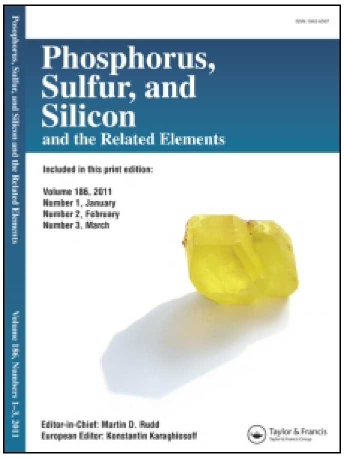

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Watanabe, Yutaka , Okazaki, Tadashi , Yamamoto, Takashi and Ozaki, Shoichiro(1996) 'Synthetic Strategies Based on Phosphite Chemistry for Inositol Phosphates and Phospholipids', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 321 — 324

To link to this Article: DOI: 10.1080/10426509608545155

URL: http://dx.doi.org/10.1080/10426509608545155

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 321–324
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SYNTHETIC STRATEGIES BASED ON PHOSPHITE CHEMISTRY FOR INOSITOL PHOSPHATES AND PHOSPHOLIPIDS

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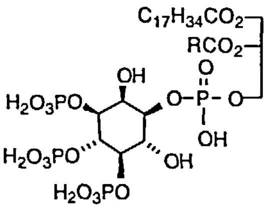
Abstract On the basis of the phosphite chemistry, new phosphorylation and glycosylation methodologies were developed. These methods were efficiently used for the syntheses of phosphatidylinositol 3,4,5-trisphosphate, and 2,6-di-*O*-mannopyranosylphosphatidylinositol.

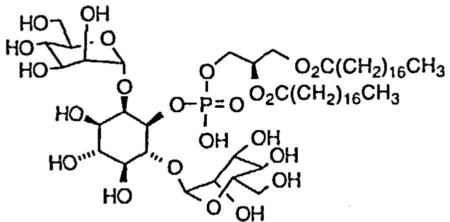
phosphorylation, glycosylation, inositol phospholipid, phosphite

INTRODUCTION

Recently, inositol phospholipids located within the plasma membrane have received much attention due to their biological interests in the intracellular signal transduction system.[1] In order to understand their physiological roles, chemical synthesis of them and analogs are very important. For the accomplishment of an efficient synthesis of inositol phosphate derivatives, new synthetic methodologies were necessary. From this standpoint, we have investigated a regioselective phosphorylation and glycosylation methodologies using the reducing and Lewis basic properties of phosphites. These synthetic methods were efficiently utilized for the synthesis of an analog **1a** of phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3] and 2,6-di-*O*-mannopyranosyl-1-phosphatidyl-*myo*-inositol [2,6-(Man)$_2$-PI]. These results are presented here.



PI(3,4,5)P$_3$: R=$(CH_2)_2(CH_2CH{=}CH)_4(CH_2)_4CH_3$
1a: R=$(CH_2)_{16}CH_3$

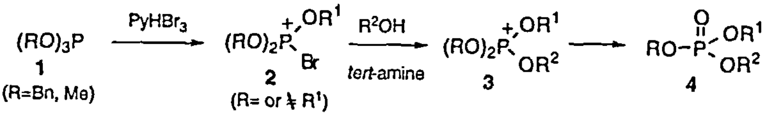


2,6-(Man)$_2$-PI

SYNTHETIC METHODOLOGIES BASED ON PHOSPHITE CHEMISTRY

A Regioselective Phosphorylation Methodology

Treatment of trimethyl and tribenzyl phosphites **1** with pyridinium tribromide in the presence of an alcohol and a *tert*-amine furnished the phosphoric triesters **4** in high yields via Arbuzov-type decomposition of **3** (**Scheme 1**). Since phosphorous mixed triesters are readily available, mixed triester products **4** can be prepared.[2]

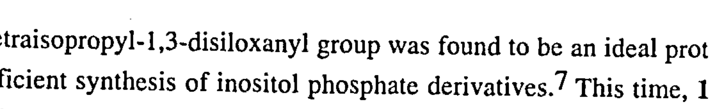


Scheme 1

This methodology was found to be effectively applicable to regioselective phosphorylation of 1,2-free inositol derivatives giving 1-O-phosphate as shown in the total syntheses (**Scheme 3** and **4**).

Glycosylation Using Glycosyl Phosphites

Finding[3] that a phosphite is protonated by 1*H*-tetrazole prompted us to investigate glycosylation using a glycosyl phosphite **5** (**Scheme 2**).[4] Lewis acids such as $ZnCl_2$-$AgClO_4$ and NIS-TfOH gave glycosides **7** in good yield. The same methodology using TMSOTf as the promoter was reported at the same period by other groups.[5] Furthermore, $BF_3 \cdot OEt_2$ was found recently to be efficient for β-selective glycosylation.[6]



Scheme 2

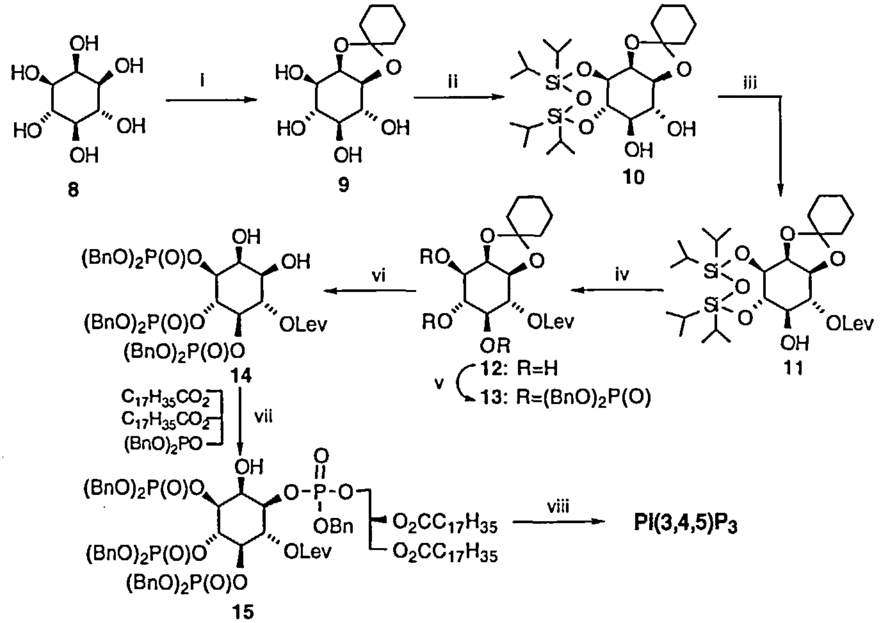
SYNTHESIS OF PHOSPHATIDYLINOSITOL DERIVATIVES

The tetraisopropyl-1,3-disiloxanyl group was found to be an ideal protecting group for the efficient synthesis of inositol phosphate derivatives.[7] This time, **10**, which can be smoothly derived from **9**, was used for the synthesis of the title compounds.

Synthesis of Phosphatidylinositol 3,4,5-trisphosphate

The disiloxanyl group in **10** functions not only to protect the hydroxyl groups at C-3 and -4 but also to prevent the reaction at C-5. Thus, 6-levulinate **11** was readily obtained.

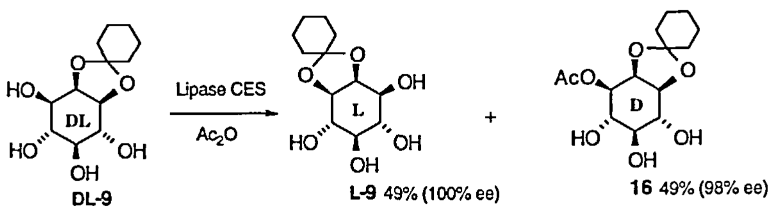
The ester was transformed to the 1,2-diol **14**, which was phosphorylated at C-1 followed by the final deprotection giving PI(3,4,5)P3 (Scheme 3).[8]



i) Cyclohexanone, TsOH (97%); ii) i-$Pr_2Si(Cl)$-O-$Si(Cl)i$-Pr_2 (94%); iii) $CH_3CO(CH_2)_2CO_2H$, DCC, DMAP (84%); iv) $^nBu_4NF{\cdot}3H_2O$, $PhCO_2H$ (85%); v) $(BnO)_2PN^iPr_2$, Tetrazole then mCPBA (72%); vi) CF_3CO_2H, CH_2Cl_2 containing MeOH (83%); vii) $PyHBr_3$, lutidine (36%); viii) 1. H_2, Pd-C, 2. NH_2NH_2

Scheme 3

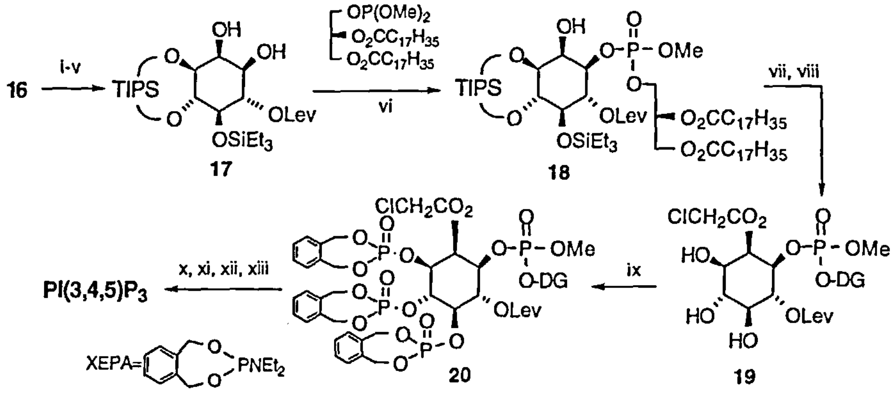
Optically active 1,2-cyclohexylidene-*myo*-inositol was enzymatically prepared via 3-acetate **16** (Scheme 4).[9] It was transformed to the pivotal intermediate D-**10**, from which chiral PI(3,4,5)P3 was obtained (Scheme 5).[10]



Scheme 4

Synthesis of 2,6-Di-*O*-mannopyranosyl-1-phosphatidyl-*myo*-inositol

The key intermediate **10** was regioselectively glycosylated at C-6 followed by, after removal of the cyclohexylidene group, regioselective phosphorylation of the resultant triol to give the 6-*O*-tetrabenzylmannopyranosyl-1-*O*-phosphatidylinositol. Selective glycosylation of the product at C-2 and deprotection (desilylation, demethylation, and debenzylation) produced concisely 2,6-(Man)2-PI.



i) MeONa (92%); ii) TIPS-Cl$_2$ (94%) ; iii) (Lev)$_2$O, DCC (84%); iv) Et$_3$Si-Cl, (100%); v) TsOH, (CH$_2$OH)$_2$ (73%); vi) C$_5$H$_5$NHBr$_3$ (96%); vii) (ClCH$_2$CO)$_2$O (100%); viii) 47% aq. HF (69%); ix) XEPA, tetrazole then mCPBA (89%); x) H$_2$, Pd/C; xi) NH$_2$NHC(S)S$^-$Et^{i}Pr$_2$NH$^+$; xii) PhSH, Et$_3$N; xiii) NH$_2$NH$_2$(21%)

Scheme 5

REFERENCES

1. M. J. Berridge, *Nature*, **361**, 315 (1993).
2. Y. Watanabe, E. Inada, M. Jinno and S. Ozaki, *Tetrahedron Lett.*, **34**, 497 (1993).
3. Y. Watanabe, S. Maehara and S. Ozaki, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1879.
4. Y. Watanabe, C. Nakamoto and S. Ozaki, *Synlett*, **1993**, 115. Y. Watanabe, C. Nakamoto, T. Yamamoto and S. Ozaki, *Tetrahedron*, **50**, 6523 (1994).
5. T. J. Martin and R. R. Schmidt, *Tetrahedron Lett.*, 33, 6123 (1992). H. Kondo, Y. Ichikawa and C.-H. Wong, *J. Am. Chem. Soc.*, 114, 8748 (1992).
6. S. Hashimoto, K. Umeo, A. Sano, N. Watanabe, M. Nakajima and S. Ikegami, *Tetrahedron Lett.*, 36, 2251 (1995).
7. Y. Watanabe, M. Mitani, T. Morita and S. Ozaki, *J. Chem. Soc., Chem. Commun.*, **1989**, 482.
8. Y. Watanabe, H. Hirofuji and S. Ozaki, *Tetrahedron Lett.*, **35**, 123 (1994).
9. L. Ling and S. Ozaki, *Carbohydr. Res.*, **256**, 49 (1994).
10. Y. Watanabe, M. Tomioka and S. Ozaki, *Tetrahedron*, in press.