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Note

Synthesis and resolution of 1,5-di-*O*-benzyl-2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzyl-*myo*-inositol

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There has been considerable research to establish which parts of the 1D-*myo*-inositol 1,4,5-trisphosphate (IP_3, **1**) molecule are essential for interaction with the IP_3-receptor (IP_3R) and the resultant liberation of calcium ions [1]. Our synthesis of the naturally occurring *myo*-inositol 1,3,4,6-tetrakisphosphate (**3** = **2**) led to the surprising discovery [2,3] that **3** was effective at liberating calcium ions. Although at first sight **3** does not resemble **1**, if it is drawn as in **2** then it can be seen that the phosphate groups at positions 1, 4, and 5 (and the hydroxyl group at position 6) in IP_3 (**1**) are replicated in **2**. Subsequently 1D-*myo*-inositol 1,4,6-trisphosphate (**5** = **4**, a simple derivative of **3**) was also shown [4,5] to be active in releasing calcium ions at the IP_3R, and this has a similar arrangement of groups as shown in **4**. Later work [6,7] also showed that DL-*myo*-inositol 1,2,4,5-tetrakisphosphate (**6**) was also active in liberating calcium ions and this too has a similar arrangement of the groups discussed above, for one of the enantiomers. A recent paper [8] showed that 1D-*myo*-inositol 1,2,4,5-tetrakisphosphate is nearly equipotent to IP_3.

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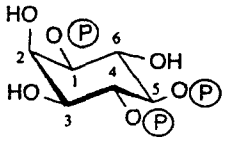
These results and many other studies on analogues of IP_3 have established that the substitutions and configurations at positions 1, 4, 5, and 6 in IP_3 (as shown in **1**) are essential for maximum activity at the IP_3R, whereas modifications at positions 2 and 3 are tolerated [1,9].



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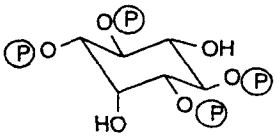

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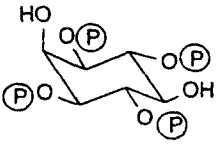

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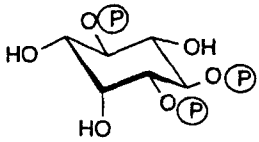

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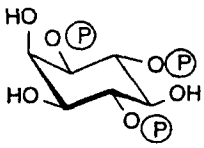

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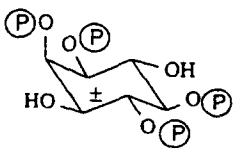

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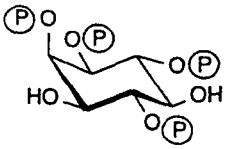

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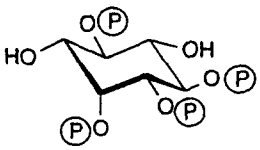

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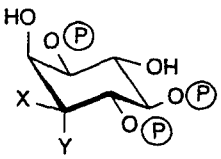
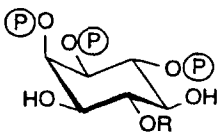


9 X = O(P) Y = H

10 X = H Y = O(P)

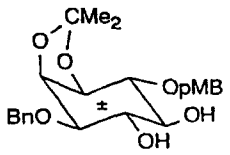


11 R = H

12 R = $(CH_2)_6CHO$

(P) = $P(O)(ONa)_2$

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



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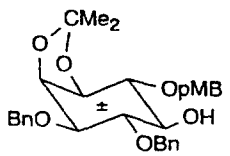

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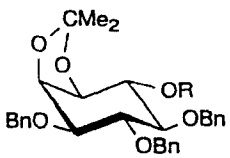
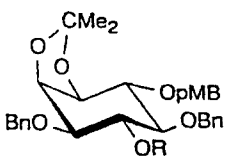


21 R = H

22 R= (-)-ω-camph

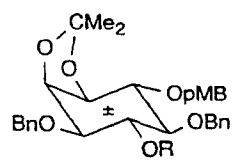


17 R= (-)-ω-camph

18 R = H

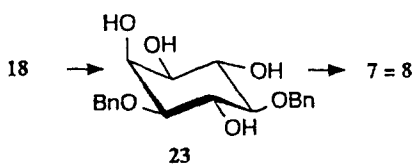
19 R = Bn

20 R = $(CH_2)_6CH{=}CH_2$



15 R = H

16 R= (-)-ω-camph



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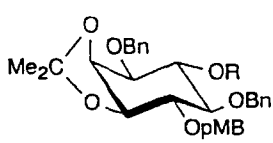
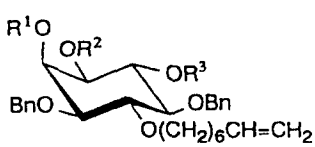


24 R = (-)-ω-camph

25 R = H

26 R = (+)-ω-camph

27 R = $(CH_2)_6CH{=}CH_2$

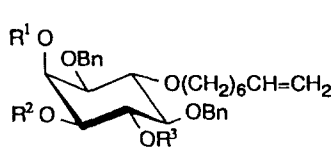


28 R^1,R^2= CMe_2; R^3= H

29 R^1= R^2= R^3= H

30 R^1= R^2= R^3= Ac

31 R^1= R^2= R^3= $P(O)(OBn)_2$



32 R^1,R^2= CMe_2; R^3= H

33 R^1= R^2= R^3= H

34 R^1 = R^2= R^3= Ac

35 R^1= R^2= R^3= $P(O)(OBn)_2$

Bn = CH_2Ph

pMB=$CH_2C_6H_4$(*p*OMe)

1D-*myo*-Inositol 1,2,4,6-tetrakisphosphate (**7** = **8**) also has this pattern but has not been tested at the IP_3R although it somewhat resembles 1D-*myo*-inositol 1,3,4,5-tetrakisphosphate (**9**) and 1L-*chiro*-inositol 1,2,3,5-tetrakisphosphate (**10**), both of which have been shown to liberate calcium ions [3,10,11], but with considerably reduced potency. It

was suggested that the bulky phosphate group (axial or equatorial) at position 3 (in **9** or **10**) was responsible for this reduction in potency. In order to prepare **7** to test its activity, an appropriately substituted chiral derivative of *myo*-inositol is required and we describe a suitable derivative here.

For studies concerned with 1D-*myo*-inositol 1,2,6-trisphosphate (**11**), which has been shown to have anti-inflammatory and analgesic properties [12], we required a derivative (such as **12**) which would allow the molecule to be coupled to a polymeric support, and for this purpose we have prepared the title *myo*-inositol derivative **15**. Because the resolution of **15**, via the camphanate ester, was readily achieved and because the enantiomers of **15** will be useful for the preparation of other *myo*-inositol phosphates (including **7**) we describe the preparation here.

Tin-mediated benzylation of **13** [13] gave a mixture of the alcohols **14** and **15** which were readily separated by chromatography. Compound **14** had been prepared previously [13] and this allowed us to distinguish between **14** and **15**. For the resolution of **15** it was converted into the diastereoisomeric mixture of (−)-ω-camphanates **16** and on recrystallisation one diastereoisomer separated preferentially. This was shown to be the camphanate **17** by the following procedure: saponification of **17** gave the alcohol **18** which was benzylated to give **19**. Treatment of **19** with dichlorodicyanoquinone (DDQ) removed the *p*-methoxybenzyl group to give syrupy **21** and this was converted into the crystalline (−)-ω-camphanate **22** which has been characterised previously [13]. Thus the enantiopure alcohol **18** is now readily available for use in the preparation of various chiral inositol phosphates including **7**, which will be available via the tetrol **23** obtainable by partial deprotection of **18**.

An almost pure sample of the other diastereoisomeric camphanate **24** was also obtained by crystallisation of the material remaining in the mother liquors after the removal of **17** and this was converted into the alcohol **25**. The alcohols **18** and **25** were converted into the octenyl ethers **20** and **27**, respectively, and these on partial deprotection gave the crystalline triols **29** and **33**, respectively. Phosphitylation of the triols **29** and **33** with dibenzyloxy(diisopropylamino)phosphine in the presence of tetrazole and subsequent oxidation of the trisphosphites [14] gave the syrupy trisphosphates **31** and **35**, respectively. Compound **31** will give access to the trisphosphate **12** after hydroxylation of the double bond with subsequent hydrogenolysis of the benzyl protecting groups and periodate oxidation.

1. Experimental

General.—The general methods were as described [13]. NMR spectroscopy was carried out on a JEOL FX90Q instrument in $CDCl_3$ solution.

*(±)-1,5-Di-*O*-benzyl-2,3-*O*-isopropylidene-4-*O*-p-methoxybenzyl*-myo-*inositol* (**15**) *and (±)-1,6-di-*O*-benzyl-2,3-*O*-isopropylidene-4-*O*-p-methoxybenzyl*-myo-*inositol* (**14**) [13].—A mixture of the diol **13** [13] (3.9 g, 9.0 mmol), dibutyltin oxide (2.3 g, 9.2 mmol), tetrabutylammonium bromide (2.97 g, 9.2 mmol), and benzyl bromide (5 mL, 41.8 mmol) in toluene (120 mL) was heated under reflux with a Soxhlet apparatus containing molecular sieve 3 Å (10 g) for 3 h. TLC (2:1 ether–light petroleum) showed

the conversion of **13** (R_f 0.1) into two products (R_f 0.5 and 0.6). Triethylamine (5 mL) was added and refluxing continued (after removing the Soxhlet) for 1 h to destroy the excess of benzyl bromide. The solution was concentrated, and ether (200 mL) and water (200 mL) were added to dissolve the products. The ether layer was separated and stirred with satd aq $NaHCO_3$ (150 mL) for 2 h, and the mixture was filtered through Celite to remove the precipitated tin derivatives. The ether layer was separated, dried (K_2CO_3), and concentrated. Column chromatography (silica gel) of the crude product using 1:3, 1:2, 1:1 ether–light petroleum, and ether gave the less polar product (R_f 0.6, 2.24 g), a mixed fraction (1.21 g), and the more polar product (R_f 0.5, 0.98 g). The mixed fraction was rechromatographed to give more of the pure isomers. The less polar, syrupy product (2.71 g, 57%) was identical (NMR, TLC) with **14** described previously [13]. The more polar product (1.66 g, 35%), mp 81–83 °C (from 1:8 EtOAc–light petroleum) with softening at 66 °C was **15**; ^{1}H NMR data: δ 1.34, 1.49 (2 s, each 3 H, CMe_2), 2.60 (s, 1 H, OH), 3.26 (t, 1 H, J 9.2 Hz), 3.79 (s, 3 H, OMe), 4.66–4.82 (m, 6 H, 3 CH_2Ph with major peaks at 4.66, 4.72, 4.76, 4.79, and 4.82), 6.78–7.35 (m, 14 H, aromatic). Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.45; H, 6.85.

*1*D-*3,5-Di*-O-*benzyl-4*-O-(−)-*ω-camphanoyl-1,2*-O-*isopropylidene-6*-O-p-*methoxybenzyl*-myo-*inositol* (**17**).—A solution of the racemic alcohol **15** (978 mg, 1.9 mmol) and (−)-*ω*-camphanoyl chloride (600 mg, 2.7 mmol) in dry pyridine (10 mL) was kept at 20 °C for 20 h. Water (1 mL) was added and the solution was left at 20 °C for 30 min and then poured into water. The oily solid which separated was extracted with 2:1 ether–CH_2Cl_2 and the extract was washed successively with ice-cold M HCl, satd aq KCl, and satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the mixed diastereoisomers **16** (1.3 g, 95%); ^{1}H NMR data: δ 0.77 (3 H), 0.88 (3 H), 0.96 (6 H), 1.04 (6 H) (4 s, 6 CMe of the camphanate portion), 1.31 (6 H) and 1.52 (6 H) (2 s, 4 Me of the isopropylidene portion), and 2 triplets centered at δ 3.47 and 3.51. The mixed diastereoisomers were dissolved in MeOH (50 mL), the solution was kept at 20 °C overnight, and crystalline **17** (400 mg, 60% of one diastereoisomer) was separated by filtration; mp 152–154 °C; $[\alpha]_D^{26}$ −15.0° (*c* 1, $CHCl_3$); ^{1}H NMR data: δ 0.78, 0.97, 1.06 (3 s, each 3 H, 3 CMe of the camphanate portion), 1.34, 1.53 (2 s, each 3 H, 2 CMe of the isopropylidene portion), and a triplet centred at δ 3.52. Anal. Calcd for $C_{41}H_{48}O_{10}$: C, 70.27; H, 6.90. Found: C, 70.34; H, 6.83.

*1*L-*3,5-Di*-O-*benzyl-4*-O-(−)-*ω-camphanoyl-1,2*-O-*isopropylidene-6*-O-p-*methoxybenzyl*-myo-*inositol* (**24**).—Recrystallisation from MeOH of the material remaining in the mother liquors, after the preparation of **17**, gave a mixture of diastereoisomers (as observed by NMR). Recrystallisation from 1:3 EtOAc–light petroleum (bp 60–80 °C) of the material remaining in the second mother liquors gave a nearly pure sample (from NMR, 300 mg) of the camphanate **24**; mp 123–124 °C with softening at 80 °C; $[\alpha]_D^{25}$ +18.5° (*c* 1, $CHCl_3$); ^{1}H NMR data: δ 0.88, 0.96, 1.04 (3 s, each 3 H, 3 CMe of the camphanate portion), with a triplet at δ 3.47. There was a small peak at δ 0.77 indicating slight contamination by the camphanate **17**. Anal. Calcd for $C_{41}H_{48}O_{10}$: C, 70.27; H, 6.90. Found: C, 70.41; H, 7.03.

*1*L-*1,5-Di*-O-*benzyl-2,3*-O-*isopropylidene-4*-O-p-*methoxybenzyl*-myo-*inositol* (**18**).—The camphanate **17** was treated with NaOH in MeOH under reflux and the product isolated in the usual way to give the alcohol **18**; mp 83–85 °C (from 1:10 EtOAc–light

petroleum); $[\alpha]_D^{25}$ −26.1° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.69; H, 7.21.

The alcohol **18** was benzylated with benzyl bromide and NaH in DMF and the product isolated in the usual way to give the tribenzyl ether **19** as a syrup which co-chromatographed with the racemic material described previously [13]. The *p*-methoxybenzyl group was removed with DDQ as described for the racemic material [13] to give the enantiopure alcohol **21** as a syrup which was described previously [13]. For characterisation this was converted into the (−)-ω-camphanate as described above for related compounds. The camphanate was identical (TLC, mp, NMR, and optical rotation) to the (−)-ω-camphanate **22** characterised previously [13], thus establishing the absolute configurations of compounds **21**, **18**, and **17**.

*1D-1,5-Di-*O*-benzyl-2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzyl*-myo-*inositol* (**25**).—The slightly impure camphanate **24** was hydrolysed with base as described above to give the alcohol **25**; mp 83–84 °C (from 1:3 EtOAc–light petroleum); $[\alpha]_D^{25}$ +24.8° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.63; H, 7.16.

The alcohol **25** should be available enantiopure from the (+)-ω-camphanate **26** [the enantiomer of the (−)-ω-camphanate **17**] by crystallisation of **26** from MeOH as described above for **17**.

*1D-3,5-Di-*O*-benzyl-4-*O*-(oct-7-enyl)*-myo-*inositol* (**29**).—The alcohol **18** (3.2 g, 6.1 mmol), sodium hydride in oil (50%, 500 mg, 10 mmol), and 8-bromooct-1-ene (1.3 mL, 7.74 mmol) in DMF (100 mL) were stirred at 20 °C for 24 h. TLC (2:1 ether–light petroleum) showed conversion of **18** (R_f 0.5) into the product (R_f 0.8) together with the excess of bromide (R_f 1.0). MeOH was added to destroy the excess of NaH, the solution was diluted with water, and the product was extracted with ether. The extract was dried (K_2CO_3) and column chromatography (silica gel) using 1:2 and 1:1 ether–light petroleum gave the ether **20** (3.5 g, 91%) as a syrup. This was treated with DDQ in aq CH_2Cl_2 in the usual way when TLC (1:1 ether–light petroleum) showed conversion of **20** (R_f 0.7) into the product (R_f 0.2). This was purified by column chromatography (silica gel), and elution with 1:1 and 1:2 ether–light petroleum gave the alcohol **28** as an oil; $[\alpha]_D^{26}$ −12.8° (*c* 1.7, $CHCl_3$). Anal. Calcd for $C_{31}H_{42}O_6$: C, 72.91; H, 8.29. Found: C, 72.57; H, 8.65.

The isopropylidene group of **28** was hydrolysed by heating with 0.1 M HCl in MeOH, an excess of $NaHCO_3$ was added, the solution was concentrated, and the product **29** was extracted with CH_2Cl_2; mp 92–95 °C (1:20 EtOAc–light petroleum); $[\alpha]_D^{26}$ +6.1° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_6 \cdot 0.5H_2O$: C, 70.12; H, 8.20. Found: C, 70.57; H, 8.20.

The triol **29** gave a syrupy triacetate **30**; $[\alpha]_D^{28}$ +21.1° (*c* 1, $CHCl_3$); ^1H NMR data: δ 1.89, 1.98, 2.13 (3 s, each 3 H, 3 Ac). Anal. Calcd for $C_{34}H_{44}O_9$: C, 68.43; H, 7.43. Found: C, 68.69; H, 7.65.

In the same way the alcohol **25** was converted into the octenyl ether **27** and the *p*-methoxybenzyl group was removed to give the alcohol **32**; $[\alpha]_D^{26}$ +9.4° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{31}H_{42}O_6$: C, 72.91; H, 8.29. Found: C, 72.58; H, 8.59.

Hydrolysis of **32** gave the triol **33**; mp 85–90 °C; $[\alpha]_D^{25}$ −5.1° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.40; H, 7.91.

This gave a triacetate **34** with a ^1H NMR spectrum identical with that of **30**.

1D-3,5-Di-O-benzyl-4-O-(oct-7-enyl)-myo-*inositol 1,2,6-tris(dibenzyl phosphate)* (**31**).—The triol **29** was converted into the tris(dibenzyl phosphite) by reaction with dibenzyloxy(diisopropylamino)phosphine in the presence of tetrazole and the product oxidised with *m*-chloroperoxybenzoic acid as described for related compounds [14]. Column chromatography (silica gel) in 2:1 ether–light petroleum gave the trisphosphate **31** as a syrup; $[\alpha]_D^{27}$ −1.0° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{70}H_{77}O_{15}P_3$: C, 67.19; H, 6.20; P, 7.42. Found: C, 67.23; H, 6.32; P, 7.46.

In the same way the enantiomer **35** was prepared from the triol **33**; $[\alpha]_D^{27}$ −0.8° (*c* 1.1, $CHCl_3$). Found: C, 67.13; H, 6.38; P, 7.37.

Acknowledgements

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