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Chiral desymmetrisation of *myo*-inositol 1,3,5-orthobenzoate gives rapid access to precursors for second messenger analogues

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Abstract—Chiral desymmetrisation of *myo*-inositol 1,3,5-orthobenzoate via the formation of diastereoisomeric bis[(1*S*)-(−)-camphanate] esters provides a convenient and fast route to precursors for biologically important inositol phosphates and lipids, and to synthetic analogues and probes modified at O-1 or O-3 of the inositol ring.

1. Introduction

myo-Inositol 1,3,5-orthoesters[1] have been widely used in recent years as intermediates in the synthesis of inositol phosphates and lipids. The introduction of the adamantane-like orthoester cage protects the O-1, O-3 and O-5 atoms of *myo*-inositol in a single step, leaving the OH groups at C-2, C-4 and C-6 free for manipulation (Fig. 1). The orthoester can also be cleaved with reducing agents to give different patterns of hydroxyl group protection,[2] and in the case of the alkyl orthoesters, acid hydrolysis can introduce an acyl ester at various positions on the inositol ring.[3] *myo*-Inositol orthoformate[4] **1** has been most extensively investigated, although *myo*-inositol orthoacetate **2**[3a,4e] and other orthoesters with alkyl chains[3b,5] have also been used. *myo*-Inositol 1,3,5-orthobenzoate **3** has not previously been exploited as a synthetic precursor, although an obvious advantage of **3** is that hydrolysis of the orthoester cage should leave a stable benzoate ester on the inositol ring, giving greater scope for subsequent elaboration.

Previously, we have shown that chiral desymmetrisation of **1**[6] and **2**[3a] by the formation of diastereoisomeric 2,4- and 2,6-bis[(1*S*)-(−)-camphanate] esters can provide rapid routes to two physiologically important inositol phosphates,[7] inositol 1,3,4,5-tetrakisphosphate [Ins(1,3,4,5)P_4][6] and inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3],[3a] respectively. For ongoing investigations into the biological roles of Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4, we required a convenient route to precursors for synthetic Ins(1,3,4,5)P_4 conjugates in which either the 1- or 3-phosphate group could be modified selectively, while retaining the 3,4,5- or 1,4,5-trisphosphate pattern. Here we show that by applying our desymmetrisation approach to *myo*-inositol orthobenzoate **3**, the methodology can be developed and extended, giving fast routes to the required chiral precursors for O-1 and O-3 modified analogues of Ins(1,3,4,5)P_4, and also for analogues of Ins(1,4,5)P_3 and phosphatidylinositol 3,4,5-trisphosphate [PtdIns(3,4,5)P_3].[8]

2. Results and discussion

2.1. General strategy

Our synthetic strategy (Scheme 1) employs chiral desymmetrisation of *myo*-inositol orthobenzoate **3** using (1*S*)-(−)-camphanic chloride, followed by isolation of the required D-2,6-bis(camphanate) **4** by crystallisation. The camphanate esters are then replaced with stable benzyl ethers in a straightforward sequence of reactions employing a methoxyisopropylidene (MIP) acetal for the transient protection of the 4-OH group, thus retaining the D-2,6 protection pattern. Acid hydrolysis of the orthobenzoate cage now allows the creation of benzoate esters at O-1 or O-3 of the *myo*-inositol ring, allowing differentiation of either the 1- or the 3-hydroxyl group from the other hydroxyl groups destined for phosphorylation. Thus, D-1-*O*-benzoyl-2,6-di-*O*-benzyl-*myo*-inositol **6** is a

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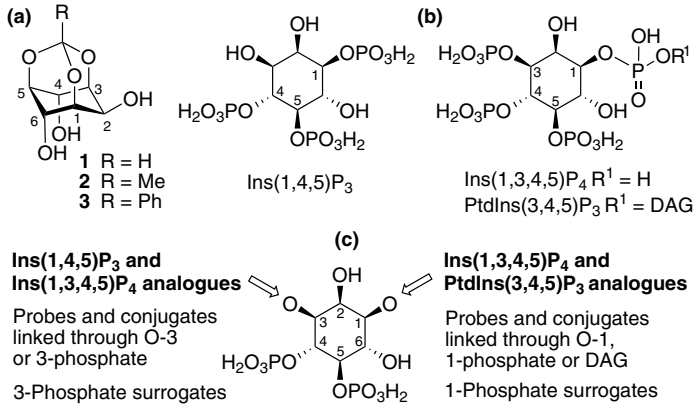
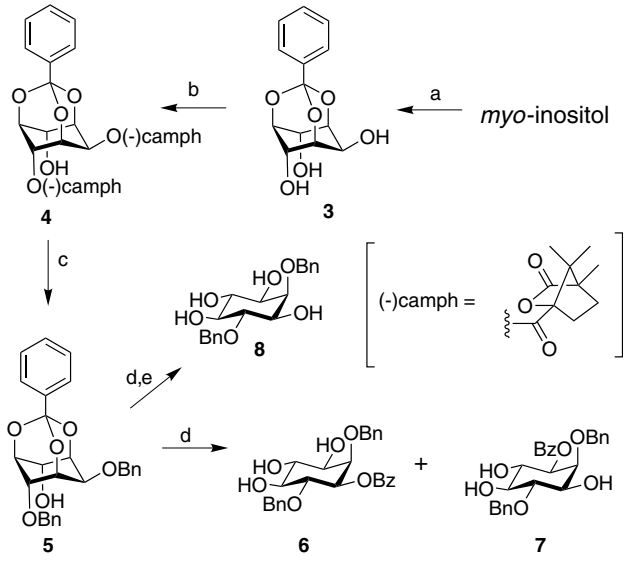


Figure 1. (a) *myo*-Inositol 1,3,5-orthoesters **1**, **2** and **3**; (b) Inositol 1,4,5-trisphosphate, inositol 1,3,4,5-tetrakisphosphate and phosphatidylinositol 3,4,5-trisphosphate; (c) Regioselectively modified analogues of $Ins(1,4,5)P_3$, $Ins(1,3,4,5)P_4$ and $PtdIns(3,4,5)P_3$ accessible from **3**. Compounds are shown with 1D-numbering. DAG = diacylglycerol.



Scheme 1. Reagents and conditions: (a) Trimethyl orthobenzoate (1.1 equiv), camphorsulfonic acid (0.02 equiv), DMSO, 80 °C, 5 h, 84%; (b) (1*S*)-(−)-camphanic chloride (2.1 equiv), triethylamine (2.3 equiv), DMAP (0.06 equiv), CH_2Cl_2, 0 °C to rt, 66%; (c) (i) 2-methoxypropene (10 equiv), PTSA (0.02 equiv), THF, 0 °C to rt; (ii) $LiOH{\cdot}H_2O$ (10 equiv), THF, MeOH, H_2O; (iii) NaH, BnBr, DMF; (iv) wet CH_2Cl_2, trace of TFA, 85% from **4**; (d) 1.0 M HCl, ethanol, 1:2, reflux, 5 h, **6**: 48%, **7**: 41%; (e) NaOH, H_2O, reflux, **8**: 98% from **5**. Bn = benzyl, Bz = benzoyl.

synthetic precursor for $Ins(3,4,5)P_3$, P-1-tethered $Ins(1,3,4,5)P_4$[8,9] and $PtdIns(3,4,5)P_3$ analogues,[8] while D-3-*O*-benzoyl-2,6-di-*O*-benzyl-*myo*-inositol **7** is a precursor for $Ins(1,4,5)P_3$ and P-3-tethered $Ins(1,3,4,5)P_4$. They are also precursors for potential $Ins(1,3,4,5)P_4$ bioisosteres, in which either the 1- or 3-phosphate group is selectively replaced by a phosphate surrogate, such as phosphorothioate,[10] or methylphosphonate.[11]

2.2. Synthesis of *myo*-inositol orthobenzoate 3

myo-Inositol orthobenzoate **3** was prepared by a method similar to that reported for the preparation of *myo*-inositol orthopentanoate,[3b] using transesterification of *myo*-inositol with a slight excess of trimethyl orthobenzoate in dry DMSO at 80 °C in the presence of a catalytic amount of camphorsulfonic acid. By distilling off formed MeOH (e.g., by carrying out the reaction in a rotary evaporator), shorter reaction times can be used. Alternatively, DMF can be used as a solvent, although higher temperatures (>140 °C) and larger amounts of catalyst and trimethyl orthobenzoate are required. After neutralisation with triethylamine and removal of solvents, a solution of the residue in hot EtOAc is filtered through a silica pad to remove coloured and polar materials, then reduced in volume and allowed to cool, giving crystals of **3** [R_f 0.40 (EtOAc); mp 213–214 °C] in 84% yield. More **3** can be obtained by flash chromatography of the mother liquor if required. A single-crystal X-ray structure of **3**[12] was obtained (Fig. 2).

2.3. Isolation of D-2,6-di-*O*-[(−)-camphanoyl]-*myo*-inositol orthobenzoate 4

Reaction of **3** with (1*S*)-(−)-camphanic chloride (2.1 equiv) in CH_2Cl_2 in the presence of triethylamine and a catalytic amount of DMAP[13] gave a mixture of the 2,6-bis(camphanate) **4**, together with the more polar 2,4-bis(camphanate).[14] The use of other solvents (pyridine, acetonitrile or DMF) was less successful, giving substantial amounts of mono- and tris(camphanate). The D-2,6-bis(camphanate) **4**, which is the required precursor for $Ins(1,4,5)P_3$, $Ins(3,4,5)P_3$, $Ins(1,3,4,5)P_4$ and $PtdIns(3,4,5)P_3$ analogues, has low solubility in most organic solvents, and can be easily isolated by crystallisation. The absolute configuration of **4** was determined as described below. Crystalline **4** is stable, although neutral or alkaline solutions of **4** show slow hydrolysis and migration of the camphanate group at O-6.

2.4. Conversion of 4 into D-2,6-di-*O*-benzyl-*myo*-inositol orthobenzoate 5

In the next step, the camphanate esters in **4** are replaced with benzyl ethers. This sequence of reactions was carried out without isolation of intermediates, requiring only a final purification step by flash chromatography. Thus, the reaction of **4** with 2-methoxypropene in the

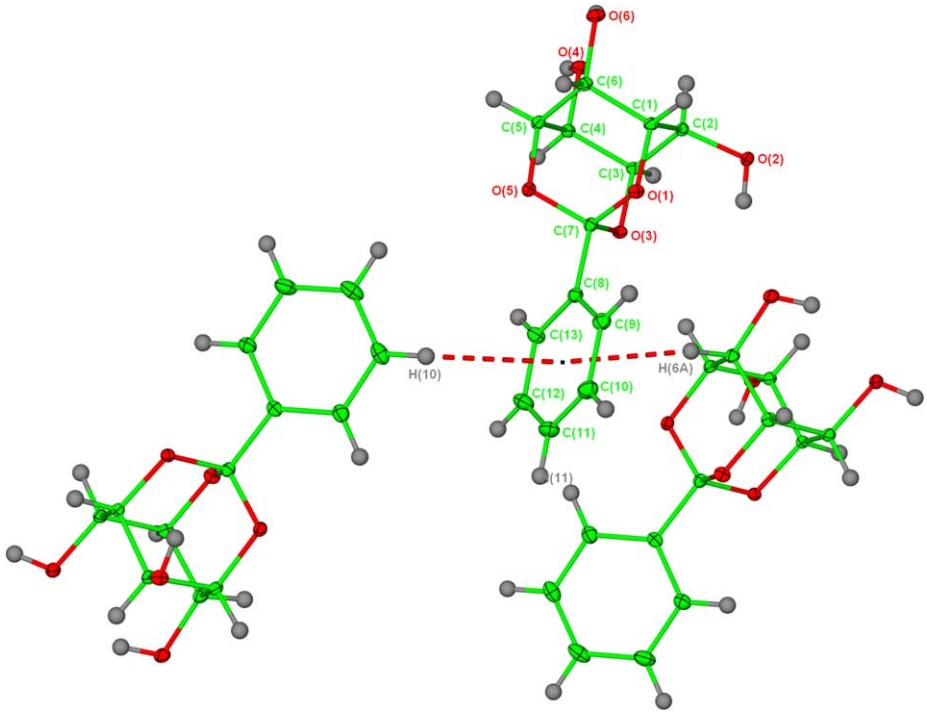


Figure 2. Portion of lattice packing in **3**, showing C–H···π interactions. Ellipsoids are represented at the 30% probability level.

presence of a catalytic amount of PTSA in THF gives the 4-*O*-MIP acetal, and addition of $LiOH{\cdot}H_2O$ in $MeOH/H_2O$ to the solution then cleaves the camphanate esters in situ. After evaporation of solvents and aqueous workup, benzylation at O-2 and O-6 followed by selective cleavage of the MIP acetal using a trace of acid gives **5**,[15] isolated by flash chromatography in 85% yield from **4**.[16] Thus, pure **5** can readily be obtained on a multi-gram scale from *myo*-inositol.

2.5. Hydrolysis and absolute configuration of 5

Hydrolysis of **5** using aqueous HCl in refluxing EtOH gave a 1.2:1 mixture of 1-*O*-benzoate ester **6** and 3-*O*-benzoate ester **7**. No 5-*O*-benzoate was detected under these conditions.[17] The triols differ strikingly in their polarity, and can be easily separated by flash chromatography, giving **6** and **7** as crystalline solids.[18] Hydrolysis of **5** followed by saponification of the resulting mixture of 1- and 3-*O*-benzoates gave D-2,6-di-*O*-benzyl *myo*-inositol **8**. The absolute configuration of **8**, and thereby that of compounds **4**, **5**, **6** and **7** was established by comparison of its specific rotation with the literature values.[19]

2.6. Synthetic utility of benzoates 6 and 7

The benzoate esters **6** and **7** are key intermediates for the synthesis of inositol phosphates and lipids. For example, phosphitylation of **6** or **7** using bis(benzyloxy)diisopropylaminophosphine and 1*H*-tetrazole, followed by oxidation of phosphites and cleavage of benzoate esters gives D-2,6-di-*O*-benzyl-*myo*-inositol-3,4,5-tris(dibenzylphosphate)[20,21,2e] and D-2,6-di-*O*-benzyl-*myo*-inositol-1,4,5-tris(dibenzylphosphate),[20] respectively, in which the 1-OH or 3-OH group is now available for selective modification. Alternatively, hydrogenolysis of **6** or **7** gives D-1-*O*-benzoyl-*myo*-inositol[22] or D-3-*O*-benzoyl-*myo*-inositol,[22,23] respectively, precursors for Ins-(2,3,4,5,6)P_5[22,24] and Ins(1,2,4,5,6)P_5.[22,24]

3. Conclusion

myo-Inositol orthobenzoate **3** is a versatile new starting material for the synthesis of *myo*-inositol phosphates and lipids. Chiral desymmetrisation of **3** allows fast access to orthogonally protected chiral intermediates, which are precursors for a range of analogues and conjugates related to Ins(1,4,5)P_3, Ins(1,3,4,5)P_4 and PtdIns(3,4,5)P_3.

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12. (a) Crystallographic data (excluding structure factors) for **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 289619. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]; While this manuscript was in preparation, an X-ray study of two polymorphs of **3** was reported: (b) Bhosekar, G.; Murali, C.; Gonnade, R. G.; Shashidhar, M. S.; Bhadbhade, M. M. *Cryst. Growth Des.* **2005**, *5*, 1977–1982; (c) The 2,4,6-tri-*O*-methyl ether of **3** has been mentioned in the literature,[2b] although no details of its preparation were given.
13. Typical procedure: *myo*-inositol orthobenzoate **3** (2.80 g, 10.5 mmol) previously dried in vacuo at 60 °C, was suspended in dry CH_2Cl_2 (40 mL). Dry triethylamine (3.3 mL, 24 mmol) and a catalytic amount of DMAP (80 mg) were added, and the mixture cooled to 0 °C. Solid (1*S*)-(−)-camphanic chloride (4.55 g, 21.0 mmol) was added in portions to the stirred mixture over 15 min. After 1.5 h, the cooling bath was removed and the mixture allowed to reach room temperature. After 2 h at room temperature, TLC (CH_2Cl_2/EtOAc 3:1) showed two products; 2,6-bis(camphanate), (R_f 0.52) and 2,4-bis(camphanate) (R_f 0.42), together with a trace of monocamphanates (R_f 0.25). A small amount of (1*S*)-(−)-camphanic chloride (approx. 100 mg) was added and stirring continued for another 1 h. This step was repeated until no trace of monocamphanates remained. The solvents were removed by evaporation under reduced pressure. The residue was taken up in CH_2Cl_2/CH_3CN (5:1, 100 mL) and the solution was washed with 0.5 M HCl (50 mL). Small amounts of CH_3CN were added, until two clear layers were obtained. The organic layer was separated, dried ($MgSO_4$) and concentrated to give a solid. Crystallisation from hot $CHCl_3$/CH_3CN gave 2,6-bis(camphanate) **4** (4.33 g, 6.91 mmol, 66%) after drying in vacuo at 30 °C; mp 238–240 °C; $[\alpha]_D^{20} = -19.4$ (*c* 0.9, DMF); ^{1}H NMR δ 0.97, 0.99, 1.06, 1.07, 1.15, 1.19 (6 × s, 18H, C*H*$_3$ of camph), 1.58–1.68 (m, 2H, C*H*$_2$ of camph), 1.98–2.14 (m, 4H, C*H*$_2$ of camph), 2.50–2.61 (m, 2H, C*H*$_2$ of camph), 4.57 (dddd, appears as dq, 1H, $J = 3.8$, 1.9, 1.9, 1.9 Hz, H-3), 4.72–4.77 (m, 3H, H-1, H-4 and H-5), 5.58 (dd, appears as t, 1H, $J = 1.6$, 1.6 Hz, H-2), 5.67 (ddd, appears as td, 1H, $J = 3.8$, 3.8, 1.6 Hz, H-6), 6.37 (d, 1H, $J = 4.6$ Hz, 4-OH), 7.42–7.46 (m, 3H, Ph) and 7.63–7.65 (m, 2H, Ph); ^{13}C NMR (100 MHz, d_7-DMF) δ 9.75, 9.80, 16.41, 16.64, 16.71 and 16.84 (6 × *C*H$_3$ of camph), 29.26, 29.32, 31.09 and 31.51 (4 × *C*H$_2$ of camph), 54.76, 54.80, 55.19 and 55.31 (4 × C_q of camph), 64.69 (*C*-2), 67.00, 70.28, 70.46 and 71.19 (4 × inositol *C*H), 73.83 (*C*-3), 91.67 and 91.69 (2 × C_q of camph), 108.13 (Ph*C*O$_3$), 126.11 and 128.56 (Ph *C*H), 130.15 (*para*-*C*H of Ph) and 138.11 (*ipso*-*C* of Ph); MS (FAB$^+$) 627 [(M+H$^+$), 100%], 429 [(M–camphO)$^+$, 10%]; Elemental analysis; calcd for $C_{33}H_{38}O_{12}$ (626.65): C, 63.25; H, 6.11. Found: C, 63.0; H, 6.10.
14. Under these conditions, the desymmetrisation reaction favours the 2,6-bis(camphanate) **4**, whose low solubility makes isolation of the minor product [2,4-bis(camphanate)] more difficult. If the method is to be used specifically for synthesis of intermediates with the 2,4-protected pattern, the reaction can be carried out using (1*R*)-(+)-camphanic chloride. This material is commercially available, although more expensive than the (1*S*)-(−)-enantiomer.
15. Data for **5**: colourless crystals from EtOAc/hexane, mp 84.5–85.5 °C; $[\alpha]_D^{20} = +3$ (*c* 1, $CHCl_3$).
16. When alcohol **5** was esterified with (1*S*)-(−)-camphanic chloride, a single product was obtained, while esterification of racemic **5** in the same way gave two diastereoisomeric products, clearly distinguishable by TLC and by ^{1}H NMR spectroscopy. Thus, no detectable migration of camphanate or MIP groups takes place during the conversion of **4** into **5**.
17. Acid hydrolysis of 2,6-di-*O*-benzyl-*myo*-inositol orthoacetate under similar conditions gives only 1-*O*-acetyl-2,6-di-*O*-benzyl *myo*-inositol and tetraol **8** (Liu, C.; Potter, B. V. L., unpublished results).
18. Data for **6**: R_f 0.32 (EtOAc); colourless crystals from ether/hexane, mp 110–110.5 °C; $[\alpha]_D^{20} = -118.9$ (*c* 1, MeOH). Data for **7**: R_f 0.70 (EtOAc); colourless crystals from EtOAc/hexane, mp 171–173 °C; $[\alpha]_D^{20} = +36.7$ (*c* 1, MeOH).
19. Data for **8**: mp 144–146 °C (from $CHCl_3$); Lit.[4b] 145.2–146.1 °C; $[\alpha]_D^{20} = -32.3$ (*c* 1, EtOH); Lit.[4b] $[\alpha]_D^{25} = -29.3$ (*c* 1, EtOH).
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