[\alpha]_D^{26}$ +34° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 0.84, 0.99, 1.07 (3 s, 3 CMe), 1.33, 1.59 (2 s, CMe_2) (Found: C, 71.47; H, 6.67%). This more polar camphanate also crystallised preferentially from a solution of the mixed camphanates in ethyl acetate–light petroleum (1:1).

*1*D-*1,4,5,6-Tetra*-O-*benzyl*-myo-*inositol* (**50**). — The camphanate **44** (R_F 0.7) was heated under reflux with sodium hydroxide in methanol for 15 min. Solid carbon dioxide was added, the solvent was evaporated, the residue was extracted with ether, and the extract was washed with water, dried (K_2CO_3), and concentrated to give the chiral alcohol **45** as an oil. This product was treated with an excess of benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide in the usual way[3], to give the crude benzyl ether **46** which was treated under reflux for 15 min with methanol (10 mL) and M hydrochloric acid (1 mL). Sodium hydrogen carbonate (500 mg) was added, the solvents were evaporated, and the crude product was extracted from the residue with dichloromethane and chromatographed on silica gel (dichloromethane–ether, 9:1) to give **50**, m.p. 148–149° (from ethyl acetate–light petroleum, 3:5), $[\alpha]_D^{26}$ +21° (*c* 1, chloroform); lit.[9a] m.p. 140–142°, $[\alpha]_D$ +25.1° (chloroform); lit.[24] $[\alpha]_D^{20}$ +18.8° (chloroform); lit.[25] $[\alpha]_D^{17}$ +24.2° (chloroform); lit.[26] m.p. 138–140°, $[\alpha]_D^{15}$ +23.2° (chloroform); lit.[27] m.p. 143°, $[\alpha]_D^{28}$ +25°; lit.[28] m.p. 146–146.5°, $[\alpha]_D^{25}$ +19.5° (chloroform).

*1*L-*1,4,5,6-Tetra*-O-*benzyl*-myo-*inositol* (**48**). — The camphanate **41** (R_F 0.8) was treated as described above, to give **48**, m.p. 148–150°, $[\alpha]_D^{26}$ −20.4° (*c* 1; chloroform); lit.[9b] m.p. 141–143°, $[\alpha]_D^{20}$ −24.3° (chloroform); lit.[25] $[\alpha]_D$ −22.3° (chloroform); lit.[29] m.p. 143–143.5°, $[\alpha]_D$ −18.6° (chloroform); lit.[30] $[\alpha]_D$ −22.3°; lit.[28] m.p. 144–145°, $[\alpha]_D^{25}$ −18.5° (chloroform).

*1*D- (**51**) *and 1*L-*1,5,6-Tri*-O-*benzyl*-myo-*inositol* (**49**). — The camphanate **44** was hydrolysed by base to give the alcohol **45**, as described above, which was treated with M hydrochloric acid–methanol (1:10) for 40 min at reflux. An excess of sodium hydrogen carbonate was added, the solvents were evaporated, and the product was extracted from the residue with dichloromethane and recrystallised from ethyl acetate–light petroleum (1:1) to give **51**, m.p. 155–156°, $[\alpha]_D^{26}$ 0° (*c* 1, chloroform) (Found: C, 70.78; H, 6.78. $C_{27}H_{30}O_6 \cdot 0.5H_2O$ calc.: C, 70.56; H, 6.80%).

In the same way, the camphanate **41** was converted *via* the alcohol **42** into **49**, m.p. 155–157°, $[\alpha]_D^{26}$ 0° (*c* 1, chloroform) (Found: C, 70.93; H, 6.89%).

The triacetates of these triols gave gels on attempted crystallisation and their n.m.r. spectra were identical to those of the racemate described above.

1D-4-O-Allyl-1,5,6-tri-O-benzyl-myo-inositol (**52**). — Hydrolysis of the camphanate **44** with base (as described above under the preparation of **50**) gave the alcohol **45**, which was treated with allyl bromide and sodium hydride in *N,N*-dimethylformamide in the usual way[3] to give the allyl ether **47** as a syrup which was heated for 30 min under reflux in M hydrochloric acid–methanol (1:9). An excess of sodium hydrogen carbonate was added, the solvents were evaporated, and the product was extracted from the residue with dichloromethane and recrystallised from ethyl acetate–light petroleum (1:4) to give **52**, m.p. 120–121°, $[\alpha]_D^{26}$ +34° (*c* 1, chloroform) (Found: C, 73.09; H, 7.19. $C_{30}H_{34}O_6$ calc.: C, 73.45; H, 6.99%).

1D-4-O-Allyl-1,3,5,6-tetra-O-benzyl-myo-*inositol* (**53**). — A mixture of **52** (750 mg), dibutyltin oxide (380 mg), tetrabutylammonium bromide (490 mg), and toluene (25 mL) was heated for 2 h under reflux with azeotropic removal of water in a Dean and Stark apparatus. Benzyl bromide (0.27 mL) was added and the solution was heated for 2 h under reflux, when t.l.c. (ether–light petroleum, 1:2) showed conversion of **52** (R_F 0.45) into major (R_F 0.7) and trace (R_F 0.6) products. The toluene was evaporated, the residue was partitioned between ether and water, the ether layer was stirred with saturated aqueous sodium hydrogen carbonate (10 mL) for 1 h, and the precipitated tin derivatives were removed. The filtrate was separated, the ether was concentrated, and the residue was chromatographed on silica gel (ether–light petroleum, 2:1) to give **53** (753 mg), m.p. 87–88° (from light petroleum), $[\alpha]_D^{26}$ +14° (*c* 1, chloroform) (Found: C, 76.36; H, 7.04. $C_{37}H_{40}O_6$ calc.: C, 76.52; H, 6.94%).

1D-1,3,5,6-Tetra-O-benzyl-4-O-(prop-1-enyl)-myo-*inositol* (**54**). — A mixture of **53** (720 mg), potassium *tert*-butoxide (500 mg), and dry methyl sulphoxide (10 mL) was kept for 2 h at 50°. T.l.c. (as above) then showed no distinction between **53** (R_F 0.7) and the product, but hydrolysis of a small portion of the solution with dilute acid showed complete removal of **53** to give a new product (R_F 0.4, see below). The solution was diluted with water, and the product was collected and recrystallised from light petroleum to give **54**, m.p. 96–98°, $[\alpha]_D^{26}$ −2.7° (*c* 1, chloroform) (Found: C, 76.52; H, 7.01. $C_{37}H_{40}O_6$ calc.: C, 76.52; H, 6.94%).

1D-1,3,5,6-Tetra-O-benzyl-myo-*inositol* (**55**). — The prop-1-enyl ether **54** was heated for 30 min under reflux in M hydrochloric acid–acetone (1:9), when t.l.c. (ether–light petroleum, 2:1) showed complete conversion of **54** (R_F 0.7) into the product (R_F 0.4). An excess of sodium hydrogen carbonate was added, the solvents were evaporated, and the product was extracted from the residue with dichloromethane and recrystallised from ethyl acetate–light petroleum (1:9) to give **55**, m.p. 97–98°, $[\alpha]_D^{27}$ +12° (*c* 0.93, chloroform) (Found: C, 75.44; H, 6.63. $C_{34}H_{36}O_6$ calc.: C, 75.53; H, 6.71%).

The bis-camphanate (**62**) had m.p. 173–174°, $[\alpha]_D^{25}$ +2.0° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.73, 0.83, 0.93, 1.035, 1.09, 1.12 (6 s, 6 CMe) (Found: C, 72.35; H, 6.73. $C_{54}H_{60}O_{12}$ calc.: C, 71.98; H, 6.71%).

(±)-1,3,4,5-Tetra-O-benzyl-myo-*inositol* (**63**). — A mixture of the racemic triol **17** (1 g), dibutyltin oxide (0.55 g), and tetrabutylammonium bromide (0.72 g) in toluene

(50 mL) was heated for 2 h under reflux with azeotropic removal of water in a Dean and Stark apparatus. Benzyl bromide (0.4 mL) was added and the solution was heated for 7 h under reflux, when t.l.c. (ether–light petroleum, 2:1) showed a major product (R_F 0.4, which co-chromatographed with **55**) and minor products (R_F 0.3, 0.7, and 0.8) which were separated by chromatography on silica gel after work-up as described above. N.m.r. spectroscopy of the acetates of the minor products (R_F 0.7 and 0.8) indicated that they were monoacetates of penta-*O*-benzyl derivatives, and the n.m.r. spectrum of the acetate of the minor product (R_F 0.3) was identical to that of the "thermosalient crystals" [3,4-di-*O*-acetyl-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol (**64**)] described previously[1]. The major product (R_F 0.4, 520 mg), which was **63**, had m.p. 116–118° (from ethyl acetate–light petroleum, 1:10) (Found: C, 75.81; H, 6.65. $C_{34}H_{36}O_6$ calc.: C, 75.53; H, 6.71%).

The acetate had m.p. 105–107° (from ethyl acetate–light petroleum) (Found: C, 73.16; H, 6.45. $C_{38}H_{40}O_8$ calc.: C, 73.06; H, 6.45%). The ^{1}H-n.m.r. spectrum was identical with that described above for **55**.

ω-Camphanates (**67**) of *(±)-1,3,4,5-tetra*-O-*benzyl*-myo-*inositol*. — The racemic diol **63** (100 mg) was converted into the diastereoisomeric bis-camphanates **67** (150 mg) in the usual way (see above). ^{1}H-N.m.r. data: δ 0.73 (3 H), 0.77 (3 H), 0.83 (3 H), 0.90 (6 H), 0.94 (3 H), 1.01 (3 H), 1.04 (6 H), 1.10 (6 H), 1.12 (3 H) for the CMe resonances of the camphanate portion. Recrystallisation from ethyl acetate–light petroleum (1:10) gave the diastereoisomer of m.p. 173–174° (54 mg) with a ^{1}H-n.m.r. spectrum identical with that described for the bis-camphanate (**62**) of 1D-1,3,5,6-tetra-*O*-benzyl-*myo*-inositol. The ^{1}H-n.m.r. spectrum of the residual crude camphanate in the mother liquor contained signals at δ 0.77 (3 H), 0.90 (6 H), 1.02 (3 H), 1.04 (3 H), 1.10 (3 H), for the CMe resonances of the camphanate portion of the bis-camphanate of 1L-1,3,5,6-tetra-*O*-benzyl-*myo*-inositol, together with small resonances due to the remaining diastereoisomer (**62**).

1D-2,4-Di-O-*methyl*-myo-*inositol* (**68**). — This chiral tetrabenzyl ether **55** was treated with methyl iodide and sodium hydride in *N,N*-dimethylformamide, and the product was isolated in the usual way[3] to give the methyl ether **56** as a syrup. This product was treated with hydrogen over Pd–C (10%) in ethanol for 12 h, and the catalyst was then collected and washed with ethanol. Evaporation of the combined filtrate and washings, with recrystallisation of the product from methanol–ether, gave **68**, m.p. 146–148°, $[\alpha]_D^{26}$ +3.4° (*c* 1, methanol) (Found: C, 46.05; H, 7.79. $C_8H_{16}O_6$ calc.: C, 46.15; H, 7.75%).

The tetra-acetate (**69**) had m.p. 166–168°, $[\alpha]_D^{26}$ −6.3° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 2.00 (3 H), 2.06 (6 H), 2.14 (3 H) (3 s, 4 Ac), 3.45, 3.52 (2 s, 2 OMe), 3.65–3.87 (m, H-2,4), 4.81–5.16 (m, H-1,3,5), 5.46 (t, *J* 9.77 Hz, H-6) (Found: C, 50.82; H, 6.52. $C_{16}H_{24}O_{10}$ calc.: C, 51.06; H, 6.43%).

1D-1,2,5,6-Tetra-O-*benzyl*-myo-*inositol* (**60**). — (*a*) A mixture of the allyl ether **52** (500 mg), dibutyltin oxide (255 mg), tetrabutylammonium bromide (330 mg), and toluene (20 mL) was heated under reflux with azeotropic removal of water in a Dean and Stark apparatus during 2 h. Allyl bromide (0.2 mL) was added and the solution was

heated for 10 h under reflux, when t.l.c. (ether–light petroleum, 2:1) showed conversion of **52** (R_F 0.3) into a product (R_F 0.8). The product was isolated in the usual way (see above) and chromatographed on silica gel (ether–light petroleum, 1:1) to give the diallyl ether **57** (450 mg) as a syrup. This compound was treated with benzyl bromide and sodium hydride in *N,N*-dimethylformamide, and the product was isolated in the usual way to give the tetrabenzyl ether **58** as a syrup which crystallised. This compound was treated with potassium *tert*-butoxide in dry methyl sulphoxide for 3 h at 50° to give the di(prop-1-enyl) ether **59**. This compound was treated with M hydrochloric acid–acetone (1:9) for 30 min at reflux, and the product was isolated in the usual way to give **60**, m.p. 152–154°, $[\alpha]_D^{25}$ −14° (*c* 1, chloroform) (Found: C, 75.41; H, 6.74. $C_{34}H_{36}O_6$ calc.: C, 75.53; H, 6.71%). ^{1}H-N.m.r. data: δ 4.60, 4.70, 4.73, 4.80, 4.84, 4.88, 4.97, 5.01, 5.10 (m, 4 CH_2Ph), 7.29, 7.32 (2 s, aromatic), identical with the spectrum of the racemic compound.

The diacetate **61** had m.p. 90–91°, $[\alpha]_D^{25}$ +5.3° (*c* 1, chloroform) (Found: C, 73.31; H, 6.67. $C_{38}H_{40}O_8$ calc.: C, 73.06; H, 6.45%). ^{1}H-N.m.r. data: δ 1.89, 1.96 (2 s, 2 Ac), 5.63 (t, *J* 10 Hz, H-4), 7.28, 7.32 (2 s, aromatic), identical with the n.m.r. spectrum of the racemic compound (**64**) described previously[1]. The chiral acetate **61** did not show the "jumping" behaviour described for the racemate[1,12].

(*b*) The racemic diol **65** was converted into the diastereoisomeric bis-camphanates (**66**) in the usual way (see above). T.l.c. (ether–light petroleum, 2:1) showed conversion of **65** (R_F 0.1) into **66** (R_F 0.5) with no separation of the diastereoisomers. Recrystallisation of the mixture **66** (1.2 g) from ethyl acetate–light petroleum (1:4) gave a pure diastereoisomer (367 mg), m.p. 200–202°, $[\alpha]_D^{25}$ −1.3° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 0.75 (3 H), 0.91 (6 H), 0.98 (3 H), 1.02 (3 H), 1.07 (3 H) (5 s, 6 CMe) (Found: C, 71.56; H, 6.81. $C_{54}H_{60}O_{12}$ calc.: C, 71.98; H, 6.71%).

Further crystallisation gave the other (crude) diastereoisomer [δ 0.83 (3 H), 0.91 (3 H), 0.95 (6 H), 1.04 (3 H), 1.06 (3 H) (5 s, 6 CMe)] together with small signals due to the other diastereoisomer described above.

The camphanate (m.p. 200–202°) was hydrolysed by base in the usual way (see above) to give **60**, m.p. 153–154°, $[\alpha]_D^{25}$ −15.5° (*c* 1, chloroform), with an n.m.r. spectrum identical with that of the compound described in (*a*).

ACKNOWLEDGMENTS

We thank Perstorp Pharma, Perstorp, Sweden for support (to J.G.), the C.S.I.C., Spain for a postdoctoral fellowship (to A.F.-M), and Miss Sheila Lathwell for the optical rotations.

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