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Use of 2-Trimethylsilylethyl as a Protecting Group in Phosphate Monoester Synthesis

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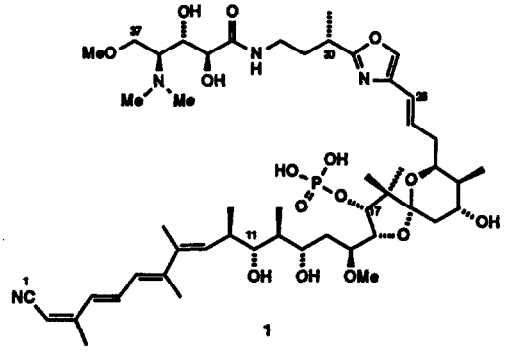
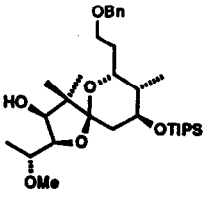
Abstract: A model study has demonstrated that phosphorylation of a highly hindered hydroxyl group can be achieved via sequential treatment with (1) 2-trimethylsilylethyl dichlorophosphite, (2) 2-trimethylsilylethyl alcohol, and (3) hydrogen peroxide. The resulting triester survives a variety of reaction conditions but may be cleaved with fluoride ion to afford the phosphate monoester.

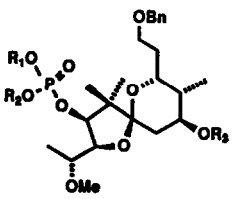
During the course of our synthesis of calyculin A (1) (see below for the structure) we encountered the problem of phosphorylating the C(17) hydroxyl group embedded in the calyculin framework. The judicious selection of a phosphorylation reagent or reagents for this purpose is not a trivial task, as the following requirements must be satisfied on the basis of our scheme designed for the target molecule 1: (1) phosphorylation of the highly hindered C(17) hydroxyl group to provide a doubly protected phosphate ester in the form of a triester, (2) survival of this triester during subsequent operations on other functionalities in synthetic intermediates (including Julia and Stille couplings), and (3) liberation of the monoester from the triester under mild conditions to complete the synthesis of 1. A literature survey[1,2] and preliminary studies[3] indicated that the first requirement could be met by an indirect method utilizing a phosphorochloridite followed by oxidation to the phosphate, rather than the direct phosphorylation with a phosphorochloridate. For requirements 2 and 3, (stability and deprotection), the use of diallyl and 2-trimethylsilylethyl phosphate esters appeared promising: the former is cleanly deprotected by a catalytic amount of Pd(0) phosphine complex[2] and the latter by fluoride ion.[4] We have examined the above indirect method, and the two protecting groups in particular, using model compound 2. The results outlined below provide a solution to our current synthetic problem and appear to be of general use for the synthesis of phosphate monoesters from hindered alcohols.



1



2



3a: R_1=R_2=allyl R_3=TIPS
3b: R_1=R_2=$CH_2CH_2Si(CH_3)_3$ R_3=TIPS
4a: R_1=H R_2=allyl R_3=TIPS
4b: R_1=H R_2=$CH_2CH_2Si(CH_3)_3$ R_3=H
4c: R_1=R_2=R_3=H

Thus, treatment [1.5h, 25°C] of compound 2 (0.02M in pyridine) with diallyl phosphorochloridite (2.2 equiv) in the presence of DMAP (2.5 equiv) provided the phosphorus (III) intermediate which was oxidized with 30% H_2O_2 (10.0 equiv) to the corresponding diallyl phosphate triester 3a in overall 85% yield.

Exposure of **3a** (0.06M in THF) to $Pd(PPh_3)_4$ (0.1 equiv) with PPh_3 (0.6 equiv) and $^nBuNH_2$ (3.0 equiv) [48h, 50°C] resulted in removal of only one allyl protecting group to afford the phosphate diester **4a**. Variation of reaction time and temperature failed to effect complete deprotection to the desired monoester.

Alternatively, to **2** (0.02M in pyridine) was added (1) 2-trimethylsilylethyl dichlorophosphite[5] (2.2 equiv) and DMAP (2.5 equiv) [stirred 1h, -10°C], (2) 2-trimethylsilylethyl alcohol (2.0 equiv) [stirred 2h, 25°C] and finally, (3) 30% H_2O_2 (10.0 equiv) to provide the triester **3b** in overall 86% yield.[6] While treatment with $^nBu_4NF$ resulted in partial cleavage to the diester **4b**, an alternative fluoride source (CH_3CN / 47% HF / H_2O = 8.5 / 0.5 / 1)[7] smoothly and fully deprotected **3b** (0.01M) [48h, 25°C] to provide **4c** in 73% yield.

With an effective protection/deprotection method established, the stability of the trimethylsilylethyl phosphate ester under various reaction conditions has been examined. The protective group was stable to amide bases, e.g., KHMDS, as well as the a-phosphonyl and a-sulfonyl carbanions to be generated en route to completion of our calyculin synthesis. It survived typical Stille coupling conditions. Furthermore, the sensitive C(1)-C(9) tetraene moiety of **1**[8] was found to be stable under the phosphate deprotection conditions. Thus, this sequence of reactions meets the requirements defined by our synthetic scheme.

This report demonstrates the first use of 2-trimethylsilylethyl as a protecting group for phosphate monoester synthesis. The synthesis of all major fragments of calyculin A, including introduction of the phosphate ester into the spiroketal moiety have been completed. This and the final coupling of the fragments to complete the synthesis will be reported in due course.[9]

Acknowledgements. This work was supported by a grant from the National Institutes of Health, (CA48175).

References and Notes

1 For examples of phosphorylation based on P(III) chemistry, see: Dialkyl N,N-dialkylphosphoramidites: (a) Watanabe, Y.; Komoda, Y.; Ebisuya, K.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 255. (b) Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175. (c) Perich, J. W.; Johns, R. B. *Synthesis* **1988**, 142. (d) Yu, K. L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979. Dialkyl phosphorochloridites and monoalkyl phosphorodichloridites: (a) Meek, J. L.; Davidson, F.; Hobbs, F. W. *J. Am. Chem. Soc.* **1988**, *110*, 2317. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964.

2 (a) Hayakawa, Y.; Wakabayashi, S.; Nobori, T.; Noyori, R. *Tetrahedron Lett.* **1987**, *28*, 2259. (b) Hayakawa, Y.; Uchiyama, M.; Kato, H.; Noyori, R. *Tetrahedron Lett.* **1985**, *26*, 6505. (c) Hayakawa, Y.; Wakabayashi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 1691. (d) Kamber, M.; Just, G. *Can. J. Chem.* **1985**, *63*, 823. (e) Bannwarth, W.; Küng, E. *Tetrahedron Lett.* **1989**, *32*, 4219. (f) Also see: Tanigawa, Y.; Nishimura, K.; Kawasaki, A. *Tetrahedron Lett.* **1982**, *23*, 5549.

3 Attempts at phosphorylation with dialkylphosphoramidites gave no reaction.

4 (a) Honda, S.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 2093. (b) Mautz, D. S.; Davisson, V. J.; Poulter, C. D. *Tetrahedron Lett.* **1989**, *30*, 7333.

5 Prepared by reaction of trimethylsilylethyl alcohol with phosphorus trichloride.

6 Attempts to purify bis(2-trimethylsilylethyl) chlorophosphite, prepared by reaction of 2-trimethylsilylethyl dichlorophosphite with 2-trimethylsilylethyl alcohol, by distillation failed, prompting us to employ the three-step procedure described.

7 (a) Newton, R. F.; Reynolds, D. P.; Finch, M. A.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981. (b) Masamune, S.; Choy, W.; Kerdesky, F.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

8 Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1937.

9 All new compounds were characterized in the standard fashion.

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