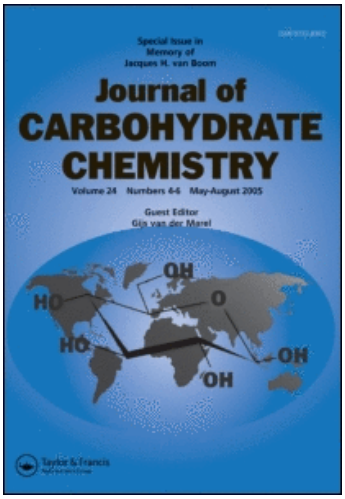


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# Analogues of 1D-*Myo*-Inositol 1,2,6-Trisphosphate. Preparation of Carboxymethyl and 2-Hydroxyethyl Phosphate Derivatives

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*COMMUNICATION*

# ANALOGUES OF 1D-*MYO*-INOSITOL 1,2,6-TRISPHOSPHATE. PREPARATION OF CARBOXYMETHYL AND 2-HYDROXYETHYL PHOSPHATE DERIVATIVES

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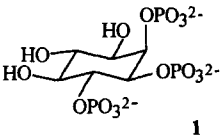
## ABSTRACT

Acylation of 1D-*myo*-inositol 1,2,6-trisphosphate (α-trinositol) followed by alkylation of the phosphate groups with benzyl bromoacetate or 2-benzyloxyethyl iodide and deprotection provides a route to analogues with modified phosphate groups. The modifications made alter steric and ionisation properties but the possibility to participate in hydrogen bonding and ionic interaction is retained.

## RESULTS AND DISCUSSIONS

α-Trinositol[2] (1D-*myo*-inositol 1,2,6-trisphosphate pentasodium salt, **1**) has antiinflammatory and analgesic properties[3] and is prepared with high optical purity (ee >99.7 %) by fermentation of phytic acid (inositol hexakisphosphate) using baker's yeast. α-Trinositol is one of few inositol phosphates prepared in kg quantities and has recently been introduced as an enantiomerically pure building block.[4]

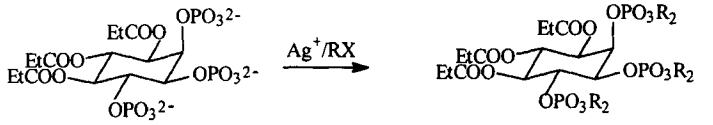



1

As part of a program dedicated to the synthesis of analogues of α-trinositol we have prepared some phosphate-modified derivatives with electrophores bioisosteric to phosphate. Hypothetically, these modifications may still permit polar interaction with a biological binding site.

Alkylation of the silver salt of propanoate **2**[5] with an excess of benzyl bromoacetate (**3a**) or 2-benzyloxyethyl iodide[6] (**3b**) in refluxing acetonitrile gave, after silica gel chromatography (heptane/ethyl acetate 1:1), the non-ionic esters **4a**[7] (8.7 g, 60 %) and **4b**[8] (2.0 g, 58 %) respectively. Hydrogenolysis (Pd(C)/HOAc) of **4b** and removal of solvent gave the expected trisdiol **5**[9] (50 mg) whereas no uniform product was formed from **4a**.





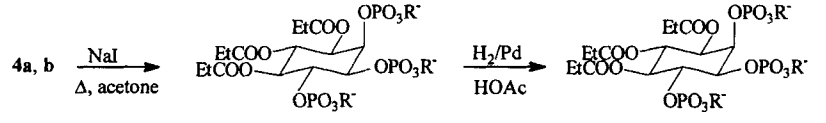

**2**

**3a**, RX = $BrCH_2COOBn$ **4a**, R = $CH_2COOBn$

**3b**, RX = $ICH_2CH_2OBn$ **4b**, R = $CH_2CH_2OBn$

**5**, R = $CH_2CH_2OH$

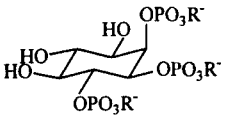
Dealkylation of **4a** and **4b** using a slight excess of sodium iodide in refluxing acetone followed by silica gel chromatography (MeCN then MeCN/MeOH 1/1) gave the sodium salts **6a**[10] (5.2 g, 90%) and **6b**[11] (0.82 g, 90 %) respectively. Hydrogenolysis (Pd(C)/HOAc) of salts **6a** and **6b,** removal of solvent and precipitation from ethanol gave the final products **7a**[12] (1.6 g, 97 %) and **7b**[13] (0.41 g, 68 %) respectively.




**6a**, R = $CH_2COOBn$ **7a**, R = $CH_2COO^-$

**6b**, R = $CH_2CH_2OBn$ **7b**, R = $CH_2CH_2O$

The propanoate **7a** was solvolyzed in ammonia/methanol, removal of solvent and precipitation from ethanol gave triol **8**[14] (0.26 g, 80%) in 90 % purity ($^1$H NMR). Aqueous sodium hydroxide or methoxide/methanol gave inferior results. Attempts to prepare amide **9** and hydroxamate **10** from ester **6a**, using liquid ammonia and hydroxylammonium chloride in trimethylamine, respectively, gave deacylation, but no product pure enough for further characterisation could be isolated.




**8**, R = $CH_2COO^-$

**9**, R = $CH_2CONH_2$

**10**, R = $CH_2CONHOH$

*In vivo* screening[15] (rat) of **7a** revealed neither analgesic nor antiinflammatory properties.



## REFERENCES AND NOTES

1. (a) Fax No +46-46-137236, E-mail mats.malmberg@mbox2.swipnet.se. (b) Present adress: Perstorp Polyols, S-284 80 Perstorp, Sweden, Fax No +46-435-37073, E-mail sepabrgn@ibmmail.com.
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7. All NMR spectra were recorded on Varian XL300.
   $^1$H NMR ($CDCl_3$) δ 7.40-7.15 (m, 30H, PhH), 5.43 (t, 1H, J = 10.2 Hz, H-4), 5.31 (dt, 1H, J = 8.9, 2.7 Hz, H-3), 5.23-5.10 (m, 12H, H-2, H-5, Ph$CH_2$), 4.70 (q, 1H, J = 9.8 Hz, H-6), 4.70-4.54 (m, 13H, $POCH_2$, H-1) 2.45-2.15, (m, 6H, $CH_3CH_2$), 1.10-0.95 (m, 9H, $CH_3CH_2$).
8. $^1$H NMR ($CDCl_3$) δ 7.45-7.15 (m, 30H, PhH), 5.47 (t, 1H, J = 10.1 Hz, H-4), 5.21 (dt, 1H, J = 8.7 , 2.2 Hz, H-3), 5.05 (t, 1H, J = 10.1 Hz, H-5), 4.86 (q, 1H, J = 9.5 Hz, H-6), 4.82 (d, 1H, J = 9.0 Hz, H-2), 4.60-4.40 (m, 13H, Ph$CH_2$, H-1), 4.35-4.08

(m, 12H, $POCH_2$), 3.72-3.50 (m, 12H, $CH_2OBn$), 2.50-2.16 (m, 12H, $CH_3CH_2$), 1.15-0.95 (m, 9H, $CH_3CH_2$).

9. $^1H$ NMR ($CD_3OD$) δ 5.53 (t, 1H, J = 9.7 Hz, H-4), 5.44 (t, 1H, J = 9.7 Hz, H-5), 5.31 (br d, 1H, J = 8.7 Hz, H-3), 5.26 (br d, 1H, J = 10.3 Hz, H-2), 4.97 (br t, 1H, J = 8.7 Hz, H-1), 4.90 (br d, 1H, J = 8.7 Hz, H-6), 4.32-4.08 (m, 12H, $POCH_2$), 3.85-3.68 (m, 12H, $OCH_2$), 2.55-2.23 (m, 6H, $CH_3CH_2$), 1.21-1.03 (overlapping triplets, 9H, J = 7.2 Hz, $CH_3CH_2$).
10. $^1H$ NMR ($CD_3COOD$) δ 7.50-7.20 (m, 15H, PhH), 5.45, (t, 1H, J = 10.0 Hz, H-4), 5.40-5.10, 4.90-4.50 (m, 17H, $POCH_2$, $PhCH_2$, H-1, H-2, H-3, H-5, H-6), 2.25-2.09 (m, 6H, $CH_3CH_2$), 1.10-0.95 (m, 9H, $CH_3CH_2$).
11. $^1H$ NMR ($CD_3COOD$) δ 7.46-7.27 (m, 15H, PhH), 5.56 (t, 1H, J = 10.0 Hz, H-4), 5.32 (t, 1H, J = 10.0 Hz, H-5), 5.20 (d, 1H, J = 10.7 Hz, H-3), 4.79 (q, 1H, J = 9.2 Hz, H-6), 4.70-4.44 (m, 8H, $PhCH_2$, H-1, H-2), 4.35-4.00 (m, 6H, $POCH_2$), 3.80-3.60 (m, 6H, $BnOCH_2$), 2.50-2.20, (m, 6H, $CH_3CH_2$), 1.12-1.00 (m, 9H, $CH_3CH_2$).
12. $^1H$ NMR ($D_2O$) δ 5.29 (t, 1H, J = 9.9 Hz, H-4), 5.10 (t, 1H, J = 9.4 Hz, H-5), 5.01 (d, 1H, 10.3 Hz, H-3), 4.79 (d, 1H, J = 9.3 Hz, H-2), 4.50 (q, 1H, J = 9.5 Hz, H-6), 4.40-3.90 (m, 7H, H-1, $POCH_2$), 2.35-2.10 (m, 6H, $CH_3CH_2$), 0.90-0.80 (m, 9H, $CH_3CH_2$); $^{13}C$-NMR ($D_2O$) δ 179.5, 179.2, 178.9, 176.5 (m), 176.4 (m), 76.9 (t, C-6), 76.7 (d, C-2), 75.5 (m, C-1), 74.9 (s, C-5), 73.5 (s, C-4), 72.7 (s, C-3), 65.6 (m), 30.3, 30.2, 30.1, 11.2, 11.0; $^{31}P$ NMR ($D_2O$) δ (not referenced) 0 (2 P), -0.4 (1 P), IR (KBr) 1750 $cm^{-1}$; $[\alpha]_D^{23}$ +15.4 (*c* 0.6, aqueous buffer pH 7.0). Anal. Found: P, 10.3.
13. $^1H$ NMR ($D_2O$) δ 5.32 (t, 1H, J = 10.2 Hz, H-4), 5.10 (t, 1H, J = 9.8 Hz, H-5), 5.0 (dd, 1H, J = 10.2 Hz, 1.4 Hz, H-3), 4.86 (d 1H, J = 9.2 Hz, H-2), 4.49 (q, 1H, J = 9.4 Hz, H-6), 4.18 (t, 1H, J = 9.6 Hz, H-1), 3.94-3.52 (m, 12H, $CH_2CH_2$), 2.40-2.15 (m, 6H, $CH_3CH_2$), 0.95-0.85 (m, 9H, $CH_3CH_2$); $^{13}C$ NMR ($D_2O$) δ 179.6, 179.4, 179.1, 76.8 (t), 76.6 (d), 75.8 (m), 75.1 (s), 73.5 (s), 72.9 (s), 70.0, 69.9, 69.8, 64.3, 64.2, 30.4, 30.2, 11.3, 11.2, 11.1; $^{31}P$ NMR ($D_2O$) δ (not referenced) 0, -0.2, -0.6; IR (KBr) 1760 $cm^{-1}$; $[\alpha]_D^{23}$ +4.8 (*c* 0.8, aqueous buffer pH 4.0). Anal. Found: P, 10.7.
14. $^1H$ NMR ($D_2O$, 40 C) δ 4.81 (d, 1H, J = 8.2 Hz, H-2), 4.50-4.16 (m, 7H, H-6, $CH_2CO$), 4.12 (t, J = 9.2, H-1), 3.72 (t, 1H, J = 9.7 Hz, H-4), 3.57 (dd, 1H, J = 9.4, 2.0 Hz, H-3), 3.51 (t, 1H, J = 9.1 Hz, H-5); $^{13}C$ NMR ($D_2O$) δ 179.8 (m), 80.0 (d), 79.7 (t), 76.6 (s), 75.9 (m), 75.3 (s), 73.5 (s), 67.2 (m); $^{31}P$ NMR ($D_2O$) one broad signal; IR (KBr) 1690 $cm^{-1}$.
15. Huntingdon Research Centre Ltd., Huntingdon, England.