

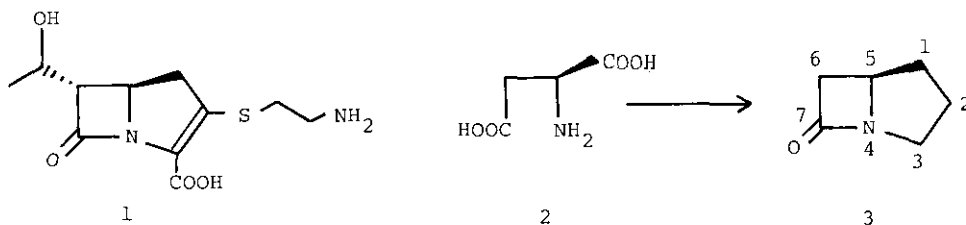
SYNTHETIC STUDIES ON OPTICALLY ACTIVE  $\beta$ -LACTAMS. CHIRAL SYNTHESIS  
 OF CARBAPENAM RING SYSTEM STARTING FROM L-ASPARTIC ACID

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

Thienamycin (1), a  $\beta$ -lactam antibiotic with a novel carbapenam ring system, is reported to exhibit a potent and broad spectrum of antibacterial activity as well as  $\beta$ -lactamase stability.<sup>2</sup> Interested in this unique biological activity, many of the synthetic approaches in the field of  $\beta$ -lactam antibiotics have recently been concerned with the synthesis of thienamycin and its derivatives.<sup>3</sup> Success in the chiral synthesis of thienamycin from aspartic acid was announced already,<sup>4</sup> and the total synthesis of (-)-homothienamycin from L-aspartic acid was reported recently.<sup>3k</sup> 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.

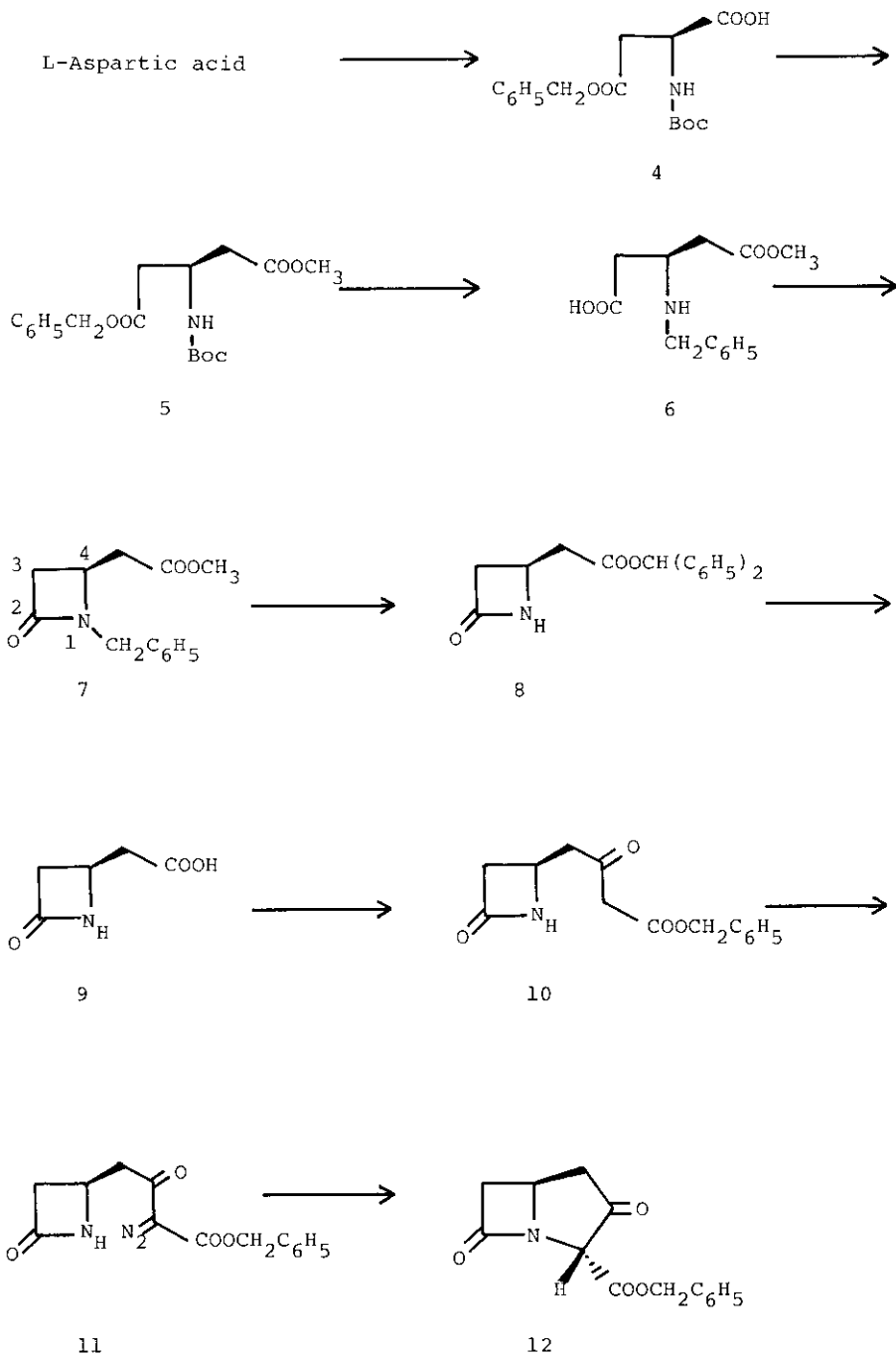


Compound 5<sup>5</sup> ( $[\alpha]_D^{20} +3.4^\circ$  ( $c=4.1$ , benzene)) was prepared in 80% yield from  $\beta$ -benzyl N-tert-butyloxycarbonyl-L-aspartate (4)<sup>6</sup> (m.p. 102-103°,  $[\alpha]_D^{22} -19.5^\circ$  ( $c=2.0$ , DMF)) by the Arndt-Eistert reaction via diazoketone (tetramethylethylenediamine,  $\text{ClCOOC}_2\text{H}_5$ , ether;  $\text{CH}_2\text{N}_2$ , ether; triethylamine,  $\text{C}_6\text{H}_5\text{COOAg}$ ,<sup>7</sup> MeOH).

Removal of the Boc group (HCl, AcOEt) afforded the corresponding amine (90%). Catalytic hydrogenation (Pd-C, H<sub>2</sub>, MeOH) of its Schiff base with benzaldehyde gave N-benzyl-β-amino acid derivative (6)<sup>5</sup> (m.p. 114-115.5°, [α]<sub>D</sub><sup>20</sup> -16.1° (c=0.98, MeOH), 71%), which was converted to the acid chloride hydrochloride (SOCl<sub>2</sub>) and then treated with triethylamine in benzene at room temperature to cyclize to the corresponding β-lactam (7)<sup>5</sup> (m.p. 43.5-44.5°, [α]<sub>D</sub><sup>20</sup> +23.8° (c=1.0, benzene), 66%, IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1755, 1745 (C=O), NMR (CDCl<sub>3</sub>) δ: 2.45-2.85 (m, 3H, C<sub>3</sub>-H<sub>β</sub>, -CH<sub>2</sub>COOCH<sub>3</sub>), 3.16 (dd, 1H, J=5 and 15 Hz, C<sub>3</sub>-H<sub>α</sub>), 3.59 (s, 3H, COOCH<sub>3</sub>), 3.9 (m, 1H, C<sub>4</sub>-H), 4.25 and 4.45 (AB-q, J=15 Hz, CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>), 7.25 (s, 5H, C<sub>6</sub>H<sub>5</sub>)). Hydrolysis of the ester group of 7 (aq. NaOH) followed by reductive debenylation (Na, liq. ammonia) afforded the corresponding acid, isolated as its benzhydryl ester (8)<sup>5</sup> (m.p. 65.5-66.5°, [α]<sub>D</sub><sup>20</sup> +46.6° (c=0.96, benzene), 73%). After hydrogenolysis of the benzhydryl ester group (Pd-C, H<sub>2</sub>, EtOH), the resulting carboxylic acid (9)<sup>5</sup> (m.p. 169-171° (decomp.), [α]<sub>D</sub><sup>20</sup> +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<sub>2</sub>NH, n-BuLi, CH<sub>3</sub>COOCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, THF) to introduce the remaining carbon framework to afford, after preparative tlc (silica gel, CHCl<sub>3</sub>:acetone=3:1), the β-keto ester (10) as an oil ([α]<sub>D</sub><sup>20</sup> +43.2° (c=0.37, benzene), 25%, IR  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 3420 (NH), 1760, 1740, 1710 (C=O), NMR (CDCl<sub>3</sub>) δ: 2.3-3.4 (m, 4H, CH<sub>2</sub>CON, CH<sub>2</sub>COCH<sub>2</sub>COOCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 3.48 (s, 2H, COCH<sub>2</sub>COOCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 3.9 (m, 1H, C<sub>4</sub>-H), 5.15 (s, 2H, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 6.30 (m, 1H, NH), 7.33 (s, 5H, C<sub>6</sub>H<sub>5</sub>)).

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

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.



## References and Notes

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Received, 26th April, 1980