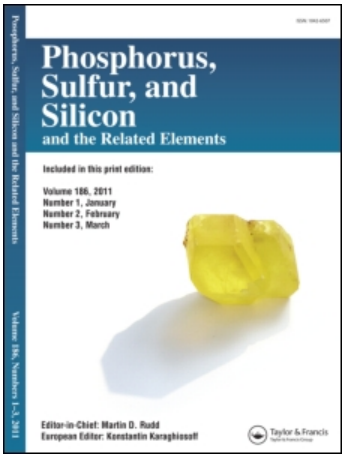

Phosphorus, Sulfur, and Silicon and the Related Elements

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Pathways for the Production of Pharmaceutical Grade Synthetic Phospholipids

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PATHWAYS FOR THE PRODUCTION OF PHARMACEUTICAL GRADE SYNTHETIC PHOSPHOLIPIDS

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Abstract Two routes are described for the synthesis of pharmaceutical grade phospholipids at the multi-kilogram scale.

Key Words: phospholipid synthesis, biocatalytic synthesis, asymmetric synthesis

In the past, kilogram and multi-kilogram amounts of phospholipids were only available by isolation from natural sources. Recently, developments in synthetic phospholipid chemistry have resulted in the creation of effective methods for the large scale production of lipid and phospholipid molecules well defined in structure and configuration.

The Sygena route was based on the work of H. Eibl [1] with D-mannitol as the source of chirality. The intermediate diacylglycerols were phosphorylated with phosphorous oxychloride and the resulting diacylglycerolphosphorous oxydichlorides were converted to the respective phospholipids by reaction with different alcohols (or protected alcohols) such as choline, ethanolamine, glycerol etc.

Genzyme [2] has developed a route based on the biocatalytic enantioselective phosphorylation of glycerol by glycerol kinase to give sn-glycerol-3-phosphate. Sn-glycerol-3-phosphate was then converted to a variety of phosphatidic acids via acylation with fatty acid anhydrides. The respective phosphatidylcholines were prepared by a chemical phosphate esterification step. Mixed chain phosphatidylcholines were prepared by the phospholipase A_2 catalyzed preparation of lyso-phosphatidylcholines followed by acylation with the appropriate fatty acid anhydride. Phospholipids with other head groups were prepared from phosphatidylcholines via phospholipase D catalyzed transesterification. Both the Sygena and Genzyme pathways are being used to prepare a range of pharmaceutical grade phospholipids at the multi-kilogram or greater scale.

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