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β-LACTAM AS SYNTHETIC INTERMEDIATE.[12] A NEW SYNTHETIC APPROACH TO OLIGOPEPTIDES THROUGH NOVEL β-LACTAMS

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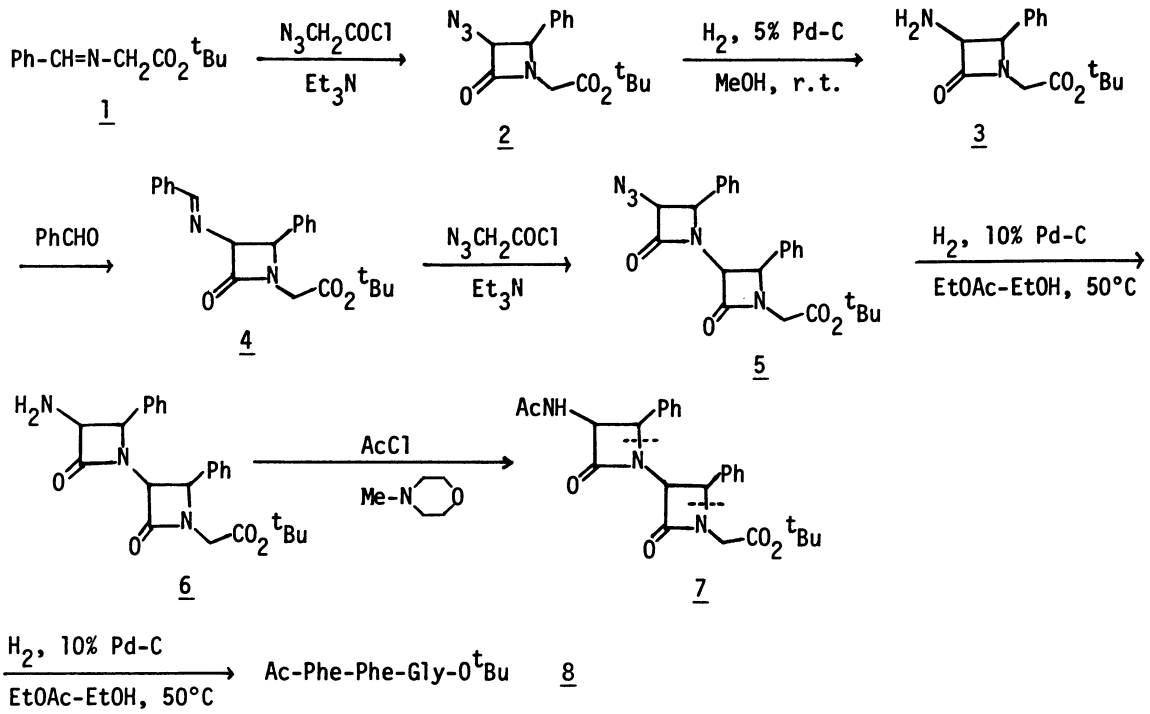
Synthetic method of a new class of β-lactams, which have two β-lactams in a single molecule, was established and subsequent cleavage upon hydrogenolysis by the use of palladium catalyst gave tri- or tetrapeptides, thus providing a new approach to oligopeptides.

Although the formation of peptide linkage has been extensively studied, most of such reactions basically involve dehydration between amine and carboxylic acid moieties of amino acids.[1] Such limited availability of synthetic manipulation toward peptides leaves us room for finding entirely new methods. For instance, we have recently reported novel routes to dipeptides by means of asymmetric hydrogenation of dehydrodipeptides,[2] and catalytic hydrogenolysis of β-lactams.[3,4] Since β-lactam ring system is essential for the antibacterial activity, little has been done on the cleavage reaction of the ring. Accordingly, the regioselective ring opening of β-lactam into peptides has revealed a new facet of this class of compound.[4]

Now, we have been able to extend our β-lactam hydrogenolysis approach to tri- and tetrapeptides. To utilize the β-lactam rings as building blocks for tri- or tetrapeptides, we put two β-lactam rings into a single molecule. Very recently, Sharma and co-workers[5] reported a preparation of, according to their terminology, a di β-lactam, similar compound of which we have prepared independently. Although our interest in this system is focused on a quite different feature of this class of compound, their report has prompted us to present thus far obtained results.

As shown in Scheme 1, the key compound, β-lactam 2, was readily prepared by using our modified Bose's method[6] from benzylidene *t*-butoxycarbonylmethylamine and azidoacetyl chloride in the presence of triethylamine in methylene chloride (56%).[7] The β-lactam 2 carries two functional groups ($-N_3$ and $-CO_2{}^tBu$) which can be converted into free amine and free acid,

Scheme 1. Synthesis of Tripeptide



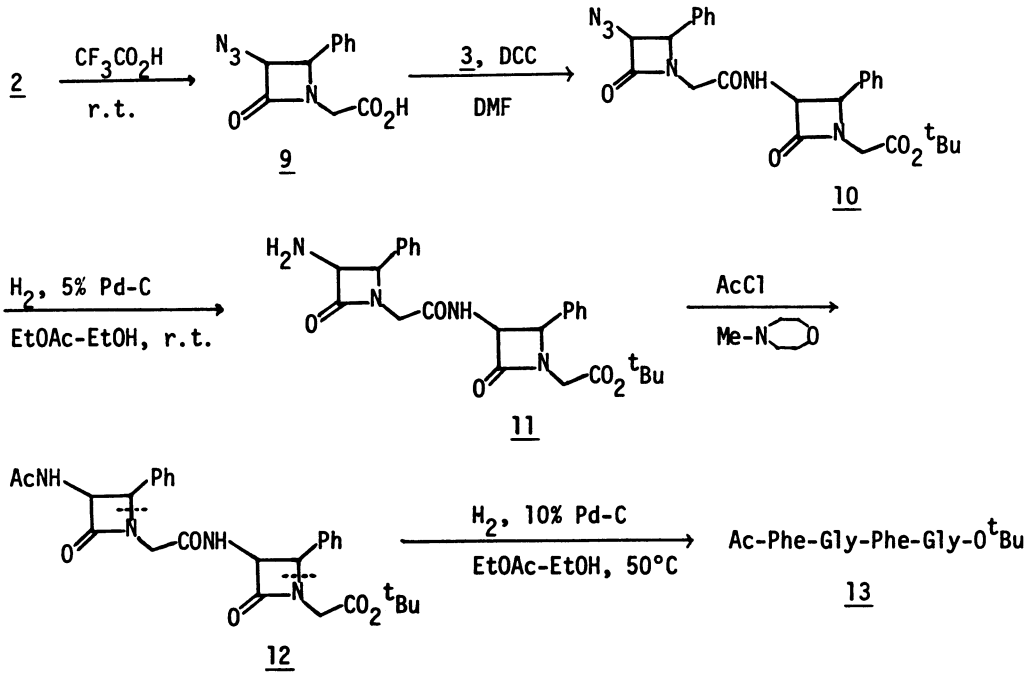
respectively for further linkage of β-lactam units. Especially, *t*-butyl group is essential for its facile cleavage into free acid under mild acidic conditions.

The azido group in 2 was readily converted to the amino group under 1 atm of hydrogen on palladium catalyst in methanol at room temperature (90%).[8] The amine 3 was condensed with benzaldehyde in the presence of sodium sulfate in benzene to form the corresponding Schiff base 4 (100%). Then, 4 was subjected to the same Bose's β-lactam forming reaction[6] (azidoacetyl chloride in the presence of triethylamine in methylene chloride) to afford compound 5 (58%), which has two β-lactam rings attached directly to each other.[9] The NMR spectrum of 5 clearly showed *cis* geometry for both β-lactam rings (J = 5.0 Hz), which is in agreement with the fact Sharma reported.[5] The compound 5 was converted to the corresponding amine in a similar manner as described above (99%), and the amino group in 6 was protected by acetyl group to give 7 by the use of acetyl chloride and N-methylmorpholine in chloroform (69%).[9] Now, all are properly set for the hydrogenolysis to tripeptide. Thus, the compound 7 was subjected to the hydrogenolysis we have developed[3,4] for the cleavage of β-lactam ring (1 atm H_2, 10% Pd-C, 50°C) to afford crystalline tripeptide Ac-Phe-Phe-Gly-O^{t}Bu 8 (100%)

after removing catalyst by filtration and evaporation of solvent. The proceeding of the reaction was easily followed by observing the disappearance of strong carbonyl stretching band (1760 cm^{-1}) of β-lactam ring and the appearance of typical amide linkage bands (3300, 1660 and 1540 cm^{-1}) in the IR spectrum. The product 8 was identified by HPLC analysis [TOYO SODA LS410K (ODS SIL), MeOH-H_2O as eluent] using authentic samples, which revealed that 8 exactly corresponds to Ac-(*L*/*D*)Phe-(*D*/*L*)Phe-Gly-O^{t}Bu: The formation of Ac-(*L*/*D*)Phe-(*L*/*D*)Phe-Gly-O^{t}Bu was not observed at all.

To show some other aspect of utilizing key compound 2, we carried out another sequence of reactions which lead to the formation of tetrapeptides, as shown in Scheme 2. *t*-Butyl group in 2

Scheme 2. Synthesis of Tetrapeptide



was successfully cleaved off leaving the β-lactam ring intact to give β-lactam carboxylic acid 9 (100%).[10] Then, 9 was successively combined with the β-lactam amine 3 by the action of dicyclohexylcarbodiimide in a usual fashion to afford 10 (42%), which also has two β-lactam rings as 5 does, but in a different way.[11] The azido group in 10 was converted to the amino group (98%), and protected as N-acetyl derivative to provide another peptide precursor 12 (68%).[11] The tandem style bis-β-lactam 12 was subjected to the hydrogenolysis to give crystalline Ac-Phe-Gly-Phe-Gly-O^{t}Bu 13 (84%) after usual work-up. The product 13 was identified by HPLC analysis (conditions: *vide supra*) using authentic samples, which turned to be a 1:1 mixture of two diastereomers.

A striking feature of this kind of tri- or tetrapeptide precursor (5, 7, 10 or 12) is that these are easily soluble in regular organic solvent such as ether, ethyl acetate, chloroform etc., and thus can be chromatographed on an ordinary silica gel column in a

usual fashion unlike other known peptide precursors. This characteristic would have a great advantage in peptide synthesis. For instance, when 10 was obtained from 3 and 9 using dicyclohexylcarbodiimide, the side product dicyclohexylurea was easily removed simply by dissolving 10 into ether in which dicyclohexylurea is virtually insoluble. Despite the well-known fact that the removal of dicyclohexylurea is always troublesome in peptide synthesis, this unusual high solubility of the tetrapeptide precursor eliminated ever-persisting problem of peptide synthesis.

As conclusion, we would like to say that we have revealed a new aspect of β-lactam chemistry besides antibacterial activity, which provides entirely new and convenient approaches to peptide synthesis as well.

Asymmetric synthesis of oligopeptides and their precursors is currently under active investigation in our group and will be reported shortly.

References and Notes

1. e.g., J. C. Sheehan and G. P. Hess, J. Am. Chem. Soc., 77, 1067 (1955); Idem, ibid., 78, 1367 (1956); G. W. Anderson, J. E. Zimmerman and F. M. Callahan, ibid., 86, 1839 (1964); R. B. Woodward, R. A. Olofson and H. Mayer, ibid., 83, 1010 (1961); H. A. Staab, Ann., 609, 75 (1957); J. C. Sheehan, J. Preston and P. A. Cruickshank, J. Am. Chem. Soc., 87, 2492 (1965); Y. Isowa, M. Ohmori, M. Sato and K. Mori, Bull. Chem. Soc. Jpn., 50, 2766 (1977) and references therein.
2. I. Ojima and T. Suzuki, Tetrahedron Lett., 21, 1239 (1980).
3. I. Ojima, S. Suga and R. Abe, Chem. Lett., 1980, 853.
4. I. Ojima, S. Suga and R. Abe, Tetrahedron Lett., 21, 3907 (1980).
5. S. D. Sharma, P. K. Gupta, J. Bindra and Sunita, Tetrahedron Lett., 21, 3295 (1980).
6. e.g., A. K. Bose, M. S. Manhas, J. C. Chib, H. P. S. Chawla and B. Dayal, J. Org. Chem., 39, 2877 (1974).
7. 2, oil: IR(neat) 2120, 1780 and 1740 cm^{-1}; NMR($CDCl_3$) δ 1.45(s, 9H), 3.87(ABq, 2H, J = 18 Hz), 5.12(ABq, 2H, J = 5 Hz) and 7.20-7.50(m, 5H).
8. 3, oil: IR(neat) 3400, 1760 and 1740 cm^{-1}; NMR($CDCl_3$) δ 1.46(s, 11H), 3.88(ABq, 2H, J = 18 Hz), 4.82(ABq, 2H, J = 5 Hz) and 7.13-7.52(m, 5H).
9. 5, mp 164-166°C: IR(KBr) 2120, 1780s, 1760 and 1730 cm^{-1}; NMR($CDCl_3$) δ 1.43(s, 9H), 3.95(ABq, 2H, J = 18 Hz), 4.16(ABq, 2H, J = 5 Hz), 4.83(ABq, 2H, J = 5 Hz) and 7.11-7.52 (m, 10H). 7, mp 120-121°C: IR(KBr) 3350, 1760 and 1740s cm^{-1}; NMR($CDCl_3$) δ 1.44(s, 9H), 1.55(s, 3H), 3.90(ABq, 2H, J = 18 Hz), 4.23(d, 1H, J = 5 Hz), 4.78(dd, 1H, J = 5 Hz, 9 Hz), 4.87(ABq, 2H, J = 5 Hz), 6.27(d, 1H, J = 9 Hz) and 7.09-7.60(m, 10H).
10. 9, oil: IR(neat) 3000(br), 2120 and 1760(br) cm^{-1}; NMR($CDCl_3$) δ 4.40(ABq, 2H, J = 18 Hz), 5.12(ABq, 2H, J = 5 Hz) and 7.17-7.55(m, 5H).
11. 10, solid, a mixture of diastereomers: IR(KBr) 3300, 2110, 1760, 1740s, 1690 and 1540 cm^{-1}; NMR($CDCl_3$) δ 1.44(s, 9H), 2.86-3.63(m, 2H), 3.88-4.43(m, 2H), 4.70-5.67(m, 4H) and 6.93-7.53(m, 11H). 11, solid, a mixture of diastereomers: IR(KBr) 3300, 1760, 1690, 1540, 1150 and 700 cm^{-1}; NMR($CDCl_3$) δ 1.79(s, 9H), 1.93 and 1.97(s, 3H), 2.80-3.67(m, 2H), 3.98-4.52(m, 2H), 4.87-5.75(m, 4H), 6.65-7.77(m, 11H) and 8.50(br d, 1H, J = 8.5 Hz).
12. Part I: see reference 3; Part II: see reference 4.

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