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INSULIN SECOND MESSENGERS: SYNTHESIS OF 6-O-(2-AMINO-2-DEOXY-α-D-GLUCOPYRANOSYL)-D-*CHIRO*-INOSITOL-1-PHOSPHATE

K. Kishta Reddy and J.R. Falck*
Departments of Molecular Genetics and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235

Jorge Capdevila
Department of Medicine
Vanderbilt University Medical School
Nashville, TN 37232

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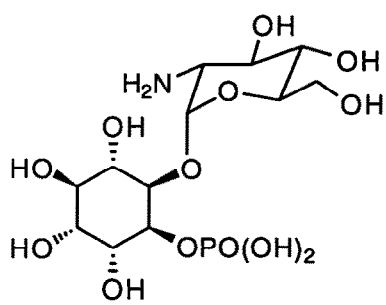
Abstract: An efficient enantiospecific route to protected *chiro*-inositol **7** from (-)-quinic acid was exploited for the synthesis of the title disaccharide which displayed insulin mimetic activity.

Insulin induces diverse and essential physiologic responses in virtually every tissue, but few details of its post-kinase mechanism are known at the molecular level.[1] Intensive worldwide investigations, however, have implicated[2] the hydrolysis of specific glycosylphosphatidylinositides (GPIs) as the source of candidate intracellular second messengers for insulin and related factors. These putative insulin mediators (PIMs), in common with the widely distributed GPI membrane anchors,[3] contain *myo*-inositol phosphate, non-N-acetylated hexosamine, and other sugars. The identification[4] of the rare cyclitol D-*chiro*-inositol[5] in place of the *myo*-isomer has revealed some stereochemical heterogeneity in the otherwise highly conserved core region. Herein, we report the first synthesis of 6-O-(2-amino-2-deoxy-α–D–glucopyranosyl)-D-*chiro*-inositol-1-phosphate (**1**), representing the PIM disaccharide moiety,[6] and its initial evaluation as part of a comprehensive program[7] to expedite the structure elucidation and pharmacologic testing of physiologically significant cyclitols.

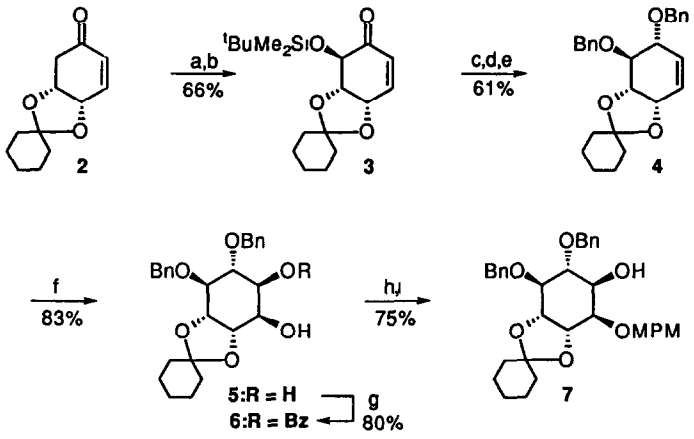


1

The cyclitol portion of **1** was efficiently constructed from enone **2**[8] (Scheme 1), available in 62% yield from commercial (-)-quinic acid. Installation of the C(4)-alcohol was readily achieved by silylation of **2** according to Corey[9] and epoxidation of the resultant enol ether exclusively from the less hindered β-face. Facile rearrangement[10] with silyl migration resulted in **3** which was converted to conduritol-F derivative **4**[11] by

sequential reduction of the ketone under Luche's conditions,[12] desilylation, and bis-benzylation. Osmium tetroxide glycolization of **4**, supported by 4-methylmorpholine N-oxide (NMO), furnished *syn*-diol **5**, mp 91-92° C, as the sole product. Differentiated benzoate **6** was obtained from **5** by selective derivatization (eq/ax 92:8) of the C(6)-hydroxyl via its cyclic stannylidene[13] in the presence of powdered 4Å molecular sieves. Trityl cation promoted[14] MPM etherification of the remaining free alcohol and benzoate saponification led to **7**.

Scheme 1



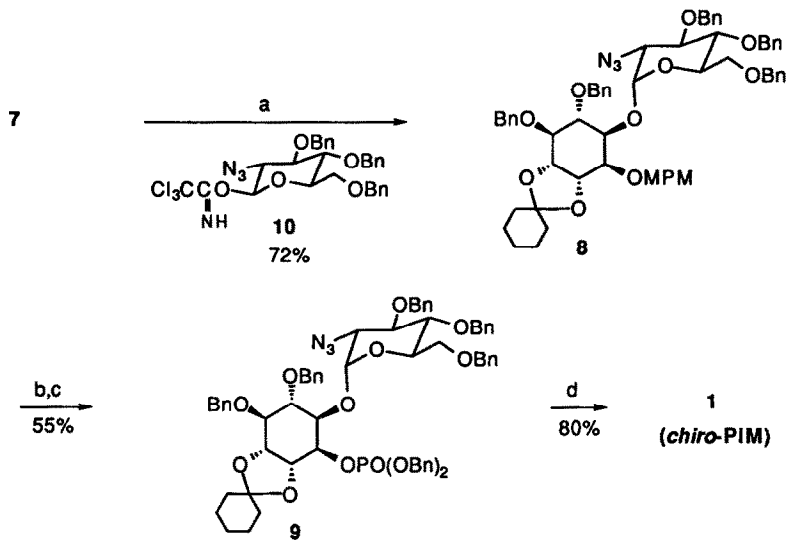
MPM = 4-$MeOC_6H_4CH_2$-

[a] *t*-$BuMe_2SiOTf$, Et_3N, CH_2Cl_2, 0->24°C, 1 h. [b] *m*-$ClC_6H_4CO_3H$, hexane, -16°C, 0.5 h. [c] $NaBH_4$, $CeCl_3$, MeOH, 0°C, 0.5 h. [d] Bu_4NF, THF, 0°->24°C, 2 h. [e] NaH, BnBr, DMF, 24°C, 2 h. [f] OsO_4, NMO, Me_2CO/H_2O (9:1), 24°C, 24 h. [g] *n*-Bu_2SnO, $PhCH_3$, 120°C, 3 h; BzCl, 4 Å MS, C_6H_6, 24°C, 8 h. [h] 4-$MeOC_6H_4CH_2OC(NH)CCl_3$, Ph_3CBF_4 (5 mole %), Et_2O, 40°C, 12 h. [i] K_2CO_3, MeOH, 24°C, 4 h.

Attachment of the masked sugar and phosphate appendages proceeded smoothly (Scheme 2) with trimethylsilyl triflate assisted[15] glycosidation of **7** using β-imidate **10**,[16] mp 84-85°C, to give the desired α-anomer **8** accompanied by a minor amount (~10%) of its chromatographically separable β-epimer: TLC (SiO_2) hexane/EtOAc (7:3), R_f~0.59 and 0.64, respectively. Mild cleavage of the MPM ether using DDQ and phosphorylation by the two-step phosphoramidite procedure of Tegge and Ballou[17] yielded **9** from whence *chiro*-PIM **1** was secured as its ammonium salt by catalytic hydrogenolysis/hydrolysis as previously described.[18]

Initial *in vitro* testing of **1** revealed weak to modest insulin agonist activity and corroborated the partial structural assignment of natural PIMs. Details of these studies as well as results from analogues of **1** will be reported elsewhere.

Scheme 2



[a] **10**, Me_3SiOTf (0.1 equiv), 4 Å MS, CH_2Cl_2, -40°C, 0.5 h.[b] DDQ, CH_2Cl_2/H_2O (9:1), 24°C, 12 h. [c] $(i\text{-Pr})_2NP(OBn)_2$ (3 equiv), 1*H*-tetrazole (7.5 equiv), CH_2Cl_2, 24°C, 1 h; *m*-$ClC_6H_4CO_3H$ (5.5 equiv), CH_2Cl_2, -40°C, 0.5 h.[d] H_2 (50 psi), 10% Pd/C, EtOH/H_2O/AcOH (80:19:1), 24°C, 24 h; AcOH/H_2O (8:2), 50°C, 3 h; NH_3(g), H_2O.

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11. Spectral data for **1**: ^{1} H NMR (250 MHz, D_2O) δ 3.19 (dd, J=3.8, 10.5 Hz, 1H), 3.35 (t, J=9.5 Hz, 1H), 3.44 (t, J=9.4 Hz, 1H), 3.54 (t, J=9.4 Hz, 1H), 3.58-3.68 (m, 2H), 3.68-3.83 (m, 2H), 3.98 (t, J=3.7 Hz, 1H), 4.39 (td, J=3.3, 10.6 Hz, 1H), 5.24 (d, J=3.8 Hz, 1H). ^{13}C NMR (250 MHz, D_2O) δ 38.5, 50.4, 53.3 (d, $J_{c,p}$=9.0 Hz) 59.5, 60.5, 60.8, 60.9, 61.6, 62.1, 62.7, 63.8 (d, $J_{c,p}$=7.5 Hz) 81.5. ^{31}P NMR (200 MHz, D_2O) 4.47 ppm (relative to 85% H_3PO_4). FAB MS (m/z): 421 (M-NH_3, 35%). **4**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32-1.48 (m, 2H), 1.52-1.73 (m, 8H), 3.63 (t, J=7.7 Hz, 1H), 4.02 (dd, J=2.7, 7.7 Hz, 1H), 4.23 (dd, J=5.0, 7.0 Hz, 1H), 4.60 (dd, J=2.7, 7.0 Hz, 1H), 4.68 (d, J=11.5 Hz, 1H), 4.75 (d, J=11.5 Hz, 1H), 4.83 (d, J=11.5Hz, 1H), 4.98 (d, J=11.5 Hz, 1H) 5.84 (dd, J=3.2, 10.7 Hz, 1H) 5.91 (dd, J=2.9, 10.7 Hz, 1H), 7.25-7.45 (m, 10H). **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33-1.47 (m, 2H), 1.54-1.73 (m, 8H), 2.55 (br s, 2H), 3.65 (br s, 2H), 3.79-3.88 (m, 1H), 4.25-4.39 (m, 3H), 4.62 (d, J=11.2 Hz, 1H), 4.73 (d, J=11.2 Hz, 1H), 4.96 (d, J=4.3 Hz, 1H), 5.02 (d, J=4.3 Hz, 1H), 7.25-7.43 (m, 10H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 23.67, 23.96, 24.95, 35.06, 37.76, 69.04, 70.99, 73.48, 74.88, 76.21, 79.03, 79.28, 83.79, 109.76, 127.55, 127.87, 127.93, 128.27, 128.54, 138.30, 138.43. **9**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25-1.42 (m, 2H), 1.42-1.70 (m, 8H), 3.34 (dd, J=3.6, 10.3 Hz, 1H), 3.46 (d, J=10.2 Hz, 1H), 3.58 (dd, J=7.4, 12.1 Hz, 1H), 3.59 (t, J=9.6 Hz, 1H), 3.65-3.72 (m, 2H), 3.81-3.94 (m, 2H), 4.20-4.26 (m, 1H), 4.29-4.41 (m, 2H), 4.43-4.72 (m, 6H), 4.74-4.90 (m, 5H), 5.01-5.17 (m, 4H), 5.22 (d, J=3.6 Hz, 1H), 7.06-7.40 (m, 35H). $[\alpha]_D^{20}$ + 56.9° (c1.2, $CHCl_3$). ^{31}P NMR (500 MHz, $CDCl_3$) -1.28 ppm (relative to 85% H_3PO_4). FAB MS (m/z) 1158 (M+H, 15%).
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