BULLETIN

OF THE KOREAN CHEMICAL SOCIETY

VOLUME 11, NUMBER 5
OCTOBER 20, 1990

BKCS 11(5) 361-470
ISSN 0253-2964

Communications

Synthesis of A δ-Lactam Analogue of Penem Carboxylate

Eun Lee*, Dong Youl Lim, and Kyung Ae Lee

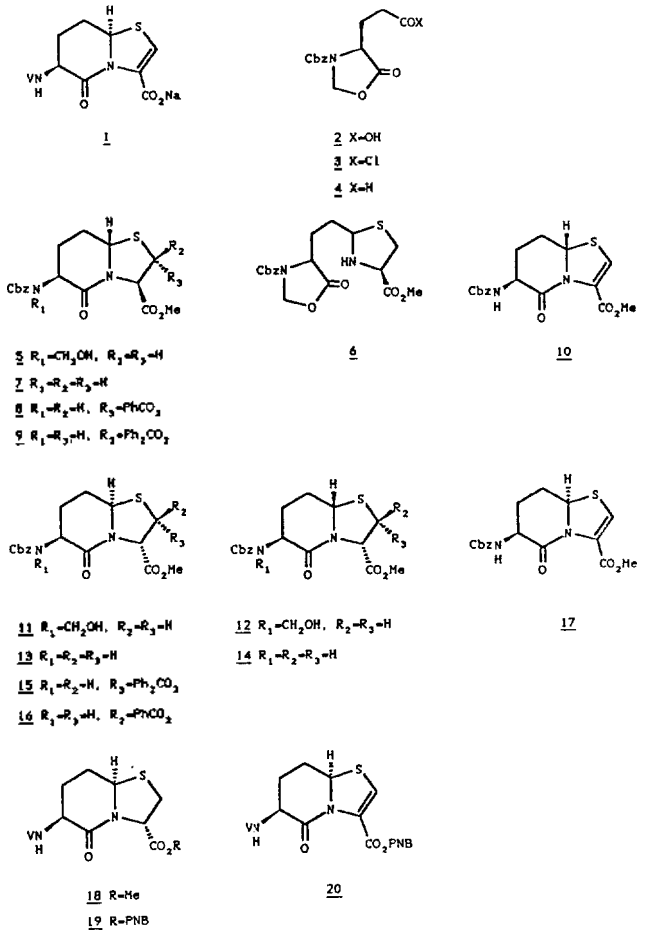
Department of Chemistry, Seoul National University, Seoul 151-742

Received April 23, 1990

Recently, several γ-lactam analogues of 6β-acylamino penems were shown to possess biological activities either as antibacterials or as β-lactamase inhibitors.[1] Herein we wish to report synthesis of a δ-lactam analogue **1** from L-glutamic acid and D-cysteine.

Acid-catalyzed condensation of α-aminocarboxylic acids with formaldehyde is known to give oxazolidinone derivatives, which represent an efficient and selevtive protection method for α-amino acid moiety.[2] Thus reaction of N-benzyloxycarbonyl-L-glutamic acid with paraformaldehyde (toluene, cat.TsOH, reflux, 5 h) produced the oxazolidinone acid **2**, which was converted to the corresponding acid chloride **3** ($SOCl_2$, reflux, 2 h). The acid chloride **3** was reduced (Bu_3SnH, EtOAc, r.t., 12 h) to the oxazolidinone aldehyde **4**.[2a] Reaction of **4** with L-cysteine methyl ester (pyridine, r.t., 3 days) resulted in the formation of the N-hydroxymethyl bicyclic δ-lactam **5** via sequential double cyclizations. The presumed thiazolidine-oxazolidinone intermediate **6** was sufficiently reactive to allow formation of the bicyclic product under mild conditions. N-Hydroxymethyl group in **5** was removed (MeOH, Na_2CO_3, r.t., 5 h) to yield the bicyclic δ-lactam **7** in 80% yield from **4**. At this point, the assignment of the absolute stereochemistry at the ring junction (5S) was only tentative; it was deduced from stereochemical considerations (methylene should be *trans* to methoxycarbonyl group) and comparison of the optical rotation value of **7** ($[\alpha]_D^{25} = -180°$, $c = 1.54$)[3] to the value of the corresponding γ-lactam ($[\alpha]_D^{20} = -199°$, $c = 0.67$).[4]

Reaction of **7** with benzoyl peroxide[5] (benzene, reflux, 3 h) produced a mixture of two epimers **8** and **9** in 31% yield, which was converted to the penem analogue **10** ($[\alpha]_D^{27} = -145°$, $c = 1.23$) in 30% yield (toluene, DBU, reflux, 0.5 h). The



stereochemical assignment was performed with the aid of 360 MHz COSY and NOE difference spectra. For example, irradiation of 6-βH (δ 2.32) resulted in the enhancement of the 5-βH (δ 5.73) signal.

The desired stereoisomer (5R) was envisioned to arise from D-cysteine. In the event reaction of **4** with D-cysteine methyl ester (pyridine, r.t., 60 h) gave the epimeric mixture of the N-hydroxymethyl bicyclic δ-lactams **11** and **12** in a 5:1 ratio (78% total yield). Removal of the one carbon appendage as before resulted in the formation of the bicyclic δ-lactams

13 ($[\alpha]_D^{25}$ = +139°, c = 1.30) and **14** ($[\alpha]_D^{25}$ = +42°, c = 1.16) in 70% yield. The major epimer **13** was reacted with benzoyl peroxide to yield a 1:1 mixture of **15** and **16**, which was converted to the olefin **17** ($[\alpha]_D^{27}$ = +196°, c = 0.59) upon treatment with DBU in THF (r.t., 0.5 h). The 5R stereochemistry was self-evident when optical rotation value of **17** was compared with that of **10**.

Having achieved the synthesis of the basic skeleton, attention was next turned to the synthesis of **1** with biologically viable phenoxyacetamide side chain. Deprotection of N-benzyloxycarbonyl group in **13** (31% HBr in HOAc, r.t., 1 h) and reprotection of the reaction product with phenoxyacetyl chloride (CH_2Cl_2-Et_3N, r.t., 27 h) resulted in the formation of V-protected bicyclic δ-lactam **18** in 56% yield. It was hydrolyzed in 91% yield (LiOH, THF-H_2O; 3:1, r.t., 0.5 h) and the corresponding PNB ester **19** ($[\alpha]_D^{28}$ = +124°, c = 2.28) was synthesized (PNBBr, $NaHCO_3$, DMF, r.t., 15 h) in 60% yield. Benzoyloxylation and elimination reactions were performed in the usual ways to produce the olefin **20** ($[\alpha]_D^{26}$ = +135°, c = 1.03) in 35% yield. The PNB group in **20** was readily cleaved off by hydrogenolysis (10% Pd/C, 38 psi, THF-pH 7 phosphate buffer 4 h) in excellent yield to give the carboxylate **1**.

Antibacterial test (MIC, 20 different strains) revealed **1** to be totally inactive.[6]

Acknowledgement. We wish to thank Korea Science and Engineering Foundation for a generous grant. Spectroscopic assistance of Dr. Y. Naya and Mr. H. Naoki of Suntory Institute of Bioorganic Research is gratefully acknowledged. We also thank Dr. E. K. Park of Korea Research Institute of Chemical Technology for performing bioassay.

References

1. (a) J. E. Baldwin, E. Lee, C. Lowe, and C. J. Schofield, *Tetrahedron Lett.*, **27**, 3461 (1986); (b) D. B. Boyd, T. K. Elzey, L. D. Hatfield, M. D. Kinnick, and J. M. Morin, *Tetrahedron Lett.*, **27**, 3453 (1986); (c) D. B. Boyd, B. J. Foster, L. D. Hatfield, W. J. Hornbark, N. D. Jones, J. E. Munroe, and J. K. Swartzendruber, *Tetrahedron Lett.*, **27**, 3457 (1986).
2. (a) B. H. Lee and M. J. Miller, *Tetrahedron Lett.*, **25**, 927 (1984); (b) S. Hanessian and S. P. Sahoo, *Tetrahedron Lett.*, **25**, 1425 (1984); (c) R. M. Freidinger, J. S. Hinkle, D. S. Perlow, and B. H. Arison, *J. Org. Chem.*, **48**, 77 (1983).
3. All optical rotation data were obtained using chloroform solutions.
4. J. E. Baldwin and E. Lee, *Tetrahedron*, **42**, 6551 (1986).
5. (a) D. J. Rawlirison and G. Sosnovsky, *Synthesis*, 1 (1972); (b) H. Matsumura, T. Yano, M. Ueyama, K. Tori, and W. Nagata, *J. Chem. Soc. Chem. Comm.*, 485 (1979).
6. Recent computer graphics/molecular mechanics energy minimizations based on the MM-2 and AMBER force fields revealed bicyclic δ-lactams like **1** should have planar amide nitrogens and too short Cohen distances. We thank professor S. K. Chung of Pohang Institute of Technology for this useful information.

Absence of Polarizability Effect on the α-Effect in Aminolyses of *p*-Nitrophenyl Acetate and S-*p*-Nitrophenyl Thioacetate

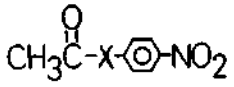
Ik-Hwan Um*, Kyung-Eun Choi, and Dong-Sook Kwon

Department of Chemistry, Ewha Womans University, Seoul 120-750

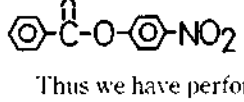
Received May 4, 1990

Basicity has most commonly been used as a measure of nucleophilicity.[1] However a group of nucleophiles often show abnormally higher reactivity toward various types of electrophiles than would be predicted from their respective basicity.[2] The enhanced nucleophilicity has been termed the α-effect and many theories have been suggested to explain the cause of the abnormal reactivity. These have focused mainly on ground-state destabilization of the α-nucleophile, transition-state stabilization, solvent effect and polarizability effect.[3]

Since the concept of Hard and Soft Acids and Bases (HSAB) principle[4] was introduced, the α-effect exhibited by a certain group of nucleophiles has been attributed to the high polarizability of them.[2] Although Pearson's concept of the HSAB principle is limited to a qualitative manner, it has often been applied successfully to many types of chemical reactions.



I: X = O, p-nitrophenyl acetate
II: X = S, S-p-nitrophenyl thioacetate



III: X = O, p-nitrophenyl benzoate
IV: X = S, O-p-nitrophenyl thiobenzoate

Thus we have performed a systematic investigation to examine the effect of polarizability on the α-effect. Firstly, we have recently demonstrated that the effect of polarizability on reactivity is significant for reactions of various anionic nucleophiles having different degree of polarizability with the esters of I, II, III and IV in H_2O.[5] We have now performed reactions of I and II with various primary amines including the so-called α-nucleophiles in H_2O. The experimental condition and method employed in the present study sre similar to the one used by Jencks *et al.*[10b] and Buncel *et al.*[12] The replacement of the ether-like oxygen in carboxylic ester by a sulfur atom has been reported to cause a significant increase in polarizability of the reaction center without changing the structure.[6] It has also been believed that amines are softer nucleophiles than oxygen centered nucleophiles, but the α-effect amines are much softer than the corresponding normal amines. Therefore the present system would be considered to be proper for a systematic study of polarizability effect on the α-effect as well as on reactivity. Futhermore, the amines employed in the present system are primary ones, and therefore any steric hindrance problems possibly caused for the reactions with secondary amines[8] would be excluded.