SYNTHETIC STUDIES ON OPTICALLY ACTIVE β-LACTAMS. CHIRAL SYNTHESIS OF CARBAPENAM RING SYSTEM STARTING FROM L-ASPARTIC ACID

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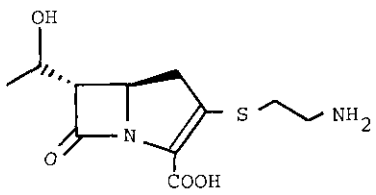
Abstract ——— Benzyl (3R,5R)-1-carba-2-oxopenam-3-carboxylate (12), a useful synthon for β-lactams having carbapenem ring system, was synthesized in optically pure state starting from L-aspartic acid.

Thienamycin (1), a β-lactam antibiotic with a novel carbapenem ring system, is reported to exhibit a potent and broad spectrum of antibacterial activity as well as β-lactamase stability.[2] Interested in this unique biological activity, many of the synthetic approaches in the field of β-lactam antibiotics have recently been concerned with the synthesis of thienamycin and its derivatives.[3] Success in the chiral synthesis of thienamycin from aspartic acid was announced already,[4] and the total synthesis of (-)-homothienamycin from L-aspatic acid was reported recently.[3k] We describe here our result on the chiral synthesis of carbapenam ring system (3) starting from L-aspartic acid (2) by the same strategy to use the chiral center of 2 as that at C-5 of 3.



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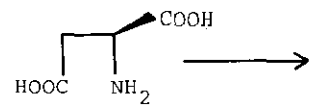

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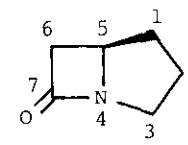

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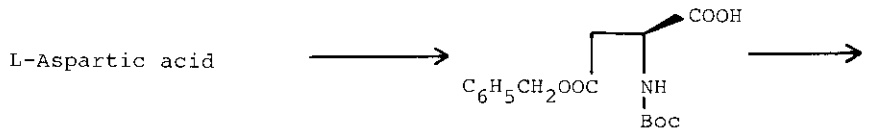
Compound 5[5] ($[\alpha]_D^{20}$ +3.4° (c=4.1, benzene)) was prepared in 80% yield from β-benzyl N-tert-butyloxycarbonyl-L-aspartate (4)[6] (m.p. 102-103°, $[\alpha]_D^{22}$ -19.5° (c=2.0, DMF) by the Arndt-Eistert reaction via diazoketone (tetramethylethylenediamine, $ClCOOC_2H_5$, ether; CH_2N_2, ether; triethylamine, C_6H_5COOAg,[7] MeOH).

Removal of the Boc group (HCl, AcOEt) afforded the corresponding amine (90%). Catalytic hydrogenation (Pd-C, H_2, MeOH) of its Schiff base with benzaldehyde gave N-benzyl-β-amino acid derivative (6)[5] (m.p. 114-115.5°, $[\alpha]_D^{20}$ -16.1° (c=0.98, MeOH), 71%), which was converted to the acid chloride hydrochloride ($SOCl_2$) and then treated with triethylamine in benzene at room temperature to cyclize to the corresponding β-lactam (7)[5] (m.p. 43.5-44.5°, $[\alpha]_D^{20}$ +23.8° (c=1.0, benzene), 66%, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1745 (C=O), NMR ($CDCl_3$) δ: 2.45-2.85 (m, 3H, C_3-$\underline{H}_\beta$, -$C\underline{H}_2COOCH_3$), 3.16 (dd, 1H, J=5 and 15 Hz, C_3-$\underline{H}_\alpha$), 3.59 (s, 3H, $COOC\underline{H}_3$), 3.9 (m, 1H, C_4-$\underline{H}$), 4.25 and 4.45 (AB-q, J=15 Hz, $C\underline{H}_2$-C_6H_5), 7.25 (s, 5H, $C_6\underline{H}_5$)). Hydrolysis of the ester group of 7 (aq. NaOH) followed by reductive debenzylation (Na, liq. ammonia) afforded the corresponding acid, isolated as its benzhydryl ester (8)[5] (m.p. 65.5-66.5°, $[\alpha]_D^{20}$ +46.6° (c=0.96, benzene), 73%). After hydrogenolysis of the benzhydryl ester group (Pd-C, H_2, EtOH), the resulting carboxylic acid (9)[5] (m.p. 169-171° (decomp.), $[\alpha]_D^{20}$ +12.3° (c=0.5, EtOH), 88%) was converted to the mixed anhydride (triethylamine, ClCOO-Bu-i, THF), which was then treated with the lithium enolate of benzyl acetate (i-Pr_2NH, n-BuLi, $CH_3COOCH_2C_6H_5$, THF) to introduce the remaining carbon framework to afford, after preparative tlc (silica gel, $CHCl_3$:acetone=3:1), the β-keto ester (10) as an oil ($[\alpha]_D^{20}$ +43.2° (c=0.37, benzene), 25%, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1760, 1740, 1710 (C=O), NMR ($CDCl_3$) δ: 2.3-3.4 (m, 4H, $C\underline{H}_2CON$, $C\underline{H}_2COCH_2COOCH_2C_6H_5$), 3.48 (s, 2H, $COC\underline{H}_2COOCH_2C_6H_5$), 3.9 (m, 1H, C_4-$\underline{H}$), 5.15 (s, 2H, $C\underline{H}_2C_6H_5$), 6.30 (m, 1H, $N\underline{H}$), 7.33 (s, 5H, $C_6\underline{H}_5$)).

The construction of the bicyclic ring system was achieved by the carbene insertion reaction.[3j,3k] Diazo exchange with p-carboxybenzenesulfonyl azide (triethylamine, CH_3CN) afforded the diazo compound (11)[5] (m.p. 99-102°, $[\alpha]_D^{20}$ +68.8° (c=0.28, benzene), 87%), which on treatment with rhodium(II) acetate (benzene, 80°) cyclized to yield the bicyclic keto ester (12)[5] (m.p. 68-69°, $[\alpha]_D^{20}$ + 298° (c= 1.54, benzene), 83%). Its NMR and IR spectra agreed well with those of the racemate reported.[3j]

Thus, the bicyclic keto ester (12) having the fundamental skeleton of thienamycin was obtained in optically pure state starting from L-aspartic acid. Further synthetic studies using this keto ester (12) as a synthon for β-lactams having carbapenem ring system are now in progress in our laboratory.



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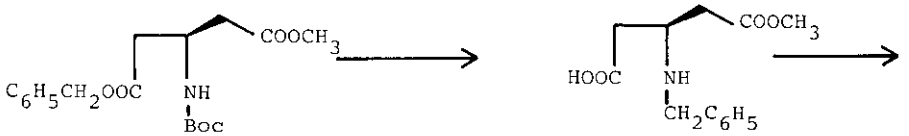

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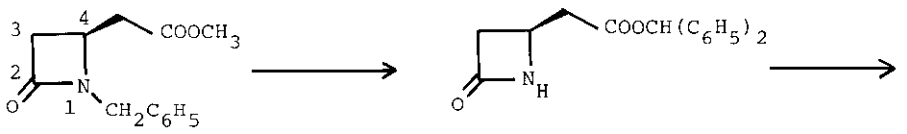

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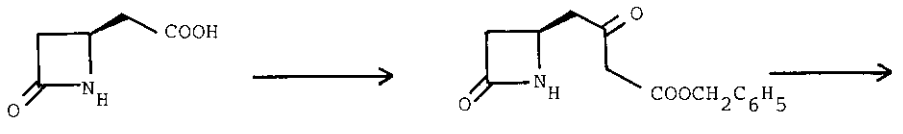

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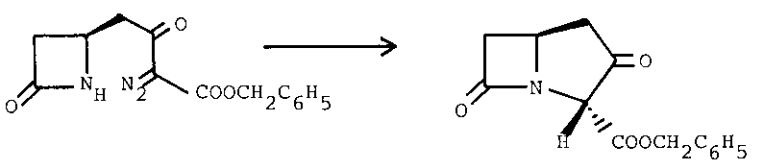

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