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THE SYNTHESIS OF HOMOCHIRAL INOSITOL PHOSPHATES FROM *MYO*-INOSITOL

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Abstract: A new synthetic procedure for efficient conversion of *myo*-inositol into homochiral inositol phosphates is presented, and is illustrated with total synthesis of *myo*-inositol 1-phosphate, 2-deoxy-*myo*-inositol 1-phosphate, *myo*-inositol 3-phosphate, *myo*-inositol 4-phosphate, *myo*-inositol 1,4-bisphosphate, *myo*-inositol 1,4,5-trisphosphate, and *myo*-inositol 3,4,5,6-tetrakisphosphate. The syntheses start with selfresolving *myo*-inositol camphanylidene *cis*-monoacetals **2a** and **2a'**, which are obtained in one step from the parent cyclitol and D- and L-camphor dimethyl acetal, respectively, and are harvested conveniently by means of a precipitation driven equilibration. The syntheses feature in the key steps the selective monophosphorylation, selective bissilylation and selective trisacylation of **2a** and **2a'**, as well as the use of dibenzyl phosphorochloridate and 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane for effecting mono and polyphosphorylations, respectively. In support of stereochemical assignments an X-ray structure of one of the intermediate fully protected inositol derivatives is also presented.

INTRODUCTION

Rapidly growing knowledge of phosphoinositides and of their role in the cell signalling systems[2] continuously widens the area of structural, bioorganic and medicinal studies of phosphoinositides and offers also novel possibilities for rational pharmacological intervention in the cell physiology. This progress is closely paralleled by intense synthetic investigations, which have already resulted in a number of viable synthetic routes to homochiral *myo*-inositol phosphates[2d,3,4] and their analogues[2d,4].

Although successful efforts to synthesize homochiral inositol phosphates from the chiral starting materials[5] or by means of the asymmetric synthesis[6], chemoenzymatic methods[7], and *via* microbial benzene oxidations[8] are already on record, the vast majority of the known syntheses of naturally occurring inositol phosphates start from the readily available parent *myo*-inositol (1).[3,4] According to one of the popular synthetic procedures[9] *myo*-inositol by treatment with ethoxycyclohexene and acid is first converted into a mixture of bisacetal derivatives which, after prerequisite separation, are then individually subjected to further protecting groups manipulation and resolution. Phosphorylation of the resolved and suitably protected inositol derivative followed finally by ultimate deprotection leads then to a homochiral inositol phosphate[3,4]. In this report we wish to present a modified approach in which instead of ethoxycyclohexene camphor dimethyl acetal is used for the first derivatization of the parent cyclitol. Such a synthetic maneuver, as originally described by Bruzik and Salamończyk[10], combines the desired inositol acetal formation with resolution in a single step and, fortunately, leads to the formation of one of the four *myo*-inositol camphor 2,3-monoacetals[11], i.e., D-2,3-*O*-(D-1,7,7)-Trimethyl[2.2.1]bicyclohept-2-ylidene)-myo-inositol (**2a**, O3-*endo*) in noticeable preference. As we have subsequently found, the preferential formation of this particular stereoisomer can be further augmented by means of a precipitation-driven equilibration of the original pool of all the four camphor derived *cis*-monoacetals affording ultimately the favored **2a** in at least 65% isolated yield, and in the form of an easily separable precipitate. Based on the ready availability of this acetal (and its enantiomer), are the developed syntheses of six naturally occurring inositol phosphates and one analogue which follow.[12]

RESULTS AND DISCUSSION

Synthesis of D-2,3-*O*-(D-1,7,7)-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (2a, O3-*endo*) and D-1,2-*O*-(D-1,7,7)-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (2a', O1-*endo*).

As reported in the pioneering report[10] sulfuric acid-catalyzed reaction of *myo*-inositol with D-camphor dimethyl acetal led to the formation of a complex mixture of positional and stereoisomers of mono and bis *myo*-inositol camphor acetals which upon subsequent partial hydrolysis gave four cis monoacetals **2a-d** in a 47:23:13:17 ratio (Scheme 1). The major isomer **2a** was shown to be chromatographically separable in the form of its tetrabenzyl ether **3a** in 33% yield, and as such has already found use as the chiral substrate in synthesis of homochiral phosphoinositides[13]. However, we have found that *p*-toluenesulfonic acid-catalyzed equilibration of the crude mixture of **2a-d** in 50:5:1 chloroform-methanol-water solvent system affords the favored acetal **2a** in the form of a precipitate and in yield increased to 65%. The solid **2a** collected afterwards by simple filtration was found to be contaminated only with minor, albeit chromatographically and spectrally detectable, amounts of the other monoacetals and of *myo*-inositol, and was judged to be of sufficiently high purity for direct synthetic use. The stereochemical integrity of this material was confirmed chemically by its conversion into the known (+)-1,4,5,6-tetrabenzyl ether **3a**[10] as well as by an X-ray analysis of one of its fully protected derivatives (**23**, *vide infra*).

It is also important to note that replacement of D-camphor dimethyl acetal with L-camphor dimethyl acetal[10] in the above synthetic sequence leads to the equally facile production of the enantiomer of **2a**, i.e., tetrol **2a'** (Figure 1).

The syntheses are conveniently carried out on a 0.01 mole scale (1.8g of *myo*-inositol), and furnish reproductively 2g of ready-to-use **2a** (or **2a'**), in each batch. Scaling up to 0.1 mole can also be done without apparent loss in yield albeit at the cost of lower isomeric purity of the collected **2a** (or **2a'**).

Scheme 1

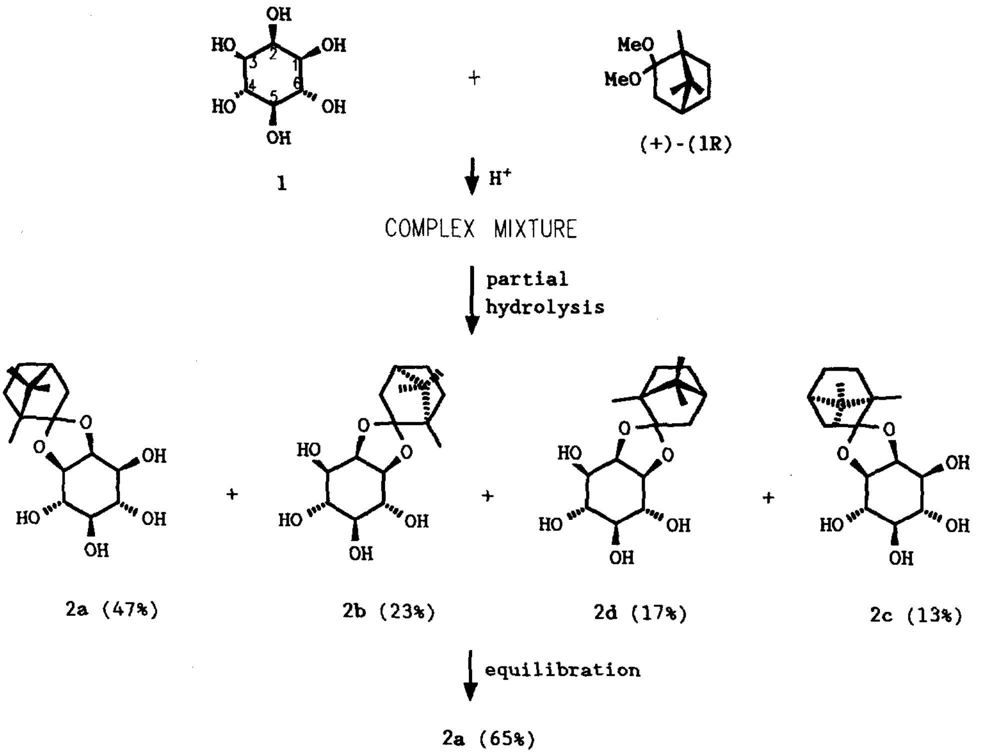
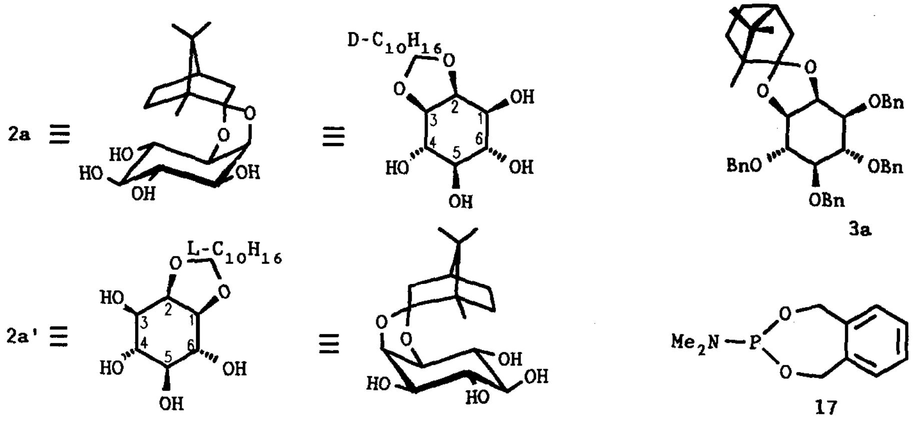


Figure 1

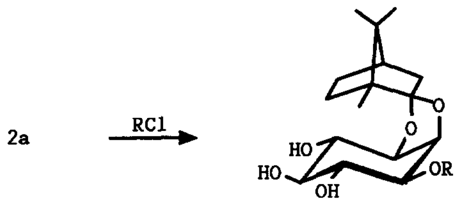


Selective protection of tetrols 2a and 2a'

After the convenient access to gram quantities of enantiomeric tetrols **2a** and **2a'** had been secured, it became apparent that advantageous use of these tetrols in synthesis of inositol phosphates hinged primarily on the possibility of their regioselective derivatization. Recent suggestions by Reese and Ward[14] regarding potentially selective blocking of the closely related cyclopentylidene *myo*-inositol 2,3-monoacetal led us however to believe, that the four hydroxy groups in **2a** and **2a'** might lend themselves to chemical distinction even though all were equatorial and secondary.

A series of exploratory experiments aimed first at the selective protection of only one hydroxy group in **2a** revealed that the relatively bulky protecting groups are placed preferentially at the Cl-hydroxyl. Treatment of **2a** with either 1.1 mol.equiv. of *tert*-butylchlorodiphenylsilane in the presence of imidazole in acetonitrile, or 1.1 mol.equiv. of pivaloyl chloride in pyridine, or 1.6 mol.equiv. of diethyl phosphorochloridate in pyridine led to the formation of the corresponding Cl-OH protected derivatives **4**, **5** and **6** in 30, 44 and 20% isolated yield, respectively (Scheme 2). Analogous reactions of **2a** with 1.1 mol.equiv. of benzyl bromide, allyl bromide, *tert*-butylchlorodimethylsilane or diphenyl phosphorochloridate gave in our hands very complex mixtures which were not studied further.

Scheme 2



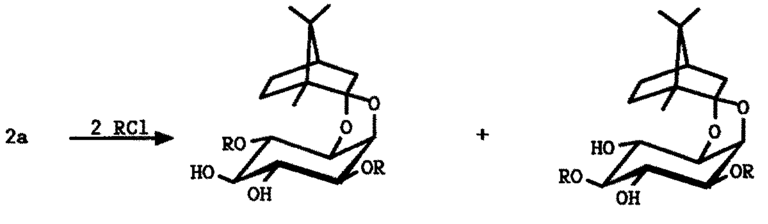
4 ($R=Ph_2Bu^tSi-$; 30%)
5 ($R=(CH_3)_3CCO-$; 44%)
6 ($R=(EtO)_2PO-$; 20%)

Interestingly, when **2a** was allowed to react with 2.2 mol.equiv. of either *tert*-butylchlorodimethylsilane or pivaloyl chloride under the above mentioned conditions, selective bis-protection of two hydroxy groups resulted. This time however, the preferred sites of protection turned out to be different for the two reagents which afforded the 1,4-bissilyl derivative **7** (50%) in the former case, and the 1,5-bispivaloyl derivative **8** (43%), in the latter case, respectively (Scheme 3).

Finally, we have found that simultaneous protection of three hydroxy groups in **2a** could also be carried out in the selective manner. This was conveniently accomplished by treatment of **2a** with an excess of pivaloyl chloride in pyridine which resulted in the prevalent formation of the 1,4,5-trispivaloyl derivative **9**, which was readily freed from the other isomers by chromatographic separation yielding pure **9** in 48% yield (Scheme 4).

Positional identification of the partially protected inositol derivatives **4-11** was primarily based on the analysis of their ^1H NMR spectra in which the downfield shift of inositol ring protons at the acylated positions and the vicinal J_{HCOH} (in DMSO-d_6) and J_{HCCH} coupling constants were found to be the most informative, especially in combination with the corresponding ^1H-^1H COSY experiments. It was usually convenient to start the analysis with the assumption that of the two small $^3J_{H_a,H_e}$ coupling constants available, the one involving H-2, H-3 protons of the ring junction should be somewhat larger than the

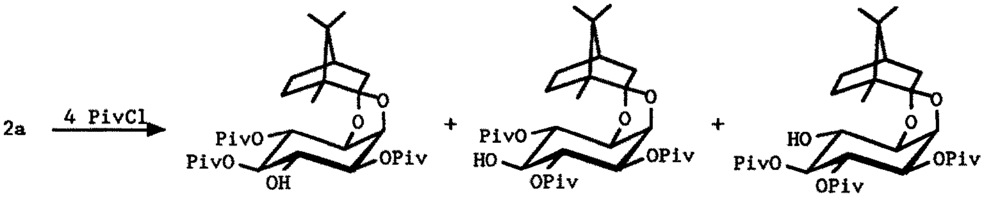
Scheme 3



7 (R=Bu^tMe_2Si- ; 50%) --

-- 8 (R=$(CH_3)_3CCO$- ; 40%)

Scheme 4



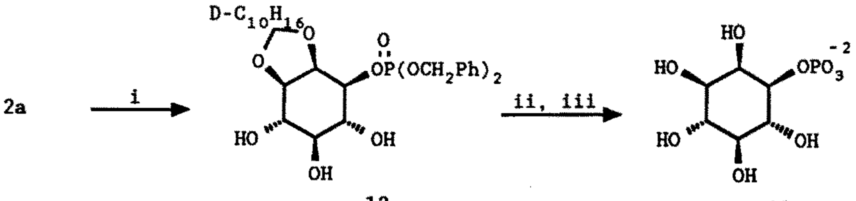
Piv=$(CH_3)_3CCO$- 9 (48%) 10 (19%) 11 (11%)

other for geometrical reasons. By the same token, $^3J_{Ha,Ha}$ involving H-3, H-4 protons was expected to be palpably smaller than all the other $^3J_{Ha,Ha}$'s in the inositol ring (cf. X-ray analysis of **23** and Table 1 listing the pertinent dihedral angles). In addition, some of the discussed partially protected inositol derivatives have had their assignment confirmed by serving as precursors in the successful syntheses of naturally occurring inositol phosphates which follow.

Synthesis of D-*myo*-inositol 1-phosphate

The discovered possibility of effecting selective monophosphorylation of **2a** led us to develop a very short synthesis of *myo*-inositol 1-phosphate (Scheme 5).

Scheme 5



12 13

(i) $ClP(O)(OCH_2Ph)_2$, pyridine, 4°; (ii) H_2, Pd/C, methanol; (iii) AcOH-H_2O (1:1).

Treatment of **2a** with 1.6 mol.equiv. of dibenzyl phosphorochloridate in pyridine afforded monophosphate **12**, practically as the only chromatographically well distinct product which accumulated in the reaction mixture in any significant amount. Facilitated by this virtue isolation of **12** provided crystalline product which after recrystallization from benzene-heptane gave analytically pure monophosphate in 23% yield. Hydrogenolysis of **12** over Pd/C in methanol, followed directly by treatment with aqueous acetic acid led to removal of the benzyl ester groups and the camphor residue, respectively, and afforded D-*myo*-inositol 1-phosphate (**13**), which was isolated in the form of its biscyclohexylammonium salt in 14% overall yield. ($[\alpha]_D$=+3.55°; δ_P= 4.64).

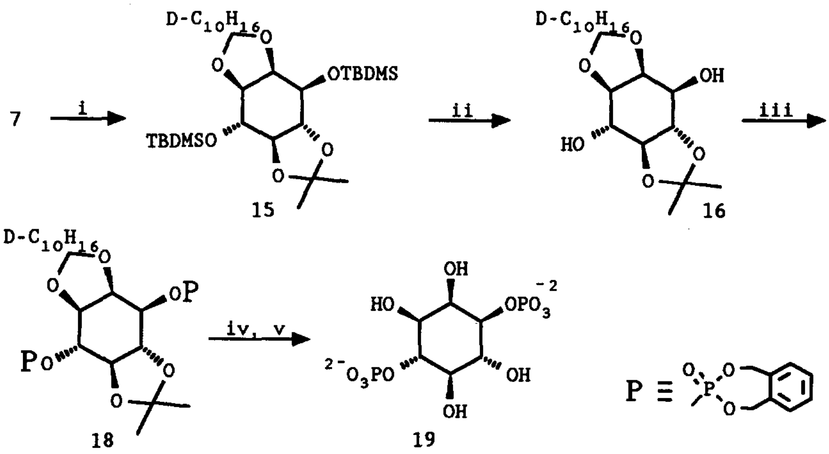
Synthesis of D-myo-inositol 3-phosphate

Starting from tetrol **2a'** and employing exactly the same methodology as above yielded D-*myo*-inositol 3-phosphate (**14**), in 16% overall yield. ($[\alpha]_D$= -3.4°; δ_P= 4.57).

Synthesis of D-myo-inositol 1,4-bisphosphate

Diol **7**, obtained directly from **2a** by selective bissilylation, was reacted with an excess of 2,2-dimethoxypropane in the presence of catalytic amounts of *p*-toluenesulfonic acid and pyridinium *p*-toluenesulfonate (PPTS) to give cleanly fully protected **15** (Scheme 6). Cleavage of silyl ethers by treatment of **15** with 1.1M Bu_4NF in tetrahydrofuran gave the 1,4-unprotected diol **16** in quantitative yield. To effect bisphosphorylation of this diol we choose a slight modification of the phosphorylation procedure reported recently by Watanabe and al.[15] Thus, treatment of **16** with 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane (**17**),[16] in the presence of tetrazole, followed by treatment with *m*-chloroperbenzoic acid (MCPBA) gave protected bisphosphate **18** in nearly quantitative yield. Successive treatment of **18** with H_2 over Pd/C and aqueous acetic acid converted it into D-*myo*-inositol 1,4-bisphosphate (**19**), isolated ultimately as its tetracyclohexylammonium salt in 35.6% overall yield. ($[\alpha]_D$=+1.8°; δ_P= 4.28, 4.92).

Scheme 6

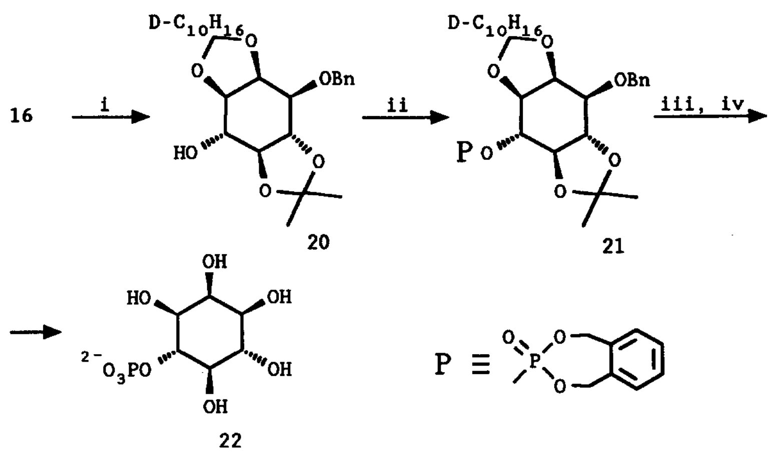


(i) 2,2-dimethoxypropane, DMF, PPTS, TsOH; (ii) Bu_4NF/THF; (iii) a: 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane, tetrazole, CH_2Cl_2, b: MCPBA; (iv) H_2/Pd/C; (v) H_2O-AcOH 1:1.

Synthesis of D-myo-inositol 4-phosphate

Our synthesis of this inositol phosphate is delineated in Scheme 7. Diol 16,

Scheme 7



(i) $PhCH_2Br/NaOH$, benzene; (ii) a: 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane, tetrazole, CH_2Cl_2; b: MCPBA; (iii) H_2,Pd/C, methanol (iv) $AcOH-H_2O$ (1:1).

available as an intermediate from the above synthesis of *myo*-inositol 1,4-bisphosphate, was benzylated selectively in the 1-position in 68% yield. The resultant alcohol **20** was then phosphorylated by means of **17** and MCPBA as above, to give fully protected phosphate **21**. Hydrogenolysis of **21** over Pd/C, followed directly by cleavage of acetals with aqueous acetic acid afforded D-*myo*-inositol 4-phosphate (**22**), isolated as its biscyclohexylammonium salt in 25% overall yield (calculated on **2a**). ($[\alpha]_D$=-1.2°; δ_P= 4.94).

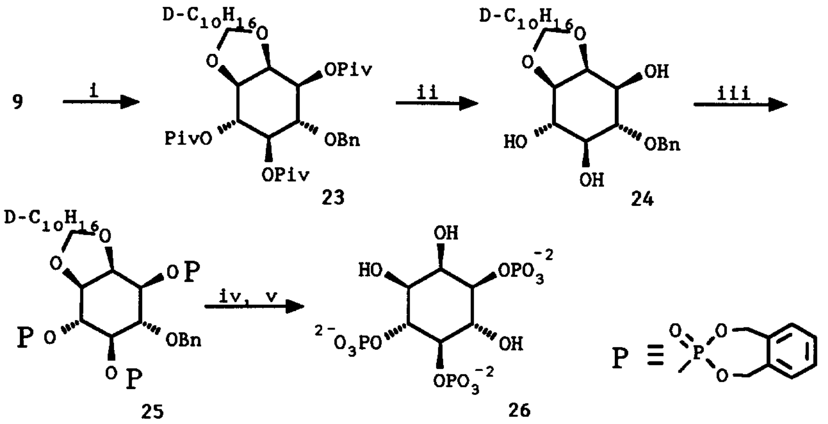
Synthesis of D-myo-inositol 1,4,5-trisphosphate

Trispivaloyl derivative **9**, obtained in one step from **2a** as described above, was treated with benzyl bromide and silver oxide to give 6-*O*-benzyl derivative **23** (Scheme 8; cf. also Figure 2). Alkaline cleavage of the ester groups in **23** led to triol **24** which was subjected to phosphorylation by means of **17** and MCPBA yielding trisphosphate **25**. Hydrogenolysis of the benzyl and ortho-xylylene groups over Pd/C, followed by acetal cleavage with aqueous acetic acid converted **25** into D-*myo*-inositol 1,4,5-trisphosphate (**26**), which was isolated as its hexasodium salt in 17.5% overall yield. ($[\alpha]_D$=-30°; δ_P= 3.63, 5.31, 5.41).

Synthesis of D-myo-inositol 3,4,5,6-tetrakisphosphate

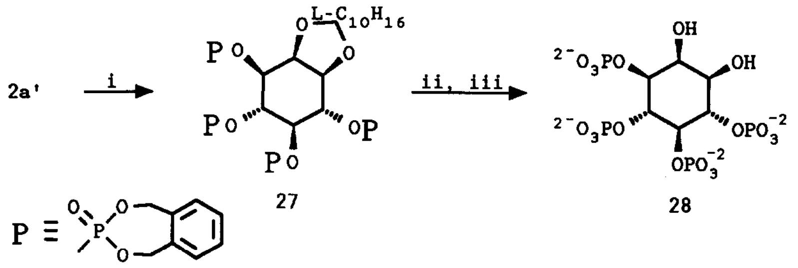
As shown in Scheme 9, exhaustive phosphorylation of **2a**' by consecutive action of an excess of **17** and MCPBA afforded protected tetrakisphosphate **27**, which after usual hydrogenolysis over Pd/C and acetal cleavage with aqueous acetic acid, gave D-*myo*-inositol 3,4,5,6-tetrakisphosphate (**28**), isolated as its octasodium salt in 56% overall yield. ($[\alpha]_D$=-6.2°; δ_P= 4.02, 4.29, 4.41, 4.93).

Scheme 8



(i) PhCH$_2$Br, Ag$_2$O, DMF; (ii) NaOH, MeOH; (iii) a: 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane, tetrazole, CH$_2$Cl$_2$; b: MCPBA; (iv) H$_2$, Pd/methanol; (v) AcOH-H$_2$O (1:1).

Scheme 9



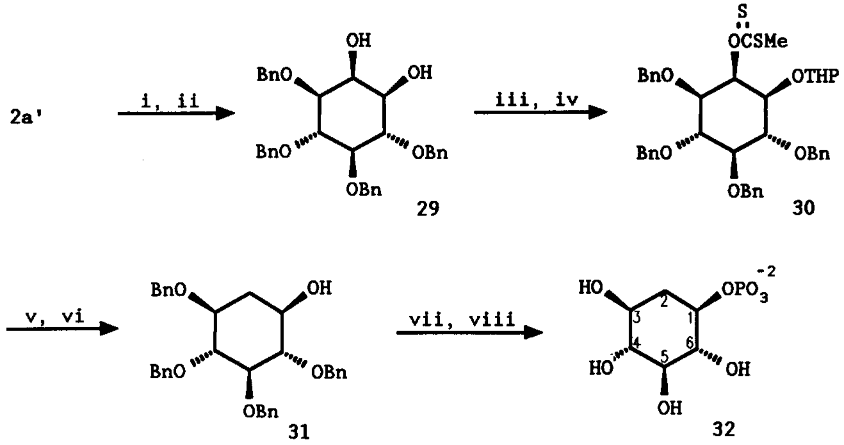
(i) a: 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane, tetrazole, CH$_2$Cl$_2$; b: MCPBA; (ii) H$_2$, Pd/C; (iii) AcOH-H$_2$O (1:1).

To the best of our knowledge, the synthesis of homochiral **28** presented above constitutes the first chemical synthesis of this inositol polyphosphate in its natural enantiomeric form.[17] Synthesis of the corresponding racemate has already been reported.[18]

Synthesis of D-2-deoxy-*myo*-inositol 1-phosphate

In order to demonstrate that versatility of tetrols **2a** and **2a'** as precursors of phosphoinositides reaches beyond the naturally occurring inositol phosphates we elected to carry out also an exemplary synthesis of an analogue, i.e., 2-deoxy-inositol 1-phosphate. According to the synthetic route delineated in Scheme 10, in order to secure placement of the phosphate group in the 1-position in the final product, it was necessary to start the synthesis with tetrol **2a'**. Exhaustive benzylation of **2a'**, followed by acetal cleavage gave

Scheme 10



(i) $PhCH_2Br$, NaH, toluene/HMPA, Δ; (ii) AcOH 80%; (iii) DHP, PPTS, CH_2Cl_2; (iv) NaH, CS_2, MeI, THF; (v) Bu_3SnH, AIBN, toluene, Δ; (vi) EtOH, PPTS; (vii) a: 2-dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane, tetrazole, CH_2Cl_2 b: MCPBA; (viii) H_2, Pd/C.

enantiomeric 3,4,5,6-tetra-*O*-benzyl inositol **29**, as described previously.[10] Treatment of **29** with 3,4-dihydro-2*H*-pyran and mild acid converted it into a mixture of two diastereomeric 1-tetrahydropyranyl ethers which were further transformed into the corresponding 2-dithiocarbonates **30** without separation. Deoxygenation[19] at the 2-position, followed directly by tetrahydropyranyl ether cleavage converted **30** into 2-deoxy-3,4,5,6-tetra-*O*-benzyl inositol **31**, in one pot. Phosphorylation of **31** by means of **17** and MCPBA, and subsequent hydrogenolytic removal of all the protecting groups gave the desired D-2-deoxy-*myo*-inositol 1-phosphate (**32**), isolated as its biscyclohexylammonium salt in 40% overall yield. ($[\alpha]_D$=+8.5°; δ_P= 4.22). Simple replacement of **2a'** with **2a** in above synthetic sequence would lead to the equally efficient production of enantiomeric 2-deoxy-*myo*-inositol 3-phosphate.

X-Ray structure of D-6-*O*-benzyl-1,4,5-tris-*O*-pivaloyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-*myo*-inositol (23)

In order to additionally support the structural assignments made in this study we decided to carry out an X-ray diffraction experiment with one of the intermediates available in the crystalline form. Attempted growing of single crystals of **12** and **23** met with success only in the case of the fully protected inositol derivative **23**. A preliminary (at R=0.089),[20] molecular structure of **23** showing also its absolute configuration is displayed in Figure 2. It supports fully the assigned stereochemistry and substitution pattern at the key inositol ring positions in **23**, and indirectly, in **9** and **2a**. Importantly, the resulted structure offers also the first direct insight into the favored configuration at the spiroacetal stereocenter in the studied 1,2- and 2,3-monoacetals. As can be seen from Figure 2, O-2 and O-3 in **23** occupy the *exo* and the *endo* position, respectively, and the bridgehead methyl faces H-4 and H-6 protons of the inositol ring. This finding confirms earlier NMR-based conclusions drawn for **3a**.[10]

The revealed conformation of **23** has no unusual features. The fully blocked inositol

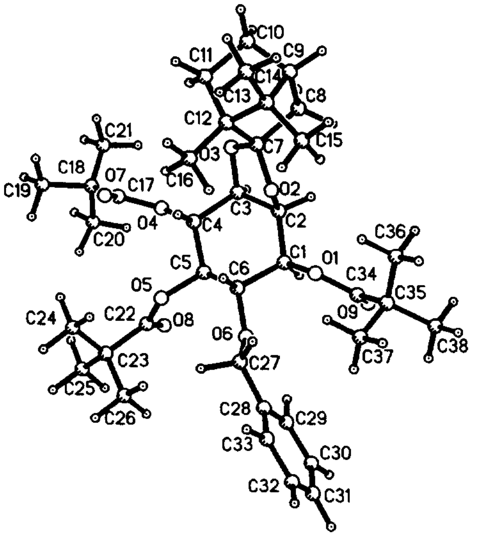


Figure 2. The crystal structure of 23 (at R=0.089)[20], with arbitrary atom labeling. Numbering of the inositol ring conforms to the IUB rules[11].

Table 1

HCCH Torsion angles (°) of the inositol ring in 23[a].

H11-C1-C2-H21	-43.3
H21-C2-C3-H31	37.6
H31-C3-C4-H41	-160.0
H41-C4-C5-H51	178.0
H51-C5-C6-H61	177.1
H61-C6-C1-H11	172.5

[a] Approximate values derived at R=0.089[20]

ring exists in a chair conformation deformed somewhat the acetal ring junction, as expected. The resulted changes in torsion angles (cf. Table 1), as reflected in the pertinent $^3J_{HH}$ coupling constants, have proven useful in facilitating the assignments discussed above. The acetal five-membered ring in 23 adopts a half-chair conformation.[20]

Conclusions

A new methodology for preparing a number of inositol phosphates was developed. It is based on the complementary use of selfresolving inositol cis-monoacetals **2a** and **2a'**, which can be obtained in quantity from *myo*-inositol and D- or L-camphor dimethyl acetal, respectively, in a single step. It is also found that the four equatorial hydroxy groups in **2a** and **2a'** can be effectively distinguished between chemically. This feature of **2a** and **2a'** has been capitalized upon extensively in the presented syntheses of inositol phosphates and is also finding use in parallel synthetic investigations.[21]

EXPERIMENTAL

General

Solvents and reagents used in this study were purified and dried (when required) by conventional methods. Dimethyl acetals of D- and L-camphor were obtained by their reactions[22] with trimethyl orthoformate. 2-Dimethylamino-5,6-benzo-1,3,2-dioxaphosphepane[16] and dibenzyl phosphorochloridate[23] were obtained by published methods. Optical rotations were measured with a Perkin-Elmer 241 MC spectrometer. NMR spectra were recorded on the Bruker MSL-300 (^{1}H 300.13MHz; ^{13}C 75.47MHz; ^{31}P 121.50MHz) and Bruker AC-200 (^{1}H 200.13MHz; ^{13}C 50.32MHz) spectrometers. Assignments of ^{1}H and ^{13}C NMR resonances were aided by 2D COSY and DEPT experiments, respectively. Chemical shifts in ^{1}H and ^{13}C NMR spectra are in ppm relative to TMS; in ^{31}P NMR spectra in ppm relative to 85% H_3PO_4. Coupling constants are in Hz. The mass spectra were measured on a Finnigan Mat 95 spectrometer. All yields are given for isolated compounds. Melting points are uncorrected. The purity of each product was checked by h.p.t.l.c (Merck, 5547), visualized by dipping in 50% solution of phosphomolybdic acid in ethanol. Preparative chromatography (short column) was carried out on Merck 230-400 mesh silica gel.

D-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (2a)

To a suspension of dry *myo*-inositol (5.4 g, 30 mmol) in anhydrous DMSO (60 mL) were added D-camphor dimethyl acetal[21] (12 g, 60 mmol) and sulfuric acid (50 μL), and the resulting heterogeneous mixture was stirred at 50-55°C until all *myo*-inositol had dissolved (ca. 3 h). Triethylamine (1 mL) was then added and the reaction mixture was concentrated *in vacuo*. To the residue chloroform-methanol-water (50:5:1, 100 mL) was added and the mixture was homogenized by sonication. *p*-Toluenesulfonic acid (20 mg) was then added and the resulting cloudy solution was stirred at room temperature overnight to yield a white precipitate. This, after addition of 0.5 mL of triethylamine, was filtered off, washed with chloroform (2x80 mL) and dried *in vacuo* at room temperature to give 6.1 g of 2a (65%). ^1H NMR (CD_3OD) δ 1.05 (s,3H), 1.07 (s,3H), 1.23 (s,3H) 1.36-1.75 (m,3H), 1.87-2.04 (m,2H), 2.17-2.95 (m,2H), 3.34 (t,J=9.6, 1H), 3.64 (dd,J=10.0, 7.1, 1H), 3.71 (t, J=9.5, 1H), 3.89 (dd, J=4.2, 9.6, 1H), 3.98 (dd, J=7.1, 5.6, 1H), 4.47 (dd, J=5.5, 4.3, 1H); ^{13}C NMR (DMSO-d_6) δ 13.32, 23.93, 24.12, 30.43, 32.79, 48.29, 48.74, 51.08, 54.69, 73.48, 75.54-76.43 (traces of free inositol, 4 lines), 77.69, 78.83, 79.19, 79.87, 80.15, 119.66.

D-1,2-*O*-(L-1,7,7-Trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (2a')

Starting with L-camphor dimethyl acetal[21] and exactly repeating the above procedure afforded 2a' in 65% yield. The NMR data for 2a' were found identical with those obtained for the enantiomeric 2a. Due to difficulties in preparing completely transparent solutions of 2a and 2a' optical rotation data for these two compounds were not obtained.

D-1,4,5,6-Tetra-*O*-benzyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (3a)

Tetrol 2a (160 mg, 0.51 mmol) was dispersed in anhydrous toluene (3 mL) by sonication (3 min.), and anhydrous HMPTA (0.5 mL) and sodium hydride (125 mg of a 50% suspension in mineral oil) were added. The dispersion was stirred at 70°C until the evolution of hydrogen ceased, and freshly distilled benzyl bromide (440 mg, 2.57 mmol) was added. Heating was continued at 100°C for 4 h and the reaction was quenched with water (2 mL). Extraction with hexane, concentration of extracts and chromatography on a short column of silica gel (hexane-ether 6:1) gave 3a (220 mg, 64%) as an oil, $[\alpha]_D$=+18° (*c* 3, chloroform)(lit.[10] +18°). This material was found identical in every respect with a sample of 3a prepared previously.[10]

D-1-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (4)

To a solution fo 2a (160 mg, 0.5 mmol) and imidazole (100 mg, 1.5 mmol) in anhydrous acetonitrile (3 mL) was added *tert*-butylchlorodiphenylsilane (600 μL, 0.6 mmol) and the mixture was stirred at room temperature for 5 h. Benzene (5 mL) was then added and the solution was separated from precipitate by decantation. The precipitate was washed again with benzene (5 mL) and decanted. The supernatant solutions were combined and evaporated, and the residue was chromatographed on a short column of silica gel (chloroform-methanol 30:1) to yield **4** (83 mg, 30%) as a foam. R_F= 0.22 (chloroform-methanol 15:1); ^{1}H NMR (DMSO-d_6) δ 0.88 (s,3H), 0.91 (s,3H), 1.10 (s,3H), 1.11 (s,9H), 1.30-2.06 (m,7H), 2.93 (dt, J=9.4, 5.2, 1H), 3.30 (ddd, J=7.1, 9.7, 4.9, 1H), 3.53-3.62 (m,2H), 3.84 (dd, J=45, 5.9, 1H), 3.97 (dd, J=4.2, 9.4, 1H), 4.86 (d, J=5.1, 1H), 4.90 (d, J=4.9, 1H), 4.99 (d, J=4.8, 1H); ^{13}C NMR (acetone-d_6) δ 9.26, 19.83, 20.10, 26.41, 44.81, 45.08, 47.53, 51.15, 72.32, 72.55, 73.76, 75.74, 76.19, 76.66, 116.70, 127.21, 127.30, 129.37, 129.47, 135.83, 136.08.

D-1-*O*-Trimethylacetyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (5)

To a solution fo **2a** (160 mg, 0.5 mmol) in anhydrous pyridine (2 mL) was added pivaloyl chloride (75 μL, 0.6 mmol) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on a short column of silica gel (chloroform-methanol 20:1) to yield **5** (90 mg, 44%) as a foam. R_F=0.2 (chloroform-methanol 10:1), ^{1}H NMR (DMSO-d_6) δ 0.87 (s,3H), 0.91 (s,3H), 1.01 (s,3H), 1.23 (s, 9H), 1.66-2.25 (m,7H), 3.17 (dt, J=9.0, 3.8, 1H), 3.35 (ddd, J=6.9, 9.0, 3.9, 1H), 3.59 (dt, J=9.2, 4.3, 1H), 3.88 (dd, J=5.6, 7.0, 1H), 4.30 (t, J=5.2, 1H), 4.89 (dd, J=9.5, 4.7, 1H), 5.02 (t, J=3.9, 2H), 5.12 (d, J=4.2, 1H); ^{13}C NMR (CD$_3$OD) δ 10.60, 21.13, 21.13, 27.87, 28.24, 30.80, 40.17, 46.72, 46.90, 52.84, 72.02, 73.85, 75.08, 75.31, 76.17, 77.36, 77.93, 119.16, 179.87.

D-2,3-*O*-(D-1,7,7-Trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol 1-diethylphosphate (6)

To a solution of **2a** (160 mg, 0.5 mmol) in anhydrous pyridine (2 mL) was added diethyl phosphorochloridate (95 mg, 0.55 mmol) and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (4 mL) and washed with aqueous sodium bicarbonate. The organic phase was evaporated and the residue was chromatographed on a short column of silica gel (chloroform-methanol 25:1) to yield **6** (45 mg, 20%) as an oil. R_F=0.23 (chloroform-methanol 15:1); $[\alpha]_D$=-14° (*c* 1.5, chloroform); ^{1}H NMR (CDCl$_3$) δ 0.83 (s,3H), 0.85 (s,3H), 0.96 (s,3H), 1.32 (dt, J=1.0, 7.1, 3H), 1.32 (dt, J=1.0, 7.1, 3H), 1.37-2.06 (m,7H), 3.36 (t, J=9.5, 1H), 3.53 (dd, J=7.1, 9.8, 1H), 3.78 (t, J=9.1, 1H), 3.90 (dd, J=6.9, 5.4,1H), 4.07-4.23 (m,4H), 4.39 (t,J=5.2, 1H), 4.47 (ddd, J=5.0, 9.2, 13.2, 1H); ^{31}P NMR (CDCl$_3$) δ -0.60.

D-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]-bicyclohept-2-ylidene)-*myo*-inositol (7)

To tetrol **2a** (1.76 g, 5.6 mmol) dispersed in anhydrous acetonitrile (5 mL) by sonication was added imidazole (1g, 14 mmol) and *tert*-butylchlorodimethylsilane (1.85 g, 12.3 mmol), and the mixture was stirred at room temperature overnight. Benzene (20 mL) was then added and the resulting mixture was washed with aqueous sodium bicarbonate. The organic phase was separated, dried (MgSO$_4$), and evaporated to afford crude product which was purified by column chromatography on silica gel (hexane-ether 4:1) to yield pure **7** (1.5 g, 50%) as an oil. R_F=0.2 (hexane-ether 3:1); $[\alpha]_D$=-10° (*c* 2.0, chloroform); ^{1}H NMR (DMSO-d_6) δ 0.14 (s,3H), 0.15 (s,3H), 0.16 (s,3H), 0.18 (s,3H), 0.89 (s,3H), 0.92 (s,3H), 0.96 (s,18H), 1.05 (s,3H), 1.21-2.10 (m,7H), 3.12 (dt, J=8.9, 4.4, 1H), 3.45 (dt,J=8.8, 4.4, 1H), 3.56 (dd, J=6.7, 9.3, 1H), 3.83 (t, J=6,6, 1H), 3.86 (dd, J=4.3, 8.7, 1H), 4.19 (dd, J=4.3, 6.2, 1H), 4.53 (d, J=4.5, 1H), 4.66 (d, J=4.4, 1H); ^{13}C NMR (C$_6$D$_6$) δ -3.85,

-3.67, -3.54, -3.29, 10.82, 19.04, 19.18, 21.27, 21.30, 26.66(3C), 26.88(3C), 28.24, 30.54, 46.13, 46.35, 48.94, 52.54, 73.06, 73.39, 75.68, 77.80, 78.38, 79.29, 118.46.

D-1,5-Di-*O*-trimethylacetyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (8)

To a solution of **2a** (35 mg, 0.08 mmol) in anhydrous pyridine (1.5 mL) was added pivaloyl chloride (24 μL, 0.17 mmol) and the resulting solution was stirred at room temperature for 3 h. After evaporation to dryness the residue was chromatographed on a short column of silica gel (chloroform-acetone 25:1) to yield **8** (29 mg, 40%) as a foam. R_F=0.24 (chloroform-acetone 10:1); ^{1}H NMR (DMSO-d_6) δ 0.92 (s,3H), 0.94 (s,3H), 1.02 (s,3H), 1.24 (s,18H), 1.27-2.16 (m,7H), 3.61 (ddd, J=7.0, 6.2, 5.9, 1H), 3.90 (ddd, J=7.7, 9.8, 5.8, 1H), 4.06 (t, J=6.3, 1H), 4.42 (dd, J=4.3, 6.4, 1H), 4.77 (t, J=7.5, 1H), 5.01 (dd, J=4.3, 9.9, 1H), 5.46 (d, J=6.0, 1H), 5.56 (d, J=5.9, 1H).

D-1,4,5-Tri-*O*-trimethylacetyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-lidene)-*myo*-inositol (9)

To a stirred solution of tetrol **2a** (3.14 g, 10 mmol) in dry pyridine (20 mL) was added pivaloyl chloride (6.03 g, 40 mmol) during 30 min. Stirring was continued for 48 h at room temperature. Hexane (100 mL) was added and the resulting mixture was washed twice with saturated sodium bicarbonate solution, then dried ($MgSO_4$) and evaporated to give an oil. This was chromatographed on a short column of silica gel (carbon tetrachloride-acetone 50:1) to yield **9** (2.7 g, 48%) as the major product. R_F=0.27 (carbon tetrachloride-acetone 20:1); mp 110-112°C; $[\alpha]_D$=-12°(*c* 2.0, chloroform); ^{1}H NMR (DMSO-d_6) δ 0.91 (s,3H), 0.97 (s,3H), 1.01 (s,3H), 1.19 (s,9H), 1.20 (s,9H), 1.26 (s,9H), 1.30-2.0 (m,7H), 3.88 (dt, J=9.6, 6.1, 1H), 4.27 (dd, J=7.3, 5.4, 1H), 4.41 (t, J=5.4, 1H), 5.01 (t, J=10, 1H), 5.07 (dd, J=10.5, 7.3, 1H), 5.14 (dd, J=9.6, 5.4, 1H), 5.71 (d, J=6.1, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 20.8, 20.9, 27.7(9C), 29.9(2C), 39.3, 39.4, 39.5, 45.5, 45.9, 48.6, 52.3, 70.8, 72.0, 73.9, 74.4, 119.0, 177.3, 178.7, 178.8.

Two minor products of the reaction, **10** and **11** were also eluted from the column and were assigned their structures by ^{1}H NMR. **10** (1 g, 19%): an oil, R_F=0.10 (carbon tetrachloride-acetone 20:1), ^{1}H NMR (DMSO-d_6) δ 0.93 (s,3H), 1.03 (s,6H), 1.15 (s,9H), 1.18 (s,9H), 1.19 (s,9H), 3.72 (ddd, J=5.4, 6.0, 6.2, 1H), 4.19 (dd, J=5.4, 6.4, 1H), 4.51 (dd, J=4.4, 6.4, 1H), 5.06 (dd, J=6.0, 8.1, 1H), 5.32 (dd, J=4.3, 10.8, 1H), 5.49 (dd, J=8.1, 10.8, 1H), 5.89 (d, J=5.2, 1H). **11** (600 mg, 11%): mp 206-208°C, R_F=0.28 (carbon tetrachloride-acetone 20:1), ^{1}H NMR ($CDCl_3$) δ 0.83 (s,3H), 0.93 (s,3H), 0.95 (s,3H), 1.16 (m,9H), 1.17 (s,9H), 1.21 (s,9H), 1.22-1.93 (m,7H), 3.54 (t, J=8.2, 1H), 4.07 (t, J=6.9, 1H), 4.46 (dd, J=4.2, 5.9, 1H), 5.02 (dd, J=6.1, 8.3, 1H), 5.10 (dd, J=4.2, 10.5, 1H), 5.33 (dd, J=8.2, 10.5, 1H).

D-2,3-*O*-(D-1.7.7-Trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol 1-dibenzylphosphate (12)

To a solution of **2a** (0.315 g, 1 mmol) in anhydrous pyridine (4 mL) chilled to 4°C was added dibenzyl phosphorochloridate (0.44 g, 1.5 mmol) and the resulting solution was stirred at that temperature for 3 h. After addition of 10 mL of ethyl acetate the solution was washed with aqueous sodium bicarbonate and concentrated *in vacuo*. The residue was subjected to chromatography on silica gel using chloroform-methanol (30:1) as eluent and gave 0.12 g of **12** (21%). R_F=0.12, mp 96-98°C; $[\alpha]_D$=-10.7° (*c* 2, chloroform). ^{1}H NMR (DMSO-d_6) δ 0.87 (s,3H), 0.89 (s,3H), 0.98 (s,3H), 1.2-2.1 (m,7H), 3.17 (dt, J=4.6, 9.2, 1H), 3.34 (ddd, J=4.8, 7.0, 9.4, 1H), 3.62 (dt, J=5.0, 9.3, 1H), 3.88 (dd, J=6.0, 6.9, 1H), 4.44 (t, J=5.0, 1H), 4.55 (ddd, J=4.4, 8.8, 10.0, 1H), 5.05-5.25 (m, 6H), 5.50 (d, J=5.0, 1H), 7.43-7.50 (m,10H); ^{13}C NMR (CDCl$_3$) δ 9.83, 20.39, 27.0, 29.63, 45.28, 48.04, 51.57, 69.71, 70.01 ($^2J_{PC}$=5.8), 71.27, 73.42, 74.72, 75.70, 75.83, 77.15 ($^2J_{PC}$=4.8), 118.4, 128.0, 128.6, 135.7; ^{31}P NMR (C$_6$D$_6$) δ -0.60.

D-*myo*-Inositol 1-phosphate (13)

To a solution of 12 (80 mg, 0.14 mmol) in methanol (5 mL) was added palladium on carbon (10%, 120 mg), and the mixture was stirred under hydrogen (baloon) at room temperature for 8 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in aqueous acetic acid (1:1 v/v, 2 mL) and the resulting solution was stirred at room temperature for 16 h. After that time aqueous acetic acid was replaced with 0.3 M aqueous cyclohexylamine (1 mL) and stirring was continued for additonal 1 h. Excess of amine and water were then evaporated and the resulting solid residue was washed with acetone-methanol mixture (1:1, 2x2 mL), and dried *in vacuo* to yield biscyclohexylammonium salt of 13 (56 mg, 88%). mp 193-195°C (lit.[24] 202°C) $[\alpha]_D$=+3.55° (*c* 2.0, H$_2$O pH 9.5) (lit.[25] +3.55°); ^{1}H NMR (D$_2$O, pD 9.5) δ 1.10-2.10 (m,20H), 3.07-3.17 (m,2H), 3.30 (t, J=9.0, 1H), 3.52-3.64 (m,2H), 3.72 (t, J=9.8, 1H), 3.87 (dt, J=2.6, 9.8, 1H), 4.19 (t, J=2.6, 1H); ^{31}P NMR (D$_2$O, pD 9.5) δ 4.64. MS (FAB) m/z: positive ion 283 (M+Na), negative ion 259 (M-H).

D-myo-Inositol 3-phosphate (14)

Starting with 2a and exactly repeating the procedures described above for 12 and 13 gave 14 as its biscyclohexylammonium salt in 80% yield. mp 194-196°C; $[\alpha]_D$=-3.4° (*c* 1.1, H$_2$O pH 9) (lit.[25] -3.45°). The NMR and MS (FAB) spectral data for 14 were found identical with those obtained above for its enantiomer (13).

D-1,4-Di-*O*-*tert*-butyldimethylsilyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-5,6-*O*-isopropylidene-*myo*-inositol (15)

To a solution of 7 (950 mg, 1.75 mmol) in dry DMF (3,5 mL) were added 2,2-dimethoxypropane (2 mL, 16 mmol), PPTS (130 mg) and *p*-toluenesulfonic acid (2 mg). The solution was stirred at room temperature for 3h. Solid sodium bicarbonate (200 mg) and benzene (20 ml) were then added and the resulting mixture was washed with aqueos sodium bicarbonate. Organic solution was dried and evaporated to dryness, and the residue was chromatographed on a short column of silica gel (hexane-ether 100:1) to give 15 (910 mg, 90%) as an oil. R_F=0.21 (hexane-ether 40:1); $[\alpha]_D$=+3.0° (c 2.0, chloroform); ^{1}H NMR (CDCl$_3$) δ 0.09 (s,3H), 0.10 (s,3H), 0.11 (s,3H), 0.12 (s,3H), 0.84 (s,3H), 0.85 (s,3H), 0.89 (s,9H), 0.90 (s,9H), 0.99 (s,3H), 1.35 (s,3H), 1,38 (s,3H), 1.42-2.18 (m,7H), 3.21 (dd, J=9.4, 10.4, 1H), 3.69 (dd, J=6.2, 10.4, 1H), 3.72 (t, J=9.4, 1H), 3.79 (t, J=6.2, 1H), 3.97 (dd, J=5.6, 10.4, 1H), 4.15 (t, J=5.9, 1H); ^{13}C NMR (C$_6$D$_6$) δ -4.13, -3.58(2C), -3.51, 10.60, 18.98, 19.07, 21.13, 21.22, 26.56(3C), 26.70, 27.54, 27.68, 28.12, 30.39, 45.88, 46.32, 48.75, 52.48, 72.11, 78.01, 78.20, 79.82, 80.24, 81.11, 111.81, 118.11.

D-5,6-*O*-Isopropylidene-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (16)

To a solution of tetrabutylammonium fluoride in dry THF (5 mL, 1.1M) was added 15 (0.8 g, 1.37 mmol) and the reaction was stirred at room temperature for 3h. Benzene (30 mL) was added and the resulting mixture was washed with aqueos sodium bicarbonate, dried (MgSO$_4$), and evaporated to dryness. The residue was purified by column chromatography on silica gel (chloroform-acetone 30:1) to yield 16 (0.48 g, 100%) as a glass. R_F=0.18

(chloroform-acetone 15:1); $[\alpha]_D$=+26.5° (c 2.2, chloroform); ^{1}H NMR (DMSO-d_6) δ 0.87 (s,3H), 0.92 (s,3H), 1.06 (s,3H), 1.43 (s,6H), 1.25-2.21 (m,7H), 3.35 (dd, J=7.3, 10.6, 1H), 3.53 (ddd, J=10.6, 5.2, 5.8, 1H), 3.66 (t, J=7.4, 1H), 3.84 (t, J=5.8, 1H), 4.02 (ddd, J=7.5, 4.9, 5.7, 1H), 4.23 (t, J=5.3, 1H), 5.32 (d, J=5.8, 1H), 5.49 (d, J=5.2, 1H); ^{13}C NMR (C_6D_6) δ 10.55, 21.14, 21.27, 27.82, 27.88, 28.06, 30.62 45.73, 46.34, 48.76, 52.50, 71.08, 76.83, 78.92, 79.33, 80.02, 80.28, 112.71, 118.50.

D-1,4-Di-*O*-(2-oxo-5,6-benzo-1,3,2-dioxaphosphep-2-yl)-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-5,6-*O*-isopropylidene-*myo*-inositol (18)

To a solution of **16** (177 mg, 0.5 mmol) and tetrazole (210 mg, 3 mmol) in anhydrous methylene chloride (3 mL) was added **17** (316 mg, 1.5 mmol) and the mixture was stirred at room temperature for 0.5h. The reaction mixture was then cooled to -60°C and a solution of 350 mg of MCPBA in 3 mL of methylene chloride was added. Stirring was continued for 10 min. at -60°C and for another 10 min at room temperature. The reaction mixture was diluted with benzene (60 mL) and washed consecutively with aqueous sodium bisulfite and aqueous sodium bicarbonate. The organic solution was dried ($MgSO_4$), and evaporated, and the residue was purified by column chromatography on silica gel (acetone-chloroform 1:10) to yield **18** (355 mg, 99%) as a glass. R_F=0.22 (chloroform-acetone 4:1); $[\alpha]_D$=+1.1° (*c* 2.2, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.87 (s,3H), 0.91 (s,3H), 1.02 (s,3H), 1.47 (s,3H), 1.49 (s,3H), 1.50-2.26 (m,7H), 3.58 (dd, J=10.8, 9.4, 1H), 4.05 (t, J=10.0, 1H), 4.15 (dd, J=6.3, 5.2, 1H), 4.58 (ddd, J=11.0, 9.3, 6.3, 1H), 4.67 (t, J=4.9, 1H), 4.86 (ddd, J=10.4, 7.0, 4.6, 1H), 4.98-5.45 (m,8H), 7.17-7.40 (m,8H); ^{31}P NMR ($CDCl_3$) δ -2.22, -1.28.

D-*myo*-Inositol 1,4-bisphosphate (19)

To a solution of **18** (350 mg, 0.488 mmol) in methanol (5 mL) was added palladium on carbon (10%, 180 mg) and the mixture was stirred under hydrogen (baloon) at room temperature for 6h. After catalyst removal and evaporation of solvent 1.5 mL of water and 1.5 mL of acetic acid were added and the resulting mixture was stirred at room temperature for 20h. The reaction mixture was evaporated to dryness, dissolved in 4 mL of 0.6 M aqueous cyclohexylamine, and stirred again for an additional 1h. Excess of amine and water were then evaporated and the resulting solid residue was washed with acetone (2x3 mL) and dried *in vacuo* to yield tetracyclohexylammonium salt of **19** (250 g, 70%). mp 178-182°C (lit.[26] 174-176°C; lit.[27] 184-194°C dec.); $[\alpha]_D$=+1.8° (*c* 5.0, water) (lit.[26] +3.1°, lit.[27] +0.12°); ^{1}H NMR (D_2O) δ 1.02-2.04 (m,40H), 2.98-3.17 (m,4H), 3.40 (t, J=9.0, 1H), 3.61 (dd, J=2.7, 9.7, 1H), 3.76 (t, J=9.4, 1H), 3.88 (dt, J=2.4, 9.8, 1H), 4.07 (bq, J=9.5, 1H), 4.17 (t, J=2.4, 1H); ^{31}P NMR δ 4.28, 4.92. MS(FAB) m/z negative ion 339 (M-H).

D-1-*O*-Benzyl-5,6-*O*-isopropylidene-2,3-*O*-(trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (20)

To a solution of **16** (40 mg, 0.113 mmol) in anhydrous benzene (4 mL) were added sodium hydroxide (powdered, 65 mg), HMPTA (30 μL) and benzyl bromide (21 μL, 0.17 mmol), and the resulting suspension was stirred at 45°C for 6h. After cooling to room temperature the reaction mixture was diluted with hexane, washed with water and evaporated to dryness. The residue was purified by column chromatography on silica gel (carbon tetrachloride-acetone 20:1) to yield **20** (34 mg, 68%) as a semisolid. R_F=0.25 (carbon tetrachloride-acetone 10:1); $[\alpha]_D$=-11.4° (*c* 2.1, chloroform), ^{1}H NMR ($CDCl_3$) δ 0.88 (s,3H), 0.94 (s,3H), 1.08 (s,3H), 1.45 (s,6H), 1.24-2.05 (m,7H), 3.56 (dt, J=5.1, 5.4, 1H), 3.76 (t, J=9.4, 1H), 3.89 (t, J=5.3, 1H), 4.08 (dd, J=9.5, 5.2, 1H), 4.53 (t, J=5.2, 1H), 4.71 (AB, J_{AB}=11.1, 2H), 5.57 (d, J=5.0, 1H), 7.40-7.49 (m,5H); ^{13}C NMR (CDCl$_3$) δ 10.67, 21.26, 21.41, 27.78, 27.90, 28.24, 30.62, 46.13, 46.48, 72.02, 76.65, 76.90, 77.38, 78.16, 80.23, 80.27, 112.7, 118.5, 128.5, 129.2, 138.9.

D-1-*O*-Benzyl-5,6-*O*-isopropylidene-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene-4-*O*-(2-oxo-5,6-benzo-1,3,2-dioxaphosphep-2-yl)-*myo*-inositol (21)

To a solution of 20 (34 mg, 0.077 mmol) and tetrazole (16 mg, 0.23 mmol) in anhydrous methylene chloride (2 mL) was added 17 (24 mg, 0.114 mmol) and the mixture was stirred at room temperature for 0.5h. The reaction mixture was then cooled to -60°C and a solution of 32 mg of MCPBA in 1 mL of methylene chloride was added. Stirring was continued for 10 min at -60°C and for another 10 min at room temperature. The reaction mixture was diluted with benzene (10 mL) and washed consecutively with aqueous sodium bisulfite and aqueous sodium bicarbonate. The organic solution was dried (MgSO$_4$), and evaporated, and the residue was purified by column chromatography on silica gel (acetone-carbon tetrachloride 1:10) to yield 21 (44 mg, 92%) as a glassy solid. R_F=0.16 (acetone-carbon tetrachloride 1:8); $[\alpha]_D$=+9.2° (*c* 2.4, chloroform); ^{1}H NMR (CDCl$_3$) δ 0.87 (s,3H), 0.89 (s,3H), 1.04 (s,3H), 1.14-1.40 (m,3H), 1.21 (s,3H), 1.25 (s,3H), 1.55-2.13 (m,4H), 3.53 (dd, J=9.1, 10.6, 1H), 3.88 (dd, J=4.2, 10.2, 1H), 4.02 (dd, J=9.0, 10.2, 1H), 4.11 (dd, J=5.3, 6.3, 1H), 4.37 (dd, J=5.2, 4.2, 1H), 4.53 (ddd, J=6.3, 10.5, 13.7, 1H), 4.76 (AB, J_{AB}=11.8, 2H), 5.10-5.36 (m,4H), 7.24-7.43 (m,9H); ^{31}P NMR (CDCl$_3$) δ -1.42.

D-*myo*-Inositol 4-phosphate (22)

To a solution of 21 (40 mg, 0.064 mmol) in methanol (2 mL) was added palladium on carbon (10%, 50 mg) and the mixture was stirred under hydrogen (baloon) at room temperature for 8h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in aqueous acetic acid (1:1 v/v, 2 mL) and the resulting solution was stirred at room temperature for 16h. After that time aqueous acetic acid was replaced with 1.5 mL of water and 25 μL of cyclohexylamine and stirring was continued for additional 0.5h. Excess of amine and water were then evaporated and the resulting solid residue was washed with methanol-aceton mixture (2:1, 2x1.5 mL), and dried to yield bis-cyclohexylammonium salt of 22 (26 mg, 88%). mp 183-188°C (dec.) (lit.[27] 180-200°C (dec)), $[\alpha]_D$=-1.2° (*c* 2.6, H$_2$O) (lit.[25] -1.3°); ^{1}H NMR (D$_2$O) δ 1.10-1.45 (m,10H), 1.53-2.10 (m,10H), 3.02-3.20 (m,2H), 3.39 (t, J=9.3, 1H), 3.52 (dd, J=3.0, 9.9, 1H), 3.60 (dd, J=2.9, 9.7, 1H), 3.68 (t, J=9.8, 1H), 4.05 (t, J=2.8, 1H), 4.10 (m, 1H); ^{13}C NMR (D$_2$O) δ 26.95, 27.51, 33.94, 53.54, 74.37, 74.58, 75.04, 75.72, 77.36, 79.13 ($^2J_{C-P}$=7); ^{31}P NMR (D$_2$O) δ 4.94 MS(FAB) m/z: positive ion 283 (M+Na), negative ion 259 (M-H).

D-6-*O*-Benzyl-2,3-*O*-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-1,4,5-tri-*O*-trimethylacetyl-*myo*-inositol (23)

To a solution of 9 (1.3 g, 2.3 mmol) in DMF (14 mL) were added silver (I) oxide (1.6 g, 6.9 mmol) and freshly distilled benzyl bromide (1.6 mL, 13.8 mmol), and the mixture was stirred at 4°C for 48h. Benzene (50 mL) was then added and the solution was separated from precipitate by decantation. After evaporation of solvents the residue was chromatographed on a short column of silica gel (carbon tetrachloride-ether 25:1) and recrystallized from heptane-benzene (20:1) to yield 23 (750 mg, 50%). R_F=0.12 (carbon tetrachloride-ether 15:1); mp 184-185°C; $[\alpha]_D$=-14° (*c* 2.1, chloroform); ^{1}H NMR (CDCl$_3$) δ 0.85 (s,3H), 0.96 (s,3H), 0.98 (s,3H), 1.12 (s,9H), 1.20 (s,9H), 1.21 (s,9H), 1.30-1.90 (m,7H), 4.03 (dd, J=7.0, 9.4, 1H), 4.05 (t, J=6.7, 1H), 4.52 (dd, J=4.5, 6.5, 1H), 4.70 (AB, J_{AB}=11.1, 2H), 5.10 (t, J=7.1, 1H), 5.19 (dd, J=4.5, 9.3, 1H), 5.21 (dd, J=6.5, 7.5, 1H), 7.21-7.40 (m,5H); ^{13}C NMR ($CDCl_3$) δ 9.75, 20.29(2C), 26.95, 27.15(9C), 29.46, 38.78(2C), 38.87, 44.17, 45.26, 47.91, 51.67, 70.79, 72.44, 72.86, 72.98, 73.57, 73.98, 77.13, 118.22, 127.22(2C), 127.61(2C), 128.31, 137.89, 176.88, 177.11, 177.65.

D-6-O-Benzyl-2,3-O-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (24)

To a solution of sodium hydroxide (600 mg) in methanol (4 mL) was added 23 (700 mg, 1.01 mmol) and the reaction mixture was stirred under reflux for 2h. The solvent was evaporated and the residue was purified by filtration through a short pad of silica gel (chloroform-methanol 70:1) to yield 24 (397 mg, 92%) as a glass. R_F=0.2 (chloroform-methanol 30:1); mp 44-45°C; $[\alpha]_D$=+16.2° (*c* 2.5, chloroform); ^{1}H NMR($CDCl_3$) δ 0.86 (s,3H), 0.87 (,3H), 1.00 (s,3H), 1.31-1.99 (m,7H), 3.47 (dd, J=7.3, 9.9, 1H), 3.61 (t, J=7.3, 1H), 3.84 (dd, J=6.9, 9.8, 1H), 3.92 (t, J=7.0, 1H), 4.02 (dd, J=4.78, 7.3, 1H), 4.35 (dd, J=4.8, 7.0, 1H), 4.8 (AB, J_{AB}=11.0, 2H), 7.25-7.40 (m,5H); ^{13}C NMR($CDCl_3$) δ 10.26, 20.96, 27.48, 30.29, 44.64, 45.72, 48.47, 52.0, 71.07, 74.21, 74.52, 75.31(2C), 76.53, 82.55, 118.43, 128.37(3C), 128.97(2C), 138.61.

D-6-O-Benzyl-2,3-O-(D-1,7,7-trimethyl[2-2-1]bicyclohept-2-ylidene)-1,4,5-tri-O-(2-oxo-5,6--benzo-1,3,2-dioxaphosphep-2-yl)*myo*-inositol (25)

To a solution of 24 (50 mg, 0.124 mmol) and tetrazole (80 mg, 1.116 mmol) in anhydrous methylene chloride (2 mL) was added 17 (118 mg, 0.558 mmol) and the mixture was stirred at room temperature for 1h. Water (3 µL) was then added and the reaction mixture was stirred for additional 15 min The reaction mixture was cooled to -60°C and a solution of 140 mg of MCPBA in 1.5 mL of methylene chloride was added. Stirring was continued for 10 min at -60°C and for another 10 min at room temperature. The reaction mixture was diluted with benzene (50 mL) and washed consecutively with aqueous sodium bisulfite and aqueous sodium bicarbonate. The organic solution was dried ($MgSO_4$), evaporated, and the residue was purified by column chromatography on silica gel (chloroform-acetone 40:1) to yield 25 (110 mg, 90%) as an oil. R_F=0.15 (chloroform-acetone 30:1); ^{31}P NMR (C_6D_6) δ -2.06, -1.55, -0.84.

D-*myo*-Inositol 1,4,5-trisphosphate (26)

To a solution of 25 (104 mg, 0.11 mmol) in methanol (4 mL) was added palladium on carbon (10%, 100 mg) and the mixture was stirred under hydrogen (baloon) at room temperature for 6h. After catalyst removal and evaporation of solvent 1.5 mL of water and 1.5 mL of acetic acid were added and the resulting mixture was stirred at room temperature for 18h. The reaction mixture was evaporated to dryness and the residue was dissolved in a minimum amount of water. Sodium hydroxide (10% solution in water, 0.77 mmol) was then added and the resulting solution was diluted with methanol to precipitate 26 as its hexasodium salt (45 mg, 73%). mp 200-202° (dec); $[\alpha]_D$=-30° (*c* 0.8, H_2O, pH 9.5)(lit.[28] -30°); ^{1}H NMR (D_2O, pD 9.5) δ 3.71 (dd, J=9.8, 3.0, 1H), 3.90 (m,3H), 4.15 (q, J=9.0, 1H), 4.33 (bt, J=2.0, 1H); ^{13}C NMR (D_2O, pD 9.5) δ 73.24, 74.34, 75.17, 77.21, 77.67, 79.86; ^{31}P NMR (D_2O, pD 9.5) δ 3.63, 5.31, 5.41; MS FAB m/z: positive ions 553 (M+H), 575 (M+Na); negative ions 551 (M-H), 529 (M-Na), 507 (M-2Na), 485 (M-3Na).

D-3,4,5,6-Tetra-O-(2-oxo-5,6-benzo-1,3,2-dioxaphosphep-2-yl)-1,2-O-(L-1,7,7-trimethyl-[2.2.1]bicyclohept-2-ylidene)-*myo*-inositol (27)

To a suspension of tetrol 2a· (105 mg, 0.33 mmol) and tetrazole (280 mg, 4 mmol) in anhydrous methylene chloride was added 17 (395 mg, 1.87 mmol) and the resulting mixture was stirred at room temperature during 1h. After cooling to -60°C a solution of MCPBA (480 mg) in anhydrous methylene chloride (3 mL) was added to the reaction mixture and stirring was continued for 10 min at -60°C and additional 10 min at room temperature. The reaction mixture was diluted with benzene (30 mL) and washed consecutively with aqeous sodium bisulfite and aqueos sodium bicarbonate. After concentration, the residue was purified by column chromatography on silica gel (chloroform-acetone 30:1) to yield **27** (210 mg, 60%) as a glass. R_F=0.16 (chloroform-acetone 30:1); $[\alpha]_D$=-16.5° (*c* 2.2, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.87 (s,3H), 1.01 (s,3H), 1.04 (s,3H), 1.41-2.16 (m,7H), 4.22 (dd, J=4.8, 6.4, 1H), 4.76 (t, J=4.8, 1H), 4.79-5.67 (m,20H), 7.22-7.48 (m,16H); ^{31}P NMR ($CDCl_3$) δ -3.72, -3.57, -3.52, -1.52.

D-*myo*-Inositol 3,4,5,6-tetrakisphosphate (28)

To a solution of **27** (150 mg, 0.14 mmol) in methanol (4 mL) was added palladium on carbon (10%, 140 mg) and the mixture was stirred under hydrogen (baloon) at room temperature for 5h. After catalyst removal and evaporation of solvent 2 mL of water and 2 mL of acetic acid were added and the resulting mixture was stirred at room temperature for 18h. The reaction mixture was then evaporated to dryness and the residue was dissolved in a minimum amount of water. Sodium hydroxide (10% solution in water, 1.26 mmol) was then added and the resulting solution was diluted with methanol to precipitate **26** as its octasodium salt (45 mg, 73%). mp 200°C (dec); $[\alpha]_D$=-6.2° (c 2.15, H_2O, pH 9.5)]. ^{1}H NMR (D_2O, pD 9.5) δ 4.09-4.17 (m,1H), 4.20 (t, J=2.9, 1H), 4.22-4.35 (m,2H), 4.45-4.67 (m,3H); ^{13}C NMR (D_2O, pD 9.5) δ 70.0, 70.67, 75.73, 77.34, 77.80, 78.24; ^{31}P NMR (D_2O, pD 9.5) δ 4.02, 4.29, 4.41, 4.93. MS(FAB) m/z: positive ions 677 (M+H), 699 (M+Na); negative ions 675 (M-H), 653 (M-Na), 631 (M-2Na), 609 (M-3Na), 587 (M-4Na).

D-3,4,5,6-Tetra-*O*-benzyl-*myo*-inositol (29)

This compound was obtained from tetrol **2a'** in 56% yield by the published procedure.[10]

D-3,4,5,6-Tetra-*O*-benzyl-1-*O*-(tetrahydropyran-2-yl)-*myo*-inositol 2-(*S*-methyl)dithiocarbonate (30)

To a solution of **29** (350 mg, 0.65 mmol) and PPTS (40 mg) in anhydrous methylene chloride was added 3,4-dihydro-2*H*-pyran (70 μL) and the resulting solution was stirred at room temperature for 2h. After this time was added another 70 μL of 3,4-dihydro-2*H*-pyran and stirring was continued overnight. Triethylamine (200 μL) was then added and the reaction mixture was evaporated to dryness. The residue was chromatographed on a short column of silica gel (hexane-ether 1:1) to give 1-*O*-tetrahydropyranyl derivative of **29**, (350 mg, 86%), R_F=0.2 (hexane-ether 1:1), ^{13}C NMR ($CDCl_3$) δ 19.25, 20.96, 25.89, 25.98, 30.98, 31.77, 61.82, 64.32, 66.40, 70.62, 73.38, 73.57, 74,48, 76.62, 79.45, 80.77, 80.86, 81.96, 84.01, 94.22, 102.39, 128.23, 128.54, 128.69, 138.30, 138.70, 139.60, 139.70. The entire amount of tetrahydropyranyl derivative (350 mg, 0.56 mmol) was dissolved in anhydrous THF (5 mL), mixed with sodium hydride (100 mg as 50% dispersion in mineral oil) and stirred under reflux until evolution of hydrogen ceased. After cooling, carbon disulfide (300 μL) was added and the reaction mixture was stirred under reflux for 1h. Methyl iodide (300 μL) was then added and stirring under reflux was continued for an additional 1h. The mixture was diluted with 30 mL of hexane-ethyl acetate (4:1) and the resulting suspension was washed twice with water. Solvents were evaporated and the residue was purified by column chromatography on silica gel (hexane-ether 4:1) to yield **30** (320 mg, 80%), as an oil. R_F=0.25 (hexane-ether 3:1); ^{1}H NMR($CDCl_3$) δ 2.65 (s,3H), 2.67 (s,3H), 3.46-3.71 (m,8H), 3.88 (t, J=3.1, 1H), 3.93-3.99 (m,3H), 4.15 (t, J=2.3, 1H), 4.55 (dd, J=2.4, 10.7, 1H), 4.78-4.96 (m,8H), 6.68 (t, J=2.7, 1H), 6.77 (t, J=2.7, 1H), 7.31-7.36 (m,20H).

D-2-Deoxy-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (31)

To a solution of 30 (310 mg, 0.43 mmol) in anhydrous toluene were added AIBN (5 mg) and tributyltin hydride (300 µL, 1.1 mmol) and the resulting solution was refluxed with stirring for 14h. After this time solvent was evaporated and the residue was dissolved in 4 mL of 96% ethanol. PPTS (60 mg) was added and the mixture was stirred at 60°C for 2.5h. After addition of solid sodium carbonate (100 mg), the reaction mixture was diluted with ethyl acetate (25 mL) and washed with water. Solvents were evaporated and the residue was chromatographed on a short column of silica gel (carbon tetrachloride-ether 4:1) to yield 31 (300 mg, 70%) as a white solid. R_F=0.3 (carbon tetrachloride-ether 3:1), mp 121-122°C, $[\alpha]_D$=-24°(*c* 2, chloroform); ^1H NMR (CD_3CN) δ 1.46 (m,1H), 2.33 (m,1H), 3.23 (bs,1H), 3.36 (t, J=8.9, 1H), 3.47 (t, J=8.9, 1H), 3.54 (t, J=1.9, 1H), 3.59 (m,2H), 4.64-4.97 (m,8H), 7.20-7.45 (m,20H); ^{13}C NMR (CD_3CN) δ 34.89, 68.67, 71.58, 74.69, 74.98, 75.16, 77.31, 83.03, 85.42, 86.01, 127.36, 127.42, 127.78, 128.20, 128.26, 129.20, 139.40.

D-2-Deoxy-*myo*-inositol 1-phosphate (32)

To a solution of 31 (80 mg, 0.15 mmol) and tetrazole (32 mg, 0.45 mmol) in anhydrous methylene chloride was added 17 (40 mg, 0.18 mmol) and the mixture was stirred at room temperature for 0.5h. The reaction mixture was cooled to -60°C and a solution of MCPBA (45 mg, 0.18 mmol) in anhydrous methylene chloride was added. Stirring was then continued at -60°C for 10 min and at room temperature for another 10 min. After addition of ethyl acetate (15 mL), the reaction mixture was washed consecutively with aqueous sodium bisulfite and aqueous sodium bicarbonate and the solvents were evaporated. The residue was purified by short column chromatography on silica gel (carbon tetrachloride-acetone 12:1) to give protected 1-phosphate derivative (100 mg, 94%) as a glass, R_F=0.24 (carbon tetrachloride-acetone 12:1); ^1H NMR ($CDCl_3$) δ 1.75 (m,1H), 2.78 (m,1H), 3.59 (m,4H), 4.44 (m,1H), 4.65-5.46 (m,12H), 7.17-7.37 (m,24H); ^{31}P NMR ($CDCl_3$) δ -0.13. The protected 1-phosphate (80 mg, 0.12 mmol) was dissolved in methanol (4 mL) and to the solution was added palladium on carbon (10%, 100 mg). The resulting mixture was stirred under hydrogen (baloon) at room temperature for 10h. After removal of catalyst and evaporation of solvent, the residue was dissolved in 0.3M aqueous cyclohexylamine (2 mL) and the solution was stirred at room temperature for 1h. Excess amine and water were then evaporated and the residue was washed with acetone (2x3 mL), and dried *in vacuo* to yield 32 (28 mg, 99%) as its biscyclohexylammonium salt. mp 173-178°C; $[\alpha]_D$=+8.5° (*c* 1, H_2O, pH 9) (lit.[29] $[\alpha]_D$=+7.1°); ^1H NMR (D_2O, pD 9) δ 1.10-1.40 (m,10H), 1.60-2.00 (m,11H), 2.23-2.37 (m, 1H), 3.03-3.20 (m,2H), 3.29 (dd, J=2.7, 7.1, 1H), 3.32 (t, J=7.0, 1H), 3.44 (dt, J=9.0, 3.0, 1H), 3.49-3.64 (m,1H), 3.85-4.03 (m,1H); ^{13}C NMR (D_2O, pD 9) δ 26.58, 27.08, 33.14, 38.99, 53.01, 53.16, 71.36, 74.41, 76.99, 77.13, 74.49; ^{31}P NMR (D_2O, pD 9) δ +4.22. MS(FAB) m/z: positive ion 267 (M+Na), negative ion 243 (M-H).

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