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# SYNTHESIS OF 1,4,5-TRISSULPHATED AND 1,4,5-TRISSULPHAMOYLATED *myo*-INOSITOLS: ISOSTERIC *myo*-INOSITOL 1,4,5-TRISPHOSPHATE ANALOGUES

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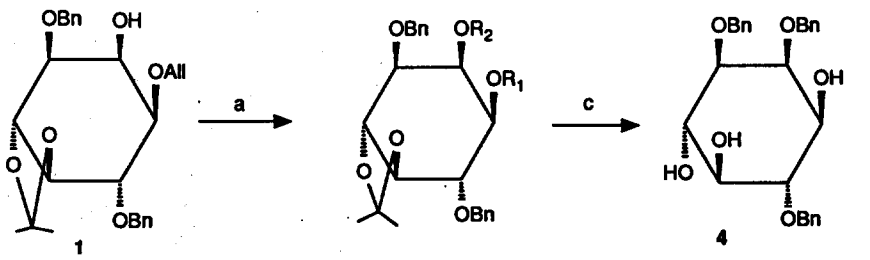
*Abstract: Synthesis of the myo-inositol 1,4,5-trisphosphate isosteric analogues (rac.) 1,4,5-trissulphate and (rac.) 1,4,5-trissulphonamido was accomplished from 1,2,4-tri-O-benzyl myo-inositol.*

It is now well understood that D-myo-inositol 1,4,5-trisphosphate ($IP_3$), generated by a receptor mediated hydrolysis of a phosphoinositide, acts as an intracellular second messenger[1]. $IP_3$ has been shown to release $Ca^{++}$ from intracellular stores, initiating a number of physiological responses. $IP_3$ is metabolized via two distinct pathways: $IP_3$ dephosphorylation by a 5-phosphatase gives inositol 1,4-bisphosphate, whereas phosphorylation by a 3-kinase yields another putative second messenger, inositol 1,3,4,5-tetrakisphosphate[2], the potential role of which is currently under investigation.

Since $IP_3$ is still the only inositol phosphate for which a clear-cut role in intracellular $Ca^{++}$ homeostasis has been demonstrated, there is a considerable interest in the synthesis[3] of $IP_3$ and derivatives thereof. In order to design $IP_3$ derivatives acting as intracellular $Ca^{++}$-antagonist, a better understanding of the mechanism of $Ca^{++}$ release at a molecular level will be essential. Mapping of the substrate specificity of the $IP_3$ receptor proteins can be performed when systematically modified analogues of the natural ligand (i.e. $IP_3$) are available. Recent advances indicated the vicinal phosphate groups[4] at position 4,5 and the 3- and 6-hydroxyl groups[5] to be essential for $Ca^{++}$ release. Additional structure activity relatonships can be



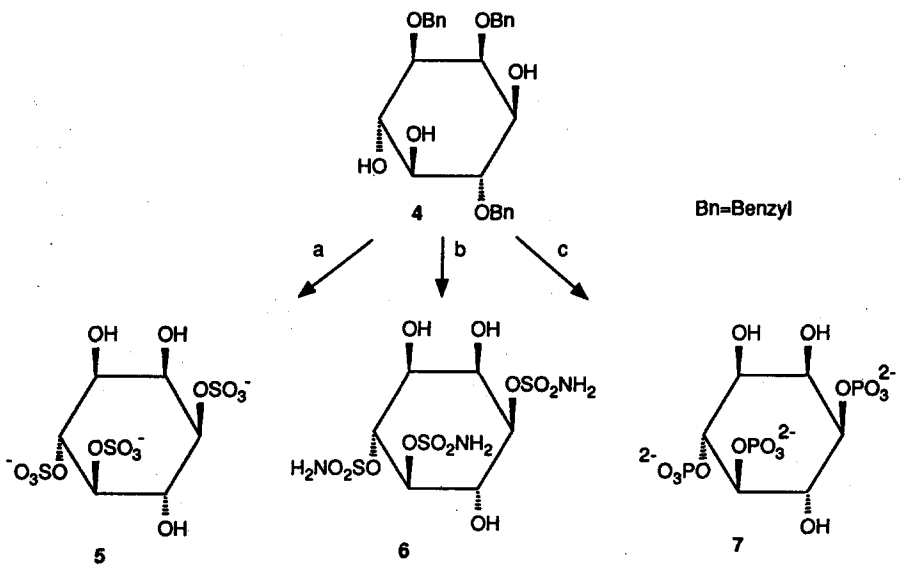

Scheme 1

*a: NaH/BnBr/DMF; b: Ir[COD(PMePh2)2]PF6/H2; c: HCl/dioxane/MeOH*

gathered from $IP_3$ analogues containing phosphate modified functions or phosphate isosteric groups. Apart from the synthesis of derivatives containing phosphorthioate moieties[6], no other report on the synthesis of isosteric $IP_3$ analogues has been published so far.

Since it has previously been shown that the sulphated polysaccharide, heparin, may compete with $IP_3$ for its receptor binding[7], the synthesis and biological testing of myo-inositol 1,4,5-trissulphate will be of considerable interest. It is not yet clear, however, whether the affinity of heparin for the $IP_3$ receptor can be attributed to a binding of sulphate groups in regions normally accomodating the $IP_3$ phosphates. The synthesis of neutral and isosteric analogues will be feasable by applying sulphonamide groups. In this communication, we wish to report the synthesis of two isosteric analogues of myo-inositol 1,4,5-trisphosphate, i.e. myo-inositol 1,4,5-trissulphate **5** and myo-inositol 1,4,5-trissulphonamide **6**.

Properly protected **1** was obtained from myo-inositol by the literature procedure[8]. Regioselective stannylene-mediated allylation[9] of **1** and subsequent benzylation afforded fully protected **2** (73% yield, see Scheme 1). Treatment of **2** with cyclooctadiene-bis(methyldiphenylphosphine)-iridium hexafluorophosphate[10] afforded **3** (100% yield), which on acid hydrolysis (dioxane/methanol/0.1 N HCl) furnished key-intermediate triol **4**[3] (96% yield).




**Scheme 2**

*a: $(CH_3CH_2)_3N.SO_3$/DMF then 10% Pd on C/$H_2$/DMF/$H_2O$; b: $NH_2SO_2Cl$/NaH/DMF then 10% Pd on C/$H_2$ in DMF/$H_2O$; c: $(CNCH_2CH_2O)_2PN(CH_2CH_3)_2$/1-H-tetrazole in $CH_2Cl_2$/$CH_3CN$ followed by tert-BuOOH/$Et_3N$ and 0.2N NaOH/dioxane/MeOH; 10% Pd on C/$H_2$/DMF/$H_2O$.*

We now turned our attention to the introduction of the different functional groups, i. e. sulphate and sulphonamide (Scheme 2). Treatment of **4** (0.2 mmol) for 16 hr at 50°C with triethylamine sulphur trioxide complex[11] (3 mmol) in DMF provided a protected sulphated inositol intermediate ($R_f$ 0.35, EtOAc: Pyr: AcOH: $H_2O$, 11: 7: 1.6: 4). The latter was purified by Sephadex LH-20 column chromatography[12] (eluent DMF containing 0.5% triethylamine) and silica gel column chromatography

(eluent: $CH_2Cl_2$/MeOH, 4:1). Subsequent hydrogenolysis (10% Pd on C in 4:1 DMF/$H_2O$) furnished myo-inositol 1,4,5-trissulphate **5** in a yield of 86% from **4**.

In order to obtain the neutral 1,4,5-trissulphamoylated derivative **6**, triol **4** (0.2 mmol) was treated with sulphamoyl chloride[13] (1.2 mmol) and NaH in DMF at 0°C for 2 hr to give, after silica gel column chromatography (eluent: $CH_2Cl_2$/MeOH, 95:5), the protected intermediate ($R_f$ 0.6, $CH_2Cl_2$/MeOH, 99:1). Subsequent debenzylation (10% Pd on C in DMF/$H_2O$) gave inositol 1,4,5-trissulphonamide **6** ($R_f$ 0.25, RP18 silica, EtOH/$H_2O$, 3:1) in 84% yield from **4**. Starting from compound **4** we also synthesized (*rac.*) $IP_3$ itself (**7**), as a reference compound, by slight modification of literature procedures[14].

The identity and homogeneity of the compounds **5**,**6** and **7** were established by NMR spectroscopy and (FAB) mass spectrometry. The $^1$H-NMR spectral data are listed in the Table[16]. The biological data on the title compounds will be reported elsewhere in due time.

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12. The combined appropriate fractions were treated with $NaHCO_3$ (1 eq./$OSO_3^-$) prior to concentration.

13. Sulphamoyl chloride was prepared from chlorosulphonyl isocyanate by controlled hydrolysis.

14. Treatment of triol **4** at 0°→20°C for 1 hr with bis(2-cyanoethyl)-*N,N*-diethyl-phosphoramidite[15] in the presence of 1*H*-tetrazole followed by oxidation for 4 hr with excess *tert*-butyl hydroperoxide in the presence of triethylamine afforded a phosphodiester intermediate, which was subjected to Sephadex LH-20 column chromatography. Base treatment (0.2 N NaOH) of the appropriate fractions and subsequent hydrogenolysis (10% Pd on C in *tert*-butanol/$H_2O$ for 16 hr) afforded crude **7**, which was applied to DEAE column chromatography (1x30 $cm^2$, 0.3-1.0 M $NH_4OAc$) to give **7** in 76% overall yield.

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16.

| inositol 1,4,5- | $H_1$ | $H_2$ | $H_3$ | $H_4$ | $H_5$ | $H_6$ |
|---|---|---|---|---|---|---|
| trissulphate (5) | 4.27 dd | 4.41 t | 3.85 dd | 4.52 t | 4.29 t | 3.96 t |
| trissulphomamide (6) | 4.55 dd | 4.57 t | 3.97 dd | 4.79 t | 4.64 t | 4.16 t |
| trisphosphate (7) | 4.10 c | 4.26 c | 3.71 dd | 4.26 c | 4.10 c | 3.88 t |

Table, $^1$H-NMR chemical shifts (360 MHz) of compounds **5**, **6** and **7**.

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