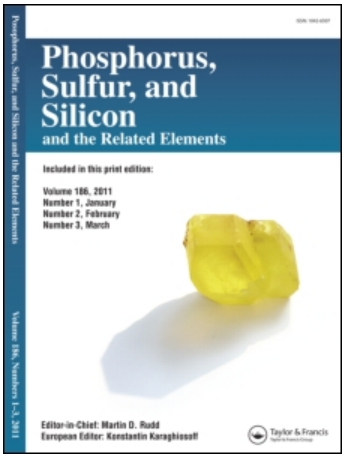

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Novel Polyphosphate Analogues of Inositol 1,4,5-Trisphosphate

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To cite this Article Riley, Andrew M. , Jenkins, David J. and Potter, Barry V. L.(1996) 'Synthesis of Novel Polyphosphate Analogues of Inositol 1,4,5-Trisphosphate', Phosphorus, Sulfur, and Silicon and the Related Elements, 111: 1, 73
To link to this Article: DOI: 10.1080/10426509608054702
URL: http://dx.doi.org/10.1080/10426509608054702

Phosphorus, Sulfur, and Silicon, 1996, Vol. 111, p. 73
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SYNTHESIS OF NOVEL POLYPHOSPHATE ANALOGUES OF INOSITOL 1,4,5-TRISPHOSPHATE

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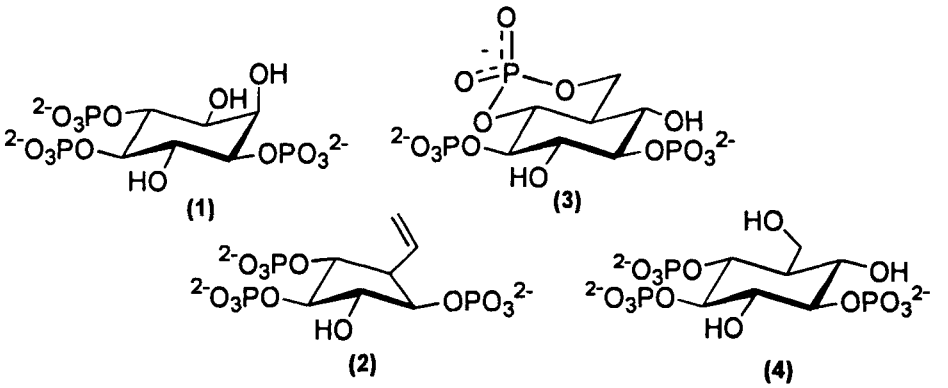
Abstract The synthesis of novel polyphosphate mimics of inositol 1,4,5-trisphosphate, including ring-contracted and conformationally restricted analogues is reported.

The binding of many hormones, neurotransmitters and growth factors to their extracellular receptors results in production of the second messenger D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3 (**1**)] *via* activation of phosphoinositidase C. Ins(1,4,5)P_3 interacts with a family of intracellular receptor-operated Ca^{2+} channels to mobilise non-mitochondrial Ca^{2+} stores in a vast array of cell types, and the synthesis of analogues of Ins(1,4,5)P_3 offers the prospect of pharmacological intervention in this ubiquitous signalling pathway. Recently, we have synthesised a number of novel polyphosphate mimics of Ins(1,4,5)P_3, including the cyclopentane-based "Pentagon IP3" (**2**).[1]

The conformationally restrained racemic analogue **3** was a full agonist at the platelet Ins(1,4,5)P_3 receptor, but 40-fold weaker than Ins(1,4,5)P_3. Racemic **4**, which bears an equatorial hydroxymethyl group, was found to be equipotent with Ins(1,4,5)P_3.



1. A. M. RILEY, D. J. JENKINS and B. V. L. POTTER, J. Am. Chem. Soc., 117, 3300-3301, (1995)