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TOTAL SYNTHESIS OF *chiro*-INOSITOL 2,3,5-TRISPHOSPHATE: A *myo*-INOSITOL 1,4,5-TRISPHOSPHATE ANALOGUE FROM BENZENE *VIA* PHOTO-OXIDATION

Howard A.J. Carless* and Kofi Busia

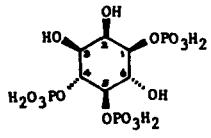
Department of Chemistry, Birkbeck College, Malet Street, London WC1E 7HX

Summary: The inositol tris- and tetrakis-phosphate analogues (4) and (14) have been synthesised from benzene by a sequence including reaction of singlet oxygen with a *trans*-cyclohexa-3,5-diene-1,2-diol (3) derivative.

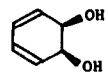
There is intense topical interest in the role of *myo*-inositol 1,4,5-trisphosphate (IP_3, 1) and related molecules as second messengers in cellular signal transduction.[1] In the last four years, there have been several successful syntheses of IP_3, both in racemic[2] and in chiral form,[3] starting from readily available *myo*-inositol or from naturally-occurring plant inositols such as pinitol or quebrachitol.[4] However, there is a need for a more versatile approach to inositols which allows greater variation in stereochemistry and substitution pattern in the synthesis of IP_3 analogues. In particular, Ley's group has reported routes to IP_3[5] and 6-deoxy analogues[6] based on microbial oxidation of benzene to *cis*-cyclohexadienediol (2), and we have published a related photochemical route to inositol intermediates.[7] Other workers have used these biotransformations of substituted aromatics to give chiral routes to cyclopentenones[8] and erythrose isomers.[9] We now describe a complementary approach, based on the *trans*-diol (3), a benzene metabolite,[10] to the total synthesis of (±)-*chiro*-inositol 2,3,5-trisphosphate (4) from benzene. The target molecule represents the epimer at C-3 of (1) in which the three biologically-important equatorial phosphate groups[11] of IP_3 are maintained.†

Diol (3) is available in six steps (40% overall yield) from benzene, *via* Birch reduction,[12] bromination, *trans*-hydroxylation, acetylation and dehydrobromination.[13] The two hydroxyl groups of (3) were protected as methoxyethoxymethyl (MEM) ethers (91% yield),[14] followed by reaction of the symmetrical diene with singlet oxygen (Methylene Blue-sensitised photo-

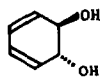
†Note the different conventional numbering of the *myo*- (1) and *chiro*- (4) inositol systems, as shown.



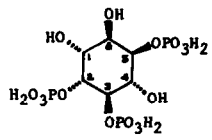
(1)



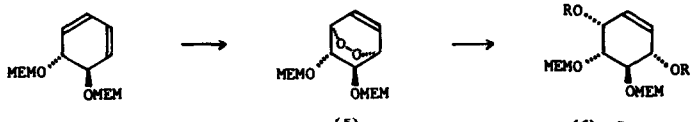
(2)



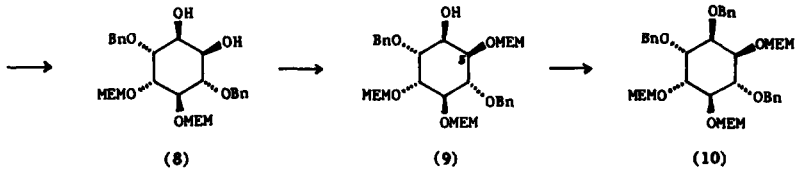
(3)



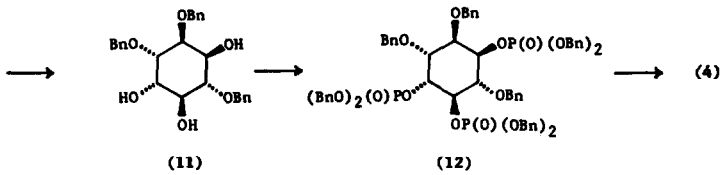
(4)



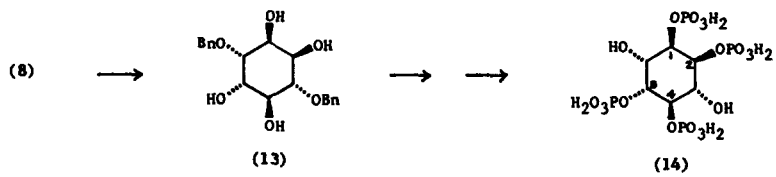
(5) (6) R = H (7) R = Bn



(8) (9) (10)



(11) (12) (4)



(8) (13) (14)

oxidation, dichloromethane, -80°C) which gave the endoperoxide (5) (82%). Stereospecific reduction of the endoperoxide by thiourea/methanol[15] led to the diol diether (6) in fair yield (70%). Subsequently, complete benzylation of this Conduritol F derivative yielded (7) (64%). Cis-hydroxylation of the remaining double bond using osmium tetroxide gave a single stereoisomer (8) of the cyclitol product,[16] isolated in 80% yield. It was possible to convert diol (8) to the tris-MEM ether (9) by preferential protection of the equatorial hydroxyl group at C-5 (60%).[17] Benzylation of the remaining hydroxyl group gave the fully protected chiro-inositol derivative (10) (88%).

Deprotection of the MEM ether groups was most successfully achieved in this example using conc. hydrochloric acid/tetrahydrofuran at 20°C, to give triol (11) (76%), and the vital phosphorylation step was accomplished using the tetrabenzyl pyrophosphate method,[1,18] to yield the trisphosphate (12) (44%).[19] Finally, hydrogenolysis (Pd-C/H_2) removed all the benzyl groups to afford the (±)-chiro-inositol trisphosphate derivative (4) (90%), isolated as its hexa-ammonium salt.[20]

The key intermediate (8) is capable of leading to other inositol phosphate analogues. Thus, conversion of (8) to the tetrol (13) by removal of the two MEM groups (HCl/THF), followed by complete phosphorylation (-40°C, BuLi, tetrabenzyl pyrophosphate) (27%) and hydrogenolysis gave (±)-chiro-inositol 1,2,4,5-tetrakisphosphate (14).[21] The latter compound is the epimer at C-3 of the recently-synthesised myo-inositol 1,2,4,5-tetrakisphosphate.[2c]

Enantiospecific synthetic routes to (4) and (14) are now available, using the resolved enantiomers of (3)[22] as chiral starting materials.

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19. Compound (12) showed inter alia δ_H (400 MHz, CD_3COCD_3) 4.41 (1H, t, J 3.6 Hz), 4.29 (1H, t, J 3.8 Hz), 3.99 (1H, t, J 9.3 Hz); δ_C 79.3, 78.8, 78.3, 76.9, 76.3, 76.1, 75.1, 74.3 (x2) p.p.m. (6 x ring carbons + 3 x benzylic); δ_P 0.33, 0.08 and -0.23 p.p.m.

20. Compound (4) (hexa-ammonium salt): δ_H (500 MHz, D_2O) 4.30 (2H, d), 4.22-4.17 (3H, m) and 3.87 (1H, t, J 9 Hz); δ_C 79.2t, 76.8d, 76.2t, 75.2d, 73.3s and 72.8s p.p.m.; δ_P 4.03, 3.74 and 3.53 p.p.m.

21. Compound (14) (octa-ammonium salt): δ_H (500 MHz, D_2O) 4.61 (1H, dm, J 10.2 Hz), 4.35-4.23 (4H, m) and 3.91 (1H, t, J 9.3 Hz); δ_C 79.5, 76.4, 76.4, 75.4, 74.8 and 73.0 p.p.m.; δ_P 3.39, 2.99 (x2) and 2.32 p.p.m.

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