The Allyl Group for Protection in Carbohydrate Chemistry. Part 20.[1a] Synthesis of 1L-1-*O*-Methyl-*myo*-inositol [(+)-Bornesitol] by Resolution of (±)-1,2,4-Tri-*O*-benzyl-*myo*-inositol

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Racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol was prepared by two new routes from (±)-1,4-di-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol, one route involving the crystalline intermediate (±)-1-*O*-allyl-3,6-di-*O*-benzyl-4,5-*O*-isopropylidene-*myo*-inositol. Oxidation of the latter and (±)-1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol with acetic anhydride–dimethyl sulphoxide gave the corresponding ketones, which were reduced with sodium borohydride to give the starting alcohols in good yield, thus providing suitable routes for the synthesis of isotopically labelled material. Racemic 1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol was resolved using (−)-ω-camphanic acid chloride to give, readily and in high yield (86%), the ω-camphanate of 1D-1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol, which was converted into 1L-1-*O*-methyl-*myo*-inositol [(+)-bornesitol] and 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol which had previously been obtained by hydrolysis of perbenzylated galactinol.

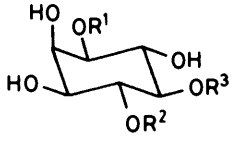
The family of inositol lipids, phosphatidylinositol (**1**), phosphatidylinositol 4-phosphate (**2**), and phosphatidylinositol 4,5-bisphosphate (**3**), are derived from *myo*-inositol with the absolute configuration as shown in structures (**1**)—(**3**).[2] Compound (**3**) is converted by receptor-mediated enzymic reactions into D-*myo*-inositol 1,4,5-trisphosphate (**4**) which acts as a 'second messenger' by mobilising intracellular calcium ions.[1,3]

We have described[1,4] a synthesis of racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol (**5**) suitable as an intermediate for the synthesis of compounds (**1**), (**3**), and (**4**), and we describe here, as well as new routes for the synthesis of the racemic triol (**5**), a resolution of the racemic isopropylidene derivative (**9**)[1] of (**5**) using (−)-ω-camphanic acid chloride {(−)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-ω-carbonyl chloride} which gave in high yield (86%), by simple crystallisation of the product, the beautifully crystalline ω-camphanate (**10**) with the absolute configuration as shown; the other diastereoisomer has not been obtained in the crystalline state. Unfortunately, the crystalline diastereoisomer (**10**) is not the one required for the synthesis of compounds (**1**), (**3**), and (**4**) but the ease of separation of the camphanate (**10**), in such high yield, from the mixture of diastereoisomers makes this a very practical resolution allowing the ready synthesis of other optically active *myo*-inositol derivatives from 1D-1,2,4-tri-*O*-benzyl-*myo*-inositol (**5**) and also considerably enriches the mother liquors with the derivative of the isomer, 1L-1,2,4-tri-*O*-benzyl-*myo*-inositol (**13**), which is required for the synthesis of compounds (**1**), (**3**), and (**4**).

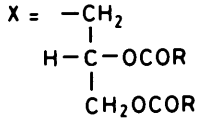
The resolution of racemic derivatives of *myo*-inositol has been studied extensively by Russian workers[5] using carbohydrate orthoesters or glycosides as resolving agents although the yields were not high and chromatographic methods were used for the separations of diastereoisomers. Classical procedures have also been used in a few cases,[6,7] as well as chromatography on chiral capillary columns[8] for the resolution of *myo*-inositol derivatives.

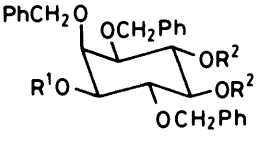
Results

The new routes for the synthesis of racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol (**5**) started from the beautifully crystalline racemic 1,4-di-*O*-benzyl-*myo*-inositol (**14**),[9] which on reaction with 2,2-dimethoxypropane (DMP) and an acid catalyst in dimethyl sulphoxide (DMSO), under kinetic conditions, gave predom-

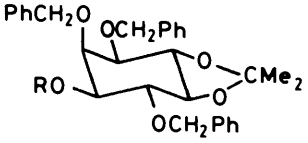


†(**1**) $R^1 = X$, $R^2 = R^3 = H$
(**2**) $R^1 = X$, $R^2 = P(O)(OH)_2$, $R^3 = H$
(**3**) $R^1 = X$, $R^2 = R^3 = P(O)(OH)_2$
(**4**) $R^1 = R^2 = R^3 = P(O)(OH)_2$

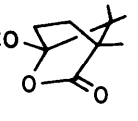




(**5**) $R^1 = R^2 = H$
(**6**) $R^1 = Me$, $R^2 = H$
(**7**) $R^1 = Allyl$, $R^2 = H$
(**8**) $R^1 = Allyl$, $R^2 = Ac$

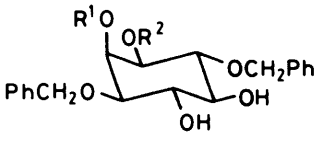


(**9**) R = H



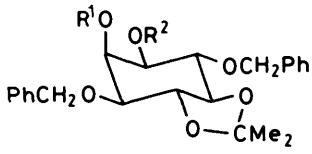
(**10**) R = −CO

(**11**) R = Me
(**12**) R = Allyl

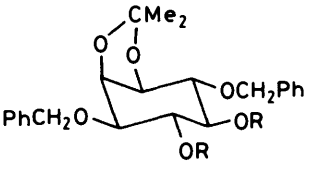


(**13**) $R^1 = CH_2Ph$, $R^2 = H$
(**14**) $R^1 = R^2 = H$
(**15**) $R^1 = H$, $R^2 = Allyl$
(**16**) $R^1 = Allyl$, $R^2 = H$

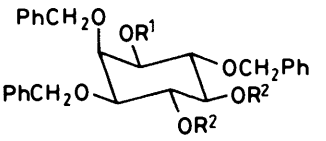
† Although the depictions of the formulae imply an absolute configuration for all of the compounds shown some of those mentioned in the text are only racemates of these.



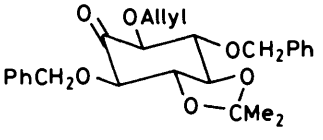
(17) $R^1 = R^2 = H$
(18) $R^1 = R^2 = Ac$
(19) $R^1R^2 = >SnBu_2$
(20) $R^1 = H, R^2 = Allyl$
(21) $R^1 = Ac, R^2 = Allyl$
(22) $R^1 = R^2 = Allyl$
(23) $R^1 = CH_2Ph, R^2 = Allyl$
(24) $R^1 = Allyl, R^2 = H$
(25) $R^1 = H, R^2 = CPh_3$
(26) $R^1 = CH_2Ph, R^2 = CPh_3$



(27) R = H
(28) R = Ac



(29) R^1 = Allyl, R^2 = H
(30) R^1 = Allyl, R^2 = Ac



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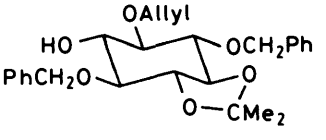

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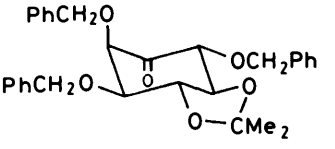

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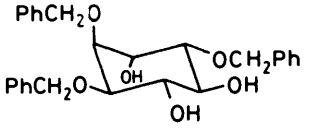
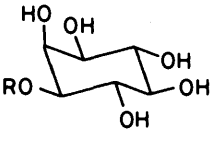
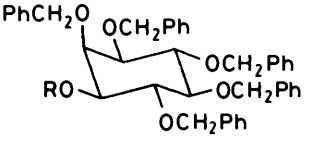


(34)



(35) R = Me
(36) R = α-D-galactopyranosyl



(37) R = Allyl
(38) R = CH=CHMe
(39) R = H
(40) R = Ac

inantly the crystalline 1,4-di-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**17**) together with some 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (**27**)[1,4] and these were readily separated by chromatography on silica gel. Crystalline diacetates (**18**) and (**28**) of the diols (**17**) and (**27**) respectively were also prepared.

The diol (**17**) was converted[10] into the dibutylstannylene derivative (**19**), which was treated with allyl bromide in *N*,*N*-dimethylformamide (DMF), resulting in allylation of the equatorial hydroxy group,[10] to give the crystalline racemic 1-*O*-allyl-3,6-di-*O*-benzyl-4,5-*O*-isopropylidene-*myo*-inositol (**20**). Proof of structure for compound (**20**) was obtained by conversion into the benzyl ether (**23**), which on acidic hydrolysis gave the syrupy diol (**29**) and this gave the crystalline diacetate (**30**), identical with the material prepared from racemic (**9**)[1] by allylation to (**23**), subsequent acidic hydrolysis to (**29**), and acetylation to (**30**). Deallylation of compound (**29**) gave racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol (**5**), identical with the material prepared previously.[1,4]

Acidic hydrolysis of the isopropylidene group of compound (**20**) gave crystalline racemic 3-*O*-allyl-1,4-di-*O*-benzyl-*myo*-inositol (**15**). A more direct route to compound (**15**) by the reaction of racemic 1,4-di-*O*-benzyl-*myo*-inositol (**14**)[9] with dibutyltin oxide and subsequent reaction of the dibutylstannylene derivative with allyl bromide was investigated; previous work[10,11] has shown that regiospecific monoalkylation of unprotected polyhydroxy compounds can be achieved in this way. Compound (**15**) was isolated in 60% yield after chromatography of the product on silica gel to remove other minor products, one of which was identified as 2-*O*-allyl-1,4-di-*O*-benzyl-*myo*-inositol (**16**) by comparison with the material obtained by direct allylation of 1,4-di-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**17**) and subsequent removal of the isopropylidene group (see below).

The ready availability of the crystalline alcohol (**20**) suggested a method for the preparation of isotopically labelled *myo*-inositol derivatives. Oxidation[12] of compound (**20**) with acetic anhydride–DMSO gave the crystalline ketone (**31**) in high yield and this was readily reduced with sodium borohydride to give predominantly the alcohol (**20**) (70%) together with the presumed, crystalline (±)-1-*O*-allyl-2,5-di-*O*-benzyl-3,4-*O*-isopropylidene-*scyllo*-inositol (**32**) (30%). Similar oxidation of racemic 1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**)[1] gave a syrupy ketone (**33**), which was also reduced in good yield to the starting alcohol (**9**) together with a small amount of the presumed, racemic *chiro*-inositol derivative. These were best separated by first removing the isopropylidene group and separation of the triol (**5**) (75%) from the presumed, crystalline, racemic 1,2,5-tri-*O*-benzyl-*chiro*-inositol (**34**) (25%) by column chromatography on silica gel. The use of tritiated sodium borohydride should provide good routes to the isotopically labelled alcohols (**20**) and (**5**) for further conversion into labelled inositol 1,4,5-trisphosphate.

Direct allylation of the diol (**17**) with one equivalent of allyl bromide and sodium hydride in DMF gave an approximately equal mixture of the monoallyl ethers (**20**) and (**24**), which were

resolved by t.l.c. and which were separated from starting material and some di-*O*-allyl ether (**22**) by chromatography on silica gel. Hydrolysis of the isopropylidene groups from the mixture of alcohols (**20**) and (**24**) gave the crystalline triols (**15**) and (**16**) respectively, which were more readily separated by silica gel chromatography than were the corresponding isopropylidene derivatives (**20**) and (**24**).

Tritylation of the diol (**17**) in refluxing pyridine containing triethylamine (which gave a more rapid reaction than did pyridine alone) gave predominantly the crystalline, equatorial trityl derivative (**25**). An improved preparation of 1,2:5,6-di-*O*-isopropylidene-3-*O*-trityl-α-D-glucofuranose[13,14] was also developed using this technique. The structure of compound (**25**) was confirmed by benzylation to give the tri-*O*-benzyl ether (**26**), which on acidic hydrolysis gave 1,2,4-tri-*O*-benzyl-*myo*-inositol (**5**), identical with the material prepared previously.[1,4]

For the resolution of the racemic triol (**5**), the isopropylidene derivative (**9**)[1] was converted into the ω-camphanate;[15] the diastereoisomer (**10**) separated spontaneously from an ether solution of the product and was recrystallised from methanol. Basic hydrolysis of compound (**10**) gave 1D-1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**), which on acidic hydrolysis gave crystalline 1D-1,2,4-tri-*O*-benzyl-*myo*-inositol (**5**). The alcohol (**9**) was converted into the methyl ether (**11**), which on acidic hydrolysis gave crystalline 1D-1,2,4-tri-*O*-benzyl-3-*O*-methyl-*myo*-inositol (**6**). Hydrogenolysis of compound (**6**) gave 1L-1-*O*-methyl-*myo*-inositol [(+)-bornesitol (**35**)]. (+)-Bornesitol has previously been isolated from Borneo rubber[16] and opepe wood,[17] and also obtained from galactinol (**36**) (after perbenzylation, methanolysis, methylation, and hydrogenolysis[18]), the absolute configuration of which had been established previously.[19] The Russian workers have also synthesised (+)-bornesitol by resolution of racemic *myo*-inositol derivatives.[5b,20] The enantiomer [(−)-bornesitol] is also a well known compound.[21-23] 1D-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**) was also converted into the allyl ether (**12**), which on acidic hydrolysis gave crystalline 1D-3-*O*-allyl-1,2,4-tri-*O*-benzyl-*myo*-inositol (**7**). The corresponding racemic compound (**7**) was non-crystalline but gave a crystalline diacetate (**8**). Benzylation of the allyl ether (**7**) gave crystalline 1L-1-*O*-allyl-2,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (**37**), which was isomerised[24] to the crystalline prop-1-enyl ether (**38**). Acidic hydrolysis of compound (**38**) gave crystalline 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (**39**) with properties similar to those reported previously for synthetic material obtained by resolution of *myo*-inositol derivatives[5b,25,26] and by hydrolysis of perbenzylgalactinol.[27] Compound (**39**) also gave a crystalline acetate, 1L-1-*O*-acetyl-2,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (**40**). The corresponding racemic acetate (**40**) was also prepared from the racemic alcohol (**39**) described previously.[27]

Experimental

T.l.c. was carried out on microscope slides coated with silica gel G. Extracts were evaporated under reduced pressure. Optical rotations were measured with a Bendix automatic polarimeter. The light petroleum used had b.p. 40—60 °C unless otherwise stated.

(±)-1,4-*Di*-O-*benzyl*-5,6-O-*isopropylidene*-myo-*inositol* (**17**).—A mixture of 1,4-di-*O*-benzyl-*myo*-inositol[9] (**14**) (6.5 g), dry DMSO (35 ml), and 2,2-dimethoxypropane (6 ml) was stirred at 20 °C and, when a clear solution was obtained, toluene *p*-sulphonic acid monohydrate (PTSA) (30 mg) was added and the mixture was stirred for a further 10 min. The solution was poured into stirred aqueous sodium hydrogen carbonate (500 mg in 250 ml) and the mixture was kept at 20 °C overnight; the crystalline products were filtered off and washed well with water. The product was triturated with dichloromethane (200 ml) which dissolved the isopropylidene derivatives and the mixture was filtered to recover the insoluble starting material (**14**) (3.2 g). T.l.c. (ethyl acetate–dichloromethane, 1:1) of the solution showed a trace of 3,6-di-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol[9] (R_F 0.9), a major product (R_F 0.75), a minor product (R_F 0.55), and a trace of starting material (**14**) (R_F 0.15). The dichloromethane solution was dried (K_2CO_3) and evaporated and the crude product was chromatographed on silica gel in ethyl acetate–dichloromethane (1:4) to remove the di-*O*-isopropylidene derivative (400 mg) and then the major product (R_F 0.75) (2.32 g, 63% based on consumed starting material); further elution with the same solvents in the ratio 1:2 gave the minor product (R_F 0.55) (740 mg, 20%). The minor product (m.p. 161—163 °C from ethyl acetate) was identical with (±)-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (**27**) prepared previously[1,4] and gave a *diacetate* (**28**), m.p. 114—116 °C (Found: C, 67.3; H, 6.9. $C_{27}H_{32}O_8$ requires C, 66.9; H, 6.7%).

The major product, (±)-1,4-*di*-O-*benzyl*-5,6-O-*isopropylidene*-myo-*inositol* (**17**), m.p. 149—151 °C [from ethyl acetate–light petroleum (b.p. 60—80 °C), 1:1] (Found: C, 69.1; H, 6.8. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.05%) gave a *diacetate* (**18**), m.p. 99—101 °C [from ethyl acetate–light petroleum (b.p. 60—80 °C), 1:1] (Found: C, 67.0; H, 6.7. $C_{27}H_{32}O_8$ requires C, 66.9; H, 6.7%).

(±)-1-O-*Allyl*-3,6-*di*-O-*benzyl*-4,5-O-*isopropylidene*-myo-*inositol* (**20**).—A mixture of the isopropylidene derivative (**17**) (12 g), dibutyltin oxide (8.4 g), and dry benzene (200 ml) was heated under reflux for 2 h in a Dean–Stark apparatus. The benzene was evaporated off and dry DMF (80 ml) and allyl bromide (4 ml) were added to the residue of the dibutylstannylene derivative (**19**). The solution was kept at 50 °C for 24 h after which time t.l.c. (ether–light petroleum, 1:1) showed almost complete conversion of the isopropylidene derivative (**17**) (R_F 0.15) into a major product (R_F 0.6). The solution was cooled, and diluted with water (500 ml), the products were extracted with ether, and the extract was dried (K_2CO_3) and evaporated. The crude product was chromatographed on silica gel (250 g) in ether–light petroleum (1:1) to give the *product* (**20**) (8.2 g, 62%), m.p. 103—105 °C [from ethyl acetate–light petroleum (b.p. 60—80 °C), 1:10] (Found: C, 71.0; H, 7.5. $C_{26}H_{32}O_6$ requires C, 70.9; H, 7.3%), which gave an *acetate* (**21**), m.p. 62—64 °C (from light petroleum) (Found: C, 70.2; H, 7.3. $C_{28}H_{34}O_7$ requires C, 69.7; H, 7.1%).

(±)-3-O-*Allyl*-1,4-*di*-O-*benzyl*-myo-*inositol* (**15**).—(*a*) A solution of the isopropylidene derivative (**20**) (500 mg) in M-hydrochloric acid–methanol (1:9; 25 ml) was heated under reflux for 20 min. Sodium hydrogen carbonate (500 mg) was added to the cooled solution and the solvents were evaporated off. The product was extracted from the residue with ether, and recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) gave the *product* (**15**), m.p. 108—110 °C (Found: C, 68.8; H, 6.9. $C_{23}H_{28}O_6$ requires C, 69.0 H, 7.05%).

(*b*) 1,4-Di-*O*-benzyl-*myo*-inositol (**14**)[9] (6 g, 16.6 mmol), tetrabutylammonium iodide (6.24 g, 16.8 mmol), and dibutyltin oxide (4.5 g, 18 mmol) were heated under reflux in toluene (150 ml) for 1 h in a Dean–Stark apparatus. Allyl bromide (3 ml, 35 mmol) was added to the cooled solution and the mixture was heated under reflux for 1 h. T.l.c. (ether) then showed a major product (R_F 0.3) and minor products (R_F 0.2, 0.5, and 0.9). The mixture was diluted with ether (300 ml), water (300 ml) was added, and insoluble material (1.5 g) was filtered off. The ether–toluene layer was washed with saturated aqueous potassium chloride and dried (K_2CO_3). Evaporation of the solvents gave a syrup, which was chromatographed on silica gel. Elution with

ether removed the minor product (R_F 0.9) and then the minor product (R_F 0.5) [400 mg, m.p. and mixed m.p. 93—94 °C with compound (**16**) prepared by direct allylation of compound (**17**) and subsequent hydrolysis of the isopropylidene group (see below)] followed by the major product (R_F 0.3) (4 g, 60%), which was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C), m.p. and mixed m.p. 107—108 °C with material prepared as described in (*a*). Treatment of the major product with DMP and PTSA in acetone gave the isopropylidene derivative (**20**), m.p. and mixed m.p. 103—105 °C with material prepared as described above.

(±)-4,5-*Di*-O-*acetyl*-1-O-*allyl*-2,3,6-*tri*-O-*benzyl*-myo-*inositol* (**30**).—(*a*) The racemic allyl ether (**20**) (480 mg) was treated with an excess of sodium hydride and benzyl bromide in DMF at 20 °C for 2 h, after which time t.l.c. (ether–light petroleum, 1:1) showed complete conversion of the starting material (**20**) (R_F 0.6) into the product (**23**) (R_F 0.85). Methanol was added to destroy the excess of sodium hydride, the solution was diluted with water, and the product was extracted with ether. The crude product (**23**) (containing benzylation by-products) was heated under reflux in methanol (18 ml) and M-hydrochloric acid (2 ml) for 30 min to remove the isopropylidene group. The solution was cooled and an excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The product was extracted from the residue with ether, the extract was dried (K_2CO_3), and the solvent was evaporated off. The crude product was chromatographed on silica gel to give the diol (**29**) (510 mg, 95%) as a syrup, which was treated with acetic anhydride–pyridine to give the *diacetate* (**30**), m.p. 134—136 °C [from light petroleum (b.p. 60—80 °C)–ethyl acetate, 10:1] (Found: C, 71.0; H, 6.7. $C_{34}H_{38}O_8$ requires C, 71.1; H, 6.7%).

(*b*) (±)-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**)[1] was treated with an excess of allyl bromide and sodium hydride in DMF at 20 °C for 2 h, after which time t.l.c. (ether–light petroleum, 1:1) showed complete conversion of the alcohol (**9**) (R_F 0.7) into the allyl ether (**12**) (R_F 0.9). Methanol was added to destroy the excess of sodium hydride, the solution was diluted with water, and the product was extracted with ether. The isopropylidene group was hydrolysed as described in (*a*) to give the diol (**29**), which was converted into the crystalline acetate (**30**), identical with the material described in (*a*).

(±)-1,4-*Di*-O-*benzyl*-5,6-O-*isopropylidene*-3-O-*trityl*-myo-*inositol* (**25**).—A solution of the diol (**17**) (1.31 g, 3.27 mmol) and trityl chloride (9.1 g, 32.3 mmol) in a mixture of dry pyridine (30 ml) and dry triethylamine (10 ml) was heated under reflux for 8 h, after which time t.l.c. (ether–light petroleum, 1:1) showed *ca.* 75% conversion of the diol (**17**) (R_F 0.15) into a major product (R_F 0.7) and a minor product (R_F 0.75). Methanol (5 ml) was added to react with the excess of trityl chloride, and after 1 h the solution was diluted with water and the products were extracted with ether. The extract was washed successively with ice-cold 3M-hydrochloric acid (to remove bases), saturated aqueous potassium chloride, and saturated aqueous sodium hydrogen carbonate, dried (K_2CO_3), and evaporated. The crude product was chromatographed on basic alumina in ether, which removed the tritylation by-products, and the products were eluted with ether–methanol (49:1). Recrystallisation of the coloured products from ethyl acetate–light petroleum (b.p. 60—80 °C) gave the *trityl derivative* (**25**) (R_F 0.7) (928 mg, 44%), m.p. 154—156 °C (Found: C, 78.3; H, 6.7. $C_{42}H_{42}O_6$ requires C, 78.5; H, 6.6%).

1,2:5,6-*Di*-O-*isopropylidene*-3-O-*trityl*-α-D-*glucofuranose*.[13,14]—A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2.07 g, 7.95 mmol) and trityl chloride (4.3 g, 15.4 mmol) in a mixture of dry pyridine (10 ml) and dry triethylamine (5 ml) was heated under reflux for 12 h. Methanol (5 ml) was added dropwise and after 1 h the solution was cooled, sodium hydrogen carbonate (2 g) was added, and the solution was evaporated to dryness. Toluene was evaporated (3 times) from the residue and the product was extracted from the residue with ether. T.l.c. (ether–light petroleum, 1:2) showed *ca.* 70% conversion of the starting material (R_F 0.05) into the trityl derivative (R_F 0.75). The product was chromatographed on silica gel in ether–light petroleum (1:1) which first eluted the tritylation by-products and then gave the title product (2.5 g, 63%) as a yellow powder. Some of the colour was removed by refluxing the product in methanol (containing a little triethylamine) with decolourising charcoal. Recrystallisation from methanol gave 1,2:5,6-di-*O*-isopropylidene-3-*O*-trityl-α-D-glucofuranose, m.p. 135—137 °C; $[\alpha]_D^{28}$ −29.5° (*c* 1 in $CHCl_3$) (Found: C, 73.9; H, 6.85. Calc. for $C_{31}H_{34}O_6$: C, 74.1; H, 6.8%) {lit.,[13] m.p. 115 °C; $[\alpha]_D$ −24.1° ($CHCl_3$); lit.,[14] m.p. 120—122 °C; $[\alpha]_D$ −19.5° (*c* 1 in $CHCl_3$)}.

(±)-1,2,4-*Tri*-O-*benzyl*-myo-*inositol* (**5**).[1,4]—(*a*) The trityl ether (**25**) was treated with an excess of benzyl bromide and sodium hydride in DMF and the product was isolated as described above [under the preparation of compound (**30**)] to give the tri-*O*-benzyl ether (**26**). This was treated with M-hydrochloric acid–acetone (1:9) under reflux for 1 h, and the product was chromatographed on silica gel in ether–light petroleum (1:1) to remove the triphenylmethanol. Recrystallisation of the product from ethyl acetate–light petroleum (b.p. 60—80 °C) (1:2) gave compound (**5**), m.p. and mixed m.p. 117—119 °C, identical with the material prepared previously.[1,4]

(*b*) The diol (**29**) [see above under the preparation of compound (**30**)] (2.18 g), PTSA (80 mg), palladium–charcoal (10% Fluka; 100 mg), ethanol (19 ml), and water (1 ml) were heated under reflux for 6 h, after which time t.l.c. (ether) showed complete conversion of the diol (**29**) (R_F 0.75) into a product (R_F 0.65). Sodium hydrogen carbonate (100 mg) was added and the solvents were evaporated off. The product was extracted from the residue with ether, and the extract was dried (K_2CO_3) and evaporated. Recrystallisation (as above) gave compound (**5**) (1.92 g), identical with the material described in (*a*).

Direct Allylation of the (±)-*Diol* (**17**).—Allyl bromide (120 mg, 1 mmol) was added to a mixture of the diol (**17**) (400 mg, 1 mmol) and sodium hydride (50 mg, 2.5 mmol) in dry DMF (5 ml) and the mixture was stirred for 2 h at 20 °C. T.l.c. (ether–light petroleum, 1:1) then showed some diol (**17**) (R_F 0.15), some di-*O*-allyl derivative (**22**) (R_F 0.9), and the monoallyl derivatives (**20**) and (**24**) (R_F 0.5 and 0.55 respectively). The slow moving isomer cochromatographed with compound (**20**) obtained from the action of allyl bromide on the dibutylstannylene derivative (**19**). The products were isolated in the usual way (see above) and chromatographed in ether–light petroleum (1:1) to isolate the mixed monoallyl ethers (**20**) and (**24**) (70 mg). These were treated with M-hydrochloric acid–acetone (1:9) at reflux for 30 min to give the two isomers (**15**) and (**16**) which were well resolved on t.l.c. (ether) (R_F 0.3 and 0.5) and were separated by chromatography on silica gel. The *fast moving isomer* (**16**) (R_F 0.5) (34 mg) had m.p. 94—96 °C (Found: C, 69.4; H, 7.3. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.1%) and was identical with the material isolated above by allylation of the dibutylstannylene derivative of the dibenzyl ether (**14**) (see above). The slow moving isomer (**15**) (R_F 0.3) (29 mg) had m.p. 108—110 °C and was identical with the material prepared by hydrolysis of the isopropylidene derivative (**20**) (see above).

(±)-1-O-*Allyl*-3,6-*di*-O-*benzyl*-4,5-O-*isopropylidene*-myo-*inosose*-2 (**31**).—A solution of 1-*O*-allyl-3,6-di-*O*-benzyl-4,5-*O*-

isopropylidene-*myo*-inositol (**20**) (4 g) in a mixture of DMSO (30 ml) and acetic anhydride (20 ml) was kept at 20 °C for 18 h after which time t.l.c. (ether–light petroleum, 1:1) showed complete conversion of (**20**) (R_F 0.5) into a major product (R_F 0.7) and a trace product (R_F 0.9) which was presumed to be the methylthiomethyl ether[28] of compound (**20**). The solution was added dropwise to a stirred mixture of sodium hydrogen carbonate (50 g) in water (250 ml) during 1 h, and the mixture was stirred for a further 2 h, when the crystalline product (3.9 g) was separated by filtration, washed well with water, and dried. Recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) gave the pure *ketone* (**31**), m.p. 123—125 °C; $\nu_{max.}$ 1 740 cm^{-1} (C=O) (Found: C, 70.8; H, 6.8. $C_{26}H_{30}O_6$ requires C, 71.2; H, 6.9%).

Reduction of the Ketone (**31**).—Sodium borohydride (500 mg) was added to a solution of the ketone (**31**) (1 g) in ethanol (50 ml) and the mixture was stirred at 20 °C for 8 h. Water (50 ml) was added and the mixture was evaporated under reduced pressure to remove the ethanol. The aqueous residue was extracted with ether, and the extract dried (K_2CO_3) and evaporated. T.l.c. (ether–light petroleum, 1:1) showed the presence of a major product (R_F 0.5) and a minor product (R_F 0.7), which were separated by chromatography on silica gel in ether–light petroleum (1:3). The slower moving product (R_F 0.5) (700 mg, 70%), m.p. and mixed m.p. 103—105 °C, was identical with the alcohol (**20**) and the faster moving product (R_F 0.7) (300 mg), m.p. 105—106 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 71.2; H, 7.6. $C_{26}H_{32}O_6$ requires C, 70.9; H, 7.3%) was presumed to be the *racemic* scyllo-*inositol derivative* (**32**) but was not further investigated.

Oxidation of the Racemic Isopropylidene Derivative (**9**) *to the Ketone* (**33**) *and Reduction of the Ketone* (**33**) *with Sodium Borohydride*.—The racemic isopropylidene derivative (**9**) (500 mg) was treated with acetic anhydride–DMSO and the products were isolated as described above under the preparation of ketone (**31**). T.l.c. (ether–light petroleum, 1:1) showed complete conversion of (**9**) (R_F 0.7) into the ketone (**33**) (R_F 0.75) and traces of faster moving products. The crude ketone was reduced with sodium borohydride and the products were isolated as described above for the reduction of ketone (**31**). T.l.c. (as above) showed a major product (R_F 0.7) and a minor product (R_F 0.75). The crude product was heated under reflux in M-hydrochloric acid–methanol (1:4; 25 ml) for 20 min. Sodium hydrogen carbonate (1 g) was added and the solvents were evaporated off. The products were extracted from the residue with ether, and the extract was dried (K_2CO_3) and evaporated. T.l.c. (ether) showed a major product (R_F 0.7) and a minor product (R_F 0.5) and these were separated by chromatography on silica gel. The major product (346 mg, 69%), m.p. and mixed m.p. 117—119 °C, was identical with the racemic triol (**5**), and the minor product (66 mg, 13%), m.p. 147—148 °C (Found: C, 72.5; H, 7.1. $C_{27}H_{30}O_6$ requires C, 72.0; H, 6.7%), was presumed to be the *racemic* chiro-*inositol derivative* (**34**) but was not further investigated.

(−)-ω-*Camphanate of* 1D-1,2,4-*Tri*-O-*benzyl*-5,6-O-*isopropylidene*-myo-*inositol*, *Compound* (**10**).—(−)-ω-Camphanic acid chloride (5 g, 23 mmol) (Aldrich) was added to a solution of racemic 1,2,4-tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**)[1] (4.9 g, 10 mmol) in dry pyridine (20 ml) and the solution was kept at 20 °C for 18 h. The solution was cooled in ice–water, water (0.5 ml) was added, and the solution was kept at 20 °C for 1 h. Ether (100 ml) and dichloromethane (50 ml) were added and the organic phase was washed successively with saturated aqueous potassium chloride, ice-cold M-hydrochloric acid (to remove the pyridine), saturated aqueous potassium chloride, and saturated aqueous sodium hydrogen carbonate and dried ($MgSO_4$). Evaporation of the solvents gave a syrup, which was taken up into ether (30 ml); crystals separated rapidly. These (2.34 g) were filtered off after 12 h, the mother liquor was evaporated, and the residue was diluted with methanol (10 ml) to give more crystals (0.54 g). The combined crystals (2.88 g, 86% of one diastereoisomer) were recrystallised from methanol (280 ml) to give the pure ω-*camphanate* (**10**) (2.5 g), m.p. 170—172 °C; $[\alpha]_D^{25}$ +53.1° (*c* 1 in $CHCl_3$) (Found: C, 71.5; H, 6.9. $C_{40}H_{46}O_9$ requires C, 71.6; H, 6.9%).

1D-1,2,4-*Tri*-O-*benzyl*-5,6-O-*isopropylidene*-myo-*inositol* (**9**).—The ω-camphanate (**10**) (1.01 g) and sodium hydroxide (300 mg) were heated under reflux in methanol (30 ml) for 1 h. The solution was cooled, solid carbon dioxide was added, the solvent was evaporated off, and toluene was evaporated from the residue. The product (810 mg) was extracted from the residue with ether and chromatographed on silica gel in light petroleum–ether (3:1) to give pure 1D-1,2,4-*tri*-O-*benzyl*-5,6-O-*isopropylidene*-myo-*inositol* (**9**), $[\alpha]_D^{25}$ +36.6° (*c* 1.4 in $CHCl_3$) (Found: C, 73.4; H, 7.2. $C_{30}H_{34}O_6$ requires C, 73.4; H, 7.0%).

1D-1,2,4-*Tri*-O-*benzyl*-myo-*inositol* (**5**).—1D-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**) (200 mg) was heated under reflux in M-hydrochloric acid–methanol (1:9; 10 ml) for 20 min. An excess of sodium hydrogen carbonate was added, the solvents were evaporated off, and toluene was evaporated from the residue. The product (180 mg) was extracted from the residue with chloroform and recrystallised from ethanol–water (3:1) to give pure 1D-1,2,4-*tri*-O-*benzyl*-myo-*inositol* (**5**), m.p. 118—120 °C; $[\alpha]_D^{25}$ −9.0° (*c* 1 in $CHCl_3$) (Found: C, 72.4; H, 7.0. $C_{27}H_{30}O_6$ requires C, 72.0; H, 6.7%) {lit.,[29] m.p. 117—119 °C; $[\alpha]_D^{16}$ +15.5° ($CHCl_3$) for the enantiomer}.

1D-1,2,4-*Tri*-O-*benzyl*-3-O-*methyl*-myo-*inositol* (**6**).—1D-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**) (250 mg) was treated with an excess of methyl iodide and sodium hydride in DMF at 20 °C for 3 h, after which time t.l.c. (ether–light petroleum, 1:2) showed complete conversion of compound (**9**) (R_F 0.3) into the methyl ether (**11**) (R_F 0.45). Methanol was added to destroy the excess of sodium hydride, the solution was diluted with water, and the product was extracted with ether, worked up, and kept with M-hydrochloric acid–methanol (1:9; 10 ml) under reflux for 20 min. An excess of sodium hydrogen carbonate was added, the solvents were evaporated off, and the product (210 mg) was extracted from the residue with chloroform and crystallised from ethanol to give the 1D-1,2,4-*tri*-O-*benzyl*-3-O-*methyl*-myo-*inositol* (**6**), m.p. 109—111 °C; $[\alpha]_D^{26}$ −25° (*c* 1 in $CHCl_3$) (Found: C, 72.2; H, 7.1. $C_{28}H_{32}O_6$ requires C, 72.4; H, 6.9%).

1L-1-O-*Methyl*-myo-*inositol* [(+)-*Bornesitol*] (**35**).—A solution of 1D-1,2,4-tri-*O*-benzyl-3-*O*-methyl-*myo*-inositol (**6**) (170 mg) in ethanol (25 ml) containing palladium–charcoal (400 mg: 10%) (Fluka) was stirred under hydrogen at 20 °C for 24 h. The mixture was filtered through Celite and the residue was washed with water. The combined filtrate and washings were evaporated, and the residue (60 mg) was recrystallised from ethanol–methanol to give 1L-1-*O*-methyl-*myo*-inositol (**35**), m.p. 205—207 °C; $[\alpha]_D^{25}$ +31.9° (*c* 1 in H_2O) (Found: C, 43.2; H, 7.3. Calc. for $C_7H_{14}O_6$: C, 43.3; H, 7.3%) {lit.,[16] m.p. 199—203 °C; $[\alpha]_D$ +31.16°; lit.,[17] m.p. 201—202 °C; $[\alpha]_D$ +31.4°; lit.,[18] m.p. 199—200 °C; $[\alpha]_D^{25}$ +34° (*c* 0.6 in H_2O); lit.,[20] m.p. 202—204 °C; $[\alpha]_D^{20}$ +32.8° (*c* 2.4 in H_2O) and for the enantiomer 1D-1-*O*-methyl-*myo*-inositol [(−)-bornesitol] lit.,[21] m.p. 205—206 °C; $[\alpha]_D^{18}$ −32.05° (*c* 3.5 in H_2O); lit.,[22] m.p.

205—205.5 °C; $[\alpha]_D$ −32.6° (*c* 1 in H_2O); lit.,[23] m.p. 203—204 °C; $[\alpha]_D$ −32° (*c* 2 in H_2O)}.

1D-3-O-*Allyl*-1,2,4-*tri*-O-*benzyl*-myo-*inositol* (**7**).—1D-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-*myo*-inositol (**9**) was treated with allyl bromide and sodium hydride in DMF and the product was isolated and the isopropylidene groups hydrolysed in the usual way (see above) to give 1D-3-O-*allyl*-1,2,4-*tri*-O-*benzyl*-myo-*inositol* (**7**), m.p. 96—98 °C [from light petroleum (b.p. 60—80 °C)], $[\alpha]_D^{26}$ −20.5° (*c* 1 in $CHCl_3$) (Found: C, 73.3; H, 6.9. $C_{30}H_{34}O_6$ requires C, 73.4; H, 7.0%).

The racemic compound (±)-3-*O*-allyl-1,2,4-tri-*O*-benzyl-*myo*-inositol [(**7**) + (**29**)] was prepared in the same way from the racemic isopropylidene derivative (**9**)[1] but did not crystallise. It gave a crystalline diacetate, (±)-4,5-*di*-O-*acetyl*-1-O-*allyl*-2,3,6-*tri*-O-*benzyl*-myo-*inositol* (**8**) [+ (**30**)], m.p. 134—136 °C [from ethyl acetate–light petroleum (b.p. 60—80 °C)] (Found: C, 71.0; H, 6.7. $C_{34}H_{38}O_8$ requires C, 71.1; H, 6.7%).

1L-1-O-*Allyl*-2,3,4,5,6-*penta*-O-*benzyl*-myo-*inositol* (**37**).—1D-3-*O*-Allyl-1,2,4-tri-*O*-benzyl-*myo*-inositol (**7**) was treated with benzyl bromide and sodium hydride in DMF and the product was isolated in the usual way (see above) to give 1L-1-O-*allyl*-2,3,4,5,6-*penta*-O-*benzyl*-myo-*inositol* (**37**), m.p. 71—72 °C (from light petroleum); $[\alpha]_D^{27}$ −2.2° (*c* 1 in $CHCl_3$) (Found: C, 79.2; H, 7.1. $C_{44}H_{46}O_6$ requires C, 78.8; H, 6.9%).

1D-1,2,4,5,6-*Penta*-O-*benzyl*-3-O-(*prop*-1-*enyl*)-myo-*inositol* (**38**).—The allyl derivative (**37**) was treated with potassium t-butoxide in DMSO and the product was isolated in the usual way[24] to give 1D-1,2,4,5,6-*penta*-O-*benzyl*-3-O-(*prop*-1-*enyl*)-myo-*inositol* (**38**), m.p. 89—90 °C (from light petroleum); $[\alpha]_D^{27}$ 0° (*c* 0.9 in $CHCl_3$) (Found: C, 79.0; H, 7.1. $C_{44}H_{46}O_6$ requires C, 78.8; H, 6.9%).

1D-1,2,4,5,6-*Penta*-O-*benzyl*-myo-*inositol* (**39**).[25–27]—A solution of the prop-1-enyl derivative (**38**) (200 mg) in M-hydrochloric acid–methanol (1:9; 10 ml) was heated under reflux for 20 min. An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The product (180 mg) was extracted from the residue with dichloromethane and crystallised from light petroleum (b.p. 60—80 °C) to give 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (**39**), m.p. 64—65 °C; $[\alpha]_D$ +10.0° (*c* 1 in $CHCl_3$) (Found: C, 78.1; H, 6.7. Calc. for $C_{41}H_{42}O_6$: C, 78.1; H, 6.7%) {lit.,[25] m.p. 59—60 °C; $[\alpha]_D$ +14.0° (*c* 0.34 in $CHCl_3$); lit.,[26] m.p. 58.8—60 °C; $[\alpha]_D^{20}$ +13.9° (*c* 0.3 in $CHCl_3$); lit.,[27] m.p. 55—58 °C; $[\alpha]_D$ +9.2° (*c* 3.25 in $CHCl_3$)}. This gave a crystalline acetate, 1L-1-O-*acetyl*-2,3,4,5,6-*penta*-O-*benzyl*-myo-*inositol* (**40**), m.p. 91—92 °C; $[\alpha]_D^{28}$ +28.2° (*c* 1 in $CHCl_3$) (Found: C, 77.0; H, 6.7. $C_{43}H_{44}O_7$ requires C, 76.8; H, 6.6%).

The *racemic acetate* (**40**) [prepared from the racemic penta-*O*-benzyl ether (**39**)[27]] had m.p. 85—87 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 77.1; H, 6.6%).

Acknowledgements

We thank Miss Sheila Lathwell for the optical rotations and Mrs. Rita Findon for typing the manuscript.

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Received 14*th July* 1986; *Paper* 6/1391