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TOTAL SYNTHESIS OF OPTICALLY ACTIVE *MYO*-INOSITOL 1,4,5-TRISPHOSPHATE AND *MYO*-INOSITOL 1,3,4,5-TETRAKISPHOSPHATE*

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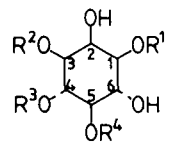
ABSTRACT:A convenient approach to the preparation of the title compounds illustrating selective protection, optical resolution and phosphorylation is presented.

Previously we reported[1,2] that the monofunctional phosphitylating reagent 1 and the phosphonylating reagent 2 could be used for the preparation of racemic *myo*-inositol 1,3,4-trisphosphate (5) and 1,4,5-tris-1-*H*-phosphonate (6), respectively.

1 $Cl\text{-}P\text{-}(OCH_2CH_2CN)_2$ 3 $Cl\text{-}P\text{-}(OCH_2CH{=}CH_2)_2$

2 $NH_4^+\ ^-OP(O)H(OBzl)$ 4 $(Et)_2N\text{-}P\text{-}(OBzl)_2$



5 $R^1{=}R^2{=}R^3{=}P(O)(OH)_2$; $R^4{=}H$

6 $R^1{=}R^3{=}R^4{=}P(O)H(OH)$; $R^2{=}H$

7 $R^1{=}R^3{=}R^4{=}P(O)(OH)_2$; $R^2{=}H$

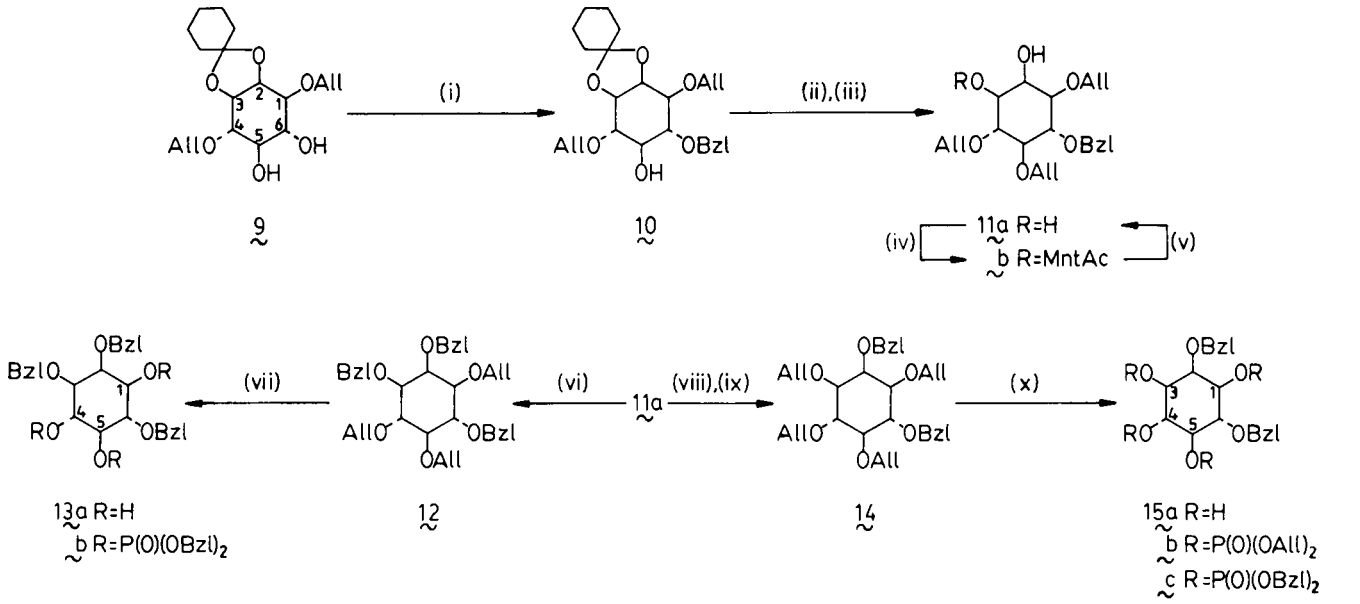
8 $R^1{=}R^2{=}R^3{=}R^4{=}P(O)(OH)_2$

As part of a continuous programme directed towards the preparation of *myo*-inositol phosphates and derivatives thereof, we now describe a convenient route to the optically active and biologically important D-*myo*-inositol 1,4,5-tris-[3] and 1,3,4,5-tetrakisphosphates[4] (*i.e.* 7 and 8, respectively).

The synthetic strategy we followed is outlined in the Scheme. Based on our earlier work[1] we used 9 as starting product. The latter was converted into racemic diol 11a by a small modification of a route originally devised by Gigg *et al*[5]. Thus partial benzylation (step i) of 9 gave, after purification by short column chromatography, homogeneous 10[6] in a yield of 38%. Allylation (step ii) of 10 followed by de-acetalization of the *cis*-cyclohexylidene function (step iii) furnished racemic diol 11a[7] (overall yield 98%). Of the several methods so far used[8] to resolve racemic *myo*-inositol derivatives, we found the procedure of Ozaki *et al*[9] to be most advantageous. Thus treatment of 11a with *l*-menthoxyacetyl chloride (MntAc-Cl) (step iv) and subsequent separation of the individual diastereomeric esters by short column chromatography afforded 11b (42% yield; $[\alpha]_D^{20}$ -18.9°, $CHCl_3$) and 11b (37% yield; $[\alpha]_D^{20}$-50.5°, $CHCl_3$). Deacetylation of the MntAc-group (step v) from the diastereomeric esters 11b yielded quantitatively the corresponding two enantiomers of 11a ($[\alpha]_D^{20}$ +20.0° and -20.0°, $CHCl_3$). The enantiomer of 11a, having $[\alpha]_D^{20}$ +20.0°, was now converted (step vi) into optically active 12 ($[\alpha]_D^{20}$ -2.9°, $CHCl_3$; mp 50.5-51.5°C) which was isolated in a yield of 88%. Removal (step vii) of the allyl protecting groups from 12 afforded 13a[7] (82% yield, mp 115-115.5°C), which was assigned the absolute D-configuration on the basis of its specific rotation[10] ($[\alpha]_D^{20}$ +8.9°, $CHCl_3$). The other optically pure precursor 15a required for the preparation of the tetrakisphosphate 8 was accessible as follows. Chemoselective tin-mediated[11] allylation (step viii) of 11a (R=H, $[\alpha]_D^{20}$ +20.0°, $CHCl_3$) afforded 11 (R=Allyl; 81% yield; $[\alpha]_D^{20}$ +12.2°, $CHCl_3$), which after benzylation (step ix) gave 14 (92% yield; $[\alpha]_D^{20}$ +0.6°, $CHCl_3$). Finally the D-*myo*-inositol 15a[7] (81% yield; $[\alpha]_D^{20}$ -22.9°, $CHCl_3$; mp 120-121.5°C) was obtained after deblocking (step x) of the four allyl groups from 14.

In a first attempt to prepare the target phosphates 7 and 8 we used the phosphitylating reagent 3[12]. In a typical example, tetrol 15a (0.5 mmol) in

*Dedicated to Prof. G.J.M. van der Kerk on the occasion of his 75th birthday.



Scheme: (i) BzlBr (1.1 eq)/NaH/DMF; (ii) AllBr/NaH/DMF; (iii) HOAc-H_2O (4:1) 95°C 2h; (iv) MntAc-Cl (1.1 eq)/ pyridine 0°C 15min; (v) NaOMe (cat)/MeOH; (vi) BzlBr/NaH/DMF; (vii) Pd(C)/TsOH (cat)/MeOH-H_2O (5:1) reflux 4h; (viii) n-Bu_2SnO (1 eq)/MeOH reflux 1.5h; AllBr (1.25 eq)/n-Bu_4NI (1.25 eq)/toluene 95°C 16h; (ix) BzlBr/NaH/DMF; (x) Pd(C)/TsOH (cat)/MeOH-H_2O (5:1) reflux 4h.

CH_2Cl_2 (5 ml) containing *N,N*-diisopropylethylamine was added dropwise to a cooled (-40°C) and stirred solution of 3 (3 mmol) in CH_2Cl_2 and left for 30 min. The intermediate phosphite triesters were then oxidized at -40°C with *t*-butyl hydroperoxide (15 mmol)[13]. Work-up, after 30 min at 0°C, and purification by short column chromatography furnished 15b in a yield of 85% (δ_P-values: -0.88, -1.09, -1.18 and -1.63 ppm). Unfortunately, selective removal[12] of the allyl groups from 15b was not successful. Analysis of 8, still having the 2- and 6-hydroxyl protected with benzyl groups, by ^{31}P-NMR showed, apart from the expected phosphate resonances, the presence of some additional phosphorus-containing impurities which could not be removed by extensive purification. We therefore decided to explore the feasibility of using *N,N*-diethyl dibenzyl phosphoramidite 4, the powerful phosphitylating properties of which were recently demonstrated by us[14] and others[15] in the preparation of phosphopeptides. Thus to a solution of 15a (1 mmol) in acetonitrile (25 ml) containing 1-*H*-tetrazole (1.25 eq/4) was added 4 (1.5 eq/OH) and left for 1 h at 20°C. Oxidation of the intermediate phosphite triesters (δ_P-values: 141.67 (1P), 141.82 (1P) and 142.91 (2P) ppm) with *t*-BuOOH[16] for 1 h at 0°C gave, after work-up and purification, homogeneous 15c[7] (82% yield; δ_P-values: -0.76, -1.06, -1.24 and -1.57 ppm). In a similar fashion 13b[7] (93% yield; δ_P-values: -1.15, -1.27 and -1.36 ppm) was prepared. Hydrogenolysis (H_2/Pd(C)/MeOH-H_2O) of 13b and 15c resulted in the D-*myo*-inositol 1,4,5-tris- and 1,3,4,5-tetrakisphosphates 7 and 8, respectively, in excellent yields. ^{1}H- and ^{31}P-NMR data of compound 7 and 8 were in complete accordance with those observed for the corresponding and naturally occurring D-*myo*-inositol tris- and tetrakisphosphates[17].

In summary, the results presented in this paper indicate that most of the problems -selective protection, optical resolution, phosphorylation- which have to be addressed in concluding a successful preparation of optically active *myo*-inositol phosphates have been resolved.

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