**SUPPLEMENTARY INFORMATION**

4-O- Allyl- myo-inositol 1,3,5-O- orthobenzoate. myo-Inositol (5.00 g, 27 mmol) was taken up in DMSO (23 mL). To the suspension was added trimethyloxide (0.61 mL, 33.3 mmol) and p-toluene sulfonic acid (56 mg, 0.29 mmol). The suspension was stirred at 100 °C for 5 h. The reaction was quenched with methyamine (0.9 mL) and the solvent removed under high vacuum. Crude myo-inositol 1,3,5-O-orthobenzoate (2, 7.6 g) was taken up in DMF (50 mL). The reaction mixture was cooled to -15 °C and sodium hydride (60 % dispersion in mineral oil, 1.08 g, 27 mmol) added portion wise. The mixture was stirred at -15 °C for 15 min, allowed to warm to rt and stirred for a further 30 min. Allyl bromide (3.24 mL, 27 mmol) was then added drop wise and the reaction stirred for 24 h. The reaction was quenched by drop-wise addition of H2O (5 mL) and the volume reduced under high vacuum. The residue was taken up in EtOAc and washed with H2O (3 x 3) and then brine. The combined aqueous layers were back-extracted with EtOAc, and this solution was washed with H2O (3 x 3) and brine. The organic layers were combined, dried (MgSO4) and the solvent evaporated under reduced pressure.

The-crude material was fractionated by chromatography on flash silica in a large sinter funnel. Elution with hexane-EtOAc (9:1 v/v) yielded the title compound (6.03 g, 73 % over 2 steps) as a pale yellow oil; Rf (EtOAc) 0.72; νmax (film)/cm -1 3570, 3495, 3054, 2927, 2856 and 1452; δ 2,6-Dibenzyl-4-(prop-1-enyl)-myo-inositol 1,3,5-O-orthobenzoate (5.40 g, 11.1 mmol) was evaporated from MeCN (3 x 5 mL), dissolved in DMSO (11 mL) and potassium t-butoxide (2.50 g, 22.2 mmol) added. The solution was stirred at 100 °C for 3 h. The reaction was cooled, diluted with H2O (5 mL) and extracted with EtOAc. The organic layer was washed with H2O (x 4), then brine, dried (MgSO4) and the solvent evaporated under reduced pressure. The title compound (5.40 g, 100 %) was isolated as a yellow oil and used without further purification; Rf (hexane-EtOAc 1:1 v/v) 0.76; νmax (film)/cm -1 3054, 2975, 2927, 2856 and 1454; δ1 (400 MHz, CDCl3) 7.66-7.72 (15H, m, Ar H), 5.82 (1H, ddt, δ 4.21-4.16 (3H, m, Ins OCH2CH2C (OCH2CH3)) ppm; δ (100 MHz, CDCl3) 138.13, 137.77, 137.18 (3 x Ar C), 134.13 (OCH2CH2C, 129.39, 128.42 (4C), 128.00 (2C), 127.94 (2C), 127.84, 127.75, 127.54 (2C), 125.39 (2C) (15 x Ar CH), 117.56 (OCH2CH2C, 107.85 (PhCO3), 73.83, 72.06, 71.92 (3 x Ins CH), 71.49, 71.29, 70.71 [(2 x OCH2Ph) + OCH2CH2C, 69.05, 66.34, 60.41 (3 x Ins CH) ppm; HRMS (Cl+) m/z (%) found [M+H]+ 487.2130 (100), C30H30O6 requires 487.2121.
afforded 3b (12.61 g, 79 %) as a colourless oil; Rf (hexane-
EtOAc 4:1 v/v) 0.16; vmax (film/cm⁻¹) 3408, 3063, 3033, 2955,
2931, 2875, 1711, 1496 and 1453; δH (400 MHz, CDCl3) 7.66-
7.19 (15H, m, 15 × Ar H), 4.82 (1H, d, J 12.5, PhCH2O),
4.68 (1H, d, J 12.5, PhCH2O), 4.58-4.53 [4H, m, (2 × Ins
CH) + PhCH₂O], 4.50-4.47 (2H, 2 × Ins CH), 4.40-4.38
(1H, m, Ins C=H), 3.94-3.93 (1H, m, Ins C=H), 3.63 (1H, bs, Ins
OH) ppm; δC (100 MHz, CDCl3) 137.81, 136.79, 135.93 (3 ×
Ar C), 129.46, 128.84 (2C), 128.75, 125.53 (2C), 128.11 (2C),
127.93 (2C), 125.37 (2C) (15 × Ar CH), 107.32 (PhCO2),
74.46, 73.41 (2 × Ins CH), 72.96 (OCH₂Ph), 71.29 (Ins CH),
70.99 (OCH₂Ph), 68.67, 67.94, 65.07 (3 × Ins CH) ppm;
HRMS (ESI) m/z (%) found [M+H]+ 447.1793 (100),
C₂₇H₂₇O₆ requires 447.1808.

15 2,4,6-Tris[phenyl-(tert-butyldimethylsilyl)-methyl]-myo-inositol
(3b), myo-Inositol 1,3,5-O-orthobenzoate (2, 200 mg, 0.75
mmol) was evaporated from MeCN (3 × 2 mL), taken up in
DMF (2 mL) and cooled to -15 °C. Sodium hydride (60 %
dispersion in mineral oil, 101 mg, 2.63 mmol) was added
portion-wise, the reaction stirred at -15 °C for 30 min then
warmed to rt and benzyl bromide (313 µL, 2.63 mmol) was added
drop-wise. The reaction was stirred at 60 °C for 12 h
then quenched with drop-wise addition of H₂O (5 mL) and
stirred for 30 min. The crude material was taken up in
EtOAc and washed with H₂O (∗3) then brine. The organic phase was
dried (MgSO₄) and the solvent evaporated under reduced
pressure. The crude material was fractionated by chromatography on flash silica in a large sinter funnel.

Elution with hexane-EtOAc (9:1 → 7:3 v/v) afforded the
*titled compound* (338 mg, 84 %) as a yellow oil; Rf (EtOAc-hexane, 1:1 v/v) 0.76; δH (270 MHz, CDCl3) 7.67-7.63 (2H, m), 7.35-
7.24 (18H, m) (20 × Ar H), 4.68 (2H, s, OCH₂Ph), 4.64 (2H,
δC (100 MHz, CDCl3) 138.10, 137.70 (2C), 137.21 (2 × Ins Ar C), 129.47,
128.48 (5C), 128.13 (3C), 128.01 (3C), 127.88 (2C), 127.69
(4C), 125.45 (2C) (20 × Ar CH), 107.93 (PhCO₂), 74.07 (2C),
71.98 (2C) (4 × Ins CH), 71.68 (2C), 71.28 (3 × OCH₂Ph),
69.11, 66.20 (2 × Ins CH) ppm; MS (Cl⁻) m/z (%) found
[M+H⁺] 537 (100), [M+N⁺H⁺] 551 (8).

### 2.6-O-Benzyl-4-O-(tert-butyldimethylsilyl)-myo-inositol

2,6-O-Benzyl-4-O-(tert-butyldimethylsilyl)-myo-inositol
1,3,5-O-orthobenzoate (3c). 2,6-O-Benzyl-4-O-(tert-butyldimethylsilyl)-myo-inositol
1,3,5-O-orthobenzoate (3b, 500 mg, 1.12 mmol) and
imidazole (164 mg, 2.46 mmol) were evaporated from MeCN
(3 × 1 mL) then taken up in dry DMF (3 mL) and Et₃N (155
µL, 1.12 mmol) was added. The reaction was cooled to 0 °C,
before adding TbdpsCl (1.16 mL, 4.48 mmol). The reaction was
heated to 100 °C and stirred for 72 h. The reaction was
quenched with H₂O (0.5 mL), stirred for a further 20 min and
the solvent was evaporated. The remaining solids were taken up
in CH₂Cl₂ (10 mL) and washed with sat. NaHCO₃, H₂O
and then brine. The organic layer was dried (MgSO₄), filtered
and the filtrate evaporated to dryness. The residue was
fractionated by chromatography on flash silica, eluting with
EtOAc-hexane (1:9 v/v), followed by sublimation of the
residual TbdpsOH contaminant (oil pump, heat gun) to give
3d (645 mg, 84 %) as fine white crystals; Rf (hexane-EtOAc,
4:1 v/v) 0.52; mp 129-131 °C (CH₂Cl₂-hexane); Found C,
57.5; H, 6.5. C₁₈H₂₄O₇Si requires C, 57.4; H, 6.5 %; δH (500
MHz, CDCl₃) 7.71-7.67 (2H, m), 7.66-7.63 (4H, m), 7.52-4.75
(4H, m), 7.46-7.32 (13H, m), 7.31-7.27 (2H, m) (25 × Ar H),
4.70 (1H, td, J 3.9, 1.7, Ins H), 4.70 (1H, d, J 12.2, OCH₂Ph),
4.67 (1H, d, J 12.6, OCH₂Ph), 4.60 (1H, d, J 12.0, OCH₂Ph),
4.48 (1H, dq, J 3.9, 1.9, 1H, Ins H), 4.48 (1H, d, J 12.0, OCH₂Ph),
4.39 (1H, td, J 3.7, 1.6, Ins H), 4.24 (1H, tt, J 3.5, 1.7, Ins 5-H),
4.22 (1H, t, J 1.7, Ins 2-H), 4.19 (1H, dq, J 3.9, 1.9, Ins H),
0.97 (9H, s, CMe₃) ppm; δC (125 MHz, CDCl₃) 138.09, 137.68,
137.16 (3 × Ar C), 135.81 (2C), 135.73 (2C) (4 × Ar CH),
133.16, 133.06 (2 × Ar C), 130.17, 130.10, 129.38, 128.51 (2C),
128.49 (2C), 128.19 (2C), 127.94 (4C), 127.85 (4C), 127.76 (2C),
125.41 (2C) (21 × Ar CH), 107.61 (PhCO₂), 74.39, 73.61 (2 × Ins CH),
72.05 (PhCH₂O), 72.05 (Ins CH), 70.99 (PhCH₂O), 70.91, 68.72,
65.33 (3 × Ins CH), 26.84 (SiCH₃), 19.14 (Me₃Si) ppm;
HRMS (TOF ES⁺) m/z (%) found [M+H⁺] 685.2970 (100),
C₃₂H₃₅O₇Si requires 685.2985; [M+K⁺] 748.3071 (32),
[M+Na⁺] 707.2792 (94).
2,4-O-Bis[2,7-dibromo-9-(3-trifluoromethylphenyl)xanthene-9-yl]-myo-inositol 1,3,5-O-orthobenzoxeato (9). To myo-inositol orthobenzoxeato (2, 99 mg, 0.37 mmol) in MeCN (2 mL) was added a solution of 9-chloro-2,7-dibromo-9-(3-trifluoromethylphenyl)xanthene (0.574 g, 1.1 mmol) in pyridine-MeCN (10 mL, 1:1 v/v). The reaction was refluxed for 6.5 h, then cooled to rt and quenched with H2O. After 30 min the solvent was stripped off and the residue dissolved in CH2Cl2. This solution was washed with sat. NaHCO3 (2×), then dried, (MgSO4), and the solvent evaporated under reduced pressure. The resultant pale yellow solids were triturated with hexane, discarding the filtrate. This material (0.336 g) was crystallised from EtOH-CH2Cl2 to give the title compound (248 mg, 46%) as fine crystallites; Rf (CHCl3-hexane, 7:3 v/v) 0.41; mp > 250 °C (EtOH-CH2Cl2); Found: C, 51.72; H, 2.50. C27H25O6 requires C, 51.73; H, 2.62 %; δ2 (360 MHz, CDCl3) 7.92 (1H, bs, 7.66-7.61 (4H, m), 7.58-7.37 (7H, m), 7.36-7.28 (8H, m), 7.15-7.12 (3H, m), 7.09 (1H, d, J = 2.3), 6.71 (1H, d, J = 2.3) (25 Ar H), 4.25 (1H, m, ex→td, J 4.0, 1.8, Ins 6-H), 4.04 (1H, t, J 4.0, Ins 7-H), 3.65 (1H, dq, J 4.0, 1.8, Ins H), 3.40 (1H, dq, J 4.0, 1.8, Ins H), 3.14 (1H, tt, J 3.7, 1.5, Ins 5-H), 2.58 (1H, d, J = 8.4, ex, Ins OH) ppm; δ2 (90.6 MHz, CDCl3) 150.16, 149.99, 149.77, 149.56, 147.74, 146.82, 136.50 (7 × Ar C), 134.21, 134.03, 133.74 (2C), 133.36, 133.09, 132.92, 131.37 (8 × Ar CH), 130.67 (2C, q, J 32.3, 2× CF3), 130.74, 129.63, 129.31, 129.00, 128.86, 128.14 (2C), 125.11 (2C) (9 × Ar CH), 125.00 (q, J 3.5), 124.63 (q, J 3.6) (2 × Ar CHFCCF3), 124.04 (Ar C), 124.01 (q, J 272.3, CF3), 123.80 (Ar C), 123.79 (q, J 272.6, CF3), 123.70-123.53 (2C, m, 2 × Ar CHFCCF3), 123.05, 121.88 (2 × Ar C), 119.15, 119.08, 118.59, 118.49 (4 × Ar CH), 116.76, 116.73, 116.40, 116.13 (4 × Ar C), 106.92 (PhCO2), 77.46, 75.45 (2 × ArCO2), 73.92, 73.70, 69.56, 68.80, 67.35, 61.66 (6 × Ins CH) ppm; MS (ESI+) m/z (%) found [M+H]+ 1230.9 (44). 35

2,6-O-Benzyl-4-methyl-5-my-o-inositol 1,3,5-O-orthobenzoxeato (10). Crude 2,6-O-Benzyl-4-methyl-inos-4-ose 1,3,5-O-orthobenzoxeato (10a) (2.0 g, 4.47 mmol) was evaporated from MeCN (3 × 5 mL) and taken up in CH2Cl2 (20 mL). Dess Martin periodinane (3.80 g, 4.94 mmol) was added followed by sufficient CH2Cl2 to allow efficient mixing, and vigorous stirring continued for 1 h. The organic layer was separated, washed with sat. NaHCO3 (2×), dried (MgSO4), and the solvent evaporated under reduced pressure. The residual gum (131 mg) was fractionated by medium pressure silica column chromatography. Elution with hexane-CHCl3 (1:0 → 0.1 v/v) afforded 9 (70 mg, 94%). 50
Cambridge, MA) at a density of approximately 4 x 10^4 cm^2.

Ins 1-H_3-C_ν/v) 0.69; cells. 20 The cells were seeded in 12-well clusters (H_2O, then brine, dried (MgSO_4) and the solvent evaporated.

exogenous expression of IP_3R1 in L fibroblasts. 19 The cells were cultured in Dulbecco’s modified Eagle’s medium containing 120 mM KCl, 30 mM imidazole hydrochloride, pH 6.8, 5 mM MgCl_2, 5 mM ATP, 0.44 mM EGTA, 10 mM Na_N_3, and 150 mM free ^45_Ca^{2+} (28 μCi/mL). The cells were then washed twice with 1 mL of efflux medium containing 120 mM KCl, 30 mM imidazole hydrochloride, pH 6.8, 1 mM EGTA, and 10 μM thapsigargin. The efflux medium was replaced every 2 min, and the efflux was performed at 30 °C. At the end of the experiment, the ^45_Ca^{2+} remaining in the stores was released by incubation with 1 mL of a 2% sodium dodecyl sulfate solution for 30 min. Ca^{2+} release is plotted as the fractional loss (i.e., the amount of Ca^{2+} released in 2 min divided by the total store Ca^{2+} content at that time). The latter value was calculated by summing in retrograde order the amount of tracer remaining in the cells at the end of the efflux and the amounts of tracer collected during the successive time intervals. The Ca^{2+} release provoked by IP_3 and 4-C-methyl IP_3 was normalized to the maximal releasable Ca^{2+}, measured by the addition of 10 μM A_23187.

6.8, 2 mM MgCl_2, 1 mM ATP, 1 mM EGTA, and 40 μg/mL saponin at 30 °C. The non-mitochondrial Ca^{2+} stores were loaded for 45 min at 30 °C in 120 mM KCl, 30 mM imidazole hydrochloride, pH 6.8, 5 mM MgCl_2, 5 mM ATP, 0.44 mM EGTA, 10 mM Na_N_3, and 150 mM free ^45_Ca^{2+} (28 μCi/mL). The cells were then washed twice with 1 mL of efflux medium containing 120 mM KCl, 30 mM imidazole hydrochloride, pH

1,3,4,5-O-Tetraacetyl-2,6-O-dibenzy1-4-C-methyl-myo-inositol. 2,6-O-Dibenzy1-4-C-methyl-myo-inositol (14, 60 mg, 0.16 mmol) and DMAP (2 mg, 0.02 mmol) were evaporated from pyridine (3 × 1 mL) and taken up in CH_2Cl_2 (1 mL). Acetic anhydride (127 μL, 1.28 mmol) and DMAP (2 mg, 0.02 mmol) were added and the reaction mixture stirred for 2 h. The reaction was quenched by drop-wise addition of H_2O (0.5 mL) and stirred for a further 30 min before it was diluted with CH_2Cl_2, washed with H_2O, then brine, dried (MgSO_4) and the solvent evaporated under reduced pressure. The crude material was fractionated by chromatography on flash silica. Elution with EtOAc-30

45^Ca^{2+} Flux Assay. L15 cells were obtained by stable exogenous expression of IP_3R1 in L fibroblasts. The cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% foetal calf serum, 3.8 mM L-glutamine, 0.9% (v/v) non-essential amino acids, 85 IU/mL penicillin, 85 μg/mL streptomycin, and 20 mM HEPES, pH 7.4. 45^Ca^{2+} fluxes were performed on saponin-permeabilized cells. The cells were seeded in 12-well clusters (Costar, Cambridge, MA) at a density of approximately 4 x 10^4 cm^2.

Experiments were carried out on confluent monolayers of cells at the seventh day after plating. The cells were permeabilized by incubating them for 10 min with a solution containing 120 mM KCl, 30 mM imidazole hydrochloride, pH

(0.53 g, 77 % over 2 steps) as a clear oil; R_f (hexane-ether, 3:7 v/v) 0.69; v_{max} (film/cm^-1) 3478, 3064, 3032, 2927, 1723, 1496 and 1455; δ_{H} (400 MHz, CDCl_3) 7.68-7.66 (2H, m), 7.46-7.34 (11H, m) 7.24-7.22 (2H, m) (15 × Ar H), 4.82 (1H, d, J 12.5, 2-OCH_3Ph), 4.69 (1H, d, J 12.5, 2-OCH_3Ph), 4.63 (1H, d, J 11.6, 6-OCH_3Ph), 4.57 (1H, d, J 11.6, 6-OCH_3Ph), 4.53 (1H, t, J 3.9, Ins 6-H), 4.46 (1H, dq, J 3.6, 1.7, Ins 1-H), 4.32 (1H, bs, Ins 4-OH), 4.19 (1H, dt, J 3.7, 1.8, Ins 3-H), 4.04 (1H, dt, J 3.8, 1.9, Ins 5-H), 4.01 (1H, t, J 1.8, Ins 2-H), 1.67 (3H, s, Ins 4-CH_3) ppm; δ_C (100 MHz, CDCl_3) 170.31, 169.70, 169.58, 169.35 (4 × OCO Me), 138.24, 137.99 (2 × Ar C), 129.44, 128.84 (2C), 128.75, 128.51 (2C), 128.10 (2C), 127.97 (2C), 127.93 (3C), 127.88, 125.35 (15 × Ar CH), 107.31 (O_CPh), 77.29, 74.67 (2 × Ins CH), 72.96 (OCH_3Ph), 72.89 (Ins CH), 71.04 (OCH_3Ph), 70.66 (Ins CH), 69.58 (Ins C), 66.20 (Ins CH), 24.27 (Ins 4-CH_3) ppm; HRMS (ESI+) m/z found [M+H]^+ 461.1959 (100). C_{23}H_{36}O_{11} requires 461.1964.