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A HIGHLY CONVERGENT PREPARATION OF PHOSPHONYLOXYACYLAMINO ACIDS:

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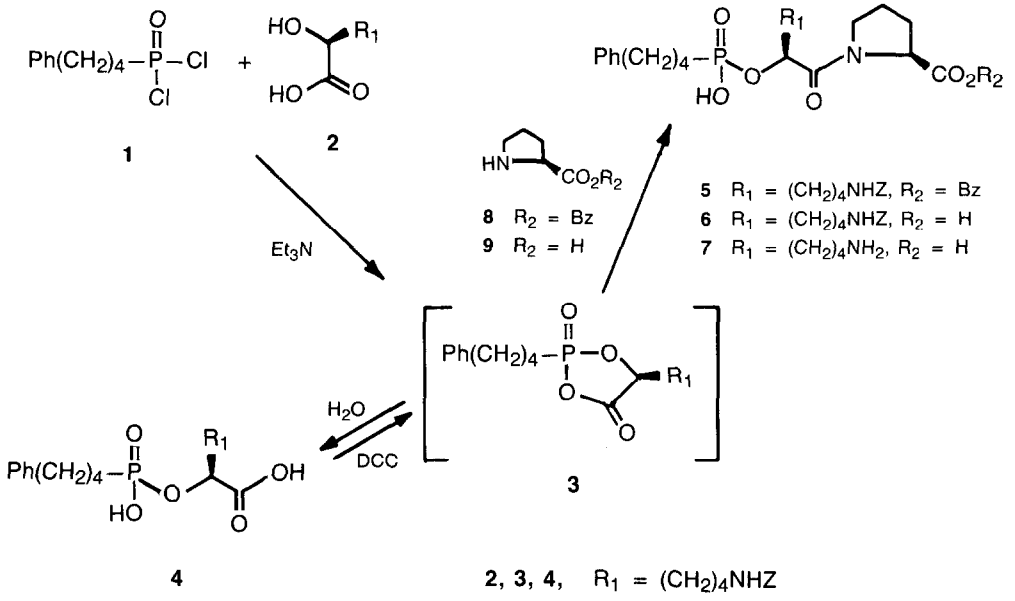
Abstract: A very simple, mild and efficient method for the preparation of phosphonyloxyacylamino acids from readily available starting materials is described.

In conjuction with our ongoing ACE Program[1] we needed a method for the rapid and efficient assembly of phsophonyloxyacylamino acids of the type 7. In this letter we describe a new, highly convergent and efficient method for the preparation of this biologically important class of compounds[2] from readily available starting materials. Thus, sequential treatment of the



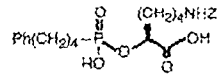
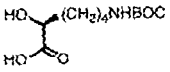
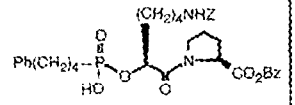
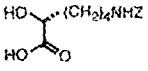
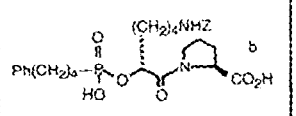
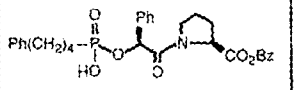
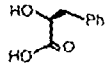
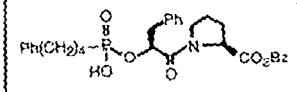
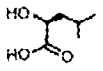
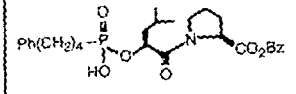
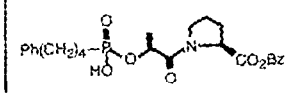
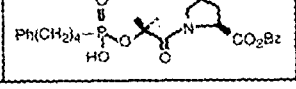
easily available phosphonyl dichloride[3] 1 with alpha-hydroxy acid 2[4] in the presence of two equivalents of triethylamine (-75°C to 0°C), and then proline benzylester hydrochloride and one equivalent of triethylamine followed by double deprotection by catalytic hydrogenolysis furnished the desired product 7 in 85% crystallized yield from 1. Similarly, addition of proline followed by deprotection and crystallization again produced 7, in 86% crystallized yield, from 1.

These remarkable transformations are due to the in situ formation and reaction of anhydride 3. Formation of the anhydride 3 by the reaction of dichloride 1 and hydroxy acid 2 was confirmed by ^{13}CNMR analysis. Intermediate 3 was formed as an almost 1:1 mixture of diastereomers, which are clearly distinguishable by the methine carbon.[5] Quenching of the intermediate 3 with water produced diacid 4, identical in every respect to a sample prepared by an alternate route.[6] Cyclodehydration of 4 with dicyclohexylcarbodiimide (DCC) produced the same mixture of diastereomers of cyclic anhydride 3 by ^{13}CNMR analysis.

Such a high yield for the formation of 7 from 1 is clearly remarkable. Even if one assumes a 100% yield for the deprotection/crystallization step, the formation of 3 from homobifunctional molecule 1 and heterobifunctional molecule 2 and the chemospecific[7] ring opening of 3 must occur in an average yield of 92.5%. Examples of this methodology using a variety of alpha-hydroxy acids and dichloride 1 are summarized in Table 1: yields are consistently high, even with a tertiary alpha hydroxy acid (Run #9).

A typical experimental procedure (Run #1) is as follows: A solution of dichloride 1 (50.0 gm, 0.199 mole) in THF (1.2 l) was cooled to -75°C and triethylamine (63.0 ml, 0.45 mole) was added to the solution. A solution of hydroxy acid 2 (56.0 gm, 0.199 mole) in THF (350 ml) was added dropwise to the dichloride solution with vigorous stirring, keeping the internal temperature at ~-75°C. After the addition was over (2 hours), the mixture was stirred for 2 hours at -78°C, allowed to warm to ambient temperature over 1 hr, and stirred 1 hr more at ambient temperature. Well powdered proline (25.0 gm, 0.21 mole) was added to the reaction mixture in one lot and the mixture was stirred at ambient temperature for 12 hours. The residue obtained after standard extractive aqueous work up was dissolved in methanol (500 ml) and 18% $Pd(OH)_2/C$ (10.0 gm) was added. Hydrogen gas was bubbled through the solution for 1 hour. Filtration and methanol evaporation followed by crystallization from water-acetone produced 7 in 86% (75.0 gm) yield, $[\alpha]_D$ = -46.2°, c = 5, MeOH; m.p. 190-195°C.[8]

Table 1

Run	Hydroxy Acid	Amine/ Nucleophile	Product	Yield %[a]	M.P. °C
1	2	9	7[b]	85[b]	190-5
2	2	8	7[b]	85[b]	190-5
3	2	H_2O		92[c]	110-113[d]
4		8		75[e]	125-130[f]
5		8		66[b]	—
6		8		88[e]	204-7[f]
7		8		88	94-6
8		8		83[e]	208-212[f]
9		8		82[e]	171-6[f]
10		8		82[e]	117-122[f]

a. Crystallized or chromatographed; b. Obtained after deprotection; c. Isolated as mono-dicyclohexylamine salt; d. Mono-dicylcohexylamine salt; e. Isolated as 1-adamantanamine salt; f. 1-Adamantanamine salt

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References and Notes:

1. E. W. Petrillo, Jr. and M. A. Ondetti, Med. Res. Rev., 2, 1-41, (1982).

2. E. W. Petrillo, Jr. et al, in "PEPTIDES: Structure and Function", Proceedings of the Eighth American Peptide Symposium, Edited by V. J. Hruby and D. H. Rich and Published by Pierce Chemical Company, 1983, Pages 541-550.

3. Dichloride 1 was prepared in 98% yield by the action of PCl_5 on the corresponding phosphonic acid and the preparation of the latter will be published elsewhere.

4. Prepared by the action Z-Cl and NaOH on the corresonding known (S)-6-amino-2-hydroxyhexanoic acid. See. K. Aketa, S. Terashima and S. Yamada, Chem. Pharm. Bull, 24, 621-631 (1976).

5. ^{13}CNMR of the Methine Carbon of 3 is : (THF-d_8), 81.23 (d, J_{P-C} = 5.8Hz) and 80.25 (d, J_{P-C} = 5.8Hz)

6. Alternate Routes for the preparation of 4 will be published elsewhere.

7. Ring opening of anhydride 3 with alcohols and other oxygen nucleophiles will be published in the future.

8. Satisfactory IR, ^{1}H and ^{13}C NMR, MS and/or elemental analysis were obtained for all new compounds.

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