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SYNTHESIS OF RACEMIC *MYO*-INOSITOL 1,4,5-TRISMETHYLPHOSPHONATE, *MYO*-INOSITOL 4,5-BISMETHYLPHOSPHONATE AND *MYO*-INOSITOL 5-METHYLPHOSPHONATE VIA A PHOSPHINATE APPROACH

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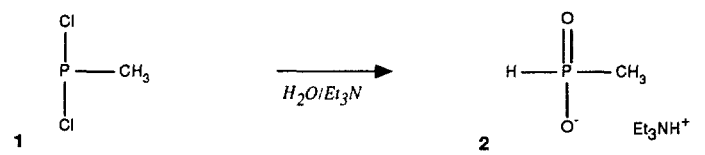
Abstract: *Synthesis of the (rac.) myo-inositol phosphate isosteric analogues 1,4,5-trismethylphosphonate, 4,5-bismethylphosphonate, and 5-methylphosphonate was accomplished using a phosphinate approach.*

The receptor mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate is now firmly established as a transmembrane signalling system, which gives rise to the formation of the two secondary messengers, i.e. diacylglycerol (DAG) and D-*myo*-inositol 1,4,5-trisphosphate (IP_3)[1]. The latter is still the only inositol phosphate for which a clear-cut role in intracellular Ca^{++} homeostasis has been demonstrated. The biological significance of the phosphatidylinositol signalling system in general and of IP_3 in particular recently evoked considerable endeavours in the chemical synthesis of (phosphatidyl)inositol phosphates[2]. Moreover, IP_3 antagonists that are cell permeable may find therapeutic application as potential drugs[3]. In order to design IP_3 analogues acting as intracellular Ca^{++}-antagonist, a better understanding of the structural and electronic requirements for high affinity towards the IP_3 active site(s) will be a prerequisite. Along this line, we recently reported on the synthesis of *myo*-inositol 1,4,5-trisphosphate- and 1,5-bisphosphate analogues containing sulphate or sulphonamide moieties as phosphate isosteric groups[4,5]. As part of an ongoing program directed towards the preparation of less negatively charged or neutral analogues of inositol phosphates, we here describe the synthesis of *myo*-inositol 5-methylphosphonate **6**, *myo*-inositol 4,5-bismethylphosphonate **10** and *myo*-inositol 1,4,5-trismethylphosphonate **14**.



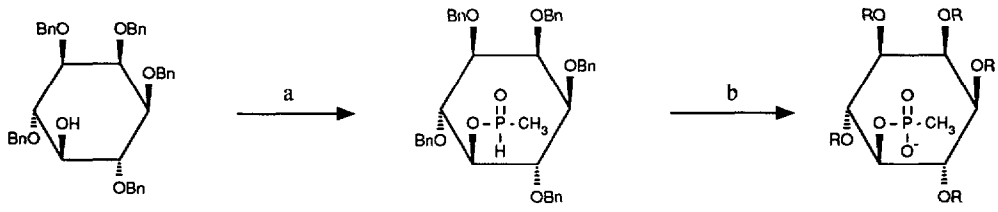
1 **2**

Scheme 1

In the course of our investigations van Boom *et al.*[6] described the application of [1-(6-trifluormethyl)benzotriazolyl]methylphosphonate as a phosphonylating agent in the synthesis of an inositol monomethylphosphonate. Analogous to bifunctional phosphorylating reagents, we expect a bifunctional P^V phosphonylating reagent not to be effective for the preparation of polyphosphonates containing vicinal diols. In general, the synthesis of vicinal bisphosphates using bifunctional P^V reagents is

hampered by the formation of cyclic phosphates[7]. In this paper we disclose that a phosphinate P^{III} approach is very suitable for the introduction of methylphosphonate functionalities in inositol derivatives[8]. In addition, the method described enabled us to synthesize 4,5-bismethylphosphonates, i.e. compounds **10** and **14**, without concomitant formation of cyclic side products.

As the appropriate phosphonylating reagent we selected methylphosphinate **2**, which was easily accessible by hydrolysis (CH_3CN-H_2O) of commercially available methyl dichlorophosphine **1**[9] and subsequent treatment with Et_3N[10] (quantitative yield, $\delta^{31}P$ 24.7 ppm), (Scheme 1). We first examined the pivaloyl chloride promoted condensation of **2** with (rac.) 1,2,3,4,6-penta-O-benzyl-*myo*-inositol **3**[11](Scheme 2). Thus, **3** (1 mmol) and **2** (2 mmol) in dry pyridine were treated with pivaloyl chloride (2 mmol). After stirring for 10 min at 20^0C, TLC indicated complete disappearance of **3** and the formation of

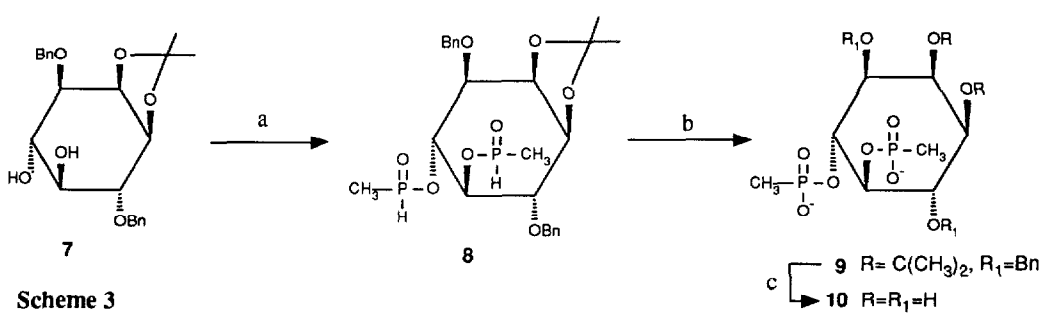


Scheme 2

*a: reagent **2** (2 eq.) and pivaloyl chloride (2 eq.), rt; b: 0.5 M I_2 in pyridine/water (4:1, v/v), rt; c: 10% Pd on C/H_2/DMF/H_2O.*

methylphosphinate **4** ($\delta^{31}P$ 37.2 ppm) having lower chromatographic mobility. Compound **4** was found to be fairly stable and could be isolated in 74% yield after silica gel column chromatography. Oxidation of **4** (0.5 M iodine in 4:1 pyridine/water, 30 min at rt) afforded methylphosphonate **5**. The latter was purified by Sephadex LH-20 column chromatography (eluent dichloromethane/methanol, 2:1, v/v) and treated with Dowex-Na^+ to give **5** as the corresponding Na^+-salt (yield 99%, $\delta^{31}P$: 25.3 ppm). Subsequent catalytic debenzylation (H_2/10%Pd-C) of **5** afforded fully deblocked (rac.) *myo*-inositol 5-methylphosphonate **6** [yield 95%, ^{31}P: δ 29.1 ppm; ^{13}C: δ (ppm) 14.33 (d, CH_3, J_{CP} 151 Hz), 81.14,(d, C-5, J_{CP} 6.6 Hz)].

The above favourable results prompted us to explore the feasibility to introduce methylphosphonate

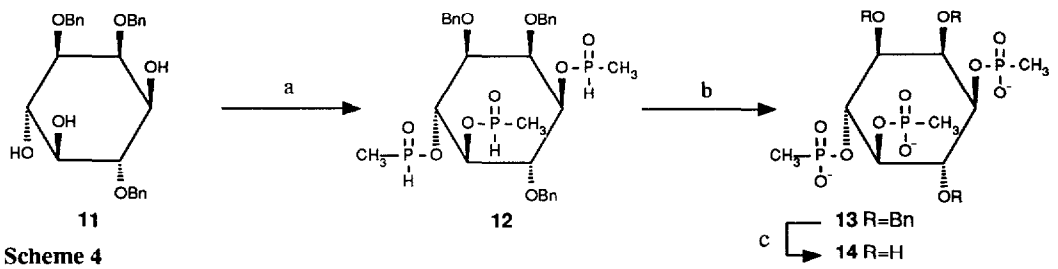


Scheme 3

*a: reagent **2** (4 eq.) and pivaloyl chloride (4 eq.), rt; b: 0.5 M I_2 in pyridine/water (4:1, v/v), rt; c: 10% Pd on C/H_2/DMF/H_2O followed by 80% aq. acetic acid at 60^0C.*

functions at the vicinal 4,5-diol. Indeed, reaction of **7**[12] (Scheme 3) with 4 equivalents of **2** in the presence of pivaloyl chloride (4 equivalents), followed by *in situ* oxidation of intermediate **8** (0.5 M iodine in 4:1 pyridine-water, 30 min at rt) afforded **9** in a yield of 60% (^{31}P: δ (ppm) 30.4, 30.7). Hydrogenolysis of **9** in the presence of 10% palladium on charcoal followed by acid hydrolysis (80% aqueous acetic acid, 60^{0}C) of the acetonide function furnished (rac.) *myo*-inositol 4,5-bismethylphosphonate **10**. The latter derivative was isolated as the corresponding Na^+-salt in 85% yield. [^{31}P: δ (ppm) 29.2, 28.6; ^{13}C: δ (ppm) 12.26, 11.90 (d, 2xCH_3, J_{CP} 139 Hz), 75.40 (d, C-5, J_{CP} 4 Hz), 76.96 (d, C-4, J_{CP} 4 Hz)].

We then turned our attention to the synthesis of rac. *myo*-inositol 1,4,5-trismethylphosphonate **14**, an isosteric analogue of IP_3. Known triol **11**[13] was reacted with **2** (6 eq.) and pivaloyl chloride (6 eq.) to give the intermediate 1,4,5-trismethylphosphinate **12**. Subsequent oxidation of **12** (0.5 M iodine in 4:1 pyridine/water, 30 min at rt) afforded the fully protected 1,4,5-trismethylphosphonate **13**. The latter was purified by Sephadex LH-20 column chromatography (dichloromethane/methanol, 2:1, v/v) and treated with Dowex-Na^+ to give **13** as the corresponding Na^+-salt [Yield 51%, ^{31}P: δ (ppm) 26.8, 26.5 (double intensity)] . Subsequent



11 12

Scheme 4

a: reagent 2 (6 eq.) and pivaloyl chloride (6 eq.), rt; b: 0.5 M I_2 in pyridine/water (4:1, v/v), rt; c: 10% Pd on C/H_2/DMF/H_2O.

hydrogenolysis (10% palladium on charcoal in DMF/H_2O for 16 hr) then provided IP_3-analogue **14** in 99% yield. [^{31}P: δ (ppm) 29.6, 28.6, 27.8; ^{13}C: δ (ppm) 11.28 (d, P_1-CH_3, J_{CP} 137 Hz), 11.81 (d, double intensity, P_4-CH_3, P_5-CH_3, J_{CP} 138 Hz), 77.02 (b, C-1), 77.67 (b, C-4), 79.12 (b, C-5)]. The ^{31}P NMR spectrum of compound **14** is shown in the Figure.

The results presented in this paper clearly illustrate that the application of the (methyl)phosphinate approach is convenient for the preparation of (methyl)phosphonate derivatives of *myo*-inositol, including 4,5-bismethylphosphonates. The identity and homogeneity of the compounds **6**, **10** and **14** were confirmed by ^{31}P, ^{13}C and ^{1}H NMR spectroscopy and (FAB) mass spectrometry. The ^{1}H spectral data are listed in the Table[14].

The biological activity of the compounds **6**, **10** and **14** was examined by two assays: *i*) a permeabilized human blood platelet aggregation model and *ii*) a radio ligand binding assay. Neither of the compounds induced platelet aggregation nor displayed any affinity for the IP_3 receptor. We previously showed that *myo*-inositol

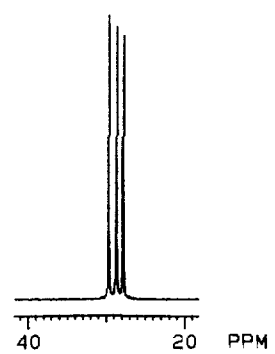


Figure. ^{31}P NMR spectrum of **14**.

1,4,5-trissulphate and *myo*-inositol 1,4,5-trissulphonamide were also biologically inactive. Hence, substitution of the phosphate moieties of IP_3 by methylphosphonate, sulphate and sulphonamide results in a complete loss of biological activity of the compounds.

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10. To a stirred mixture of CH_3CN/H_2O (11 ml, 10:1, v/v) is added dropwise at 0^0C methyl dichlorophosphine (1 ml, ≈ 11.3 mmol). After 25 min. the mixture is concentrated and coevaporated with CH_3CN and CH_3CN/Et_3N (3:1, v/v).
11. 1,2,3,4,6-penta-O-benzyl-*myo*-inositol **3** was isolated as a side product (14% yield) in our synthesis (ref. 4) towards 1,2,4,6-tetra-O-benzyl-*myo*-inositol.
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14.

myo-inositol	H_1	H_2	H_3	H_4	H_5	H_6
5-methylphosphonate (**6**)	3.72 dd	4.18 t	3.72 dd	3.84 t	3.90 q	3.84 t
4,5-bismethylphosphonate (**10**)	3.68 dd	4.04 t	3.57 dd	4.18 q	3.93 q	3.77 t
1,4,5-trismethylphosphonate (**14**)	4.01 ddd	4.21 t	3.74 dd	4.24 q	3.98 q	3.87 t

Table, ^{1}H-NMR chemical shifts (360 MHz) of compounds **6**, **10** and **14**.

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