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Synthesis from quebrachitol of 1L-*chiro*-inositol 2,3,5-trisphosphate, an inhibitor of the enzymes of 1D-*myo*-inositol 1,4,5-trisphosphate metabolism *

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ABSTRACT

L-Quebrachitol was *O*-demethylated to give 1L-*chiro*-inositol which, on treatment with dibutyltin oxide, benzyl chloride, and tetrabutylammonium iodide in acetonitrile, gave mainly crystalline 1L-2,3,5-tri-*O*-benzyl-*chiro*-inositol (**5a**) together with 1L-2,3,5,6-tetra-*O*-benzyl-*chiro*-inositol. Catalytic hydrogenolysis of the 1,4,6-tribenzoate (**6a**) of **5a** afforded crystalline (−)-1L-1,4,6-tri-*O*-benzoyl-*chiro*-inositol (**7**). Phosphitylation of **7** with either bis(2-cyanoethyl) *N*,*N*-diisopropylphosphoramidite or chlorodiethoxyphosphine followed by oxidation gave the respective 2,3,5-trisphosphate derivatives. Deprotection with either sodium in liquid ammonia or bromotrimethylsilane followed by sodium hydroxide then gave (−)-1L-*chiro*-inositol 2,3,5-trisphosphate (**2**).

INTRODUCTION

1D-*myo*-Inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] (**1**) is a second messenger, generated by agonist-stimulated, receptor-mediated, phospholipase C-catalysed cleavage of the minor membrane lipid, phosphatidylinositol 4,5-biphosphate[1]. Ins(1,4,5)P_3 releases sequestered Ca^{2+} from an intracellular store in the endoplasmic reticulum and its generation is a key event in signal transduction for numerous extracellular agonists. Ins(1,4,5)P_3 acts through a receptor which has been isolated[2], cloned and sequenced[3,4], and reconstituted[5].

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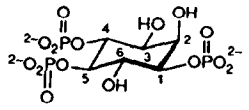
* Dedicated to Professor Fritz Eckstein on the occasion of his 60th birthday.



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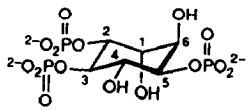

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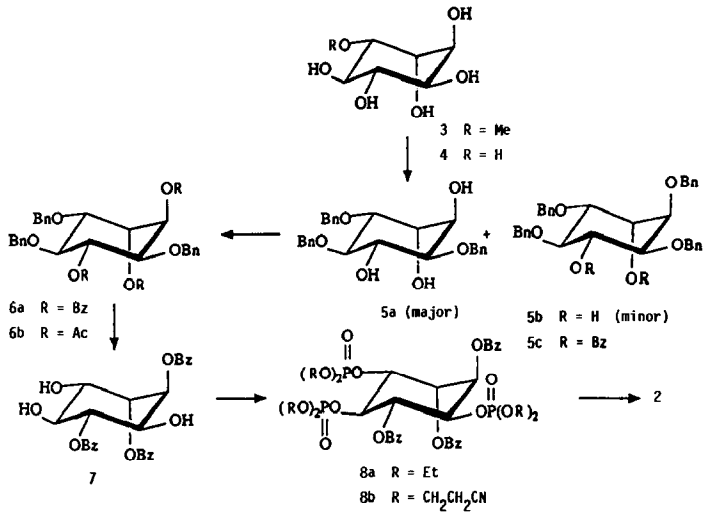
There is significant potential[6] for the design and chemical synthesis of novel receptor ligands and inhibitors for the enzymes Ins(1,4,5)P_3 5-phosphatase, which deactivates Ins(1,4,5)P_3 by dephosphorylation, and the 3-kinase which phosphorylates the equatorial HO-3. Such compounds may have potential therapeutic value. Indeed, there is a need for chemically modified analogues of Ins(1,4,5)P_3 in order to aid investigations of structure–activity relationships for all three binding proteins[6,7]. Few useful analogues have been reported. We have prepared potent analogues of Ins(1,4,5)P_3, including non-hydrolysable phosphorothioates[6–8] and fluoro analogues[9,10].

Although some success in the development of 5-phosphatase inhibitors has been achieved[11–14], it is a particular challenge to explore the design of 3-kinase inhibitors, since, in contrast to the 5-phosphatase which is relatively non-specific in its binding of inositol phosphates, the 3-kinase appears to be more specific in its recognition of such ligands than the receptor itself. 1L-*chiro*-Inositol 2,3,5-trisphosphate (**2**)*, which may be visualised as Ins(1,4,5)P_3 with the configuration at position 3 inverted, is of interest as a potential inhibitor of 3-kinase and a route for the synthesis of optically active **2** has been developed. Whilst this work was in progress, a synthesis of racemic **2** from benzene via a photo-oxidation procedure was published[15], but no biological data on **2** have been reported. The synthesis and activity of 1D- and 1L-*chiro*-inositol 1,3,4-trisphosphate have been reported[16], and our results have been reported in preliminary form[17].

A major problem in the synthesis of inositol polyphosphates concerns the multiple regiospecific protection of the various hydroxyl groups in inositol to afford intermediates suitable for polyphosphorylation[7]. This requirement invariably involves extensive manipulations with various permanent and temporary protecting groups, and a simplified procedure would be of great utility. If the strategy of tin-mediated alkylation[18] of the equatorial hydroxyl group in a vicinal *cis*-diol were to be applied to 1L-*chiro*-inositol (**4**), the symmetry of the molecule would lead to multiple protection at positions 2, 3, and 5. Thus 1L-*chiro*-inositol, which has axial hydroxyl groups at positions 1 and 6, should initially undergo rapid benzylation at HO-2*eq*,5*eq* to afford the 2,5-di-*O*-benzyl derivative via the corresponding *cis*-dibutylstannylene derivatives. Further benzylation at either positions 3 or 4 in a *trans*-diequatorial dibutylstannylene derivative affords the 2,3,5- or 2,4,5-tri-*O*-benzyl derivative, which are identical. A similar approach has been employed to

* Note the different conventional numbering of the *myo* (**1**) and *chiro*-inositol (**2**) systems.



Scheme 1.

generate allyl-protected *myo*-inositol intermediates[19]. We now report the synthesis of **2** via regiospecific tri-*O*-benzylation of 1L-*chiro*-inositol.

RESULTS AND DISCUSSION

L-Quebrachitol (**3**) was *O*-demethylated[20] with hydriodic acid to give 1L-*chiro*-inositol (**4**) (Scheme 1). Treatment of **4** under reflux with 4 mol equiv each of dibutyltin oxide and tetrabutylammonium iodide in acetonitrile, followed by 5 mol equiv of benzyl chloride, afforded crystalline 1L-2,3,5-tri-*O*-benzyl-*chiro*-inositol (**5a**, 32%) and 1L-2,3,5,6-tetra-*O*-benzyl-*chiro*-inositol (**5b**, 6%) together with very small amounts of other polybenzylated products. Treatment of **5a** with an excess of benzoyl chloride in pyridine gave the syrupy 1,4,6-tribenzoate **6a** in quantitative yield. The structure of **5a** was assigned unambigiously by ^{1}H COSY NMR spectroscopy of **5a** and its 1,4,6-triacetate **6b**. The ^{1}H COSY spectrum of **6b** is illustrated in Fig. 1. The signals of H-1 and H-6 appeared as an overlapping 2-proton multiplet (δ 5.41–5.42) and were assigned easily since they exhibited only the smaller $^3J_{eq,eq}$ and $^3J_{ax,eq}$ couplings for H-1,6, H-1,2, and H-5,6. The protons coupled to H-6 (δ 3.68 and 3.88), as indicated by the COSY spectrum, were then assigned as H-2 or H-5, which was confirmed by their appearance as dd with large $^3J_{ax,ax}$ and small $^3J_{ax,eq}$ values. The signals (pseudo-triplets) at δ 5.35 and δ 3.70 were then assigned to H-4 or H-3. The signals of H-1, H-6, and H-4 (or H-3) appeared at relatively low field in contrast to those of the other protons, reflecting deshielding by the neighbouring acetyl groups. Therefore, the structure of **6b** could be assigned as either (−)-1L-1,4,6-tri-*O*-acetyl-2,3,5-tri-*O*-benzyl-*chiro*-inositol or (−)-1L-1,3,6-tri-*O*-acetyl-2,4,5-tri-*O*-benzyl-*chiro*-inositol, which are identical. The structure of **5b** was confirmed in a similar fashion via the ^{1}H COSY spectrum of

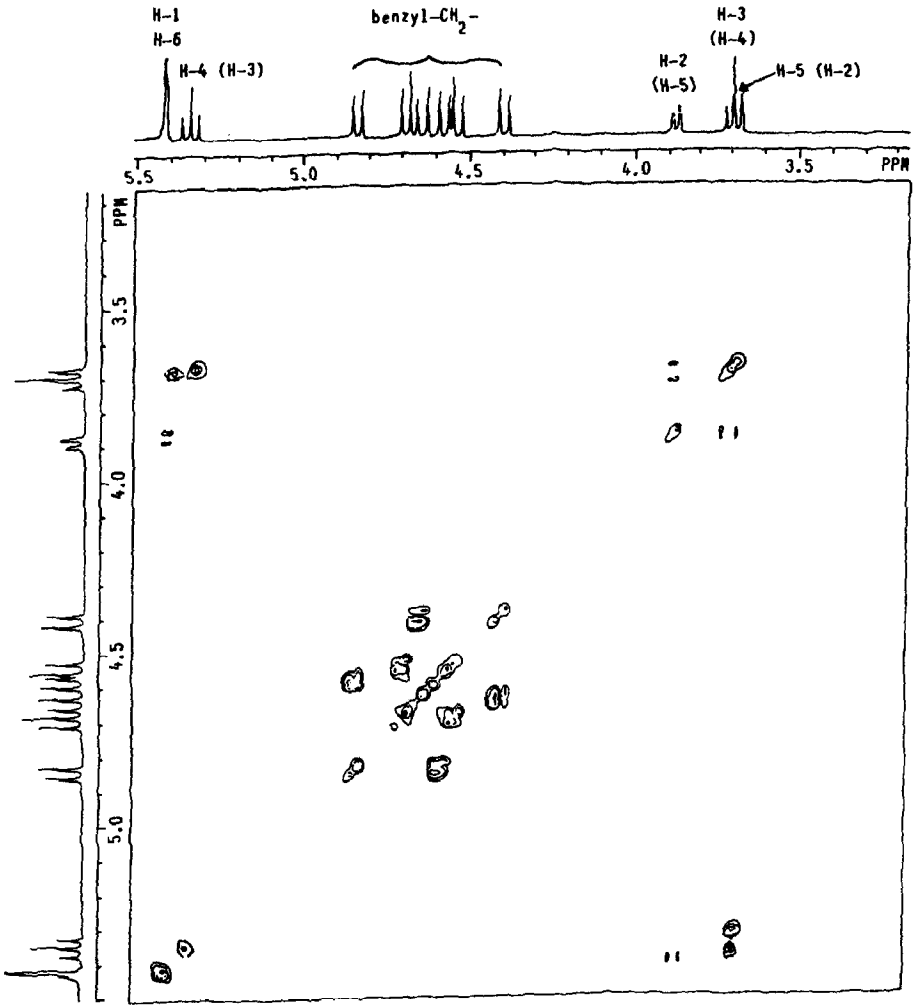


Fig 1. ^1H COSY NMR spectrum (400 MHz) of a solution of 1L-1,4,6-tri-*O*-acetyl-2,3,5-tri-*O*-benzyl-*chiro*-inositol (**6b**) in $CDCl_3$.

the 1,4-dibenzoate **5c** as (−)-1L-1,4-di-*O*-benzoyl-2,3,5,6-tetra-*O*-benzyl-*chiro*-inositol.

Catalytic hydrogenolysis (Pd/C) of **6a** gave crystalline 1L-1,4,6-tri-*O*-benzoyl-*chiro*-inositol (**7**, 94%). The minor polybenzylated *chiro*-inositols, formed in the original reaction, were isolated, but the small quantities precluded characterisation.

Phosphitylation of **7** using chlorodiethoxyphosphine gave a trisphosphite derivative which was not isolated but oxidised immediately with *tert*-butyl hydroperoxide to the syrupy 2,3,5-tris(diethyl phosphate) **8a** (73% from **7**). The ethyl groups were removed from **8a** using bromotrimethylsilane and then the benzoyl groups were removed using aqueous sodium hydroxide to give the target 2,3,5-trisphosphate **2**,

which was purified by ion-exchange chromatography and quantified (87%) as a glass using the Briggs phosphate assay[21].

A modified route to **2** employed bis(2-cyanoethyl) *N,N*-diisopropylphosphoramidite[22] as the phosphitylating agent. Oxidation of the resulting tris[di-(2-cyanoethyl) phosphite] gave **8b**, and deblocking with sodium in liquid ammonia followed by purification gave 80% of **2**.

The 2,3,5-trisphosphate **2** was a potent agonist for the release of intracellular Ca^{2+} from permeabilised human neuroblastoma cells, being only 5–10-fold less potent than Ins(1,4,5)P_3. Ca^{2+} was released by **2** in a sustained fashion similar to inositol 1,4,5-trisphosphorothioate[6,23], suggesting resistance to metabolism. The K_i values for the inhibition of human erythrocyte membrane Ins(1,4,5)P_3 5-phosphatase-catalysed dephosphorylation of 5[^{32}P]-Ins(1,4,5)P_3 and crude rat-brain 3-kinase-catalysed phosphorylation of Ins(1,4,5)P_3, measured as we described for other analogues[9,14], were 7.7 and 7.1 μM, respectively. Although, as expected, **2** was not a substrate for the 3-kinase but a potent inhibitor, it was not dephosphorylated by 5-phosphatase. The biological results will be presented in detail elsewhere[24].

Removal[14] of HO-6 from Ins(1,4,5)P_3 to give 6-deoxy-Ins(1,4,5)P_3 generates a moderately potent inhibitor of 5-phosphatase. However, the finding that **2** is a potent inhibitor of this enzyme poses the question as to how a change in orientation of a hydroxyl group remote from the site of action of the enzyme can have such a radical effect. Whether this effect is the result of subtle changes in conformation or of non-productive binding of **2** to the enzyme merits further investigation (see ref. 24).

EXPERIMENTAL

TLC was performed on Silica Gel 60F (Merck) with detection by UV light or with methanolic phosphomolybdic acid. Flash-column chromatography was performed on silica gel (SORBSIL C60). The ^{1}H NMR spectra (internal Me_4Si) were recorded with a Bruker AM-300, Jeol JMN-GX270, or JMN-GX400 spectrometer. The ^{31}P NMR spectra (external aq 85% phosphoric acid) were recorded with a Jeol FX-90Q, JMN-GX400, or Bruker AM-300 spectrometer. Mass spectra were recorded at the S.E.R.C. Mass Spectrometry Service Centre (Swansea) or at the Mass Spectrometry Service, University of Bath. Microanalysis was carried out at Butterworth Laboratories Ltd. or by the Microanalysis Service, University of Bath. Melting points (uncorrected) were determined using a Reichert-Jung Thermo Galen Kofler Block. Optical rotations at 589 nm were measured with an Optical Activity Ltd. Polarimeter Type-AA-10. Ion-exchange chromatography was performed on DEAE Sephadex A-25 by elution with a gradient of triethylammonium hydrogen carbonate (TEAB) buffer at pH 8.0. Quantitative analysis of phosphate was performed using the Briggs phosphate assay[21].

1L-chiro-Inositol (**4**).—A mixture of quebrachitol (10 g, extracted from crude rubber by-product, which was a kind gift of The Malaysian Rubber Company, Kuala Lumpur) and aq 47% HI (25 mL) was boiled under reflux for 2 h, then poured into boiling EtOH (160 mL), and cooled. The product was collected and washed twice with EtOH to give **4** (80%)[20], mp 215–220°, $[\alpha]_D$ −64° (*c* 3.8, H_2O); lit.[25] mp 240°, $[\alpha]_D$ −64°.

(−)-1L-2,3,5-Tri-O-benzyl-chiro-inositol (**5a**).—A mixture of **4** (3.6 g, 20 mmol), Bu_2SnO (19.94 g, 80 mmol), Bu_4NI (29.53 g, 80 mmol), and dry MeCN (250 mL) was boiled under reflux for 15 h, benzyl chloride (11.5 mL, 100 mmol) was added, and boiling was continued for 24 h. The solvent was evaporated, the residue was partitioned between ether (100 mL) and M HCL (100 mL), and the ether layer was washed twice with satd aq $NaHCO_3$ (2 × 1 L), dried ($MgSO_4$), filtered through Celite, and concentrated. Flash-column chromatography (light petroleum then ether–EtOH 95:5) of the residue gave **5a** (32%) and 1L-2,3,5,6-tetra-*O*-benzyl-*chiro*-inositol (**5b**, 6%) which were crystallised from light petroleum–EtOAc.

Compound **5a** had mp 96–97°, $[\alpha]_D$ −47° (*c* 2.3, EtOH). ^1H NMR data ($CDCl_3$, 300 MHz): δ 2.62 (d, 1 H, *J* 2.3 Hz, OH), 2.65 (s, 1 H, OH), 2.69 (s, 1 H, OH), 3.68 (t, 1 H, *J* 9.3 Hz, CH), 3.70 (dd, 1 H, *J* 9.4 and 2.7 Hz, CH), 3.82 (dd, 1 H, *J* 9.3 and 2.5 Hz, CH), 3.90 (td, 1 H, *J* 9.3 and 2.2 Hz, CH), 4.06–4.15 (m, 2 H, 2 CH), 4.59 and 4.65 (ABq, 2 H, J_{AB} 11.3 Hz, CH_2), 4.60 and 4.66 (ABq, 2 H, J_{AB} 11.3 Hz, CH_2), 4.77 and 4.88 (ABq, 2 H, J_{AB} 11.3 Hz, CH_2), 7.20–7.35 (m, 15 H, 3 Ph). Mass spectrum: *m/z* 468.2386 [$(M + NH_4)^+$, 8%; calcd 468.2385], 359 (25), 288 (10), 269 (15), 198 (26), 181 (35), 108 (100), 91 (70).

Anal. Calcd for $C_{27}H_{30}O_6$ (450.53): C, 71.98; H, 6.71. Found: C, 72.00; H, 6.95.

Compound **5b** had mp 114°, $[\alpha]_D^{20}$ −28° (*c* 6.4, $CHCl_3$). ^1H NMR data ($CDCl_3$, 400 MHz): δ 2.48 (s, 1 H, OH), 2.56 (s, 1 H, OH), 3.68 (t, 1 H, *J* 9.4 Hz, H-3 or H-4), 3.74 (dd, 1 H, *J* 2.8 and 9.8 Hz, H-2 or H-5), 3.79 (dd, 1 H, *J* 3.0 and 9.1 Hz, H-2 or H-5), 3.94 (t, 1 H, *J* 3.5 Hz, H-1 or H-6), 4.01 (t, 1 H, *J* 3.7 Hz, H-1 or H-6), 4.07 (t, 1 H, *J* 9.5 Hz, H-3 or H-4), 4.49 and 4.71 (ABq, 2 H, J_{AB} 12.1 Hz, CH_2), 4.57 and 4.71 (ABq, 2 H, J_{AB} 11.6 Hz, CH_2), 4.64 (s, 2 H, CH_2), 4.86 (s, 2 H, CH_2), 7.24–7.39 (m, 20 H, 4 Ph). FAB-mass spectrum: *m/z* 539 [$(M - H)^-$, 89%], 449 (65), 431 (100), 359 (21), 334 (35), 272 (50), 244 (35), 182 (58), 141 (25), 93 (22).

Anal. Calcd for $C_{34}H_{36}O_6$ (540.66): C, 75.53; H, 6.71. Found: C, 75.20; H, 6.77.

(−)-1L-1,4-Di-O-benzoyl-2,3,5,6-tetra-O-benzyl-chiro-inositol (**5c**).—To a solution of **5b** (0.054 g, 0.1 mmol) in pyridine (5 mL) was added benzoyl chloride (0.05 mL, 0.6 mmol). The solution was stirred at room temperature for 2.5 h, then concentrated, and the residue was partitioned between ether (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Flash-column chromatography (light petroleum–ether 2:1) of the residue gave **5c** in quantitative yield as a syrup, $[\alpha]_D^{20}$ −13° (*c* 7.5, $CHCl_3$). ^1H NMR data ($CDCl_3$, 400 MHz): δ 3.86 (dd, 1 H, *J* 2.7 and 10.1 Hz, H-5), 3.92 (t, 1 H, *J* 9.5 Hz, H-3), 3.96 (t, 1 H, *J* 3.4 Hz, H-6), 4.14 (dd, 1 H, *J* 3.4 and 9.8 Hz, H-2), 4.43 and 4.52 (ABq, 2 H, J_{AB} 12.2 Hz, CH_2), 4.57 and 4.85 (ABq, 2 H, J_{AB} 11.1 Hz, CH_2), 4.61

and 4.66 (ABq, 2 H, J_{AB} 11.6 Hz, CH_2), 4.60 and 4.77 (ABq, 2 H, J_{AB} 11.0 Hz, CH_2), 5.64 (t, 1 H, *J* 3.7 Hz, H-1), 5.89 (t, 1 H, *J* 9.8 Hz, H-4), 7.04–8.18 (m, 30 H, 6 Ph). FAB-mass spectrum: *m/z* 749 [(M + H)$^+$, 48%], 641 (80), 551 (25), 371 (20), 181 (33), 91 (100).

*(−)-1L-1,4,6-Tri-O-acetyl-2,3,5-tri-O-benzyl-*chiro*-inositol* (**6b**).—A solution of **5a** (0.135 g, 0.3 mmol) and acetic anhydride (0.4 mL, 4.4 mmol) in dry pyridine (3 mL) was heated at 100° for 1 h, then cooled to room temperature, and concentrated in vacuo. Toluene then EtOH were distilled from the residue, which was recrystallised from cyclohexane to give **6b** (0.16 g, 90%), mp 136–138°, $[\alpha]_D^{20}$ −100° (*c* 2, $CHCl_3$). ^{1}H NMR data ($CDCl_3$, 400 MHz): δ 1.95, 2.08, 2.10 (3 s, each 3 H, Ac), 3.68 (dd, 1 H, *J* 2.2 and 9.8 Hz, H-5 or H-2), 3.70 (dd, 1 H, *J* 9.6 Hz, H-3 or H-4), 3.88 (dd, 1 H, *J* 2.2 and 9.5 Hz, H-2 or H-5), 4.40 and 4.64 (ABq, 2 H, J_{AB} 11.9 Hz, CH_2), 4.54 and 4.69 (ABq, 2 H, J_{AB} 11.0 Hz, CH_2), 4.58 and 4.84 (ABq, 2 H, J_{AB} 11.3 Hz, CH_2), 5.35 (dd, 1 H, J_{AB} 9.8 Hz, H-4 or H-3), 5.41–5.42 (m, 2 H, H-1 and H-6), 7.23–7.35 (m, 15 H, 3 Ph). FAB-mass spectrum: *m/z* 577 [(M + H)$^+$, 47%], 517 (39), 469 (92), 427 (34), 379 (81), 337 (19), 181 (15), 91 (100).

Anal. Calcd for $C_{33}H_{36}O_9$ (576.64): C, 68.74; H, 6.29. Found: C, 68.40; H, 6.21.

*(−)-1L-1,4,6-Tri-O-benzoyl-2,3,5-tri-O-benzyl-*chiro*-inositol* (**6a**).—To a solution of **5a** (1.35 g, 3 mmol) in pyridine (30 mL) was added benzoyl chloride (2.1 mL, 27 mmol). The solution was stirred at room temperature for 2 h, then concentrated, and the residue was partitioned between ether (250 mL) and satd aq $NaHCO_3$ (250 mL). The organic layer was dried ($MgSO_4$) and concentrated. Flash-column chromatography (light petroleum–ether 2 : 1) of the residue gave **6a** in quantitative yield as a syrup, $[\alpha]_D^{20}$ −34.5° (*c* 8.9, EtOAc). ^{1}H NMR data ($CDCl_3$, 300 MHz): δ 3.99 (t, 1 H, *J* 9.5 Hz, H-3 or H-4), 4.05 (dd, 1 H, *J* 2.2 and 9.9 Hz, H-2 or H-5), 4.17 (dd, 1 H, *J* 2.2 and 9.6 Hz, H-5 or H-2), 4.48 and 4.66 (ABq, 2 H, J_{AB} 12.4 Hz, CH_2), 4.62 and 4.79 (ABq, 2 H, J_{AB} 11.1 Hz, CH_2), 4.62 and 4.81 (ABq, 2 H, J_{AB} 11.2 Hz, CH_2), 5.83 (t, 1 H, *J* 9.6 Hz, H-4 or H-3), 5.86–5.87 (m, 2 H, H-1 and H-6), 7.02–8.07 (m, 30 H, 6 Ph). FAB-mass spectrum: *m/z* 763 [(M + H)$^+$, 17%], 655 (96), 641 (100), 565 (97), 551 (45), 475 (41), 461 (48), 371 (26), 271 (37).

Anal. Calcd for $C_{48}H_{42}O_9$ (762.29): C, 75.58; H, 5.55. Found: C, 75.40; H, 5.66.

*(−)-1L-1,4,6-Tri-O-benzoyl-*chiro*-inositol* (**7**).—To 5% Pd/C (3.9 g), freshly prepared by hydrogenation in EtOH (30 mL) at atmospheric pressure for 1 h at room temperature, was added a solution of **6a** (1.90 g, 2.40 mmol) in EtOH (20 mL). After shaking the mixture under H_2 for a further 12 h at room temperature, it was filtered and concentrated in vacuo, and the residue was crystallised from EtOH–H_2O to give **7** (1.151 g, 94%), mp 189–190°, $[\alpha]_D^{20}$ −37° (*c* 1, EtOH). ^{1}H NMR data ($CDCl_3$, 300 MHz): δ 3.13–3.20 (broad s, 1 H, OH), 3.50–3.57 (broad s, 1 H, OH), 3.57–3.65 (broad s, 1 H, OH), 4.13 (t, 1 H, *J* 8.4 Hz, H-3), 4.15–4.20 (dd, 1 H, H-2), 4.32 (dd, 1 H, *J* 2.8 and 9.8 Hz, H-5), 5.52 (t, 1 H, *J* 9.3 Hz, H-4), 5.63–5.68 (m, 2 H, H-1 and H-6), 7.28–8.03 (m, 15 H, 3 Ph). FAB-mass spectrum: *m/z* 493 [(M + H)$^+$, 28%], 371 (98), 249 (24), 233 (25), 122 (20), 105 (100), 94 (13), 78 (15).

Anal. Calcd for $C_{27}H_{24}O_9$ (492.49): C, 65.85; H, 4.91. Found: C, 65.82; H, 4.96.

*1L-1,4,6-Tri-O-benzoyl-*chiro*-inositol 2,3,5-tris(diethyl phosphate)* (**8a**).—Compound **7** (0.098 g, 0.2 mmol), from which dry acetonitrile had been distilled twice, was dissolved in dry acetonitrile (5 mL), and treated with *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) followed by chlorodiethoxyphosphine (0.18 mL, 1.2 mmol) dropwise at −4°. After 30 min, the mixture was allowed to warm to room temperature during 2 h, ^{t}BuOOH (1 mL, 70% in H_2O) was added, and stirring was continued overnight at room temperature. The resulting solution was partitioned between satd aq $NaHCO_3$ and CH_2Cl_2 (50 mL each), and the organic layer was dried ($MgSO_4$) and concentrated. Flash-column chromatography [light petroleum (bp 40–60°), EtOAc, and 1:10 EtOH–EtOAc] gave **8a**, isolated as an oil (0.132 g, 73%). NMR data ($CDCl_3$): ^{1}H (300 MHz), δ 0.75–1.30 (m, 18 H, 6 CH_3), 3.60–4.21 (m, 12 H, 6 CH_2), 4.90–5.00 (broad, 1 H, CH), 5.07 (td, 1 H, *J* 2.6 and 9.3 Hz, CH), 5.17 (m, 1 H, CH), 5.91–5.97 (m, 3 H, 3 CH), 7.41–8.24 (m, 15 H, 3 Ph); ^{31}P (121.5 MHz), δ −1.35 (s, 1 P), −1.48 (s, 1 P), −2.03 (s, 1 P).

*(−)-1L-1,4,6-Tri-O-benzyl-*chiro*-inositol 2,3,5-tris[di-(2-cyanoethyl) phosphate]* (**8b**).—To a mixture of **7** (0.059 g, 0.12 mmol) and 1*H*-tetrazole (0.125 g, 1.8 mmol) in dry CH_2Cl_2 (3 mL) was added bis(2-cyanoethyl) *N,N*-diisopropylphosphoramidite (0.27 g, 1.2 mmol). The mixture was stirred at room temperature for 1 h, ^{t}BuOOH (0.5 mL, 70% in H_2O) was added, and the resulting solution was stirred overnight, then washed with satd aq $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated. Flash-column chromatography of the residue, as for **8a**, gave **8b** (0.102 g, 81%), isolated as an oil, $[\alpha]_D^{20}$ −11° (*c* 3.1, $CHCl_3$). NMR data ($CDCl_3$): ^{1}H (270 MHz), δ 2.79–2.84 (m, 12 H, 6 CH_2), 4.31–4.38 (m, 12 H, 6 CH_2), 5.13–5.22 (m, 3 H, 3 CH), 5.98–6.03 (m, 3 H, 3 CH), 7.55–7.72 (m, 9 H, Ph), 8.11–8.26 (m, 6 H, Ph); ^{31}P (162 MHz), δ −3.03 (s, 1 P), −3.15 (s, 1 P), −3.22 (s, 1 P). Mass spectrum: *m/z* 1051 (M^+, 51%), 631 (9), 608 (11), 564 (9), 447 (13), 258 (14), 149 (43), 105 (100), 95 (67), 83 (90).

*(−)-1L-*chiro*-Inositol 2,3,5-trisphosphate* (**2**).—(*a*) To a solution of **8a** (0.1 g, 0.111 mmol) in dry CH_2Cl_2 (0.5 mL) was added bromotrimethylsilane (0.24 mL, 2.7 equiv). The solution was stirred at room temperature overnight and then concentrated, the residue was stirred with H_2O (1 mL) for 1 h at room temperature, and the mixture was concentrated in vacuo to give the free acid. 0.5 M NaOH (4 mL) was added to the free acid, the solution was left overnight at room temperature, the cations were removed by treatment with Dowex 50 (H^+) resin, and the acidic solution was extracted with $CHCl_3$ in order to remove benzoic acid, and then subjected to ion-exchange chromatography on DEAE Sephadex A-25, using a gradient from H_2O to M TEAB (pH 8.0), to give **2** (0.045 g, 86.5%); **2** was eluted at ca. 800 mM TEAB.

(*b*) To liquid ammonia (40 mL) was added a solution of **8b** (0.060 g, 0.057 mmol) in dry dioxane (1.8 mL), followed by Na (0.1 g, 4.3 mmol) in small pieces. The solution was stirred for 5 min, the reaction was quenched with EtOH, and the ammonia was evaporated in a stream of N_2. A solution of the residue in H_2O was

treated with Dowex (H^+) resin until it became slightly acidic, then filtered, basified with triethylamine, and concentrated. Ion-exchange chromatography of the residue as in (*a*) gave **2** (0.044 g, 80%), $[\alpha]_D^{20}$ −13° (*c* 0.5, H_2O, pH 9). NMR data (D_2O): ^1H (300 MHz), δ 4.02 (t, 1 H, *J* 8.5 Hz, CH), 4.36–4.48 (m, 5 H, 5 CH); ^{31}P (121.5 MHz), δ 0.07 (s, 1 P), 0.34 (s, 1 P), 0.68 (s, 1 P). FAB-mass spectrum: *m/z* 419 [$(M - H)^-$, 100%], 401 (27), 352 (34), 325 (27).

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