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MICROBIAL OXIDATION IN SYNTHESIS: PREPARATION OF 6-DEOXY CYCLITOL ANALOGUES OF *MYO*-INOSITOL 1,4,5-TRISPHOSPHATE FROM BENZENE

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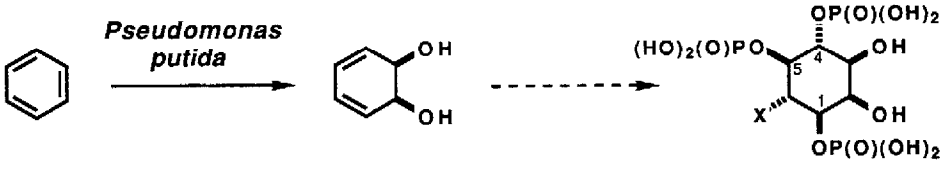
Summary: *The novel 6-deoxy, 6-deoxy-6-fluoro and 6-deoxy-6-methyl myo-inositol 1,4,5-trisphosphate derivatives (4), (5) and (6) were derived from benzene via microbial oxidation to cis-1,2-dihydroxycyclohexa-3,5-diene (2) and conversion through to the key epoxyacetonide (7).*

There is currently considerable interest in the synthesis of cyclitol compounds and particularly in systems related to the cellular second messenger inositol 1,4,5-trisphosphate (IP_3) (1). [1,2b] Since *myo*-inositol is cheap and readily available most syntheses of inositol phosphates to date have begun with the parent cyclitol and have proceeded through a multistep protection - deprotection sequence to set up the desired pattern of substitution. We have already described a conceptually different strategy[2] starting from benzene and making use of a microbial oxidation using *Pseudomonas putida*[2,3] to afford the cyclohexadiene diol (2). This approach is especially well suited to the preparation of a range of novel analogues[2b] modified at sites other than the phosphate group, in contrast to previously reported approaches which are not readily amenable for such analogue preparation.[4] Biological evaluation of these compounds will hopefully lead to a more detailed understanding of the phosphatidylinositol (PI) cycle regulating cellular functions as diverse as secretion, proliferation and smooth muscle contraction. We have previously published routes to IP_3 (1) and 6-*O*-methyl IP_3 (3) from (2)[2b] and here we report the syntheses of other novel IP_3 derivatives (4)-(6).

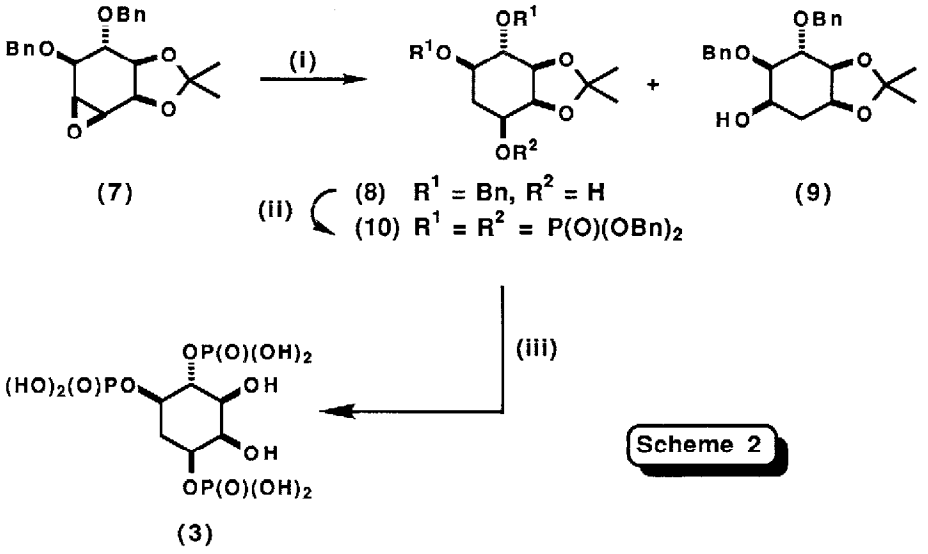


(2)

(1) X = OH
(3) X = OMe
(4) X = H
(5) X = F
(6) X = Me

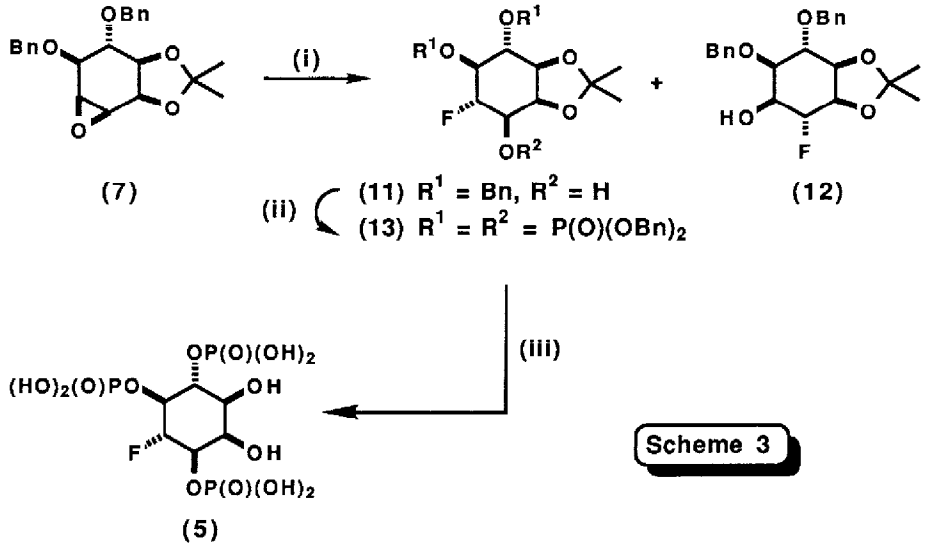
Scheme 1

In all of these syntheses use is made of the epoxy acetonide (7) which in turn is readily derived from (2). For the preparation of the 6-deoxy compound (4) the epoxide (7) was reacted with lithium aluminium hydride in boiling ether to afford the alcohol (8) (76%), accompanied by a small amount of the alternative ring opened product



Scheme 2

(i) $LiAlH_4$, Et_2O, reflux, 2h, 88%; (ii) a. H_2, 10% Pd-C, EtOH, 39h; b. ^nBuLi, $^iPr_2NH$, THF, tetrabenzylpyrophosphate, 56% overall; (iii) a. TMSBr, CH_2Cl_2, RT, 65 min; b. H_2O, 80 min, 79% overall.



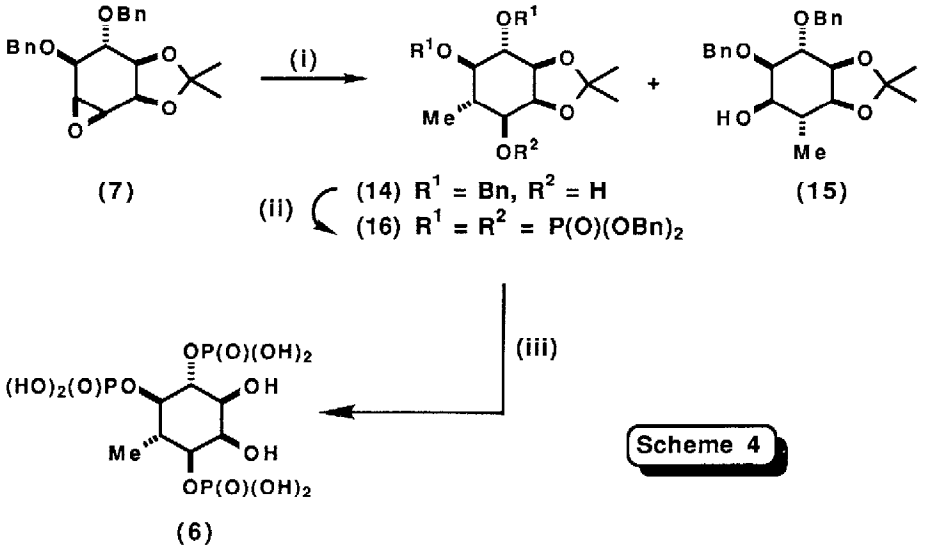
Scheme 3

(i) TASF, THF, reflux, 4 days, 74%; (ii) a. H_2, 10% Pd-C, EtOH, 18h; b. ^nBuLi, $^iPr_2NH$, THF, tetrabenzylpyrophosphate, 77% overall; (iii) a. TMSBr, CH_2Cl_2, RT, 65 min; b. H_2O, 80 min, 93% overall.

(9) (12%). Debenzylation of the major product (8) by hydrogenolysis and subsequent phosphorylation with ^{n}BuLi/tetrabenzylpyrophosphate gave the 1,4,5-trisphosphate (10). Total deprotection of this trisphosphate was readily achieved using Meek's TMSBr protocol.[1g] Purification of the product by anion exchange HPLC (Spherisorb S5SAX column, 0.2M ammonium formate buffer at pH 4) furnished 6-deoxy IP_3 (3)[5] in 79% overall yield from (8).

Replacement of an hydroxyl group with a fluorine atom has been considered a simple isosteric substitution in inositol synthesis,[6] and thus analogue (5) was considered an attractive target for synthesis. Treatment of the previously described epoxy acetonide (7) with tris(dimethylamino)sulphonium difluorotrimethylsilicate (TASF)[7] in THF at reflux afforded the fluorohydrins (11) and (12) as a 4:1 mixture readily separable by silica gel chromatography. In a similar fashion to that described above, compound (11) was hydrogenolysed and phosphorylated to afford (13). Subsequent deprotection with TMSBr and purification by anion exchange HPLC produced the novel 6-fluoro derivative of IP_3 (5) in 93% overall yield from (13).

This very versatile sequence towards a range of unique IP_3 analogue compounds was also applicable to the synthesis of the 6-deoxy-6-methyl derivative (6). Nucleophilic ring opening of (7) using lithium dimethyl(cyano)copper (I) furnished the alcohols (14) and (15) as a 21:1 mixture (76% combined yield). The alcohol (14) was then elaborated to the fully protected trisphosphate (16) in a manner analogous to that used above. Treatment with TMSBr followed by purification afforded the desired 6-deoxy-6-methyl IP_3 (6).[9]



Scheme 4

(i) $Me_2Cu(CN)Li_2$, THF, -30°C, 22h, 76%; (ii) a. H_2, 10% Pd-C, EtOH,16h; b. ^{n}BuLi, $^{i}Pr_2NH$, THF, tetrabenzylpyrophosphate, 41% overall; (iii) a. TMSBr, CH_2Cl_2, RT, 65 min; b. H_2O, 80 min, 82% overall.

The above syntheses of these IP_3 analogues further illustrates the important strategic advantage that can be gained by using microbial oxidation methodology for cyclitol preparation from aromatic substrates.

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5. ^{1}H-NMR δ (500 MHz, D_2O, pH 9.4; HOD = 4.63) 4.01 (1H, s, 2-H), 3.91 (2H, br s, (CHOP(O)(OH)$_2$)$_2$), 3.76 (1H, br s, CHOP(O)(OH)$_2$), 3.47 (1H, d, J 6.9 Hz, 3-H), 2.17 (1H, d, J 10.5 Hz, 6 eq-H), 1.74 (1H, q, J 10.5 Hz, 6 ax-H); ^{31}P-NMR δ (101 MHz, D_2O, pH 9.0) 5.93 (3P, br s).
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8. ^{1}H-NMR δ (500 MHz, D_2O, pH 9.0; HOD = 4.63) 4.44 (1H, dt, J 52.1 and 7.7 Hz, 6-H), 4.09 (1H, br s, 2-H), 3.99-3.95 (3H, m, (CHOP(O)(OH)$_2$)$_3$), 3.59 (1H, d, J 5.8 Hz, 3-H); ^{31}P-NMR δ (101 MHz, D_2O, pH 9.0), 6.85 (1P, br s), 5.86 (1P, s), 5.27 (1P, br s); ^{19}F-NMR δ (84 MHz, D_2O, pH 9.0) -196.4 (d, J 53.7Hz).
9. ^{1}H-NMR δ (500 MHz, D_2O, pH 9.0; HOD = 4.63) 4.09 (1H, s, 2-H), 3.97 (1H, br s, CHOP(O)(OH)$_2$), 3.59 (1H, br s, CHO(P)(O)(OH)$_2$), 3.52 (1H, dd, J 8.8 and 9.1 Hz, CHO(P)(O)(OH)$_2$), 3.47 (1H, br s, 3-H), 1.81 (1H, br s, 6-H), 0.97 (3H, d, J 4.9 Hz, Me); ^{31}P-NMR δ (101 MHz, D_2O, pH 9.0), 6.74 (1P, br s), 5.47 (1P, br s), 3.90 (1P, br s).

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