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SYNTHESIS OF 6-*O*-(2-AMINOETHYL)-D,L-*MYO*- INOSITOL-1,2-CYCLIC PHOSPHATE: A MODEL OF A PUTATIVE INSULIN SECOND MESSENGER

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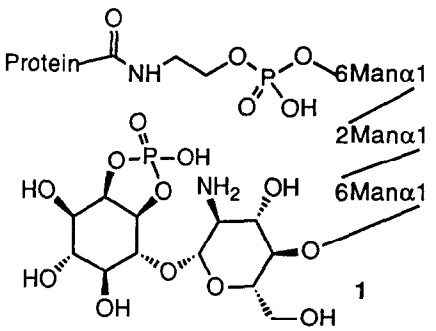
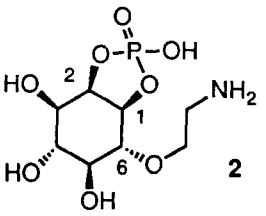
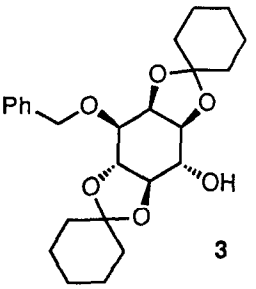
Abstract - The synthesis of the titled compound **2** is described. This material was synthesized to aid in the structural elucidation of a putative insulin second messenger. It was designed to be a potential insulinomimetic as well.

The hydrolysis of phosphatidylinositol-4,5-bisphosphate to yield the second messengers diacylglycerol and inositol-1,4,5-trisphosphate (IP_3) has been implicated in the mechanism of action of a number of hormones and neurotransmitters.[1] Recently another inositol phosphate messenger system has been reported[2] in connection with the mechanism of action of the anabolic hormone insulin. This latter system differs in that this putative second messenger is, apparently, a glycosylinositol phosphate (**GIP**) which mediates some of insulin's actions in insulin sensitive tissues such as muscle, liver and fat. **GIP** has even been reported to mimic some of insulin's actions. In particular, Saltiel et al[3] have reported that lipogenesis from glucose in intact rat adipocytes is stimulated by **GIP** alone; this is a characteristic of insulin. Although the complete structure of **GIP** has not yet been determined, there is general agreement that it is a polysaccharide of approximately five glucose units in size containing an aminosugar glycosidically linked to an inositol phosphate.

We were interested in seeing if we could generate a small molecule agonist of **GIP** as it could be a potentially useful therapeutic agent for diabetes. As a basis for starting chemistry in this area we chose the apparently similar glycosylphosphatidylinositol anchor of *Trypanosoma brucei* as a model[4] for **GIP** as its complete structure is known.[5] Both **GIP** and the anchor are released from cell membranes by the action of glycosylphosphatidylinositol specific phospholipase(s) C.[6] In the latter case the result of this cleavage is thought to be an inositol-1,2-cyclic phosphate.[7] The 'core'[8] polysaccharide (**1**) of this material is shown



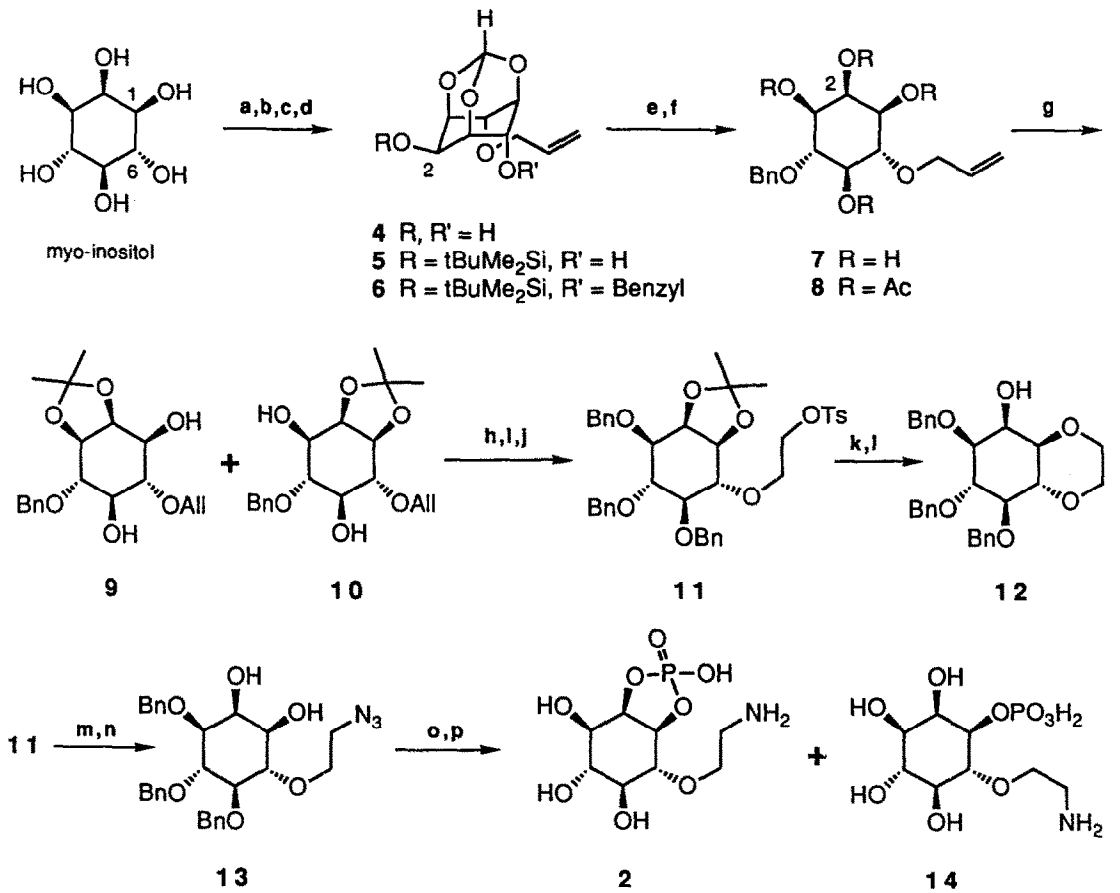




above. We have assumed that the cyclic phosphate moiety is also present in **GIP** and proposed the compound **2** as a potential small molecule mimic of it. Synthesis of **2** may also serve as a model study for the synthesis of **GIP** and may also provide useful spectral data for its structure elucidation. We collapsed the putative polysaccharide aminosugar portion of **GIP** to an aminoethyl moiety for synthetic expediency as it is the smallest group that we could attach to the inositol ring that still bears an analogously situated amino group. This amino group serves to maintain the local environment about the cyclic phosphate in a no net charge (zwitterionic) situation at physiological pH. This charge distribution may be important in molecular recognition of **GIP**.

The inositol literature provides no routes to the 1,2,6-substituted inositol required for **2** probably because most synthetic work has focused on the 1,4,5-substituted system of IP_3. Compound **3** is reported[9] to be accessible from *myo*-inositol in ca. 18% yield in two steps and would provide a suitably differentiated inositol for conversion to **2** by appropriate manipulation of its free hydroxyl group followed by selective hydrolysis of the *trans*-cyclohexylidene ketal. The downside of this approach is that the first step produces three regioisomeric bis-cyclohexylidene ketals from *myo*-inositol whose separation by recrystallization/flash chromatography is tedious especially on the scale required for a first step.[10] We thought instead that the ortho ester **4** would be a more attractive starting material as it can be obtained with ca. 100% regioselectivity from *myo*-inositol in two steps in > 80% yield[11] and is suitably functionalized for further elaboration. The allyl group of **4** also seemed to be a convenient surrogate for the aminoethyl group needed for **2**.

Attempts to selectively convert the axial hydroxy of **4** to a benzyl ether with NaH and benzyl bromide in DMF were not successful[11] (ax / eq selectivity = 3). On the other hand the equatorial hydroxy could be



Scheme 1

Reagents and Conditions: (a) $(EtO)_3CH$, H^+, DMSO, 100° (b) allyl bromide, NaH, DMF (c) $tBuMe_2SiCl$, imid., DMF (d) benzyl bromide, NaH, DMF (e) Aq HCl, MeOH (f) Ac_2O, Py, DMAP (g) from **7**: 2,2-dimethoxypropane, H^+, THF (h) tBuOK, benzyl bromide, THF (i) OsO_4, NMO; $NaIO_4$; $NaBH_4$ (j) Ts_2O (k) HCl, MeOH (l) NaH, THF (m) NaN_3, DMSO, 60° (n) aq HCl, MeOH (o) methyl dichlorophosphate, pyridine (p) H_2, 10% Pd / C

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silylated with apparent 100% regioselectivity with *tert*-butyldimethylsilyl chloride to give **5**[12] The axial hydroxy could then be benzylated to give **6** which was converted to the tetraol **7** with aqueous HCl.

These three transformations were carried out in 94% overall yield. The assignment of the site of benzylation to O(4) rather than O(2) was confirmed by inspection of the ^1H NMR of the tetraacetate derivative **8**. This spectrum clearly shows the inositol ring in a chair conformation and the C(2) hydrogen is easily assigned as it is the only equatorial hydrogen present. It shows a downfield shift of 1.4 ppm upon acetylation and is, thus, consistent with the assigned structure. Not surprisingly, submission of **7** to standard acetonide forming conditions gave two acetonides, **9** and **10**, in near equal amounts. These two compounds, however, were easily separated by flash chromatography on silica gel (2:1-hexane:EtOAc). The faster eluting compound was identified as the desired **10** (*vide infra*). The unwanted **9** could be recycled to **10** by acid hydrolysis and resubmission to the acetonidation conditions. Thus, one recycle provided a 56% yield of **10**. A fully protected inositol was next obtained by perbenzylation. This was followed by oxidative cleavage of the allyl group, reduction and tosylation to produce **11** in 65% overall yield. Acidic hydrolysis of **11** followed by brief treatment with base gave the bicyclic compound **12**. This facile cyclization is consistent with the acetonide regiochemistry assigned to **10**. The synthesis was continued after this brief digression by replacing the tosylate group of **11** with that of azide and cleaving the acetonide with HCl to give **13**. This diol was treated with *in situ* prepared dichlorophosphate[13] to give an unstable cyclic phosphate which was immediately hydrogenolysed to a mixure[14] (3.5:1) of **2** and the inositol-1-phosphate **14**.[15] Ion exchange chromatography on Dowex 1X2-200 (HCO_3^- form) provided **2**[16] in 52% yield.

Thus, we obtained the desired 1,2,6-substituted inositol in a reasonably concise and selective manner. This route requires only one separation of regioisomers and as they can be recycled little material is lost. This is in contrast with the alternative route proposed from **3**. Our route is amenable to producing more complicated 6-substituted-1,2-cyclic phosphates by utilizing the allyl group as a protecting group to be removed as required for further elaboration to form , for example, the glycosidic linkage found in **GIP**. This route also could easily be modified to produce alternatively substituted inositols by differential treatment, for example, of compounds **5** or **9**.

Treatment of freshly isolated rat adipocytes with 1 mM **2** using Saltiel's procedure[3,17] gave no stimulation of lipogenesis in the presence of glucose. Compound **14** was similarly inactive in this assay. Thus, these compounds do not achieve our goal of agonists of **GIP**.

EXPERIMENTAL:

NMR spectra were taken on a Varian VXR-300 with ^{1}H, ^{13}C and ^{31}P spectra taken at 300, 75 and 121 MHz respectively. ^{1}H spectra in $CDCl_3$ were referenced to TMS at δ 0.0 and those in D_2O to internal acetone at δ 2.23. ^{13}C spectra in $CDCl_3$ were referenced to $CDCl_3$ at δ 77.0 and those in D_2O to internal acetone at δ 33.1. ^{31}P spectra were referenced to external 85% H_3PO_4 at δ 0.0. Chemical ionization (CI) mass spectra were taken on a HP-5988A mass spectrometer. FAB mass spectra were performed by M-Scan, Westchester PA. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. All flash chromatography was performed on 32-63 μ silica gel using HPLC grade solvents. All reactions were performed under a stream of N_2. Tetrahydrofuran (THF) was distilled just prior to use from sodium benzophenone ketyl. Aldrich anhydrous DMF was used as received. All other reaction solvents were Fisher HPLC grade and used as received. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

2-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-1,3,5-*O*-methylidyne-4-*O*-(2-propenyl)-D,L-*myo*-inositol (5). To a solution of the diol **4**[11] (4.29 g, 18.6 mmol) in 40 mL DMF was added imidazole (1.90 g, 27.9 mmol) and *tert*-butyldimethylsilyl chloride (3.93 g, 26.1 mmol). After stirring for 18 hours the DMF was removed by rotary evaporation and the residue taken up in 700 mL EtOAc. This solution was washed with 200 mL 0.5 M HCl and 100 mL brine, dried over $MgSO_4$ and concentrated to a pale yellow oil. This material was flash chromatographed on 250 g silica gel with EtOAc/hexane (1/4) to yield **5** as a colorless oil (6.02 g, 94%): ^{1}H NMR ($CDCl_3$) δ 5.94-5.81 (m, 1H), 5.51 (s, 1H), 5.35-5.28 (m, 2H), 4.47-4.13 (m, 8H), 3.63 (d, J= 10.3 Hz, 1H), 0.95 (s, 9H), 0.16 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 132.7, 119.2, 102.5, 74.9, 74.8, 72.5, 71.8, 68.3, 67.4, 60.8, 25.8, 18.3, -4.7, -4.8; MS (CI, *i*-butane) 345 (M+1). Anal. Calcd for $C_{16}H_{28}O_6Si_1$: C, 55.79; H, 8.19. Found: C, 55.81; H, 8.20.

2-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-1,3,5-*O*-methylidyne-6-*O*-(phenylmethyl)-4-*O*-(2-propenyl)-D,L-*myo*-inositol (6). To a solution of the alcohol **5** (6.04 g, 17.5 mmol) and benzyl bromide (2.40 mL, 19.3 mmol) in 60 mL DMF maintained at 0° was added NaH (60% oil dispersion- 772 mg, 19.3 mmol). The resulting solution was stirred for 30 minutes at 0° and for 90 minutes at room temperature. The reaction was then quenched with 10 mL of pH 7 phosphate buffer and the solvents removed by rotary evaporation. The residue was partitioned between 500 mL EtOAc and 75 mL water. The organic layer was washed with 50 mL brine, dried over $MgSO_4$ and concentrated to a pale yellow oil. This material was flash chromatographed on 250 g silica gel with EtOAc/hexane (1/8) to afford **6** as a colorless oil (7.58 g, 100%): ^{1}H NMR ($CDCl_3$) δ 7.35-7.27 (m, 5H), 5.91-5.79 (m, 1H), 5.53 (d, J= 1.2 Hz, 1H), 5.29-5.14 (m, 2H), 4.67 and 4.58 (ABq, J= 12.0 Hz, 2H), 4.41-4.26 (m, 4H), 4.16-4.02 (m, 4H), 0.93 (s, 9H), 0.13 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.7, 134.1, 128.3, 127.7, 127.3, 117.1, 103.1, 74.1(2), 73.3(2), 71.3, 70.5, 68.0, 61.7, 25.9, 18.4, -4.7(2); MS (CI, *i*-butane) 435 (M +1). Anal. Calcd. for $C_{23}H_{34}O_6Si_1$: C, 63.56; H, 7.89. Found: C, 63.63; H,

7.95.

4-*O*-(Phenylmethyl)-6-*O*-(2-propenyl)-D,L-*myo*-inositol (7). A solution of **6** (6.04 g, 13.9 mmol) in 150 mL MeOH containing 7.6 mL of 2.0 M aq HCl was refluxed for 6 hours. The solution was then neutralized with Amberlite (OH^- form) and filtered. Concentration of the filtrate afforded **7** (4.35 g , 100%) as a white foam. A portion of this material was recrystallized from ether/hexane giving tiny white crystals: mp: 119-120°; ^1H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5H), 6.02-5.89 (m, 1H), 5.32-5.16 (m, 2H), 4.88 and 4.81 (ABq, J= 11.2 Hz, 2H), 4.34-4.27 (m, 2H), 4.09 (s, 1H), 3.70-3.44 (m, 5H), 3.04 (s, 1H), 2.75-2.64 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 134.9, 128.6, 128.0, 117.3, 81.4, 81.2, 75.0, 74.6, 73.9, 71.7(2), 71.5; MS (CI, *i*-butane) 311 (M+1). Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.68; H, 7.21.

4-*O*-(Phenylmethyl)-6-*O*-(2-propenyl)-D,L-*myo*-inositol-1,2,3,5-tetra-acetate (8). A solution of **7** (33.0 mg, 106 μmol) in 1.0 mL pyridine/Ac_2O (2/1) containing 1 mg DMAP was stirred for 18 hours. The solvents were then removed by rotary evaporation and the residual solid flash chromatographed on 500 μg silica gel with EtOAc to afford **8** (44.6 mg, 88%) as an amorphous white solid: mp: 134-136°; ^1H NMR ($CDCl_3$) δ 7.36-7.22 (m, 1H), 5.85-5.72 (m, 1H), 5.54 (t, J=2.8 Hz, 1H), 5.24-4.98 (m, 5H), 4.67 and 4.59 (ABq, J=11.7 Hz, 2H), 4.16-4.00 (m, 2H), 3.87 (t, J=10.0 Hz, 1H), 3,76 (t, J=9.8 Hz, 1H), 2.17 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H); MS (CI, *i*-butane) 479 (M+1).

2,3-*O*-(1-Methylethylidene)-4-*O*-(phenylmethyl)-6-*O*-(2-propenyl)-D,L-*myo*-inositol (9) and 1,2-*O*-(1-methylethylidene)-4-*O*-(phenylmethyl)-6-*O*-(2-propenyl)-D,L-*myo*-inositol (10). A solution of **7** (4.24 g, 13.7 mmol) in 100 mL THF/2,2-dimethoxypropane (3/1) containing 45 mg *p*-toluenesulfonic acid was stirred for 100 minutes. The reaction was then quenched with Amberlite (3 g, OH^- form) and filtered. Concentration of the filtrate gave an oil which was flashed chromatographed on 500 g silica gel with hexane/EtOAc (2/1) to afford **9** (2.17 g, 45%) and **10** (1.93 g, 40%). Compound **10** elutes first under these conditions.

Data for **9**: mp: 82-83° (ether/hexane); ^1H NMR ($CDCl_3$) δ 7.39-7.29 (m, 5H), 6.01-5.90 (m, 1H), 5.35-5.19 (m, 2H), 4.92 and 4.67 (ABq, J=11.5 Hz, 2H), 4.45 (dd, J=3.9,6.1 Hz, 1H), 4.41-4.34 (m, 1H), 4.27-4.21 (m, 2H), 3.89 (app. q, J=3.8 Hz, 1H), 3.70 (dd, J=6.6,9.0 Hz, 1H), 3.63 (t, J=7.5 Hz, 1H), 3.57-3.50 (m, 1H), 2.60 (d, J=2.7 Hz, 1H), 2.52 (d, J=3.7 Hz, 1H), 1.53 (s, 3H), 1.40 (s, 3H); ^{13}C NMR($CDCl_3$) δ 138.1, 134.7, 128.4, 127.9, 127.8, 117.3, 109.9, 81.9, 80.7, 78.7, 75.4, 73.7, 73.1, 72.9, 69.7, 27.4, 25.3; MS (CI, *i*-butane) 351 (M+1). Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.99; H, 7.51.

Data for **10**: mp: 75.5-76° (ether/hexane); ^1H NMR ($CDCl_3$) δ 7.41-7.25 (m, 5H), 6.01-5.88 (m, 1H), 5.34-5.19 (m, 2H), 4.93 and 4.75 (ABq, J=11.5 Hz, 2H), 4.44 (dd, J=3.9,6.1 Hz, 1H), 4.41-4.35 (m, 1H), 4.21-4.14 (m, 2H), 3.92 (app q, J=3.8 Hz, 1H), 3.74 (t, J=7.4 Hz, 1H), 3.64 (dd, J=6.6,9.0 Hz, 1H), 3.59-3.53 (m, 1H), 2.62 (d, J=2.7 Hz, 1H), 2.50 (d, J=3.7 Hz, 1H), 1.55 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.2, 134.6, 128.5, 127.9(2), 117.3, 109.8, 81.6, 81.1, 78.6,

75.4, 74.0, 73.8, 72.1, 69.7, 27.4, 25.2; MS (CI, *i*-butane) 351 (M+1). Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.17; H, 7.53

1,2-*O*-(1-Methylethylidene)-4-*O*-(phenylmethyl)-6-*O*-[2-(*p*-toluenesulfonyloxy)ethyl]-D,L-*myo*-inositol (11). To a solution of the diol **10** (2.60 g, 7.42 mmol) in 150 mL THF containing 60 mg 18-Crown-6 was added 1.0 M potassium *tert*-butoxide (17.8 mL, 17.8 mmol) and benzyl bromide (2.20 mL, 18.6 mmol). The reaction was quenched after stirring for one hour with the addition of 25 mL water. This mixture was then extracted with 300 mL EtOAc and the extract washed with 50 mL brine, dried over $MgSO_4$ and concentrated to a yellow oil. This material was flashed chromatographed on 250 g silica gel with hexane/EtOAc (8/1) to afford the tribenzyl ether (3.76 g, 96%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 7.40-7.27 (m, 5H), 6.01-5.88 (m, 1H), 5.31-5.14 (m, 2H), 4.87-4.72 (m, 6H), 4.37-4.20 (m, 3H), 4.01 (t, J=6.2 Hz, 1H), 3.92 (t, J=8.7 Hz, 1H), 3.67 (m, 2H), 3.36 (t, J=9.0 Hz, 1H), 1.55 (s, 3H), 1.35 (s, 3H); ^{13}C NMR($CDCl_3$) δ 138.6, 138.1, 135.1, 128.3, 128.0, 127.7, 127.6, 116.7, 109.7, 82.2(2), 80.8, 79.0, 77.0, 75.3, 75.2, 74.5, 73.3, 72.9, 27.7, 25.7; MS (CI, *i*-butane) 531 (M+1). Anal. Calcd. for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found: C, 74.65; H, 7,23.

To a solution of the above product (3.74 g, 7.05 mmol) in 200 mL acetone/water (4/1) was added OsO_4 (200 mg) and N-methylmorpholine-N-oxide (908 mg, 7.75 mmol). The resulting solution was stirred for eight hours and an additional 100 mg of OsO_4 and 450 mg NMO was added. After stirring for 16 more hours the solution was concentrated to 20 mL and diluted with 500 ml EtOAc. This solution was washed with 50 mL each of 10% $NaHSO_3$, 1.0 M HCl and brine, dried over $MgSO_4$ and concentrated to 4.6 g of a pale yellow oil. This material was dissolved in 150 mL of dioxane/water (3/1) and treated with $NaIO_4$ (1.66 g, 7.75 mmol) After stirring for 25 hours the solution was concentrated to 30 mL and diluted with 100 mL water. This solution was extracted with 2X 500 mL EtOAc. These extracts were washed with 50 mL brine, dried over $MgSO_4$ and concentrated to 5.1 g of a yellow oil. This material was immediately taken up in 150 mL THF/*i*PrOH (1/1) cooled to 0^o and treated with $NaBH_4$ (270 mg, 7.05 mmol). This solution was allowed to warm to room temperature while stirring for one hour. The reaction was quenched with acetone and concentrated to a white semi-solid which was partitioned between 600 mL EtOAc/water (8/1). The EtOAc layer was washed with 50 mL brine, dried over $MgSO_4$ and concentrated to a pale yellow oil which was flash chromatographed on 250 g silica gel with EtOAc/hexane (2/3) to afford the hydroxyethyl ether (2.51 g, 67% from the tribenzyl ether) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.40-7.27 (m,15H), 4.86-4.71 (m, 6H), 4.25 (dd, J=4.2,5.6 Hz, 1H), 3.99 (dd, J=5.6,7.6 Hz, 1H), 3.93-3.85 (m, 3H), 3.72-3.63 (m, 4H), 3.33 (dd, J=8.3,10.0 Hz, 1H), 2.92 (t, J=6.6Hz, 1H), 1.57 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.3, 138.0(2), 128.4, 127.9(2), 127.8(2), 127.7, 127.6, 110.0, 83.0, 81.9, 81.1, 78.9, 76.9, 75.2, 75.0, 74.2, 73.9, 73.3, 62.1, 27.7, 25.6; MS (CI, *i*-butane) 535 (M+1). Anal. Calcd. for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 71.93; H, 7.16.

To a solution of the above compound (2.50 g, 4.68 mmol) in 100 mL CH_2Cl_2 maintained at 0° was added pyridine (756 µL, 9.35 mmol) and *p*-toluenesulfonic anhydride (2.29 g, 7.01 mmol). The resulting solution was stirred at 0° for 30 minutes and then for one hour at room temperature and was then quenched with 100 mL 1.0 M $NaHCO_3$. The resulting heterogeneous solution was stirred for 10 minutes and then extracted with 500 mL EtOAc. This extract was washed with 100 mL 0.5 M HCl and 50 mL brine, dried over $MgSO_4$ and concentrated to give **11** (3.27 g, 100%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.75 (d, J=8.5 Hz, 2H), 7.39-7.25 (m, 17H), 4.82-4.68 (m, 6H), 4.21-4.09 (m, 3H), 4.00-3.83 (m, 4H), 3.64 (dd, J=3.9,8.5 Hz, 1H), 3.56 (dd, J=7.1,9.8 Hz, 1H), 3.27 (dd, J=8.3,9.5 Hz, 1H), 2.39 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.5, 138.3, 138.0, 129.7, 128.3(3), 128.0, 127.9(2), 127.8, 127.6(2), 109.8, 83.9, 81.6, 80.7, 78.7, 76.8, 75.2, 75.0, 74.4, 73.3, 69.3, 69.2, 27.7, 25.6, 21.5; MS (CI, *i*-butane) 689 (M+1). Anal. Calcd. for $C_{35}H_{44}O_9S_1$: C, 68.00; H, 6.44. Found: C, 67.89; H, 6.47.

Preparation of (12). To a solution of **11** (76.0 mg, 110 µmol) in 5 mL MeOH/THF (1/1) was added 150 µL 0.5 M aq HCl. The resulting suspension was refluxed for 3 hours and then neutralized with Amberlite ($^-$OH form). This suspension was filtered and concentrated to a colorless oil which was taken up in 5 mL THF. This solution was treated with NaH (4.8 mg- 60% oil dispersion, 120 µmol) and stirred for 15 minutes. The reaction was then quenched with 5 mL water and extracted with 40 mL EtOAc. This extract was washed with 5 mL brine, dried over $MgSO_4$ and concentrated to a white solid. Flash chromatography on 10 g silica gel with EtOAc/hexane (1/1) afforded **12** (49.4 mg, 95%) as an amorphous white solid. Recrystallization from ether/hexane gave small white crystals: mp: 128-129°; ^1H NMR ($CDCl_3$) δ 7.39-7.25 (m, 15H), 4.93-4.68 (m, 6H), 4.16 (t, J=2.6 Hz, 1H), 3.96-3.71 (m, 6H), 3.49 (dd, J=2.9,9.5 Hz, 1H), 3.46 (t, J=9.3 Hz, 1H), 3.17 (dd, J= 2.4,9.8 Hz, 1H), 2.41, (s, 1H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.7, 137.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8(2), 127.5, 127.4, 81.3(2), 79.9, 76.7, 76.1, 75.8, 75.2, 72.7, 68.5, 67.2, 66.2; MS (CI, i-butane) 519 (M+1). Anal. Calcd. for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 73.12; H, 6.77.

6-*O*-(2-Azidomethyl)-3,4,5-*tris*-*O*-(phenylmethyl)-D,L-*myo*-inositol (13). A solution of **11** (3.15 g , 4.57 mmol) in 30 mL DMSO containing NaN_3 (446 mg, 6.86 mmol) was stirred for 110 minutes at 60°. This solution was then diluted with 50 mL 0.5 M NaOH and extracted twice with 400 mL EtOAc. These extracts were washed twice with 100 mL water, dried over $MgSO_4$ and concentrated to a pale yellow oil. Flash chromatography on 100 g silica gel with hexane/EtOAc (6/1) afforded the azide (2.50 g, 98%) as a colorless oil. This material was refluxed for 70 minutes in 150 mL MeOH containing 10 mL 0.5 M aq HCl. The solution was then neutralized with 2.0 M NaOH; 25 mL of pH 7 phosphate buffer added and the solution concentrated to about 35 mL. This solution was extracted with 400 mL EtOAc. This

extract was washed with 25 mL brine, dried over $MgSO_4$ and concentrated to give **13** (2.31g, 100%) as an amorphous solid. A small amount of this material was recrystallized from ether/hexane to give an amorphous white solid: m.p.: 76-77°; ^1H NMR ($CDCl_3$) δ 7.36-7.27 (m, 15H), 4.93-4.72 (m, 6H), 4.21 (br s, 1H), 4.07-4.01 (m, 1H), 3.94 (t, J=9.5 Hz, 1H), 3.84-3.77 (m, 1H), 3.65 (t, J= 9.4 Hz, 1H), 3.50-3.38 (m, 5H), 2.93 (d, J=4.2 Hz, 1H), 2.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 138.5(2), 137.7, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6(2), 82.9, 82.2, 81.5, 79.8, 75.8, 75.5, 72.7, 71.7(2), 69.1, 51.5; MS (CI, *i*-butane) 492 (M+1-N_2). Anal. Calcd. for $C_{29}H_{33}N_3O_6$: C, 67.04; H, 6.40; N, 8.09. Found: C, 67.04; H, 6.39; N, 8.04.

6-*O*-(2-Aminoethyl)-DL-*myo*-inositol-1,2-cyclic-hydrogen phosphate (2). Dichloromethyl phosphate (96.3 µL, 962 µmol) was added to 2.0 mL pyridine. A suspension was formed after stirring for a few minutes and after 30 minutes **13** (200 mg, 385 µmol) was added in one portion. This suspension was stirred for 80 minutes and the reaction quenched with 4.0 mL saturated $NaHCO_3$. This mixture was rotary evaporated to dryness and quickly taken up in 10 mL water. This solution was acidified to pH 1 with 2.0 M HCl and extracted with 2X 60 mL EtOAc. These extracts were dried over $MgSO_4$ and concentrated to a white crystalline solid pure by ^1H NMR. This material was immediately taken up in 10 mL H_2O/THF/EtOH (1/1/1) containing 400 µmol $NaHCO_3$ and 300 mg 10% Pd on carbon. This mixture was shaken for 42 hours under 50 psi H_2 in a Parr hydrogenator. The resulting material was filtered through a pad of 500 mg Celite with an aqueous wash. Concentration gave 104 mg of a colorless glass. A portion of this material (17.3 mg) was immediately submitted for assay as the stability of this material was unknown. A ^1H NMR spectrum of this material showed it to be about 3.5:1 (**2**:**14**). The remainder of the material was loaded on a column of 8.0 g Dowex 1X2-200 resin ($^-HCO_3$ form) and elution with H_2O afforded **2** (47.9 mg, 52%) as an amorphous white solid and further elution with 100 mM ammonium bicarbonate afforded **14** (21.2 mg, 14%) as a colorless glass.

Data for **2**: ^1H NMR (D_2O, pD=7) δ 4.71 (t, J=4.2 Hz, 1H), 4.46 (ddd, J=4.6,8.1,20.0 Hz, 1H), 4.08-4.03 (m, 2H), 3.74-3.65 (m, 3H), 3.40 (t, J=9.6 Hz, 1H), 3.27-3.17 (m, 2H); ^{13}C NMR (D_2O pD=7) δ 85.4, 82.2, 80.1 (d, J=2.5 Hz), 74.6, 74.2, 72.5 (d, J=10.1 Hz), 71.4, 42.4; ^{31}P NMR (D_2O, pD=7, H coupled) δ 18.7 (d, J=20.1 Hz); MS (FAB+) 286 (M+1). HRMS (FAB) Calcd for $C_8H_{16}N_1O_8P_1$: 286.06920. Found: 286.07080.

Data for **14** (ammonium salt): ^1H NMR (D_2O, pD=7) δ 4.22 (t, J=2.7 Hz, 1H), 4.13-4.06 (m, 1H), 3.97-3.89 (m, 2H), 3.65 (t, J=9.5 Hz, 1H), 3.54 (dd, J=2.7,9.8 Hz, 1H), 3.51 (t, J=9.8 Hz, 1H), 3.41 (t, J=9.3 Hz, 1H), 3.27-3.08 (m, 2H); ^{13}C NMR (D_2O, pD=7) δ 84.0 (d, J=5.0 Hz), 77.1, 76.2 (d, J=5.0 Hz), 75.1, 74.5, 73.6, 71.6, 42.3; ^{31}P NMR (D_2O, pD=7, H coupled) δ 6.67 (d, J=9.7 Hz); MS (FAB+) 304 (m+1). Anal. Calcd. for $C_8H_{18}N_1O_9P_1 \cdot 2\ H_2O$: C, 28.41; H, 6.85, N, 8.28. Found: C, 28.22; H, 6.69; N, 8.59.

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14. Ring opening of the cyclic phosphate occurs during the reaction. Presumably some of the inositol-2- phosphate is also formed but it was not detected. The final product **2** is reasonably stable at neutral pH.
15. Compound **14** was also made from **13** using the following route: (a) MOMCl, DIPEA, CH_2Cl_2 (b) NaH, BnBr, DMF (c) HCl, MeOH (d) Tetrabenzylpyrophosphate, NaH, THF (e) H_2 (50 psi), 10% Pd/C, THF/EtOH/ water in 24% unoptimised overall yield.
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