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Preliminary communication

Synthesis of (±)-1,2,4-tri-*O*-benzyl-*myo*-inositol*

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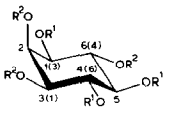
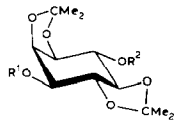
D-*myo*-Inositol 1,4,5-trisphosphate (**1**) is released from the membrane lipid phosphatidylinositol 4,5-bisphosphate on receptor-mediated enzymic hydrolysis and may act as a "second messenger" by mobilising intracellular calcium ions[2–7].

For synthetic work, suitably protected derivatives of *myo*-inositol were required, and we now describe the synthesis of crystalline racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol (**2**), which should be resolvable by known techniques[8] and converted into **1** by the phosphorylation methods described previously[9,10].

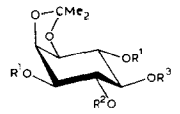
(±)-1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol[11] (**5**) was converted[11] into the dibenzyl ether **6**. A crystalline monobenzyl derivative (**7**, m.p. 167–169°) was isolated after partial benzylation and this gave the known[12,13] 1-*O*-benzyl-*myo*-inositol on acid hydrolysis.



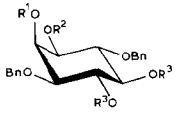
1 $R^1 = -P(O)(OH)_2, R^2 = H$
2 $R^1 = H, R^2 = Bn$
3 $R^1 = -CH_2-CH=CH_2, R^2 = Bn$
4 $R^1 = Ac, R^2 = Bn$



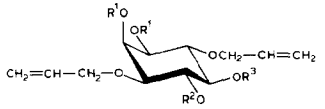
5 $R^1 = R^2 = H$
6 $R^1 = R^2 = Bn$
7 $R^1 = Bn, R^2 = H$
8 $R^1 = R^2 = -CH_2-CH=CH_2$



9 $R^1 = Bn, R^2 = R^3 = H$
10 $R^1 = Bn, R^2 = R^3 = -CH_2-CH=CH_2$
11 $R^1 = Bn, R^2 = R^3 = -CH_2-CH=CMe_2$
12 $R^1 = -CH_2-CH=CH_2, R^2 = R^3 = H$
13 $R^1 = -CH_2-CH=CH_2, R^2 = R^3 = Bn$
14 $R^1 = -CH_2-CH=CH_2, R^2 = Bn, R^3 = H$
15 $R^1 = -CH_2-CH=CH_2, R^2 = H, R^3 = Bn$
16 $R^1 = R^3 = -CH_2-CH=CH_2, R^2 = Bn$



17 $R^1 = R^2 = H, R^3 = -CH_2-CH=CH_2$
18 $R^1 = R^2 = H, R^3 = -CH_2-CH=CMe_2$
19 $R^1 = H, R^2 = R^3 = -CH_2-CH=CH_2$



20 $R^1 = H, R^2 = R^3 = Bn$
21 $R^1 = R^3 = H, R^2 = Bn$
22 $R^1 = R^2 = H, R^3 = Bn$

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Partial hydrolysis [a solution of **6** (10 g) and toluene-*p*-sulphonic acid monohydrate (1 g) in acetone (200 mL) and water (5 mL) at 20° for 45 min] of **6** gave a readily separable mixture of **6** (soluble in ether), 1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (**9**; m.p. 161–163°, soluble in chloroform but poorly soluble in ether), and 1,4-di-*O*-benzyl-*myo*-inositol[11] (poorly soluble in chloroform and ether). Compound **9** was converted into the allyl ether **10** and the "prenyl" ether **11** and these, on acid hydrolysis, gave the crystalline diols **17** (m.p. 106–108°) and **18** (m.p. 91–93°), respectively.

The dibutylstannylidene derivative of **17** was treated with allyl bromide in *N,N*-dimethylformamide[14] to give the tri-*O*-allyl derivative **19**, benzylation of which gave (±)-1,4,5-tri-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol (**3**, m.p. 53–55°). Removal of the allyl groups by isomerisation with potassium *tert*-butoxide in methyl sulphoxide and subsequent acid hydrolysis[15], or by the action of Pd/C in the presence of acid[16], gave (±)-1,2,4-tri-*O*-benzyl-*myo*-inositol (**2**, m.p. 116–118°) which was characterised as the acetate **4** (m.p. 123–125°).

Partial hydrolysis [a solution of **8** (2.5 g) and toluene-*p*-sulphonic acid monohydrate (270 mg) in acetone (55 mL) and water (1.4 mL) at 20° for 1 h] of the allyl ether **8** (m.p. 85–87°) of **5** gave a readily separable mixture of **8** (soluble in light petroleum), **12** (m.p. 130–132°, extracted from an aqueous solution with chloroform), and 1,4-di-*O*-allyl-*myo*-inositol (not extracted from water by chloroform). Reaction of **12** with 1 equiv. of benzyl bromide and sodium hydride in *N,N*-dimethylformamide gave a mixture of **13–15** in approximately equal proportions and these were readily isolated by column chromatography on Merck silica gel 60 (70–230 mesh). Elution with ether–light petroleum (b.p. 40–60°) (1:2) gave **13** followed by **14**, and further elution with these solvents (ratio, 1:1) gave **15**. Acid hydrolysis of **13–15** gave **20** (m.p. 78–80°), **21** (m.p. 107–109°), and **22** (m.p. 162–164°), respectively. Removal of the allyl groups from **21** and **22** by the action[16] of Pd/C gave 4-*O*-benzyl-*myo*-inositol[9,12] (from **21**) and 5-*O*-benzyl-*myo*-inositol[12] (from **22**).

Allylation of **14** gave **16** which, on acid hydrolysis followed by benzylation, gave (±)-1,4,5-tri-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol (**3**) identical with the material prepared as described above.

The 1,4-di-*O*-allyl-5,6-di-*O*-benzyl-*myo*-inositol (**20**) is being used as an intermediate for the synthesis of 2,4,5-tri-*O*-benzyl-*myo*-inositol, which should provide inositol 1,3,4-trisphosphate which has also been observed in stimulated cells[2,17]

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