Scalable and Cost-effective Synthesis of Inositol Heptakisphosphate (IP_7)

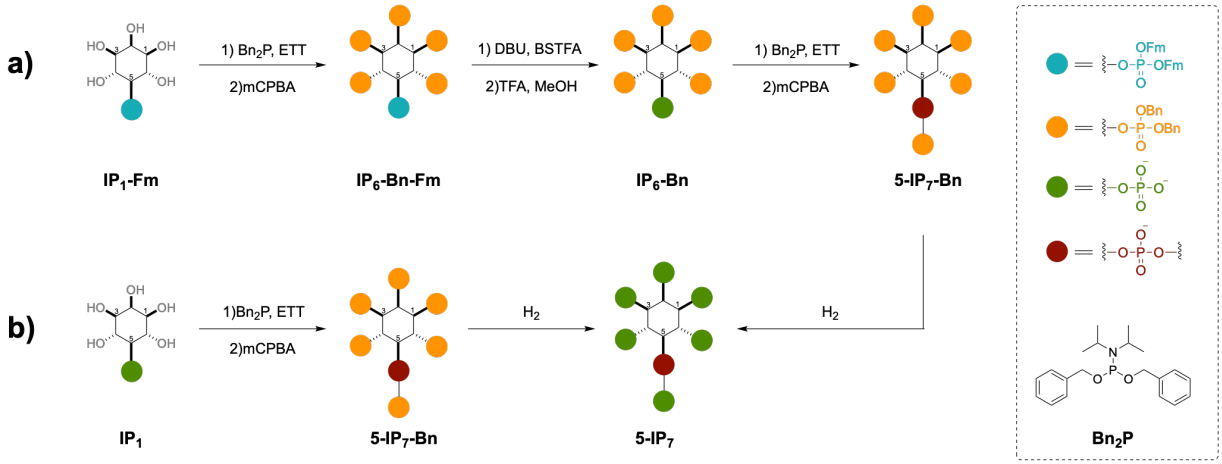
Dr.Mengsi Lu, Prof.Henning Jessen

Institute of Organic Chemistry, Universität Freiburg, Albertstr. 21,Freiburg i. B., Germany

mengsi.lu@ocbc.uni-freiburg.de

Inositol phosphates (IP) are key molecules in cellular signaling, phosphate storage and metabolism. [1-4] The synthetic feasibility enables the external mimicry of bioactivities and serve as a powerful probe for tracing. However, the conventional synthesis of highly phosphorylated inositol derivatives, such as IP_7, is insufficient. The stepwise synthetic route starts from IP_1 to IP_6, followed by deprotection, phosphorylation and final hydrogenation (scheme 1, a).

During the process, two challenges arise:
1) Laborious steps due to the protection/deprotection process
2) Dependence on moisture-sensitive reagent (BSTFA) for deprotection, which increases the risk of reaction failure



Scheme 1, synthetic routes of 5-IP_7.

To address these issues, a new, one-pot global phosphorylation strategy was developed, enabling a direct phosphorylation from IP1 to IP7 precursors followed by final hydrogenation (scheme 1,b). By closely monitoring the reaction and controlling the parameters, the reaction was successfully optimized:
1) The product overall yield increased threefold with decreased workflow time
2) Excellent reproducibility was achieved without the need for moisture-sensitive reagents

This approach not only improves the synthesis of 5-IP_7 but also provides a scalable, cost-effective method for obtaining phosphorylated inositol derivatives (IP_2-IP_8), reducing redundancy while increasing efficiency.

[1] L. Nagpal, S. He, F. Rao, S. H. Snyder, *Annu. Rev. Biochem*, **2024**, *93*, 317.
[2] S. G. Thota, R. Bhandari, *J. Biosci,* **2015**, *40*, 593.
[3] M. K. Ried, R. Wild, D. Fiedler, et al, *Nat. Commun,* **2021**, *12,* 384.
[4] D. Qiu, A. Saiardi, H. J. Jessen, et al, *Nat. Commun,* **2020**, *11*, 6035.