2-O-Acetyl-3,4,5,6-tetra-O-benzyl-D-myoinosityl diphenylphosphate: A new useful intermediate to inositol phosphate and phospholipids

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Abstract
Inositol phosphates and inositol phospholipids are ubiquitous in biochemistry and play a central role in cell signaling and regulation events. For this reason, their synthesis has attracted widespread interest. This paper describes the preparation of a new optically active inositol phosphate derivative, 2-O-acetyl-3,4,5,6-tetra-O-benzyl-D-myoinosityl diphenylphosphate (6), and its characterization by spectroscopic methods. Compound (6) represents a useful intermediate for the preparation of inositol phosphate and phospholipids, in particular of glycerophosphoinositol (GPI), a natural anti-inflammatory agent.

KEYWORDS
anti-inflammatory activity, desymmetrization, l-camphor dimethyl acetal, myo-inositol phosphate, myo-inositol phospholipids

1 | INTRODUCTION

The inositols are the nine stereoisomeric forms of cyclohexanexehol belonging to the class of cyclitols, that is, cyclolkanes in which three or more ring atoms are each substituted with one hydroxyl group.1,2 myo-Inositol, or cis-1,2,3,5-trans-4,6-cyclohexanexehol, is the most common isomeric form in nature that also uses at least five of the others (scylo-, epi-, neo-, D-chiro-, and muco-inositol).3 It constitutes the structural core of a group of important metabolites, that is, inositol phosphates and inositol phospholipids, that are involved in numerous important biological processes including cellular signal transduction, membrane transport, protein anchoring, and cytoskeletal regulation.1-4 Specifically, phosphatidylinositols, which constitute approximately 1% of the phospholipids in cell membranes, are selectively phosphorylated by multiple kinases at the C-3, C-4 and C-5 positions to generate a number of endogenous phosphatidylinositol phosphates which are in turn converted into various inositol phosphates differing for the phosphorylation pattern of the inositol ring.3,5

Concentrations of inositol derivatives in biological systems are very low, thus strongly limiting their analytical detection and the isolation from natural sources in useful amounts to fully elucidate their physiological functions. For this reason, numerous synthetic efforts are still in progress to prepare biologically relevant inositol phosphates...
and inositol phospholipids as well as many of their analogs to be used as chemical probes in biological studies.\(^5\)-\(^7\)

Most of the synthetic routes to inositol phosphates and phospholipids commenced from myo-inositol, a cheap and readily available starting material, and involve properly protected chiral derivatives of myo-inositol as key intermediates. Such derivatives have been prepared both by resolution of myo-inositol (a meso compound) and by stereoselective synthesis using chemical and/or enzymatic approaches and exploiting many selective protection and deprotection schemes of inositol hydroxyl groups.\(^8\)-\(^12\)

Among the known inositol phosphates, glycerophosphoinositols have recently attracted much attention due to their distinctive biological activity.\(^13\) These water-soluble ubiquitous cellular metabolites, produced through the deacylation of the membrane phosphoinositides by receptor-activated cytosolic phospholipase A2,\(^13\) include non-phosphorylated \(sn\)-glycerol-3-phosphoinositol (glycerophosphoinositol [GPI]) and its phosphorylated derivatives glycerophosphoinositol 4-phosphate and glycerophosphoinositol 4,5-bisphosphate. GPI has been found to play a role as an endogenous mediator in the inflammatory response, being part of a negative feedback loop that inhibits the de novo synthesis of pro-inflammatory and pro-thrombotic compounds. The anti-inflammatory activity of exogenous GPI has been investigated both in vitro and in an in vivo model in comparison with dexamethasone, showing that GPI parallels the anti-inflammatory effect of the corticosteroid drug.\(^13\) Moreover, the anti-inflammatory effect of GPI in counteracting blood–brain barrier (BBB) failure has been found at lower doses than dexamethasone and without cytotoxic effects, thus suggesting the use of GPI as a natural anti-inflammatory agent and a “BBB enhancer” for neurodegenerative diseases such as multiple sclerosis and Alzheimer’s dementia.\(^14\)

As a part of our studies on the synthesis of GPI, here we report the chemical synthesis and the characterization of optically active 2-\(O\)-acetyl-3,4,5,6-tetra-\(O\)-benzyl-myoinositol diphenylphosphosphate (6), a new useful building block for the synthesis of inositol phosphates and phospholipids.

**2 MATERIALS AND METHODS**

All solvents and reagents were purchased from Sigma-Aldrich and Scharlab and used without further purification. Analytical TLC was performed on silica gel F\(_{254}\) precoated aluminum sheets (0.2-mm layer, Merck). Silica gel 60, 40–63 µm (Merck, Darmstadt, Germany) was used for flash column chromatography. \(^1\)H, \(^13\)C, and \(^31\)P NMR spectra were recorded at 400.13, 100.61, and 161.96 Hz, respectively, on a Bruker AVANCE 400 (Bruker, Karlsruhe, Germany) spectrometer equipped with the TOPSPIN software package (Bruker, Karlsruhe, Germany) at 300 K, unless stated otherwise. MestReNova (v. 14.2) from Mestrelab Research was used for NMR processing. \(^1\)H and \(^13\)C chemical shifts (\(\delta\)) are given in parts per million and are referenced to the solvent signal (\(\delta_H\) 7.26–\(\delta_C\) 77.16 ppm from tetramethylsilane [TMS] for CDCl\(_3\)). \(^31\)P chemical shifts (\(\delta\)) are given in parts per million and are referenced to standard \(\text{H}_3\text{PO}_4\) (aq) 85% (0 ppm). \(^1\)H NMR signals were assigned with the aid of \(^1\)H–\(^1\)H correlation spectroscopy (\(^1\)H–\(^1\)H COSY). \(^13\)C NMR APT (attached proton test) signals were assigned by \(^1\)H–\(^13\)C correlation experiments (heteronuclear multiple quantum correlation spectroscopy [HSQC] and heteronuclear multiple bond correlation spectroscopy [HMBC]). Optical rotations were measured on a Jasco P-1030 polarimeter (LabX, Midland, Ontario, Canada). Electrospray ionization mass spectra (ESI-MS) were recorded on the Thermo Finnigan LCQ Advantage spectrometer (Hemel Hempstead, Hertfordshire, UK). For NMR and MS spectra, see Supporting Information.

**3 SYNTHESIS OF 2-\(O\)-ACETYL-3,4,5,6-TETRA-\(O\)-BENZYL-D-MYO-INOSITYL DIPHENYLPHOSPHATE (6) FROM MYO-INOSITOL (1)**

\(d-1,2-O-(\text{1,7,7-Trimethyl[2,2,1]}\text{bicyclohept-2-ylidene})\) myo-inositol (2). 1-Camphor dimethyl acetal (7) (220 mg, 1.11 mmol) and PTSA (8 mg, 0.04 mmol) were added to a dispersion of dry myo-inositol (1, 100 mg, 0.56 mmol) in anhydrous DMSO (2.0 mL) under inert atmosphere. The resulting mixture was stirred at 55°C for 4 h until complete dissolution of the substrate was observed. The reaction was cooled to room temperature, neutralized with Et\(_3\)N, and concentrated under reduced pressure. The residue was suspended in a mixture of CHCl\(_3\)/MeOH/H\(_2\)O (50:5:1, 10 mL), PTSA (5 mg) was added, and the resulting mixture was stirred at room temperature overnight. After neutralization with Et\(_3\)N, the resulting precipitate was filtered and washed with CHCl\(_3\). The resulting crude was purified by flash chromatography (CHCl\(_3\)/MeOH 9:1, Rf 0.22), and 2 was obtained as the major component of a mixture of diastereoisomers, which was used in the next reaction without further purification (90 mg, 0.29 mmol, 49%).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\), 6) major isomer: 4.81–4.74 (m, 3H, OH), 4.69 (d, \(J = 4.1\) Hz, 1H, OH), 4.09 (dd, \(J = 5.7\), 4.1 Hz, 1H, CH sugar), 3.66 (t, \(J = 7.0\), 5.6 Hz, 1H, CH sugar), 3.52 (dt, \(J = 8.9\), 4.3 Hz, 1H, CH sugar), 3.31–3.15 (m, 2H, 2 × CH sugar), 2.93 (td, \(J = 9.4\), 3.9 Hz, 1H, CH sugar), 2.00–1.84 (m, 2H, 2 × CH\(_2\) camphor), 1.72–1.61 (m, 2H, CH and CH\(_2\) camphor), 1.40 (d,
$J = 12.8$ Hz, 1H, CH$_2$ camphor), 1.31 (td, $J = 13.0, 12.4, 4.9$ Hz, 1H, CH$_2$ camphor), 1.18–1.08 (m, 1H, CH$_2$ camphor), 0.97 (s, 3H, CH$_3$), 0.83 (2, 3H, CH$_3$), 0.77 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, DMSO-$_d_6$, $\delta$) 116.4 (Cq camphor), 77.1 (CH sugar), 76.7 (CH sugar), 76.1 (CH sugar), 74.4 (CH sugar), 72.3 (CH sugar), 70.2 (CH sugar), 51.6 (Cq camphor), 47.9 (Cq camphor), 45.7 (CH$_2$ camphor), 45.1 (CH camphor), 29.6 (CH$_2$ camphor), 27.3 (CH$_2$ camphor), 21.0 (CH$_3$ camphor), 20.8 (CH$_3$ camphor), 10.2 (CH$_3$ camphor); MS (ESI, m/z): [M + H]$^+$ calcd for C$_{14}$H$_{24}$O$_6$Na, 313.17; found, 313.04.

d-3,4,5,6-Tetra-O-benzyl-1,2-O-(tetramethylenoxy)-myo-inositol (3). NaH (60% dispersion in mineral oil, 2.46 g, 61.50 mmol) was added in one portion to a solution of 2 (1.20 g, 3.82 mmol) in dry DME (50 mL) at 0°C under inert atmosphere. After stirring at 0°C for 30 min, BnBr (2.8 mL, 23.54 mmol) was added, and the mixture was stirred at room temperature for 24 h. The reaction was quenched first with MeOH and then with H$_2$O under vigorous stirring at 0°C. After evaporation of the solvent under reduced pressure, the residue was dissolved in AcOEt (30 mL) and washed with H$_2$O (2 × 15 mL) and brine (1 × 10 mL). The organic layer was dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The resulting crude was purified by flash chromatography (n-hexane/AcOEt 9:1, Rf 0.31) to get 3 as a light-yellow oil (2.17 g, 32.22 mmol, 84%).

$^1$H NMR (400 MHz, CDCl$_3$, $\delta$) 7.45–7.28 (m, 20H, 4 × Ph), 4.95 (d, $J = 11.4$ Hz, 1H, CH$_2$Ph), 4.87–4.72 (m, 7H, CH$_2$Ph), 4.35 (dd, $J = 6.2, 4.1$ Hz, 1H, CH sugar), 4.01 (dd, $J = 7.1, 6.2$ Hz, 1H, CH sugar), 3.88 (t, $J = 8.2$ Hz, 1H, CH sugar), 3.84–3.75 (m, 2H, 2 × CH sugar), 3.48 (dd, $J = 9.6, 7.9$ Hz, 1H, CH sugar), 2.07–1.94 (m, 2H, 2 × CH$_2$ camphor), 1.83–1.73 (m, 2H, CH, and CH$_2$ camphor), 1.53 (d, $J = 12.9$ Hz, 1H, CH$_2$ camphor), 1.43 (td, $J = 12.6, 4.9$ Hz, 1H, CH$_2$ camphor), 1.37–1.25 (m, 1H, CH$_2$ camphor), 1.13 (s, 3H, CH$_3$ camphor), 0.92 (s, 3H, CH$_3$ camphor), 0.90 (s, 3H, CH$_3$ camphor); $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$) 138.8, 138.7, 138.5 (4 × Cq phenyl), 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.59, 127.55, 127.5 (20 × CH phenyl), 117.7 (Cq camphor), 83.3 (CH sugar), 82.2 (CH sugar), 80.8 (CH sugar), 77.4 (CH sugar), 76.3 (CH sugar), 75.2 (CH$_2$Ph), 75.0 (CH$_2$Ph), 74.0 (CH$_2$Ph), 73.7 (CH sugar), 72.5 (CH$_2$Ph), 51.6 (Cq camphor), 48.0 (Cq camphor), 45.2 (CH$_2$ camphor), 45.0 (CH$_2$ camphor), 29.8 (CH$_2$ camphor), 27.1 (CH$_2$ camphor), 20.7 (CH$_3$ camphor), 20.4 (CH$_3$ camphor), 10.2 (CH$_3$ camphor); MS (ESI, m/z): [M + Na]$^+$ calcd for C$_{34}$H$_{36}$O$_6$Na, 563.24; found, 563.15.

2-O-Acetyl-3,4,5,6-tetra-O-benzyl-1,2-O-(tetramethylenoxy)-myo-inositol (5). A solution of 4 (300 mg, 0.55 mmol), PTSA-H$_2$O (10 mg, 0.05 mmol) and trimethyl orthoacetate (0.30 mL, 2.74 mmol) in acetonitrile (20 mL) was stirred at room temperature for 2 h. The reaction was cooled to −40°C and H$_2$O (0.30 mL) was added; then the mixture was stirred at −40°C for 4 h, neutralized with pyridine and concentrated under reduced pressure. The residue was dissolved in AcOEt (20 mL), washed with H$_2$O (2 × 10 mL), dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The resulting crude was purified by flash chromatography (n-hexane/EtOAc 8:2, Rf 0.30) to get 5 as a colorless oil (290 mg, 0.50 mmol, 91%).

$[a]_D^{20} = −1.78$ deg cm$^3$ g$^{-1}$ dm$^{-1}$ ($c = 2.00$ g cm$^{-3}$ in CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$, $\delta$) 7.41–7.28 (m, 20H, 4 × Ph), 5.75 (t, $J = 2.8$ Hz, 1H, CH sugar), 5.04–4.95 (m, 3H, 3 × CH$_2$Ph), 4.87 (d, $J = 10.6$ Hz, 1H, CH$_2$Ph), 4.83 (d, $J = 10.7$ Hz, 1H, CH$_2$Ph), 4.79 (d, $J = 5.0$ Hz, 1H, CH$_2$Ph), 4.76 (d, $J = 5.1$ Hz, 1H, CH$_2$Ph), 4.54 (d, $J = 11.2$ Hz, 1H, CH$_2$Ph), 3.92 (t, $J = 9.5$ Hz, 1H, CH sugar), 3.82 (t, $J = 9.6$ Hz, 1H, CH sugar), 3.64 (br d, $J = 9.6$ Hz, 1H, CH sugar), 3.60–3.54 (m, 2H, 2 × CH$_2$ sugar), 2.34 (br s, 1H, OH), 2.18 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, DMSO-$_d_6$, $\delta$) 170.5 (C–O), 138.6, 138.3, 137.6 (4 × Cq phenyl), 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7 (4 × CH phenyl), 83.3 (CH sugar), 82.0 (CH sugar), 81.5 (CH sugar), 78.5 (CH sugar), 76.0, 76.0, 75.6, 72.2 (4 × CH$_2$Ph), 70.2 (CH sugar), 69.3 (CH sugar), 21.1 (CH$_3$); MS (ESI, m/z): [M + Na]$^+$ calcd for C$_{36}$H$_{38}$O$_7$Na, 605.25; found, 605.53.
2-O-Acetyl-3,4,5,6-tetra-O-benzyl-D-myoinositol diphenylphosphate (6). DMAP (2.3 mg, 0.02 mmol), Et3N (210 μL, 152 mg, 1.50 mmol), and DPC (160 μL, 207 mg, 0.77 mmol) were added to a solution of 5 (107 mg, 0.18 mmol) in CH2Cl2 (10 mL), and the resulting mixture was stirred at room temperature for 24 h. The reaction was washed with H2O (20 mL) and brine (20 mL). The organic phase was dried over Na2SO4 and concentrated under reduced pressure to get a yellow oil crude, which was purified by flash chromatography (hexane/AcOEt 9:1, Rf 0.31) to get 6 as a light-yellow oil (105 mg, 0.13 mmol, 70%).

\[ [\alpha]_D^{20} = +0.95 \text{deg cm}^2 \text{g}^{-1} \text{dm}^{-1} \] (c = 1.53 g cm\(^{-3}\) in CHCl3);

\[ ^1H \text{NMR} (400 \text{MHz}, \text{CDCl}_3, \delta) \] 7.43–7.06 (m, 30H, 2 × Ph and 4 × Bn), 5.98 (t, J = 2.8 Hz, 1H, H-2), 4.94–4.75 (m, 7H, CH₂Ph), 4.67 (ddd, J = 10.1, 8.4, 2.8 Hz, 1H, H-1), 4.47 (d, J = 10.9 Hz, 1H, CH₂Ph), 4.05 (t, J = 9.6 Hz, 1H, H-6), 3.87 (t, J = 9.5 Hz, 1H, H-4), 3.62–3.54 (m, 2H, H-3 and H-5), 2.11 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3, δ) 169.4 (C=O), 150.5, 150.4 (2 × Ph), 138.5, 138.2, 138.1, 137.5 (4 × Bn), 129.8, 129.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 125.4, 125.3 (2 × Ph and 4 × Bn), 120.2, 120.0 (2 × Ph), 82.6 (C-5), 81.1 (C-4), 80.0 (C-6), 78.2 (C-3), 77.4 (C-1), 76.3, 76.0, 75.7, 72.4 (4 × CH₂Ph), 68.6 (C-2), 20.9 (CH3); 31P NMR (162 MHz, CDCl3, δ) –12.30; MS (ESI, m/z): [M + H]\(^+\) calcd for C₄₉H₄₉O₁₀P, 815.30; found, 815.24; [M + Na]\(^+\) calcd for C₄₉H₄₉O₁₀PNa, 837.28; found, 837.45; Anal. calcd for C₄₉H₄₉O₁₀P: C 70.75, H 5.81; found: C 69.99, H 6.20.

\[ ^1H \text{NMR} (400 \text{MHz}, \text{CDCl}_3, \delta) \] 3.11 (s, 3H, OCH₃), 2.14 (ddd, J = 12.9, 4.6, 3.0 Hz, 1H, CH₂), 1.74–1.61 (m, 3H, CH and 2 × CH₂), 1.36–1.27 (m, 1H, 2 × CH₂), 1.17–1.11 (m, 1H, 2 × CH₂), 1.08 (d, J = 12.7 Hz, 1H, CH₂), 0.91 (s, 3H, CH₃), 0.87 (s, 3H, CH₃), 0.79 (s, 3H, CH₃); 13C NMR (100 MHz, CDCl3, δ): 108.1 (C [OCH₃]), 53.0 (Cq), 50.2 (OCH₃), 49.9 (Cq), 47.2 (OCH₃), 44.3 (CH), 41.0 (CH₂), 29.3 (CH₂), 27.3 (CH₂), 20.8 (CH₃), 20.5 (CH₃), 12.4 (CH₃); MS (ESI, m/z): [M]\(^+\) calcd for C₁₂H₂₃O₂, 198.16; found, 198.07.

**4 | RESULTS AND DISCUSSION**

Several methods have been reported in the literature for the preparation of enantiopure myo-inositol derivatives by resolution of myo-inositol. Among them, we followed the methodology based on introduction of D- or L-camphor as chiral auxiliaries into the myo-inositol structure. Such an approach, first described by Bruzik et al., results both in the desymmetrization of myo-inositol and in the regioselective protection of its hydroxyl groups in C-1 and C-2 positions.

As illustrated in Scheme 1, we adopted the procedure reported by Nkambule, with some modifications, to obtain 2-O-acetyl-3,4,5,6-tetra-O-benzyl-D-myoinositol (5), which was then converted to enantiomerically pure 2-O-acetyl-3,4,5,6-tetra-O-benzyl-D-myoinositol diphenylphosphate (6). This strategy enabled us to synthesize the target molecule in five steps from myo-inositol (1) in an overall 19% yield.

More in details, 1 was transketalized by treatment with 4 equivalents of L-camphor dimethyl acetal (7), prepared by treatment of L-camphor with trimethyl orthoformate), and PTSA in dry DMSO at 55°C. The selectivity of the reaction led to the formation of cis

**SCHEME 1 Synthesis of 2-O-acetyl-3,4,5,6-tetra-O-benzyl-D-myoinositol diphenylphosphate (6) from myo-inositol (1).**
monoacetate 2 as the major product in a complex mixture of diastereoisomers. The PTSA-catalyzed equilibration of the crude mixture allowed to further increase the amount of the desired isomer 2, protected at 1 and 2 positions and having the D configuration. After precipitation in dichloromethane, the mixture containing 2 was directly treated with benzyl bromide and NaH in dry DMF to protect the remaining four hydroxyl groups as benzyl ethers to give 3. The latter intermediate was easily purified from the traces of diastereoisomers generated in the previous step by flash chromatography. The chiral auxiliary was then removed with concentrated acetic acid (80% v/v solution in water) at 100°C, and the resulting crude product 4 was used in the next step without further purification.

To complete the synthetic sequence, 5 was reacted with excess diphenyl phosphoryl chloride (DPC), a catalytic amount of 4-dimethylaminopyridine and triethylamine in dichloromethane, followed by simple aqueous workup and chromatographic purification to give the target product 6 in 70% yield.

The 1H-NMR spectrum of 6 recorded in CDCl₃ (Figure 1) showed the expected pattern of signals. In details, the typical signal of the equatorial proton H-2, usually located slightly downfield with respect to the others, is further shifted to 5.98 ppm. Similarly, the axial proton H-1 was also shifted downfield to 4.66 ppm with respect to the corresponding signal in myo-inositol (1).
5  |  CONCLUSION

To sum up, this short note reports the synthesis of 2-O-acetyl-3,4,5,6-tetra-O-benzyl-d-myoinositol diphenylphosphate (6), a new optically active inositol phosphate derivative that may be a useful building block for the synthesis of inositol phosphates and phospholipids such as the anti-inflammatory agent GPI. It is worth noting that, to the best of our knowledge, no chemical synthesis of GPI and its phosphorylated derivatives has been reported to date. Starting from 6, GPI might be simply prepared by treatment with a properly protected glycerol synthon, followed by removal of all protective groups.  

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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