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Convenient synthesis of 3- and 6-deoxy-D-*myo*-inositol phosphate analogues from (+)-*epi*- and (−)-*vibo*-quercitols

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Abstract—Starting from (+)-*epi*- and (−)-*vibo*-quercitols readily produced by bioconversion of *myo*-inositol, some biologically interesting phosphate and polyphosphate analogues, including the Ins(1,4,5)P_3 derivatives of 3-deoxy- and 6-deoxy-D-*myo*-inositol, could be readily prepared in a conventional manner. In addition, chemical modification at C-2 of the 3-deoxy Ins(1,4,5)P_3 provided 2-epimer, and 2-deoxy and 2-deoxy-2-fluoro forms. Eight polyphosphate analogues obtained were assayed for biological activity against PDH-Pase and PDH-K, and G6Pase, but none proved positive.

In recent years, D-*myo*-inositol-1,4,5-trisphosphate Ins(1,4,5)P_3, as well as its bis and tetrakisphosphates, have been demonstrated[1] to play important roles as second messengers which control many cellular processes by generating internal calcium signals, which then diffuse through the cytosol and bind to receptors on the endoplasmic reticulum causing the release of calcium ions (Ca^{2+}) into the cytosol. Therefore, it is feasible that inhibitors of enzymes of the phosphoinositide cascade, involved in biosynthesis and degradation of Ins(1,4,5)P_3, could be of medicinal interest and also invaluable tools to elucidate the individual roles of metabolites in the regulation of cell function. In order to study biochemical and medicinal properties of these polyphosphates, a large number of analogues and derivatives have so far been synthesized[2] and their biological activity tested. Recent findings[3] of insulin-like and anti-inflammatory properties have also stimulated us to develop means for routine synthesis of these compounds (Fig. 1).

Bioconversion[4] of *myo*-inositol readily provides some inaccessible optically active deoxyinositols,[5] such as (+)-*epi*- and (−)-*vibo*-quercitols (**1** and **2**), in quantity, which might allow their application as starting materials for development of novel biologically active cyclitol derivatives. In preceding papers, we reported the synthesis of several anhydro[5] and some *C*-(aminomethyl)deoxyinositols,[6] and *O*-methyl-deoxyinosamines[7] as

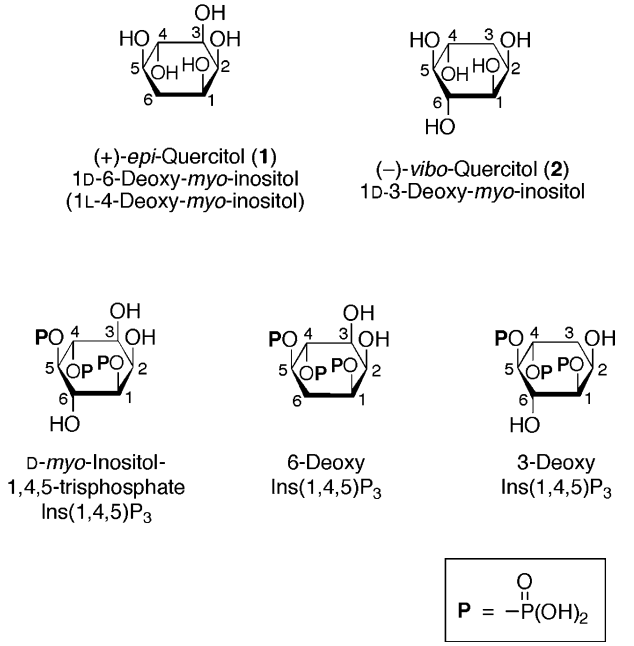

Figure 1. Deoxyinositols **1** and **2**, and Ins(1,4,5)P_3 and its deoxy derivatives.

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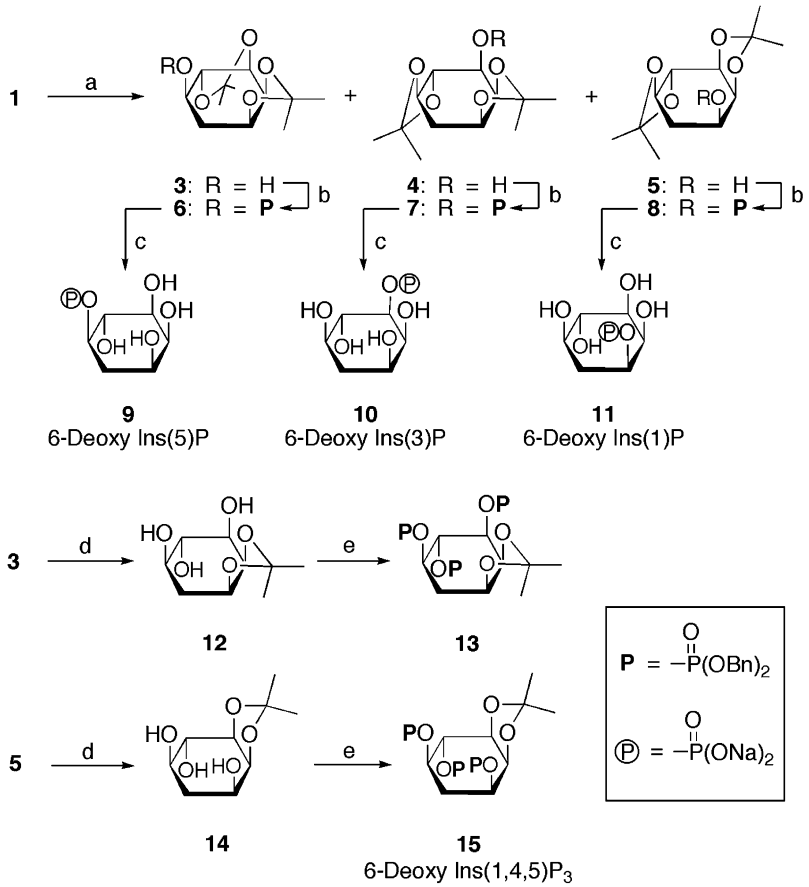
potential candidate new glycosidase inhibitors. In this letter, we describe convenient synthesis of a number of mono-, tris-, and tetrakisphosphate derivatives of 3- and 6-deoxy-D-*myo*-inositols. In addition, chemical modification at C-2 of the 3-deoxy Ins(1,4,5)P_3 was carried out to prepare 2-epimer, and 2-deoxy and 2-deoxy-2-fluoro derivatives. Furthermore, in order to provide certain trisphosphate mimics[8] designed by analogy with adenophostines,[9] the most potent agonists of Ins(1,4,5)P_3 receptor, the 1-phosphate function of the 3-deoxy Ins(1,4,5)P_3 was replaced with (phosphinyl)alkyloxyl groups (Schemes 1 and 2).

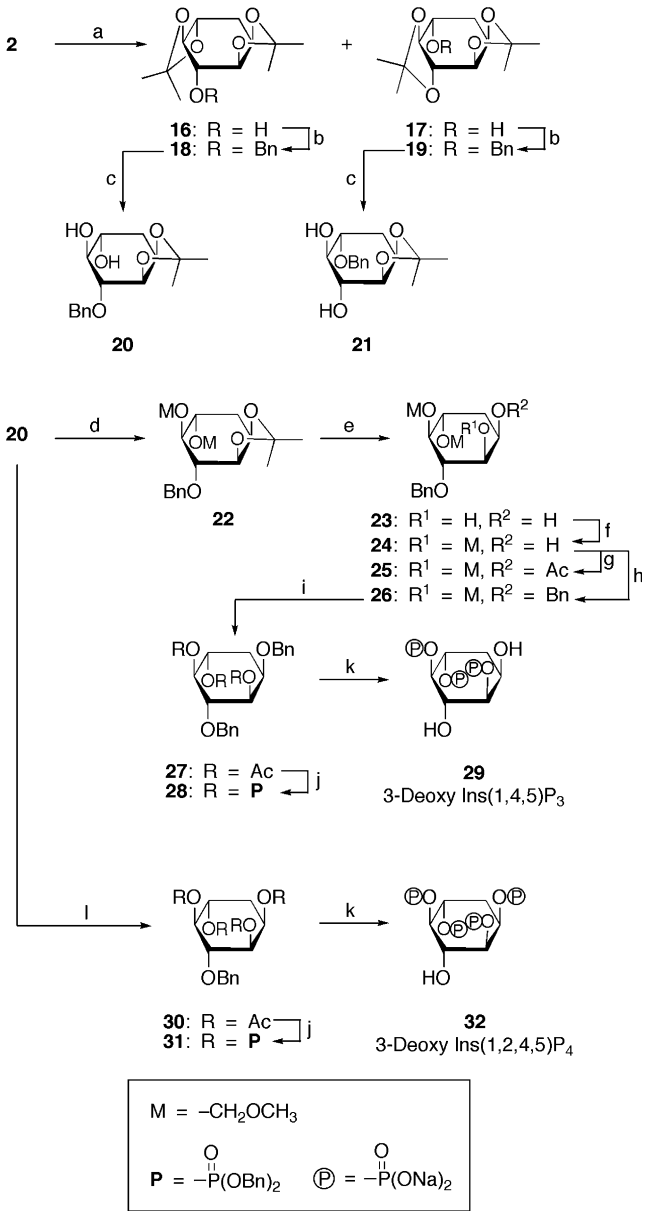
Recently, synthesis of several polyphosphate derivatives of 6-deoxy-D-*myo*-inositol[10] (**1**) has been elaborated[11] from precursors derived from D-galactose, and their biological activity assayed. 6-Deoxy Ins(1,4,5)P_3 is recognized by the highly selective 3-kinase,[12] the kinetics of its metabolism indicate that it is a substrate for this enzyme, with resultant competitive inhibition of phosphorylation of Ins(1,4,5)P_3.

We here describe a convenient preparative route from (+)-*epi*-quercitol[4] (**1**). Isopropylidenation[6] of **1** with an excess of 2,2-dimethoxypropane and TsOH in DMF was carried out at room temperature to give three readily separable di-*O*-isopropylidene derivatives **3** (24%), **4** (26%), and **5** (31%). These were treated with dibenzylphosphoryl chloride in pyridine at room temperature to give the respective dibenzylphosphates **6** (77%), **7** (86%), and **8** (87%), hydrogenolysis of which with PtO_2 in ethanol produced, after neutralization with cyclohexylamine, the respective phosphates as crystalline amine salts. Treatment of the salts with Dowex 50 W × 2 (H^+) resin gave the free phosphates **9** (88%), **10** (70%), and **11** (80%), isolated as bis-sodium salts.

Furthermore, compounds **3** and **5** could be partially de-O-isopropylidenated with TsOH in EtOH at 0 °C to give the triols **12** (70%) and **14** (78%), respectively. Possible contamination of **12** and **14** due to acid-catalyzed migration of the *cis*-isopropylidene groups was not observed. Compound **14** was similarly phosphorylated to give the protected precursor **15** (60%) of 6-deoxy Ins(1,4,5)P_3.[11] The structure of **15** was indirectly confirmed by the fact that ^{1}H NMR spectrum of isomeric trisphosphate **13** obtained for reference from **12** showed coupled signals (δ 4.31, ddd, J = 5.6, 8.9, and 13.9 Hz) and (δ 4.62, J = 5.1, and 8.9 Hz) due to H-1 and H-2 bonded to carbon atoms of the O-isopropylidene group. Thus, five biologically interesting phosphate analogues could be demonstrated to be readily available from (+)-*epi*-quercitol (**1**).



Scheme 1. Synthesis of some mono- and trisphosphates of 6-deoxy-D-*myo*-inositol. Reagents and conditions: (a) $(MeO)_2CMe_2$–DMF (1:2, v/v), TsOH, 6 h, rt; (b) $(PhO)_2POCl$ (1.5 M equiv), pyridine, 1 h, rt; aqueous 80% AcOH; (c) H_2, PtO_2, EtOH, rt; $C_6H_{11}NH_2$; Dowex 50 W × 2 (H^+) resin, 1 M NaOMe, MeOH; (d) TsOH, EtOH, pH ~ 4, 0 °C; (e) $(PhO)_2POCl$, DMAP, pyridine, rt; aqueous 80% AcOH.



Scheme 2. Synthesis of some tris- and tetrakisphosphates of 3-deoxy-*myo*-inositol. Reagents and conditions: (a) $CH_2{=}C(OMe)CH_3$, TsOH (0.1 M equiv), DMF, 3 h, rt; (b) NaH, BnBr, DMF; (c) CSA, MeOH, pH ~ 4, rt; (d) $MeOCH_2Cl$ (4 M equiv), diisopropylethylamine, DMF; (e) aqueous 80% AcOH; (f) Bu_2SnO (2 M equiv), tetrabutylammonium bromide; (g) Ac_2O, pyridine; (h) NaH, BnBr, DMF, rt; (i) 4 M HCl, 50 °C; Ac_2O, pyridine; (j) NaOMe, MeOH; i-$Pr_2NP(OBn)_2$ (6 M equiv), DMF, rt; *m*CPBA (10 M equiv), rt; (k) H_2, 10% Pd/C, aqueous EtOH; $C_6H_{11}NH_2$; Dowex 50 W × 2 (H^+) resin, NaOMe, MeOH; (l) aqueous 80% AcOH, 50 °C.

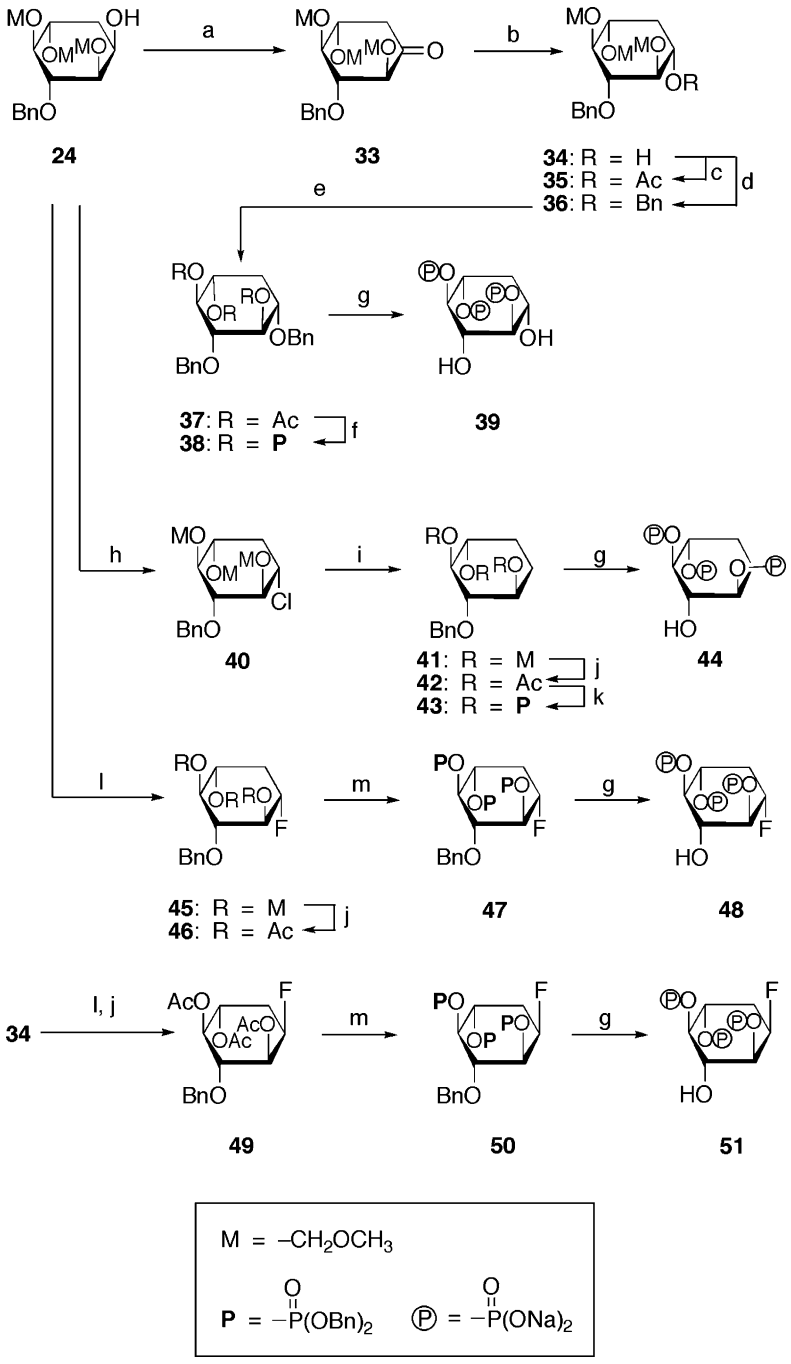
3-Deoxy-D-*myo*-inositol-(1,4,5)P_3 was first synthesized[13,14] from L-quebrachitol through a multi-step sequence and shown to be a good substrate of Ins(1,4,5)P_3-5-phosphatase (Schemes 2 and 3).

Isopropylidenation[5] of (−)-*vibo*-quercitol (**2**) was carried out by treatment with 2-methoxypropene in the presence of TsOH in DMF at room temperature. A mixture of the 1,2:4,5- **16** and 1,2:5,6-di-*O*-isopropylidene derivatives **17** was, without separation, treated with NaH in DMF and then with an excess of BnBr to give the benzyl ethers **18** and **19**, which were partially de-O-isopropylidenated under the influence of CSA in MeOH to afford, after separation over a silica gel column, the 4- and 6-*O*-benzyl derivatives **20** (55%) and **21** (42%). Compound **20** was treated with chloromethyl methyl ether and diisopropylethylamine to give the di-*O*-methoxymethyl derivative **22** (89%), de-O-isopropylidenation of which with 80% aqueous acetic acid gave the diol **23** (88%). Treatment of **23** with dibutyltin oxide and tetrabutyl ammonium bromide at 120 °C, and subsequent similar etherification, gave crude methoxymethyl ether **24** (87%). The structure of **24** could be fully characterized with the ^{1}H NMR spectrum of the *O*-acetyl derivative **25** (~100%) obtained. In addition, **24** was conventionally benzylated to give the 2-*O*-benzyl derivative **26** (91%). The methoxymethyl groups of **26** were removed by treatment with 4 M hydrochloric acid, and the product was subsequently acetylated to give the tri-*O*-acetyl derivative **27** (90% over-all yield). Compound **27** was treated with methanolic sodium methoxide under Zemplén conditions, and the resulting triol was phosphorylated with dibenzyl diisopropylphosphoro-amidite in DMF, and, then the reaction mixture was treated with *m*CPBA. The product was isolated by chromatography on silica gel to afford the 1,4,5-tris(dibenzylphosphate) **28** (93% over-all yield). Hydrogenolysis of **28** in the presence of 10% Pd/C in aqueous ethanol at room temperature gave the trisphosphate, which was purified by treatment with cyclohexylamine to produce a crystalline salt. This compound was deaminated by passage through a column of Dowex 50 × 2 (H^+) resin to afford the free phosphate isolated as a bis-sodium salt **29** (97%).

The tetra-*O*-acetyl derivative **30** (98%), obtained similarly from **20**, was deacetylated and a crude alcohol was dibenzylphosphorylated to give tetrakisbenzylphosphate **31** (70% over-all yield). It was deprotected and the product was obtained as a bis-sodium salt[15] **32** (83%).

Oxidation of compound **24** with pyridinium chlorochromate in the presence of molecular sieves 4 Å in CH_2Cl_2 gave the deoxyinosose derivative **33** (96%), which was reduced with sodium borohydride to give the 2-epimer **34** (56%) as a major product. The structure of **34** was confirmed by the ^{1}H NMR spectrum of the 2-*O*-acetyl derivative **35**. Compound **34** was converted into the 2-epimer, 3-deoxy-*scyllo* Ins(1,4,5)P_3 **39**, following the standard sequence of reactions [→**36** (95%) →**37** (90%) →**38** (56%) →**39** (97%)].

Treatment of **24** with sulfuryl chloride in pyridine in the presence of DAMP gave the chloride **40** (70%). This compound was treated with tributyltin hydride in the presence of AIBN to provide the 2-deoxy derivative **41** (94%). Starting from **41**, 2,3-dideoxy Ins(1,4,5)(P_3)[14] **44** was obtained [→**42** (96%) →**43** (86%) →**44** (~100%)] in a conventional manner. Fluorination of **24** with dimethyl amino sulfur trifluoride (DAST) in CH_2Cl_2 afforded the 2-deoxy-2-fluoro derivative **45** (70%), which was converted into the tri-*O*-acetyl derivative **46** (95%). This acetate **46** was deacylated and conventionally phosphorylated to give the trisphosphate **47**, which was deprotec-

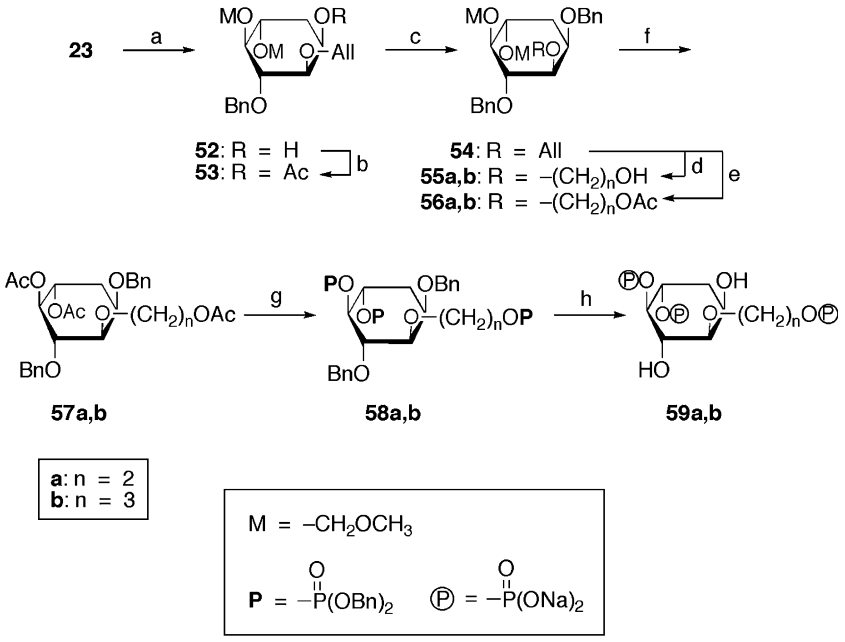


Scheme 3. Chemical modification at C-2 of 3-deoxy Ins(1,4,5)P_3. Synthesis of deoxy and deoxyfluoro derivatives. Reagents and conditions: (a) PCC, MS 4 Å, CH_2Cl_2, rt; (b) $NaBH_4$, EtOH; (c) Ac_2O, pyridine; (d) NaH, BnBr, DMF; (e) $MeOCH_2Cl$, diisopropylethylamime, DMF; Ac_2O, pyridine; (f) NaOMe, MeOH; dibenzyldiisopropylphosphoro-amidite, DMF; (g) H_2, 10% Pd/C, aqueous EtOH; $C_6H_{11}NH_2$, Dowex 50 W × 2 (H^+) resin, NaOMe, MeOH; (h) $SOCl_2$, DAMP, pyridine; (i) Bu_3SnH, AIBN, toluene, 120 °C; (j) Ac_2O, pyridine; (k) 4 M HCl, THF; phosphorylation; (l) DAST, CH_2Cl_2, rt; (m) aqueous 80% AcOH; $(PhO)_2POCl$.

ted to give the deoxyfluoro derivative[15] **48** (70% over-all yield). Similarly, the alcohol **34** was transformed into the deoxyfluoro derivative[15] **51** (80% over-all yield) via **49** and **50**.

Next, adenophosphine[9] analogues of 3-deoxy Ins(1,4,5)P_3 were prepared. Several permeant analogues of Ins(1,4,5)P_3 have been synthesized[8] and their ability to cross the membrane tested with vasopressin cells (Scheme 4).

Compound **23** was treated with dibutyltin oxide in toluene, and then after addition of allyl bromide, the mixture was heated at reflux temperature to give the allyl ether **52** (90%), which was characterized as the acetate **53** (96%) as a syrup. Compound **52** was converted into the benzyl ether (→**54**, 82%), which was subjected to ozonolysis in CH_2Cl_2/MeOH, followed by reduction with $NaBH_4$ (→**55a**) and conventional acetylation to give the 2-acetoxyethyl derivative **56a** (60% over-all yield). Hydrolysis of **56a** with 4 M



Scheme 4. Chemical modification of the C-2 function of 3-deoxy Ins(1,4,5)P_3. Reagents and conditions: (a) Bu_2SnO, TBAB, toluene, 120 °C; CH_2=CHBr; (b) Ac_2O, pyridine; (c) NaOMe, MeOH; NaH, BnBr, DMF; (d) (→**55a**) O_3, CH_2Cl_2/MeOH, −78 °C; $NaBH_4$, MeOH; (→**55b**) BH_3/THF, THF; H_2O_2; (e) Ac_2O, pyridine; (f) 4 M HCl, THF; Ac_2O, pyridine; (g) NaOMe, MeOH; i-$Pr_2NP(OBn)_2$, 1*H*-Tetrazole, DMF; mCPBA; (h) H_2, 10% Pd/C, aqueous 30% EtOH; $C_6H_{11}NH_2$, Dowex 50 W × 2 (H^+) resin, 1 M NaOMe, MeOH.

hydrochloric acid in THF gave, after conventional acetylation, the acetate **57a** (80%). Conventional de-O-acetylation of **57a** gave the diol, which was treated with 1*H*-tetrazole in DMF and then with dibenzyliso-propylphosphoro-amidite to give the protected tris-phosphate **58a** (72% over-all yield). Hydrogenolysis of **58a** in aqueous ethanol in the presence of 10% Pd/C gave the trisphosphate[15] **59a** (∼100%) isolated as a syrupy sodium salt.

Hydroboration of **54** was accomplished with boran–THF complex in THF, and then the reaction was quenched by addition of water, followed by treatment with 35% aqueous hydroperoxide for 30 min (→**55b**). The product was isolated as the acetate **56b** (∼100%) and similarly converted in turn into the trisphosphate[15] **59b**.

None of the eight compounds **29**, **32**, **39**, **44**, **48**, **51**, and **59a**,**b** activated pyruvate dehydrogenase phosphatase (PDH-Pase), or inhibited pyruvate dehydrogenase kinase (PDH-K) significantly. None of the compounds tested inhibited glucose 6-phosphatase (G6Pase) significantly.

Compounds **59a** and **59b** appeared to inhibit lipogenesis (Multi-Well Plate cell based assay). However, the inhibition decreased with increasing concentrations of the test compounds. When tested in vivo in streptozotocin diabetic mice (a model of type I diabetes) at a dose of 1 mg/kg, neither **59a** nor **59b** had any acute lowering effect on blood glucose. Furthermore, when administered chronically at a dose of 1 mg/kg/day for 10 days, **59a** did not significantly lower blood glucose.

Acknowledgments

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15. ^{1}H NMR (300 MHz) data for compound **32** (in D_2O); $[\alpha]_D^{21}$ −19 (*c* 3.7, H_2O); δ 4.50–4.47 (m, 1H, H-2), 4.23–4.12 (m, 1H, H-4), 3.90–3.81 (m, 2H, H-1, H-5), 3.70 (dd, 1H, $J_{5,6}$ = 9.2 Hz, $J_{1,6}$ = 9.6 Hz, H-6), 2.27 (ddd, 1H, $J_{2,3eq}$ = 4.4 Hz, $J_{4,3eq}$ = 4.7 Hz, J_{gem} = 14.4 Hz, H-3eq), 1.52 (m, 1H, H-3ax). [M−H] *m*/*z* 482, [M+Na−2H] *m*/*z* 505, $[M-2H]_2$ *m*/*z* 241; for compound **48** (in D_2O); $[\alpha]_D^{21}$ +7.3 (*c* 2.5, H_2O); δ 4.53–4.29 (m, 1H, H-5), 4.06–3.85 (m, 3H, H-1, H-2, H-4), 3.43 (dd, 1H, $J_{2,3}$ = 8.5 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 2.41–2.35 (m, 1H, H-6eq), 1.75–1.65 (m, 1H, H-6ax). [M−H] *m*/*z* 405, [M+Na−2H] *m*/*z* 427, $[M-2H]_2$ *m*/*z* 202; for compound **51** (in D_2O); $[\alpha]_D^{21}$ +7.5 (*c* 1.4, H_2O); δ 4.90 (d, 1H, $J_{2,F}$ = 48.6 Hz, H-2), 4.16–4.02 (m, 1H, H-4), 3.98–3.82 (m, 2H, H-1, H-5), 3.67 (dd, 1H, $J_{1,6} = J_{5,6}$ = 9.5 Hz, H-6), 2.41–2.30 (m, 1H, H-3eq), 1.60 (dddd, 1H, $J_{2,3ax}$ = 2.2 Hz, $J_{3ax,4}$ = 12.9 Hz, J_{gem} = 13.7 Hz, $J_{3ax,F}$ = 46.9 Hz, H-3ax). [M−H] *m*/*z* 405, [M+Na−2H] *m*/*z* 427, $[M-2H]_2$ *m*/*z* 202; for compound **59a** (in $CDCl_3$); $[\alpha]_D^{23}$ +17 (*c* 2.4, $CHCl_3$); δ 7.34–7.01 (m, 40H, 8 × Ph), 5.08 and 4.44 (m, 18H, H-4, H-5, 8 × CH_2Ph), 4.03–3.98 (m, 2H, 2 × H-2′), 3.89 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{2,3}$ = 9.8 Hz, H-3), 3.78 (br, 1H, H-1), 3.60–3.55 (m, 2H, 2 × H-1′), 3.26 (dd, 1H, $J_{1,2}$ = 2.7 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 2.61 (ddd, 1H, $J_{1,6eq} = J_{5,6eq}$ = 4.4 Hz, J_{gem} = 13.9 Hz, H-6eq), 1.39–1.28 (m, 1H, H-6ax); and for compound **59b** (in $CDCl_3$); $[\alpha]_D^{26}$ −129 (*c* 1.3, $CHCl_3$); δ 7.36–7.01 (m, 40H, 8 × Ph), 5.08 and 4.56 (m, 17H, H-5, 8 × CH_2Ph), 4.52 (dd, 1H, $J_{4,5}$ = 9.0 Hz, $J_{3,4}$ = 9.3 Hz, H-4), 4.05–3.95 (m, 2H, 2 × H-3′), 3.87 (dd, 1H, $J_{3,4}$ = 9.3 Hz, $J_{2,3}$ = 9.5 Hz, H-3), 3.76 (br, 1H, H-1), 3.75–3.38 (m, 2H, 2 × H-1′), 3.22 (dd, 1H, $J_{1,2}$ = 2.7 Hz, $J_{2,3}$ = 9,5 Hz, H-2), 2.65 (ddd, 1H, $J_{1,6eq} = J_{5,6eq}$ = 4.4 Hz, J_{gem} = 14.4 Hz, H-6eq), 1.83–1.79 (m, 2H, 2 × H-2′), 1.39–1.30 (m, 1H, H-6ax).