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

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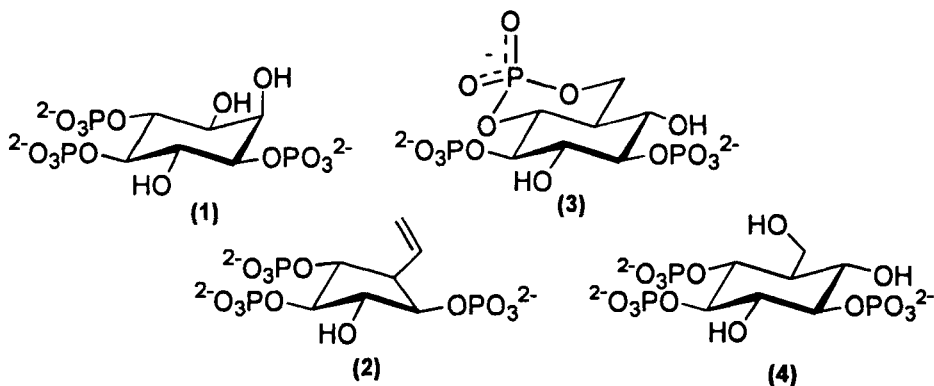
## SYNTHESIS OF NOVEL POLYPHOSPHATE ANALOGUES OF INOSITOL 1,4,5-TRISPHOSPHATE

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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 [ $\text{Ins}(1,4,5)\text{P}_3$  (1)] *via* activation of phosphoinositidase C.  $\text{Ins}(1,4,5)\text{P}_3$  interacts with a family of intracellular receptor-operated  $\text{Ca}^{2+}$  channels to mobilise non-mitochondrial  $\text{Ca}^{2+}$  stores in a vast array of cell types, and the synthesis of analogues of  $\text{Ins}(1,4,5)\text{P}_3$  offers the prospect of pharmacological intervention in this ubiquitous signalling pathway. Recently, we have synthesised a number of novel polyphosphate mimics of  $\text{Ins}(1,4,5)\text{P}_3$ , including the cyclopentane-based "Pentagon IP3" (2).<sup>1</sup>

The conformationally restrained racemic analogue 3 was a full agonist at the platelet  $\text{Ins}(1,4,5)\text{P}_3$  receptor, but 40-fold weaker than  $\text{Ins}(1,4,5)\text{P}_3$ . Racemic 4, which bears an equatorial hydroxymethyl group, was found to be equipotent with  $\text{Ins}(1,4,5)\text{P}_3$ .



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