A few examples are also known for niobium,[9] viz. $[Nb_6HI_8]^{n+}$ (n = 2 or 3) containing H as the centering element.[10] Up till now, it has been considered that these centered cluster species are stabilized by addition of electrons from the valence orbitals of the centering element to the bonding metal-metal orbitals of the cluster unit.[7] Thus, with few exceptions, these clusters exist only when the centering atom is present. However, in the case of $Mo_6O(OEt)_{18}$, which has 16 electrons for Mo-Mo bonding, the central oxygen atom should not be required for stability.[11] Addition of the 6 valence electrons from the central O atom gives a total of 22 electrons for the cluster unit. Presumably, these 6 additional electrons are placed at such a low energy relative to the metal-metal orbitals that they may be considered only as weakly interacting with the Mo-Mo bonding orbitals.

Another approach to the bonding of this cluster unit is to consider the latter as if it were two "independent" M_3X_{13} units, each with 8 electrons available for Mo-Mo bonding. Of main significance is the Mo-Mo distance of 2.6108 (3) Å, which is slightly greater than that of other 6-, 7-, or 8-electron M_3X_{13} clusters. For example, the 8-electron cases, $[Mo_3OCl_3(O_2CCH_3)_3(H_2O)_3]^{2+}$ [12] and $Zn_3Mo_3O_8$,[13] have d(Mo-Mo) of 2.550 (5) and 2.580 (2) Å, respectively. These distances are known to be influenced to some degree by interaction of the "capping" O atom with the Mo cluster orbitals of the triangular unit.[14] In the latter species, the Mo-O(cap) distances are 2.03 (1) and 2.06 (1) Å, respectively, whereas in **2**, this distance is 2.1073 (4) Å. The longer Mo-O1 distance is understandable because in **2** the O atom is 6-coordinate and in the other examples it is 3-coordinate.

Another significant difference between the triangular subunits of **2** and other M_3X_{13} clusters is the very short terminal Mo-O4 distance of 1.948 (3) Å. In the other known 8-electron M_3X_{13} examples, the corresponding distance is greater than 2.10 Å, viz. 2.13 (1) Å in $[Mo_3OCl_3(O_2CCH_3)_3(H_2O)_3]^{2+}$ and 2.160 (8) Å in $Zn_3Mo_3O_8$. This suggests that significant Mo-O π interactions occur in the Mo-O terminal bonds of **2**, and this may in turn weaken the Mo-Mo bonding.

In another view, the structure of the cluster unit of **2** can be related to that of the isopolyanions $[M_6O_{19}]^{n-}$ (M = Mo or W, n = 2; M = Nb or Ta, n = 8).[15] Essentially, **2** is a reduced ethoxy analogue of the oxo anion. Specifically, the $[Mo_6O_{19}]^{2-}$ anion consists of an undistorted octahedral arrangement of Mo atoms centered by one O atom, bridged on each edge by twelve O atoms, and multiply bonded to six terminal O atoms. The isopolyanion is fully oxidized, and thus it has no d electrons available for Mo-Mo bonds. Electrons provided by the reduced oxidation state of molybdenum in the $Mo_6O(OEt)_{18}$ cluster, viz. Mo(3.33), are then utilized to form the Mo-Mo bonds of the distorted cluster.

Conceivably, it should be possible to oxidize the cluster unit by 1 and 2 electrons, leaving 15 and 14 electrons for metal-metal bonding. In the case of a 1-electron oxidation, the extent of delocalization of the unpaired electron over the entire cluster unit, as opposed to localization on one of the triangular subunits, would be of interest. At present, further efforts are underway to develop rational syntheses of compounds of this type and to elucidate their spectroscopic and chemical properties.

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Supplementary Material Available: A listing of crystal data, bond lengths and angles, and positional and thermal parameters for **2** (5 pages); tables of observed and calculated structure factors for **2** (4 pages). Ordering information is given on any current masthead page.

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Synthesis of the First Optically Pure, Fluorinated Inositol 1,4,5-Trisphosphate of *myo*-Inositol Stereochemistry and Its Effect on Ca^{2+} Release in Swiss 3T3 Cells

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The importance of inositol phosphates for intracellular signalling is now well established.[1,2] Stimulation of cell surface receptors by a variety of ligands initiates the hydrolysis of a membrane-located phosphoinositide to give D-*myo*-inositol 1,4,5-trisphosphate (Ins 1,4,5P_3) and diacylglycerol. Ins 1,4,5P_3 releases Ca^{2+} from intracellular stores associated with the endoplasmic reticulum, causing an increase in cytoplasmic free Ca^{2+} concentration.[3] A large number of inositol phosphates, apart from Ins 1,4,5P_3, have been found in eukaryotic cells, but their role remains to be elucidated.[1,2,4-7] The complexity in inositol phosphate metabolism arises primarily because of the phosphorylation of Ins 1,4,5P_3 by a 3-kinase to give D-*myo*-inositol 1,3,4,5-tetrakisphosphate (Ins 1,3,4,5P_4).[8] In some, but not all, systems, Ins 1,3,4,5P_4 may control intracellular Ca^{2+} movement,[9-11] thus regulating the amount of Ca^{2+} available to Ins 1,4,5P_3. The extent to which the anabolism of Ins 1,4,5P_3 occurs in different cell preparations used for studying inositol phosphate second messenger action is not clear, but an agent that could prevent metabolism by the 3-kinase pathway would be a useful probe for studying inositol phosphate function.[12-14]

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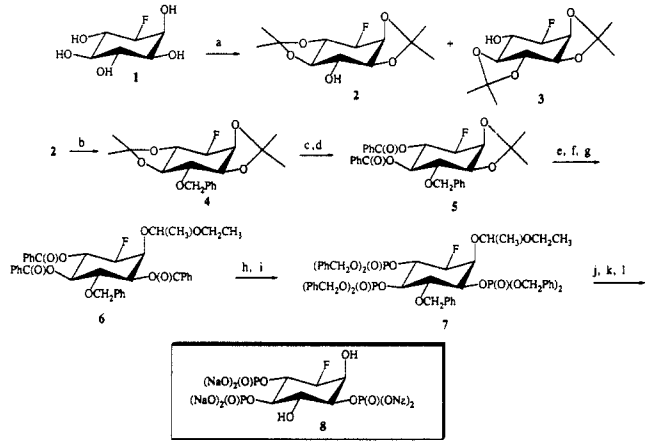
Scheme I. Synthesis of D-3-Deoxy-3-fluoro-*myo*-inositol 1,4,5-Trisphosphate[a]



[a] Reagents and conditions: (a) 2-methoxypropene, camphorsulfonic acid (cat.), DMF, 80 °C, 4 h, 83%, (ratio **2**:**3** = 1:2.3); (b) NaH, then $PhCH_2Br$, THF, 0 → 23 °C, 12 h, 96%; (c) CH_3COCl (cat.), $MeOH/CH_2Cl_2$ (1:2), 23 °C, 40 min, 86%; (d) PhCOCl, pyr, DMAP (cat.), 23 °C, 12 h, 92%; (e) concentrated HCl (cat.), MeOH, 23 °C, 6 h, or $AcOH/H_2O/THF$ (2:1:1 v/v), 80 °C, 14 h, 92%; (f) PhCOCl, pyr, 0 °C, 22 h, 76%; (g) $H_2C{=}CHOCH_2CH_3$, CH_2Cl_2, PPTS, 0 → 23 °C, 12 h, 86%; (h) K_2CO_3, MeOH, 23 °C, 14 h, 83%; (i) tetrabenzylpyrophosphate, NaH, DMF, 0 °C, 8–10 h, 95%; (j) p-TSA, MeOH, 23 °C, 14 h, 82%; (k) PtO_2/H_2, EtOH, 23 °C, 14 h; (l) 1 N NaOH (6 equiv), 80%.

We have shown previously that D-3-deoxy-3-fluoro-*myo*-inositol (**1**) is an inhibitor of the growth of transformed fibroblasts.[15] From additional experiments employing [^{3}H]-3-deoxy-3-fluoro-*myo*-inositol we have been able to show that this particular analogue is taken up by cells and is incorporated into cellular phospholipids (unpublished observations).

To address the question of whether the D-3-deoxy-3-fluoro-*myo*-inositol 1,4,5-trisphosphate (3-F $InsP_3$), if formed, could lead to modified cellular responses through a differing role as an agonist vis-à-vis natural Ins 1,4,5P_3, we synthesized 3-F $InsP_3$ to directly investigate its effects on intracellular Ca^{2+} mobilization.

The synthesis of 3-F $InsP_3$ was accomplished starting from quebrachitol. Quebrachitol was converted in two steps to **1**,[16] and **1** was reacted with 2-methoxypropene and camphorsulfonic acid to afford a 1:2.3 mixture of **2** and **3**. Compounds **2** and **3** were separated by silica gel chromatography. The free hydroxyl group of compound **2** was protected by benzylation, the trans acetonide was selectively cleaved by HCl in methanol, and the newly freed hydroxyl groups were benzoylated to give **5**. The remaining acetonide was cleaved by aqueous acid treatment, the equatorial hydroxyl group was selectively benzoylated, and the remaining axial alcohol was protected as its ethoxyethyl derivative. The benzoate groups of **6** were cleaved by methanolic potassium carbonate treatment in preparation for phosphorylation at the same sites. The phosphorylation reaction was best carried out by using sodium hydride and freshly prepared tetrabenzylpyrophosphate in DMF at 0 °C.[17] Lastly, the ethoxyethyl group of **7** was cleaved by reaction with *p*-toluenesulfonic acid (*p*-TSA) in methanol, and complete debenzylation was effected by hydrogenolysis over platinum oxide. Titration of the crude mixture with 6 equiv of sodium hydroxide led to the stable hexasodium salt **8** of 3-F $InsP_3$ as a white powder [$[\alpha]^{23}_D$ −8.5° (*c* 3.75 mg/mL, H_2O, cyclohexylamine added to insure basicity)]. The ^{1}H, ^{19}F, and ^{31}P NMR

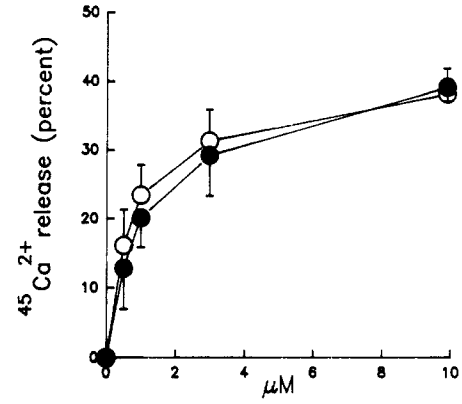


Figure 1. Concentration-response curve for the release of $^{45}Ca^{2+}$ from nonmitochondrial stores of saponin-permeabilized Swiss 3T3 cells by (●) 3-F Ins 1,4,5P_3. $^{45}Ca^{2+}$ release is expressed as a percent of the total $^{45}Ca^{2+}$ in the cells at 6 min. Values are mean of five determinations, and bars are SD. Also shown is $^{45}Ca^{2+}$ release (○) by Ins 1,4,5P_3 in saponin-permeabilized Swiss 3T3 cells as reported previously.[18]

and FAB mass spectra of **8** were fully consistent with its assigned structure.

To investigate the effect of 3-F $InsP_3$ on Ca^{2+} release, we used saponin-permeabilized Swiss 3T3 cells as described previously.[18] Preliminary studies showed that the uptake of $^{45}Ca^{2+}$ by the cells reached a plateau by 6 min. Ins 1,4,5P_3 (Molecular Probes, Irvine, CA) or 3-F Ins 1,4,5P_3 was added at 6.25 min, and the $^{45}Ca^{2+}$ remaining in the cells was measured at 7 min.

As can be seen from the dose–response curve presented in Figure 1, 3-F $InsP_3$ acts as a full agonist in releasing $^{45}Ca^{2+}$ from the 3T3 cells. The unnatural fluorinated $InsP_3$ analogue is equipotent to natural $InsP_3$. Dextran sulfate, a potent blocker of the release of Ca^{2+} by Ins 1,4,5P_3,[18] also blocked the release of Ca^{2+} induced by 3-F Ins 1,4,5P_3 (data not shown). From our studies it is apparent that interaction of Ins 1,4,5P_3 with its receptor on the endoplasmic reticulum does not require the 3-hydroxyl group either for recognition or for functional activity.[19]

While the present work further supports the notion that the D-3 substituted *myo*-inositol isosteres could owe their antiproliferative effects to their inability to form Ins 1,3,4,5P_4, other modes of action such as the inability to form 3-phosphorylated phosphatidylinositols[20] are clearly possible, and further biochemical studies are needed. The findings gleaned from this study are nonetheless significant. 3-F $InsP_3$ exhibits the same agonist effects as Ins 1,4,5P_3 on Ca^{2+} release, but its role is not further complicated by a possible simultaneous action of 3-kinase(s) to produce Ins 1,3,4,5P_4. This compound may thus have a role in place of Ins 1,4,5P_3 in studying intracellular Ca^{2+} release.[21,22]

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Supplementary Material Available: Full experimental details including optical rotations, melting points, ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR, IR, and HRMS data for new compounds reported herein (10 pages). Ordering information is given on any current masthead page.

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