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Application of the Arbuzov Reaction for the Synthesis of Phosphonate Analogues of *Myo*-inositol 1,2-bis- and 1,2,6-trisphosphates and Methyl α-D-mannopyranoside 2,3,4-trisphosphate

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Abstract: The reaction of perbenzylated (±)-*myo*-inositol 1,2-bis- and 1,2,6-tris-phosphites with benzyl bromoacetate, followed by catalytic (Pd/C) hydrogenolysis affords (±)-*myo*-inositol 1,2-bis- and 1,2,6-tris(carboxymethylphosphonate). The same procedure is used for the synthesis methyl α-D-mannopyranoside 2,3,4-tris(carboxymethylphosphonate).

Recognition of Ins(1,4,5)P_3 as a second messenger[1] has stimulated interest in the chemistry of inositol phosphates. Initially, most effort was put into biological aspects of this discovery[2] and into the synthesis of natural inositol phosphates.[3] Recently, the focus of synthetic activity has been drifting towards structurally modified myo-inositol phosphates with novel biological properties.[4] Ins(1,2,6)P_3 is an inositol trisphosphate regioisomer,[5] produced in kg quantities (Perstorp Pharma, Sweden) by partial degradation of phytic acid with phytase.[6] Ins(1,2,6)P_3 exhibits biological activity such as inhibition of inflammatory reactions and edema in skin burn injury,[7] and is also effective in treeting acute abnormalities of nerve function in early experimental diabetes.[8]

This work describes the synthesis of the modified derivative of Ins(1,2,6)P_3 containing three carboxymethylphosphonate groups, -O-P(O)(OH)CH_2COOH. Several examples of phosphonate analogues of *myo*-inositol phosphates have been described: 5-methylenephosphonate analogue of Ins(1,4,5)P_3,[9] 5-methylphosphonate and 5-(difluoromethyl)-phosphonate analogues of Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4,[10] rac. 3-methylphosphonate analogues of Ins(3,4)P_2 and Ins(1,3,4)P_3,[11] methylphosphonate analogue of D-Ins(1)P,[12] rac. *myo*-inositol-1-O-methylphosphonate-4,5-bis-phosphate,[13] rac. *myo*-inositol 1,4,5-tris(methylphosphonate), *myo*-inositol 4,5-bis(methylphosphonate) and *myo*-inositol 5(methylphosphonate).[14] Synthetic procedures leading to this type of modified phosphoinositols involve either bis[6(alkyl)benzotriazole-1-yl] alkylphosphonates[10-13] or triethylammonium hydrogen methylphosphinate.[14]

Our main target compound was *myo*-inositol 1,2,6-tris(carboxymethylphosphonate), hexasodium salt, **11**. Other targets were *myo*-inositol-1,2-bis(carboxymethylphosphonate), tetrasodium salt, **10** and α-methyl mannopyranoside-

2,3,4-tris(carboxymethylphosphonate) hexasodium salt, **14.** The starting materials for the syntheses were: commercial α-methyl mannopyranoside **3a**, the relatively readily available 3,4,5,6-tetra-O-benzyl *myo*-inositol **1**[15] and 3,4,5-tri-O-benzyl *myo*-inositol **2**.[16]

For the synthesis of the target compounds we chose a new strategy involving the following reaction sequence:

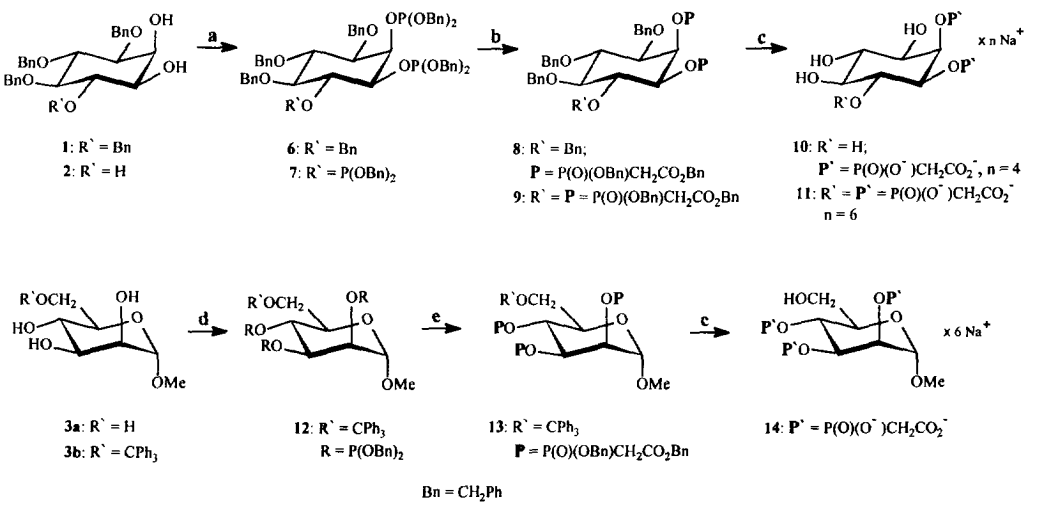
(i) Phosphitylation of the *myo*-inositols (sugar), duly protected by benzyl groups to form inositol (sugar) dibenzyl phosphites;

(ii) Arbuzov reaction of the *myo*-inositol (sugar) phosphites with benzyl bromoacetate;

(iii) Deprotection of all benzyl groups.

The starting materials **1**, **2** and **3b** were phosphitylated by known phosphitylating reagents, **17** R_2N-$P(OBn)_2$ **4**: R=Et or **5**: R=Pr^i.[17] Yields and rates of the phosphitylation by both reagents are comparable. Phosphites **6**, **7** and **12** were purified by a short column silica-gel chromatography and characterized by ^{31}P NMR.[18]

Arbuzov reaction of **6**, **7** and **12** with benzyl bromoacetate was carried out at 75°C - 80°C. An excess of benzyl bromoacetate acted as solvent (Scheme 1).



Scheme 1. **Reagents and conditions**: a) **4** or **5**, (3 eq. for **1**, 4.6 eq. for **2**), CH_2Cl_2 (2-5 ml/1 mmol of **1** or **2**), tetrazole (5 eq. for **1**, 6 eq. for **2**), r.t., 2h, 71-90%; b) $BrCH_2COOBn$ (excess), 80°C, 1-2h, 71-85%; c) Pd/C, H_2, methanol, 12h, r.t. then NaOH aq., 71-92%; d) **4**, (4.5 eq.), CH_2Cl_2 (4 ml/1 mol of **3b**), tetrazole (6 eq.), r.t. 1h, 72%; e) $BrCH_2COOBn$ (excess), 75°C, 12h, 45%.

The reaction products **8**, **9** and **13** were purified by repeated column chromatography (Silica-gel, $CHCl_3$-CH_2Cl_2-acetone, 15:15:1).

The structure of **8**, **9** and **13** were confirmed by ^{31}P NMR spectroscopy.[19]

^{31}P, ^{13}C and ^{1}H NMR spectra of **10**, **11** and **14** are listed in reference (20).

In the view of the mentioned above biological activity of α-trinositol [7,8] it seemed useful to test this property of the compound **11** in the similar, following assays:[21]

(i) Irwin test,[22]

(ii) inhibition of edema,[23]

(iii) acetic acid-induced writhing,[24]

(iv) shock sensitivity.[25]

Myo-inositol 1,2,6-tris(carboxymethylphosphonate) hexasodium salt **11** and the parent α-trinositol exhibited no change in the Irwin test (mice) at dose 256 mg/kg; At dose 512 mg/kg both compounds resulted in the death of one in three mice. In the test of inhibition of edema both compounds showed at dose 64 mg/kg a statistically significant effect (95%). For phosphonate **11** no statistically significant effect was seen in acetic acid-induced writhing whereas α-trinositol exhibited an activity in this test. Neither phosphonate **11** nor α-trinositol were active in the shock sensitivity test.

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18. **6** δ_p (C_6D_6): 140.4 (J_{AB} 1.8 Hz, 2P);

7 δ_p (C_6D_6): 140.2 (d, $^5J_{P1P2}$ 2.1 Hz, P-2); 140.8 (dd, $^5J_{P1P2}$ 2.1 Hz, $^5J_{P1P6}$ 3.9 Hz, P-1); 143.2 (d, $^5J_{P1P6}$ 3.9 Hz; P-6).

12 δ_p (C_6D_6): 140.3; 141.6 (2P).

19. **8** ^{31}P NMR δ_p (C_6D_6): 20.8-22.6 ppm (m).

9 ^{31}P NMR δ_p (C_6D_6): 21.0 - 22.5 (m), 24.0, 24.3, 24.4 ppm.

13 ^{31}P NMR δ_p (C_6D_6): 20.5 - 23.5 ppm (m).

20. **12** ^{31}P NMR δ_p (C_6D_6): 19.71, 19.04 ppm.

^{13}C NMR δ: 178.4 (t, $^2J_{P-C}$ 5.2 Hz); 79.2 (d, $^2J_{P-C}$ 7.0 Hz); 76.8 (d, J unmeasured); 76.2 (s); 74.8(s); 73.5 (d, J_{P-C} 5.2); 73.2(s); 51.0 (CH_3OH); 41.1 (d, $^1J_{P-C}$ 123.8 Hz); 40.2 (d, $^1J_{P-C}$ 122.1 Hz).

^{1}H NMR δ: 4.67 (dt, 1H, H-2); 4.01 (dddd, partially overlaped, 1H, H-1); 3.89 (t, 1H, H-6); 3.75 (t, 1H, H-4); 3.50 (ddd, 1H, H-3); 3.33 (t, 1H, H-5); 2.88-2.62 (m, 4H, P-CH_2). $J_{1,2}$=$J_{2,3}$= 2.5 Hz, $J_{1,6}$=$J_{5,6}$=$J_{4,3}$ 9.5 Hz; $^3J_{P-O-H2}$ = 9.3 Hz; $^4J_{P-O-C4H4}$= 1 Hz, $^3J_{P-O-H1}$= 9.5 Hz; $^2J_{P-C-H}$= 21.6 Hz; $^2J_{P-C-H}$=19.2 Hz.

13 ^{31}P NMR δ(D_2O): 18.88; 19.37; 20.70 ppm.

^{13}C NMR δ: 178.4-178.7 (m); 78.90(s); 78.46; 78.52; 75.68; 74.40; 73.15; 42.14 (m, J_{P-C} 19 Hz); 39.78 (m).

^{1}H NMR δ: 4.65 (dm, $^3J_{PH}$ 10 Hz, 1H); 4.30 (dd, J 9.0 and 9.5 Hz, 1H); 4.10 (t, J 9.0 Hz, 1H); 3.78 (t, J 9.5 Hz, 1H); 3.53 (m, 2H), 3.33; 2.6-3.0 (m, 6H, P-CH_2).

14 ^{31}P NMR δ (D_2O): 21.29; 20.68; 19.69 ppm.

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