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USE OF A β-TRIMETHYLSILYLETHOXYMETHYL ESTER AS A PROTECTING GROUP. A FACILE PREPARATION OF 1-HYDROXYCYCLOPROPANECARBOXYLIC ACID PHOSPHATE

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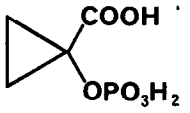
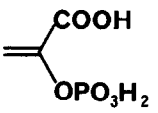
Summary: The potential use of β-trimethylsilylethoxymethyl (SEM) esters for temporary carboxyl blocking is illustrated in a preparation of the title compound.

1-Hydroxycyclopropanecarboxylic acid phosphate, 1, is a potent reversible inhibitor[1] of enzymes utilizing phosphoenolpyruvate (PEP), such as phosphoenolpyruvate carboxylase (EC 4.1.1.31)[2], which catalyzes the carboxylation of PEP, 2, to give oxaloacetate, 3. We recently had need for an alternative to the previously published synthesis[1], which proceeds in low overall yield and requires the use of ion-exchange chromatography. We report herein a facile synthesis of 1 which utilizes a β-trimethylsilylethoxymethyl (SEM) ester as a temporary, easily removable carboxyl protecting group.



1



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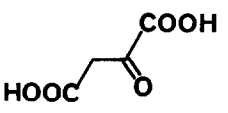

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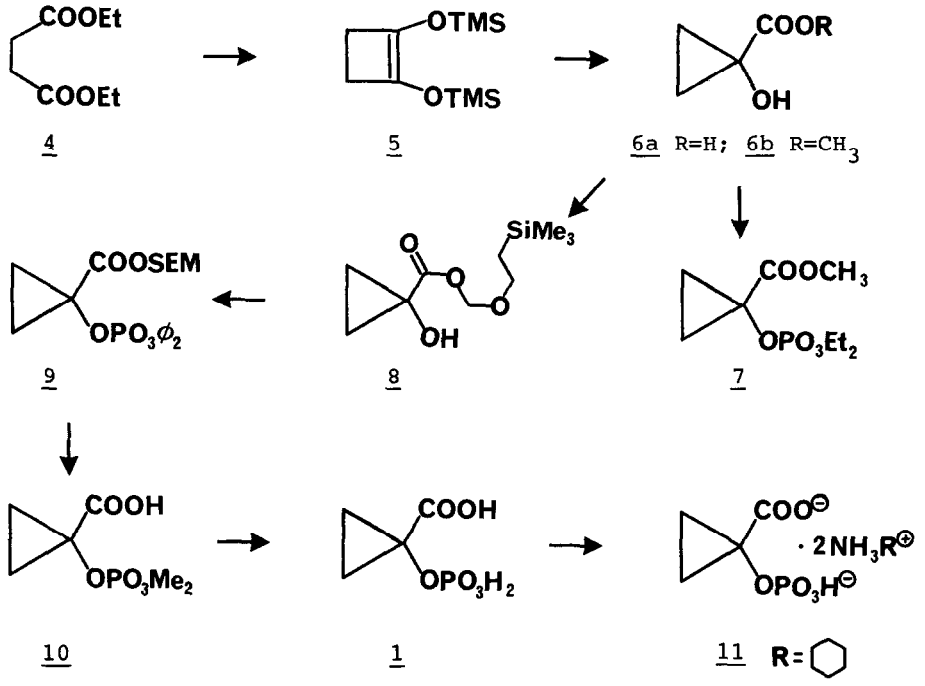
Synthesis of 1 commences with the known 1-hydroxycyclopropanecarboxylic acid (6a, Scheme 1). The latter is prepared by bromination of 1,2-bis(trimethylsiloxy)cyclobutene 5[3], followed by workup with aqueous sodium hydroxide.[4] Attempts to phosphorylate 6a directly failed to yield a clean product, and while ester 6b (diazomethane; bp 105-108°, 20 mm Hg) could be phosphorylated (NaH, THF, diethyl chlorophosphate), only the phosphate group of 7 could be de-esterified in good yield (TMS iodide). It occurred to us that a reasonable alternative approach would be to free the carboxyl group first (Scheme 2), since the phosphate group could then

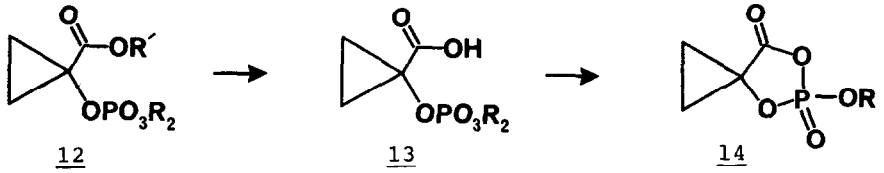
be expected to undergo facile solvolysis via the intermediacy of a cyclic anhydride (12→13→14).[5] Similar accelerated solvolyses occur in the case of phosphoenolpyruvate[6] and analogs.[7]

The choice of esters suitable for a compound of type 12 was restricted somewhat by the destruction undergone by 6a under DCC-mediated esterification conditions, which suggested the use of an alkoxymethyl ester.[8] While most are accessible through mild alkylations, considerations of stability or deprotection influenced us to apply the β-trimethylsilylethoxymethyl (SEM) group[9] to our purposes.

SCHEME 1



SCHEME 2



Thus 8 (Scheme 1) was readily obtained by treatment of 6a with triethylamine (1.15 eq) and SEM chloride (1.05 eq) in dry THF at 0°. Ester 8 could be isolated in 80% yield by MPLC on silica gel[10], but further reaction with additional triethylamine (1.15 eq), diphenyl chlorophosphate (1.1 eq) and N,N-dimethylaminopyridine (0.05 eq) afforded, after aqueous workup, the phosphate 9. The latter could be isolated in 70% yield by MPLC on silica gel[10], but the crude product was sufficiently pure for use in the next step. Thus exposure of 9 to methanol-D_4 at ambient temperature effected solvolysis at the acetal carbon of the SEM group of 9, with a t1/2 of about 12 hr [^{1}H NMR shift of acetal singlet from 5.2 ppm to 4.5 ppm (downfield) relative to the SEM trimethylsilyl group]. Only a slight loss (10%) of one phenol from 9 was observed in 12 hr [^{31}P NMR shift from -13.4 ppm to -6.8 ppm (upfield) relative to 85% H_3PO_3]. Complete displacement of the SEM group occurred between 2 hr and 5 hr at reflux[11], accompanied by 60% consumption of the diphenyl phosphate group [^{31}P NMR relative intensities of peaks at -13.4, -6.8 and 0.6 ppm: 37%, 56%, 7%]. Complete conversion to 10 [0.6 ppm] required about 48 hr of reflux. Acid-base extraction with ether (cold dilute $NaHCO_3$, HCl) and trituration of the solid crude product with cold ether afforded pure 10 as a hygroscopic white solid, mp 71-73°.[10,12] The overall yield of 10 from 6a, without purification of intermediates, was 60%.

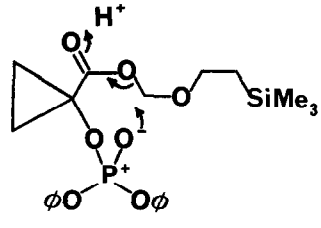
The free acid 10 was dissolved in water and was allowed to stand for several days, or was heated at 40° for a shorter period, until ^{31}P NMR indicated complete hydrolysis of 10. Removal of water on the rotary evaporator and drying *in vacuo* over magnesium perchlorate furnished 1 as a colorless foam. Treatment of 1 in cold acetone with cyclohexylamine (3 eq) and recrystallization of the resulting solid from methanol-acetone afforded the bis-cyclohexylamine salt 11, mp 173-175°, in 65% yield from 10.[10,13]

In conclusion, it should be noted that the use of β-trimethylsilylethoxymethyl (SEM) esters to mask carboxyl groups affords compounds sufficiently stable for chromatography and routine manipulation, but which may be readily deprotected without affecting either acid or base-sensitive functionalities.

References and Notes

1. M. H. O'Leary, W. J. DeGooyer, T. M. Dougherty and V. Anderson, Biochem. Biophys. Res. Commun., 1981, 100, 1320.
2. M. H. O'Leary, Ann. Rev. Plant. Physiol., 1982, 33, 297.
3. J. J. Bloomfield and J. M. Nelke, Org. Synth., 1973, 53, 158.

4. Bayer AG, U.S. Pat. 3,813,432, and reference 1 above. Crude 6a is best obtained by continuous extraction, and purified by sublimation (80-90°, 0.1 mm Hg).
5. N. E. Jacobsen and P. A. Bartlett, J. Am. Chem. Soc., 1983, 105, 1613.
6. B. L. Hirschbein, F. P. Mazenod and G. M. Whitesides, J. Org. Chem., 1982, 47, 3765.
7. J. A. Stubbe and G. L. Kenyon, Biochemistry, 1971, 10, 2669.
8. T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1981, Chapter 5.
9. B. H. Lipshutz and J. J. Pegram, Tetrahedron Lett., 1980, 21, 3343.
10. Spectral data: ^{1}H NMR spectra (60 MHz) were recorded on a Varian EM 360 spectrometer. Shifts reported as ppm downfield from tetramethylsilane. ^{31}P NMR spectra (40 MHz) were recorded on JEOL FX-100 fourier transform spectrometer using proton irradiation and external deuterium lock. Shifts reported as ppm downfield (positive) and upfield (negative) from 85% H_3PO_4. 8 ^{1}H ($CDCl_3$): 0.05 (9H, s), 0.7-1.5 (6H, m), 3.65 (2H, t, J = 4), 5.30 (2H, s). 9 ^{1}H ($CDCl_3$): 0.05 (9H, s), 0.90 (2H, t, J = 4), 1.5 (4H, m), 3.65 (2H, t, J = 4), 5.25 (2H, s), 7.30 (10H, s); ^{31}P ($CDCl_3$): -13.3. 10 ^{1}H ($CDCl_3$): 1.5 (4H, m), 3.85 (6H, d, J = 5.5); ^{31}P ($CDCl_3$): 0.03. 1 ^{1}H (CD_3OD): 1.4 (m); ^{31}P (CD_3OD): 1.67. 11 ^{1}H (CD_3OD): 1.2-2.3 (12H, m), 2.8-3.4 (14, m); ^{31}P (CD_3OD): 1.54.
11. No decomposition of the SEM group to yield ethylene was observed under these conditions. As pointed out by a referee, the remarkably accelerated solvolysis of the SEM group in the present instance may be due to anchimeric assistance by the neighboring phosphate group, as illustrated below:



12. Calculated for $C_6H_{11}O_6P_1$: C, 34.30; H, 5.28. Found: C, 34.46; H, 5.18.
13. Calculated for $C_{16}H_{33}N_2O_6P_1$: C, 50.52; H, 8.74; N, 7.36. Found: C, 49.92; H, 8.63; N, 6.99.

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