

Total Synthesis of the 5-Methylenephosphonate Analogue of *D*-*myo*-Inositol 1,4,5-Trisphosphate

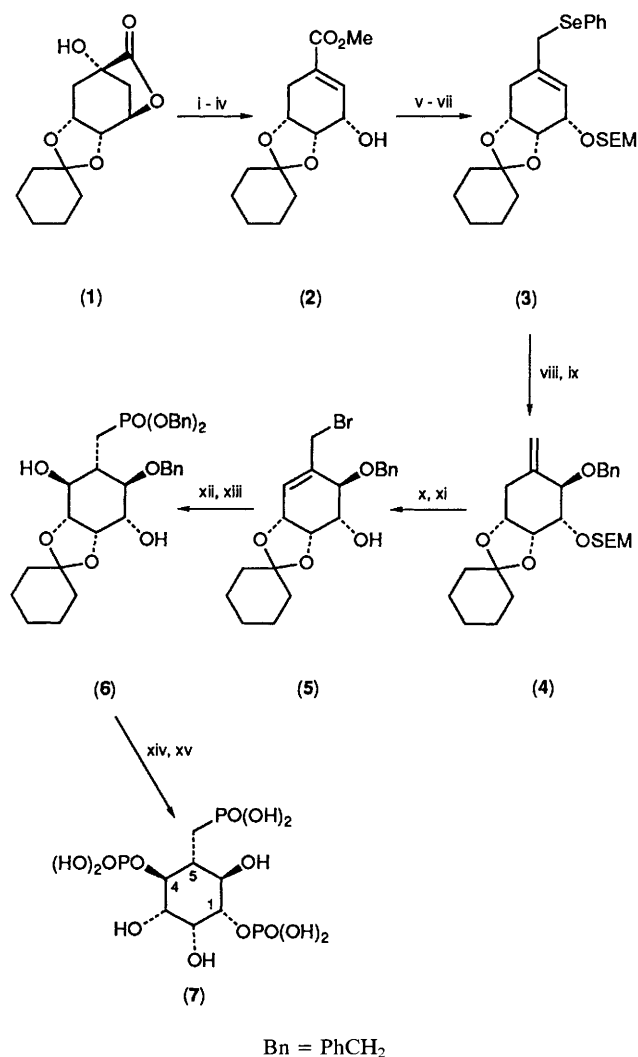
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The 5-methylenephosphonate analogue of *D*-*myo*-inositol 1,4,5-trisphosphate has been prepared from (–)-quinic acid and shown to be a long-lived agonist of calcium mobilization.

D-*myo*-Inositol 1,4,5-trisphosphate (1,4,5-IP₃), the calcium mobilizing intracellular second messenger of the phosphatidylinositol (PI) cycle, is rapidly metabolized *in vivo* by either of two divergent pathways: (a) initial phosphorylation by a 3-kinase followed by hydrolysis of the C(5)-phosphate, or (b)

direct dephosphorylation by a specific 5-phosphatase.¹ Intervention in these pathways may provide new insights into the function and possible therapeutic manipulation of the PI cycle. In particular, it has been deemed of value to prepare inositol (poly)phosphates modified with metabolically more



Scheme 1. Reagents and conditions: i, mesyl chloride (1.5 equiv.), Et₃N, CH₂Cl₂, 0 °C, 20 min; ii, NaOMe (0.15 M), MeOH/THF (1 : 2), 0 °C, 30 min; iii, PCC (1.5 equiv.), 3 Å molecular sieves, HOAc (0.2 equiv.), 4 h at 0 °C, then 1.5 h at 24 °C; Et₃N (1.5 equiv.), 24 °C, 15 min; iv, NaBH₄, MeOH/THF (3 : 1), 0 °C, 1 h, 68% overall from (1); v, SEM-Cl (2 equiv.), Pr₂NEt (5 equiv.), THF, 45 °C, 12 h, 85%; vi, DIBAL-H (3.5 equiv.), PhMe, -78 °C, 3 h, 76%; vii, *N*-(phenylseleno)phthalimide (2 equiv.), Bu₃P (2 equiv.), THF, 0 °C, 45 min, 65%; viii, NaIO₄ (2 equiv.), 1,4-dioxane/pH 7 buffer (1 : 1.6), 0 °C, 6 h, 85%; ix, KH (2.2 equiv.), PhCH₂Br (2 equiv.), THF, 12 h, 90%; x, Buⁿ₄NF (0.25 M, 3 equiv.), HMPA, 105 °C, 65 min, 92%; xi, PhSeBr (1.1 equiv.), Na₂CO₃ (1.4 equiv.), CH₂Cl₂, -78 °C, 1 h; *m*-ClC₆H₄CO₃H (1.3 equiv.), C₅H₅N (2.6 equiv.), -78 → 0 °C, 0.5 h, 95% (crude); xii, NaPO(OCH₂Ph)₂ (2.8 equiv.), 18-crown-6 (1 equiv.), PhMe, 0 °C, 20 min, 65%; xiii, BH₃ (3 equiv.), THF, 0 → 24 °C over 1.25 h, then 24 °C for 1.5 h; *m*-ClC₆H₄CO₃H (9 equiv.), 25 °C, 14 h, 95%; xiv, Pr₂NP(OCH₂Ph)₂ (4 equiv.), 1H-tetrazole (16 equiv.), CH₂Cl₂, 0 → 24 °C, 2 h; *m*-ClC₆H₄CO₃H (6 equiv.), -78 → 0 °C, 3 h, 91%; xv, 10% Pd/C, H₂ (3.5 atm), EtOH/H₂O (4 : 1), 25 °C, 5 h; EtOH/H₂O/HOAc (24 : 6 : 1), 24 °C, 16 h; NaOH, MeOH, 67%.

stable phosphorus functionalities.² Herein, we describe the total synthesis of (7), the 5-methylenephosphonate analogue of 1,4,5-IP₃, utilizing a strategy³ that exploits both the chirality and complete carbon framework of commercial (-)-quinic acid.

Lactone (1), obtained⁴ from (-)-quinic acid in 86% yield, was converted to the known³ ester (2) (68% overall) by an improved procedure involving sequential mesylation of the tertiary alcohol, lactone methanolysis using NaOMe, and pyridinium chlorochromate (PCC) oxidation. Following elimination of methanesulphonate using triethylamine in methanol/tetrahydrofuran (THF) (1 : 2), the newly generated enone was reduced *in situ* by sodium borohydride exclusively from the less hindered β-face (Scheme 1). Protection of the C(1)-alcohol (inositol numbering) in (2) as its β-trimethylsilyl-ethoxymethyl (SEM) ether (85%), low temperature di-*iso*-butylaluminium hydride (DIBAL-H) reduction of the ester (76%), and selenylation⁵ (65%) of the resultant primary alcohol generated selenide (3).[†] Stereoselective [2,3]-sigmatropic rearrangement (85%) of the allylic selenoxide derived from (3) and benzylation (90%) gave rise to (4) as the sole product.

Fluoride ion induced desilylation (92%) of (4) in hexamethylphosphoric triamide (HMPA) and kinetically controlled addition⁶ of phenylselenenyl bromide to the exocyclic alkene provided mainly the anti-Markovnikov adduct. The latter underwent smooth oxidative elimination to the somewhat labile allylic bromide (5)[‡] (95%), which was sufficiently pure to be used directly in the next step. Michaelis-Becker phosphorylation⁷ (65%) of (5) using excess sodium dibenzyl phosphite in the presence of 18-crown-6 and hydroboration of the alkene with 3-chloroperoxybenzoic acid work-up furnished a single stereoisomer (95%) identified by ¹H NMR analysis (250 MHz, COSY, *J*-resolved) as (6)[‡] with the desired all-*trans* configuration between the substituents on C(3)-C(6). Introduction of the C(1) and C(4) phosphates (91%) by the two-step phosphite method according to Tegge and Ballou⁸ and removal of the protecting groups afforded (7)[‡] (67%), isolated as its sodium salt.

Initial biological evaluation suggests that (7) acts as a long-lived agonist of 1,4,5-IP₃ activity. It elicits contraction of bovine tracheal smooth muscle permeabilized with saponin^{9a} and stimulates a sustained release of calcium from a microsomal preparation of bovine adrenal gland.^{9b} The details of these studies will be presented elsewhere.

This work was financially supported by a Grant-in-Aid from

[†] Satisfactory analytical data were obtained for all new, stable intermediates.

[‡] Selected data for (5): m.p. 143–144 °C (Et₂O/hexane); [α]_D²³ -52.5° (c 1.30, CHCl₃); δ_H (250 MHz, CDCl₃) 1.31–1.68 (m, 10H), 2.33 (d, 1H, *J* ~6.8 Hz), 3.88 (d, 1H, *J* ~9.8 Hz), 3.93 (ddd, 1H, *J* ~2.6, 3.0, 7.0 Hz), 4.35 (d, 1H, *J* ~9.8 Hz), 4.43 (d, 1H, *J* ~7.5 Hz), 4.48 (ddd, 1H, *J* ~1.0, 2.6, 5.2 Hz), 4.59 (ddd, 1H, *J* ~1.5, 3.4, 5.2 Hz), 4.88 (d, 1H, *J* ~10.8 Hz), 4.96 (d, 1H, *J* ~10.8 Hz), 5.79 (br. s, 1H), 7.29–7.46 (m, 5H). For (6): [α]_D²³ +21° (c 1.24, CHCl₃); δ_H (250 MHz, CDCl₃) 1.33–1.80 (m, 1H), 1.85 (dddd, 1H, *J* ~6.0, 6.2, 8.3, 26.9 Hz), 2.12 (dd, 1H, *J* ~6.0, 18.8 Hz), 2.30–2.55 (br. s, 2 × OH), 3.66 (dd, 1H, *J* ~6.2, 8.3 Hz), 3.92 (dd, 1H, *J* ~8.3, 11.1 Hz), 3.95 (dd, 1H, *J* ~4.4, 6.2 Hz), 4.06 (dd, 1H, *J* ~6.3, 8.3 Hz), 4.41 (dd, 1H, *J* ~4.3, 6.3 Hz), 4.47 (d, 1H, *J* ~11.3 Hz), 4.68 (d, 1H, *J* ~11.3 Hz), 4.88–5.08 (m, 4H), 7.14–7.44 (m, 15H); FAB MS (*m/z*) 610 (M + H, 100%), 519 (M + H - PhCH₂, 25%). For (7) (hexasodium salt): δ_H (500 MHz, D₂O) 1.25 (dt, 1H, *J* ~10.6, 15.0 Hz), 1.57–1.66 (m, 1H), 2.05 (apparent dd, 1H, *J* ~15.0, 20.1 Hz), 3.53–3.59 (m, 2H), 3.68–3.78 (m, 2H), 4.20 (apparent t, 1H, *J* ~2.2 Hz); ³¹P NMR (81 MHz, D₂O, pH 12, ¹H decoupled) δ 3.05 (s, 1P), 4.73 (s, 1P), 21.58 ppm (s, 1P); FAB MS (*m/z*) 551 (M + H, 25%), 529 (24%), 507 (12%).

the American Heart Association and the Robert A. Welch Foundation.

Received, 14th February 1990; Com. 0/00685H

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