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Enantioselective synthesis of some 6-deoxy-halodeoxy inositol derivatives

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Abstract

Total synthesis of 3-*O*-benzoyl-2,6-dideoxy-2,2-difluoro-D-*myo*-inositol **1**, 2,3,6-trideoxy-2,3-difluoro-D-*neo*-inositol **2**, 2,6-dideoxy-2-fluoro-D-*scyllo*-inositol **3** and 2-*O*-benzyl-3,6-dideoxy-3-chloro-D-*myo*-inositol **4** in optically pure form is described.

Inositol phosphates are generated in living cells as a response to external signals such as drugs, hormones, or neuropeptides.[1] They act principally by the control of the calcium-signaling process in which the released *myo*-inositol 1,4,5-trisphosphate (1,4,5-IP_3) causes the mobilization of calcium from intracellular stores triggering complex biochemical processes. As part of our ongoing program to understand better, and gain deeper insight into the biological role of inositol derivatives, we were interested in the preparation of structural analogues of inositol phosphates. The primary goal of this work was to afford chemical tools to probe the biochemical pathways involved. The manipulation of the signaling system indeed, may result in new therapies for a number of disease states. Some possible targets are, for example, diseases which arise from pathologic stimulation of phospholipase C and a number of kinases, resulting in uncontrolled cell proliferation and growth factor activation, respectively.[2] It seemed to us worthy to address the question of the biochemical relevance of halogenated isoster analogues of *myo*-inositol derivatives which may act as antagonists on inositol phosphate receptors and thus may inhibit such pathological processes. The design of the target molecules arose from enzyme-substrate recognition mechanism-based models. Considering the close similitude of the RNA cleavage mechanism of ribonuclease A,[3] it was hypothesized that the phospholipase C and the phosphodiesterase might require the participation of the *cis*-hydroxy group of the inositol ring adjacent to the phosphodiester in PtdIns(4,5)P_2 for adequate enzymatic activity. The D-3 and D-6-position of the *myo*-inositol ring are particularly relevant for biological activity. First, the phosphorylation by PI-3′-kinase gives a class of

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† Deceased November 16th 1998. This article is dedicated to his memory.

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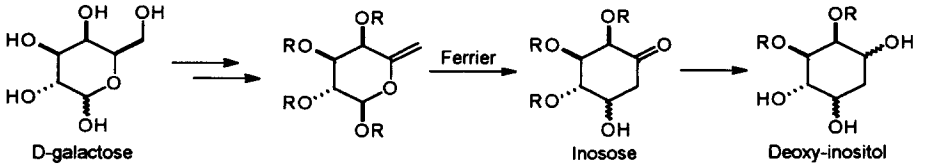
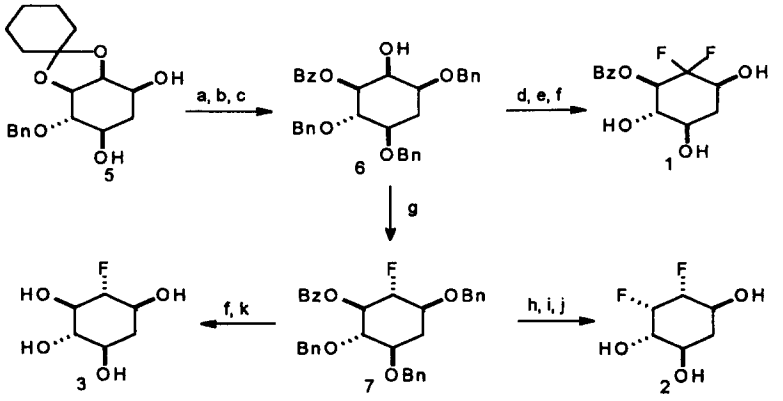


Figure 1.

phosphoinositides that is not a substrate for PI-PLC. Furthermore, it was shown that D-3-substituted *myo*-inositol analogues are selective inhibitors of the growth of v-*sis*-transformed NIH 3T3 cells.[4] Also, the 6-deoxy Ins(1,4,5)P_3 has already been demonstrated to be a full agonist for Ca^{++} release in permeabilized SH-SY5Y human neuroblastoma cells, a relatively potent Ins(1,4,5)P_3 5-phosphatase inhibitor and a weak substrate for Ins(1,4,5)P_3 3-kinase.[5,6]

Over the last decade a number of deoxy *myo*- and *scyllo*-Ins(1,4,5)P_3 analogues have been prepared and tested.[7] The preparation of the 3-*O*-benzoyl-2,6-dideoxy-2,2-difluoro-D-*myo*-inositol **1**, 2,3,6-trideoxy-2,3-difluoro-D-*neo*-inositol **2**, 2,6-dideoxy-2-fluoro-D-*scyllo*-inositol **3** and 2-*O*-benzyl-3,6-dideoxy-3-chloro-D-*myo*-inositol **4** were, therefore, chosen as synthetic targets.[8] The optically active starting material was prepared from D-galactose (Fig. 1) according to our earlier developed methodology, using Ferrier rearrangement in the stereoselective sugar to cyclitol transformation step.[9]

Synthesis of 2,2-difluoro **1**, 2,3-difluoro **2** and 2-fluoro **3** were realized as outlined in Scheme 1. The protected 6-deoxy Ins(1,5) diol **5** was prepared from the Ferrier rearrangement product according to our earlier work (Fig. 1).[9] Dibenzylation of the suitably protected diol **5**, and removal of the ketal protecting group, gave rise to the vicinal diol, which, after selective benzoylation of the equatorial hydroxyl using benzoyl chloride and pyridine, gave the alcohol **6**. Then the free hydroxy of **6** was converted to the corresponding 2-inosose by oxidation using TPAP/NMO. Conversion of this keton into the 2,2-difluoro derivative was accomplished using (diethylamino)sulfurtrifluoride (DAST). Finally, the desired molecule **1** was liberated by hydrogenolysis.[10]

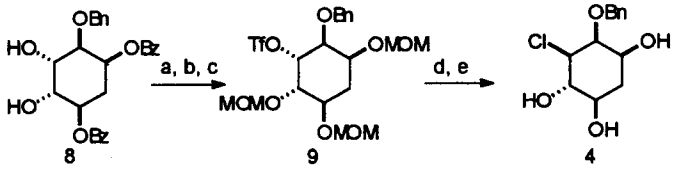


Scheme 1. (a) BnBr, NaH, DMF, rt, 12 h (95%); (b) HCl, MeOH, rt, 15 h (95%); (c) BzCl, Py, 10°C, 20 min (80%); (d) TPAP, NMO, CH_2Cl_2, rt, 12 h (80%); (e) DAST, CH_2Cl_2, rt, 20 h (62%); (f) H_2, Pd/C 10%, AcOEt:EtOH (8:2), rt, 2 h (93%); (g) DAST, CH_2Cl_2, rt, 2 h (90%); (h) NaOH, AcOEt:MeOH (1:1), rt, 24 h (76%); (i) DAST, CH_2Cl_2, 0°C, 10 h (75%); (j) H_2, Pd/C 10%, AcOEt:MeOH (8:2), rt, 3 h (90%); (k) NaOH, MeOH, rt, 2 h (95%)

To generate the difluorinated compound **2** from **7**, the benzoyl protecting group was removed and the liberated hydroxyl function was transformed to fluorine by complete inversion of configuration using DAST. The final deprotection was performed by hydrogenolysis of the benzyl group affording 2,3-difluoro-D-*neo*-inositol **2**[11] (Scheme 1).

As Scheme 1 shows, the common intermediate **6** was also used to prepare the 2-fluoro derivative **3**. The free hydroxy was treated with DAST. The final deprotection of the intermediate **7** was performed in two steps. Reductive cleavage of the benzyl group followed by saponification afforded the desired 2-fluoro-D-*scyllo*-inositol derivative **3**.[12]

The chlorinated inositol **4** was prepared from diol **8**[13] as follows (Scheme 2). Removal of the benzoate groups and selective protection using methoxymethylene chloride (MOMCl) followed by transformation of the remaining OH into triflate gave rise to **9**. Conversion of the triflate into chloro derivative was accomplished by simple substitution reaction using lithium chloride in HMPT. Deprotection of the MOM groups afforded the desired 2-*O*-benzyl-3,6-dideoxy-3-chloro-D-*myo*-inositol **4**.[14]



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Scheme 2. (a) NaOH, MeOH:AcOEt (1:1), rt, 4 h (80%); (b) $[(CH_3)_2CH]_2NC_2H_5$, MOMCl, DMF, rt, 10 h (50%); (c) $(Tf)_2O$, CH_2Cl_2, Py, –60°C, 3 h (76%); (d) HMPT, Me_2SO, LiCl, rt, 3 h (53%); (e) HCl, MeOH, 50°C, 10 h (70%)

In summary, the enantioselective total synthesis of 3-*O*-benzoyl-2,6-dideoxy-2,2-difluoro-D-*myo*-inositol **1**, 2,3,6-trideoxy-2,3-difluoro-D-*neo*-inositol **2**, 2,6-dideoxy-2-fluoro-D-*scyllo*-inositol **3** and 2-*O*-benzyl-3,6-dideoxy-3-chloro-D-*myo*-inositol **4** were realized.[15] These compounds are actually used in our laboratory to prepare isoster analogues of inositol 1,4,5-trisphosphate derivatives. The synthesis and the results of the biological tests of these compounds will be described elsewhere.

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10. Compound **1**: mp 194–196°C, $[\alpha]_D^{25}$ 9.1 (*c* 0.6, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ ppm: 5.2 (dd, 1H, H-3, J_{3-4}=10 Hz), 4.5–4.3 (dt, 1H, H-2, J_{2-F}=52 Hz), 3.9 (m, 1H, H-5), 3.6 (m, 1H, H-1), 3.5 (t, 1H, H-4, J_{4-5}=10 Hz), 2.2 (m, 1H, H-6eq, $J_{6ax-6eq}$=12 Hz), 0.8 (q, 1H, H-6ax, J_{6ax-1}=12 Hz); ^{13}C NMR (75.50 MHz, CD_3OD) δ ppm: 169 (*C*=O), 136–130 (Ph), 122-119-115 (C-2, J_{2-F}=244 Hz), 77 (C-4), 75 (C-3), 71 (C-5), 69 (C-1), 32 (C-6); (found: C, 54.31; H, 5.05. $C_{13}H_{14}O_5F_2$ requires: C, 54.19; H, 4.90%).
11. Compound **2**: mp 193–196°C, $[\alpha]_D^{20}$ −11.1 (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 4.9 (m, 1H, H-3), 4.2 (m, 1H, H-2), 3.9 (m, 1H, H-1), 3.6 (m, 1H, H-5), 3.3 (m, 1H, H-4), 2.1 (m, 1H, H-6eq), 1.2 (q, 1H, H-6ax); ^{13}C NMR (75.50 MHz, $CDCl_3$) δ ppm: 96 (C-2, J_{2-F}=168 Hz), 93 (C-3, J_{3-F}=168 Hz), 75 (C-4), 69 (C-5), 68 (C-1), 38 (C-6, J_{6-F}=9.4 Hz).
12. Compound **3**: mp 195–198°C, $[\alpha]_D^{25}$ −3.5 (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ ppm: 4.2–3.9 (td, 1H, H-2, J_{2-3}=10 Hz, J_{2-F}=52 Hz, J_{2-1}=10 Hz), 3.7 (m, 1H, H-4), 3.5–3.3 (m, 2H, H-5,1), 3.2 (t, 1H, H-3, J_{3-4}=J_{4-5}=10 Hz), 2.1 (m, 1H, H-6eq), 1.4 (q, 1H, H-6ax, $J_{6ax-6eq}$=J_{6ax-5}=12 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ ppm: 101–97 (C-2, J_{2-F}=178 Hz), 78 (C-4), 74 (C-1, J_{1-F}=17 Hz), 70 (C-5), 69 (C-3, J_{3-F}=18 Hz), 38 (C-6); (found: C, 43.28; H, 6.27. $C_{13}H_{15}O_5F$ requires: C, 43.37; H, 6.67%).
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14. Compound **4**: mp 237–240°C, $[\alpha]_D^{25}$ −2.3 (*c* 1.0, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ ppm: 7.2 (m, 5H, Ph), 4.6 (dd, 2H, OCH_2Ph), 3.9 (m, 1H, H-2), 3.7–3.4 (m, 3H, H-1,4,5), 3.3 (m, 1H, H-3), 1.9 (dt, 1H, H-6eq, $J_{6eq-6ax}$=12 Hz), 1.8 (q, 1H, H-6ax, J_{6ax-1}=12 Hz).
15. The structures of all new compounds were unequivocally established by ^1H and ^{13}C NMR, MS and elementary analysis. In cases of compounds **1**, **2**, **3** and **4**, COSY ^1H–^1H correlations were performed.