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TOTAL SYNTHESIS OF MYO-INOSITOL POLYPHOSPHATES FROM BENZENE VIA CONDURITOL B DERIVATIVES

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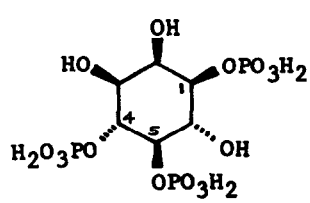
Summary: The four (±)-myo-inositol phosphates 1,4,5-IP_3 (1), 2,4,5-IP_3 (15), 1,2,4,5-IP_4 (17) and 4,5-IP_2 (19) have been synthesised from benzene, using the protected conduritol B (10) as the key intermediate.

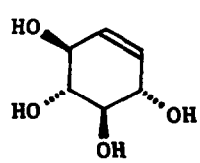
There is considerable activity in the synthesis of myo-inositol phosphates, in view of the role played by the 1,4,5-trisphosphate (1) as a secondary cell messenger in the release of calcium from intracellular stores.[1,2] Many synthetic approaches to (1) have begun by selective manipulation of the hydroxyl groups of abundant myo-inositol,[1,3] or from the naturally-occurring plant inositols, pinitol and quebrachitol.[4] The need for adaptable routes to (1) and its analogues has led to the development of total syntheses which begin with benzene.[5,6]

One obvious approach to the myo-inositol phosphates relies on cis-hydroxylation of a suitable derivative of conduritol B (2). In fact, conduritol B and related compounds are proving to be valuable synthetic targets,[7] since the epoxide (3) is a β-glycosidase inhibitor (particularly of the mammalian enzyme, defective in Gaucher's disease, which cleaves glucosylceramide),[8] and cyclophellitol (4) has very recently been found as a novel β-glucosidase inhibitor.[9] Derivatives of (2) may also act as convenient intermediates in the synthesis of aminocyclitol antibiotics.[10]

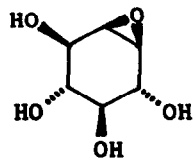
We now describe a route from benzene, via the trans-diol (5),[11] which is capable of providing a general route to conduritol B derivatives, and which we have developed into the total syntheses of four specific myo-inositol phosphates (1), (15), (17) and (19).



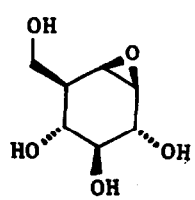
(1)



(2)



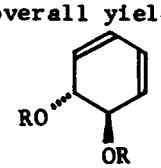
(3)



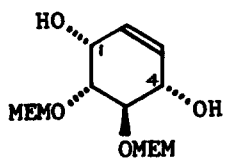
(4)

The MEM-protected trans-benzene diol (6), available in seven steps in ca. 35% yield from benzene, provides the diene which undergoes [4+2] addition to singlet oxygen, followed by thiourea reduction to afford diol (7).[6]

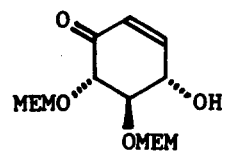
The key step which allows inversion at C-1 of (7) is an oxidation-reduction sequence: pyridinium chlorochromate (PCC, 1.5 equiv.) oxidation yields the separable hydroxyenones (8) and (9) (50% and 20%, respectively). Reduction of (8) by $NaBH_4/CeCl_3$[12] gives the symmetrical conduritol B derivative (10) (90%).[13] The unusual enedione (11), which did not undergo tautomerisation to the corresponding aromatic system under the reaction conditions,[14] was found to be a more beneficial intermediate; thus, oxidation of (7) (3 equiv. PCC) followed by isolation of the enedione and its subsequent reduction ($NaBH_4/CeCl_3$) leads to (10) in 70% overall yield.



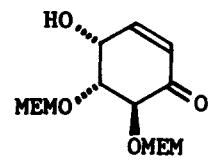
(5) R = H
(6) R = MEM ($CH_2OCH_2CH_2OCH_3$)



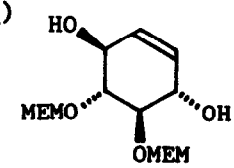
(7)



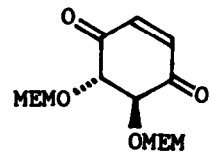
(8)



(9)

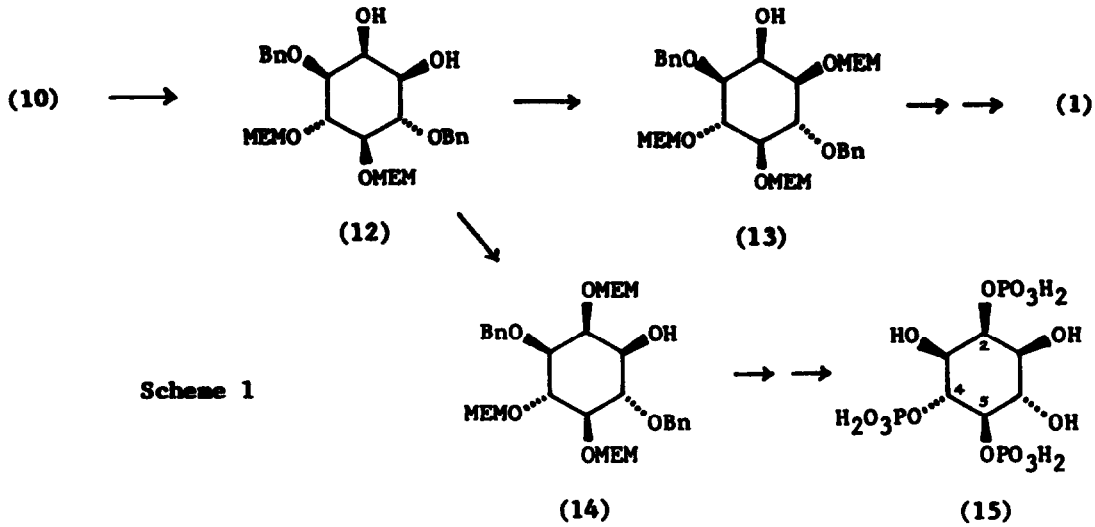


(10)



(11)

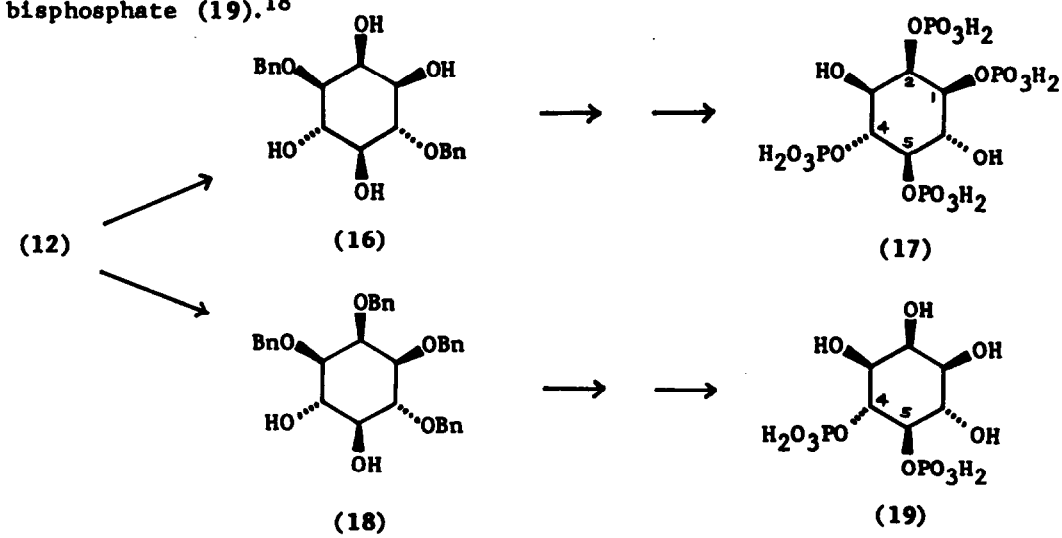
Several (±)-myo-inositol phosphate isomers were prepared from diol (10) by the following reactions (**Schemes** 1 and 2). Smooth dibenzylation of (10) ($NaH/PhCH_2Br$, 95% isolated yield) was easily achieved, followed by osmium tetroxide-catalysed cis hydroxylation (OsO_4/N-methylmorpholine-N-oxide, 96%), leading to protected cyclitol (12). Selective (equatorial) addition of a third MEM ether grouping gave (13) and (14) as separated major and minor products (60% and 10%, respectively). A final benzylation of (13) (86%), and subsequent MEM deprotection (6M HCl, THF, 20°C) produced a triol (59%) which was phosphorylated using the tetrabenzyl pyrophosphate/sodium hydride method (47%);[1] ultimately, hydrogenolysis of the benzyl groups (Pd/H_2) gave myo-inositol 1,4,5-trisphosphate (1), having ^1H, ^{13}C and ^{31}P spectra comparable with those in the literature.[15] The minor isomer (14) from the above selective etherification (**Scheme** 1) was taken through an identical sequence of reactions: benzylation (78%), deprotection (82%), phosphorylation (53%) and hydrogenolysis (85%), to afford the recently reported myo-inositol 2,4,5-trisphosphate (15).[3a,16]



Scheme 1

Compound (12) is a versatile intermediate in the synthesis of other biologically-relevant myo-inositol phosphates, as shown in **Scheme 2**. For example, MEM-deprotection of diol (12), phosphorylation of the resulting tetrol (16) and hydrogenolysis gave the IP_4 isomer, racemic myo-inositol-1,2,4,5-tetrakisphosphate (17).[17]

Alternatively, further benzylation of (12) and removal of the MEM groups gave the tetrabenzyl derivative (18) which was then phosphorylated (TBPP/BuLi/THF) and deprotected to give racemic myo-inositol 4,5-bisphosphate (19).[18]



Scheme 2

Acknowledgement

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13. Compound (10): δ_H (270 MHz, CD_3COCD_3) 5.53 (2H, s, =CH) 4.92, 4.83 (each 2H, d, J 7 Hz, OCH_2O), 4.35 (2H, d, OH), 4.16 (2H, m, H-1, H-4), 3.88-3.45 (10H, m) and 3.31 (6H, s, OCH_3); δ_C 129.9 (=CH), 97.5 (OCH_2O), 84.4 (C-2, C-3), 72.5, 68.1 (OCH_2CH_2O), 72.5 (C-1, C-4), and 58.7 (OCH_3) ppm.

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16. We can now report the ^{13}C nmr data for (15): δ_C (D_2O, ammonium salt) 80.2t, 78.0t, 77.5d, 76.5s, 74.7s and 74.5t ppm.

17. Compound (17) (ammonium salt, D_2O): δ_H (500 MHz) 4.62 (1H, d, J 8 Hz), 4.24 (1H, q, J 9 Hz), 4.00 (1H, t, J 9 Hz), 3.95 (1H, t, J 9 Hz), 3.87 (1H, q, J 8-9 Hz) and 3.65 (1H, t, J 8-9 Hz); δ_C 80.8m, 78.8t, 78.3d, 76.1t, 75.1d and 74.6s ppm.

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