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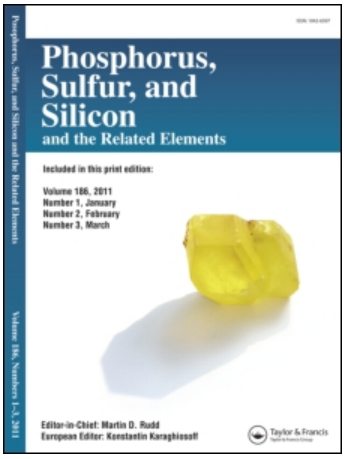

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General Synthesis of Phosphatidylinositol Phosphates

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To cite this Article Kubiak, Robert J. and Bruzik, Karol S.(1996) 'General Synthesis of Phosphatidylinositol Phosphates', Phosphorus, Sulfur, and Silicon and the Related Elements, 111: 1, 70
To link to this Article: DOI: 10.1080/10426509608054699
URL: http://dx.doi.org/10.1080/10426509608054699

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Phosphorus, Sulfur, and Silicon, 1996, Vol. 111, p. 70
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GENERAL SYNTHESIS OF PHOSPHATIDYLINOSITOL PHOSPHATES

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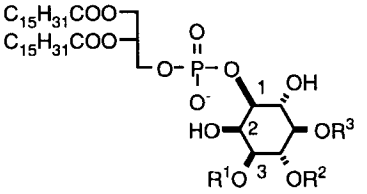
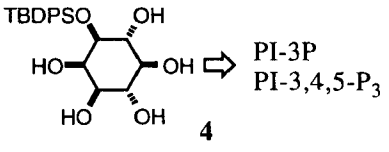
Abstract A general method for synthesis of 3-phosphorylated phosphatidylinositols is described.

Phosphatidylinositol (PI) and phosphatidylinositol phosphates (PIP_n), such as PI-4-P, PI-4,5-P_2 undergo receptor-mediated cleavage by phosphatidylinositol-specific phospholipase C, and are precursors of second messengers important in diverse cellular signaling pathways. In contrast, the 3-phosphorylated phosphatidylinositols, such as PI-3-P (**1**), PI-3,4-P_2 (**2**) and PI-3,4,5-P_3 (**3**), which are formed in response to signals of growth factors, are resistant to hydrolysis by this enzyme, and their cellular function is only beginning to emerge [1,2]. These compounds are formed in minute quantities, and therefore have to be synthesized for many practical applications.

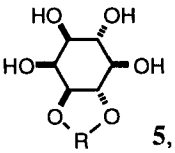


1, $R^1 = PO_3^{2-}$, $R^2 = R^3 = OH$
2, $R^1 = R^2 = PO_3^{2-}$, $R^3 = OH$
3, $R^1 = R^2 = R^3 = PO_3^{2-}$

Here, we describe the first general approach to all 3-phosphorylated phosphatidyl-inositols starting from easily accessible intermediates **4** and **5** [3]. This approach could also be extended to all inositol phospholipids and their phosphorothioate analogs. The common difficulty associated with syntheses of PI phosphates is the necessity to discern between phosphorylation sites leading to phosphomono- and phosphodiesters. Using precursors **4** and **5** these sites were differentiated by regioselective low temperature benzoylation of inositol hydroxyl groups. Depending on the starting compound selective benzoylation at 3, 3,4- and 3,4,5-positions could be achieved. Further redesign of protective groups led to several enantiomerically pure precursors of phospholipids featuring the same protective groups and differing only in their number and positions in the inositol ring.



PI-3P
PI-3,4,5-P_3



PI-3,4-P_2

4

5, R = tetraisopropyldisiloxanedi-1,3-yl

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