Synthetic Studies of Carbapenem and Penem Antibiotics. VI. 1) Stereoselective Reduction of Enamino Ketone and Lactonization of the Reduction Product for the Synthesis of 1β-Methylcarbapenem

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The synthesis of the 1β-methylcarbapenem key intermediate 2 from the enamino ketone 6 was investigated. Stereoselective reduction of 6 and effective lactonization of the crude reduction product are described. The methyl group in 6 was shown to play an important role in these steps.

Keywords enamino ketone; stereoselective reduction; δ-lactone; 3-(1-hydroxyethyl)-2-azetidinone; 1β-methylcarbapenem

Much effort has been directed toward the synthesis of 1β-methylcarbapenem antibiotics (1), because of their excellent characteristics: good chemical and metabolic stability, in addition to potent and broad-spectrum antibacterial activity. 2) In the synthesis of 1, a (3S,4S)-4-[(R)-1-carboxyethyl]-3-[(R)-1-hydroxyethyl]-2-azetidinone derivative (2) is a key intermediate, and a number of synthetic methods for 2 have been developed. 3) In the practical synthesis of thienamycin starting from 1,3-acetonedicarboxylate, Melillo et al. reported that reduction of the enamino ketone (3a) proceeded stereoselectively to afford the amino alcohol (4) as an all-syn single isomer, which was easily converted to the δ-lactone (5) by treatment with hydrogen chloride. 4) We considered that this method would be applicable to a practical synthesis of 1β-methylcarbapenemems, if the reduction of 6 stereoselectively afforded an all-syn amino alcohol isomer. Therefore, we initiated studies on the approach to racemic 2 from the enamino ketone (6) by the application of Melillo's method and found that the methyl group in 6 played a significant role not only in the stereoselective reduction of dimethyl 2-acetyl-3-benzylamino-4-methyl-2-pentenedioate (6), but also in the formation of the δ-lactone (8) from the amino alcohol (7). The present paper describes these results.

Stereoselective Reduction of the Enamino Ketone (6) The reduction of 6, which was easily prepared from dimethyl 2-acetyl-3-benzylamino-2-pentenedioate (3b) by treatment with methyl iodide and sodium hydride in tetrahydrofuran (THF) at 45°C, was carried out with...
NaBH₃CN (2.0 eq) in AcOH at 10 °C for 2 h to give the saturated amino alcohol as a mixture of two isomers (7a and 7b) in 77% yield. The ratio of the two isomers was determined to be 3:1 based on the integration of the H-3 signal in the ¹H-NMR spectrum, and no other isomers could be observed. The stereochemistry at C1, C2 and C3 in 7a and 7b was expected to be all-syn from literature precedents, and the relative configuration of C3 and C4 was assigned as syn in 7a and anti in 7b on the basis of the coupling constant between H-3 and H-4 in the ¹H-NMR spectra. The stereochemistry of 7a and 7b was confirmed by transforming 7a,b into a mixture of azetidinones (10a and 10b) as follows. It was reported that aqueous barium hydroxide in THF hydrolyzed a less hindered ester more rapidly, so the selective saponification of the 3:1 mixture of 7a and 7b was examined with Ba(OH)₂. As expected, the sterically congested ester was not hydrolyzed and a mixture of terminal carboxylic acids (9a and 9b) was obtained in 50% yield. The ratio of 9a and 9b was 10:3 by ¹H-NMR analysis. Subsequently, the mixture of 9a and 9b was cyclized with 2,2'-dipyridyl disulfide and triphenylphosphine to afford a mixture of 10a and 10b in 62% yield and in the ratio of 7:2 on the basis of the ¹H-NMR spectrum. Comparing the NMR spectra of 10a and 10b in the mixture, the coupling constant between H-3 and H-4 of the major product (10a) was 5.3 Hz, which showed that 10a was a cis-β-lactam, while that of the minor product (10b) was 2.0 Hz, showing a trans-β-lactam. Consequently, 7a was the (all-syn) compound and 7b was the (syn-syn-anti) compound (Chart 2).

In order to improve the stereoselectivity, we attempted the reduction at lower temperature using catecholborane and then NaBH₃CN in AcOH. Treatment of 6 with catecholborane (1.1 eq) in THF at −78 °C gave the 1,4-adduct (11), whose NMR spectrum showed it to be almost the sole product. Subsequently 11 was subjected to further reduction with NaBH₃CN (2 eq) in AcOH at 10 °C to afford a 98:2 mixture of 7a and 7b in 80% yield from 6 (Chart 3).

From these results, the stereoselectivity of reduction was due to the effect of the methyl substituent at C4, but it could not be explained just in terms of the formation of a rigid hydrogen-bond in the enamine ketone moiety of 6. It seemed that a bicyclic chelation system as shown in 6' was constructed in the reduction step, and the steric hindrance of the methyl group caused the higher stereoselectivity in the rigid system.

**Lactonization of the Amino Alcohols**

When HCl gas was passed through a solution of the 3:1 mixture of 7a and 7b in CH₂Cl₂ at room temperature, the desired lactone (8a) was obtained as a sole product, which was isolated as its HCl salt by crystallization from Et₂O in 65% yield (87% yield from 7a). The other stereoisomer (8b) was not observed in the reaction mixture. This result showed that the course of the lactonization could be controlled by the stereochemistry of the methyl group and kinetic separation of 7a and 7b could be easily achieved. Consequently, 8a was obtained from 6 without purification by column chromatography. The relative configuration of 8a was determined by leading 8a to the azetidinone (10) using the same procedure as described above, after ring cleavage by treatment with Ba(OH)₂. The obtained...
azetidine was identical with 10a derived from 7a. It was found that 8a possessed the desired relative configuration for the synthesis of 2, except for that of the hydroxy group (Chart 4).

Finally the stereochemistry of 7a and 8a was confirmed by transforming them into the known key intermediate (2). The conversion of 8a to 2 was accomplished as shown in Chart 5. Acid hydrolysis of 8a with concentrated HCl followed by esterification with benzyl bromide gave the benzyl ester (8d) in 63% yield from 8a. Conversion of 8d to the amino acid (7d) was achieved in 72% yield by hydrolysis with Ba(OH)₂, esterification and then hydrogenolysis over Pd–C. Cyclization of 7d with dicyclohexylcarbodiimide (DCC) afforded the azetidine (12) in 60% yield. The inversion of hydroxyl group was performed by using the Mitsunobu reaction to give the benzoate (2a), which was then treated with sodium methoxide in a mixture of CH₃CN and MeOH to afford the racemic 3-[1-hydroxyethyl]-2-azetidine (2b) in 64% yield from 12. The spectral data of 2b were identical with reported values.

**Conclusion**

We have demonstrated that the synthetic route to thienamycin starting from 1,3-acetonedicarboxylate was applicable to a practical synthesis of 1β-methylcarba-
penems (1). Owing to the effect of the methyl group, the reduction of the enamino ketone (6), which is the key step of this route, proceeded stereoselectively to give the desired amino alcohol (7a). Furthermore, the isomerically pure lactone (8a) was easily isolated as crystals after lactonization of the crude reduction product. The highly stereoselective reduction of 6 strongly suggested the formation of a bicyclic ring system (6') by chelation.

A synthetic study of optically active analogues of 2 using this established procedure will be reported in the near future.

**Experimental**

Melting points were determined with a Thomas-Hoover capillary melting points apparatus without correction. Infrared (IR) spectra were measured with a Hitachi 260-10 spectrophotometer. ¹H-NMR spectra were recorded with a JEOL GX-270 FT spectrometer in the designated solvent using tetramethylsilane as an internal reference. Thin layer chromatography (TLC) was performed on Silica gel 60F₂₅₄ TLC plates (E. Merck). Column chromatography was done on Silica gel 60 (70—230 mesh, E. Merck). The organic solutions were dried over MgSO₄ before vacuum evaporation.

**Dimethyl 2-Acetyl-3-benzylamino-4-methyl-2-pentene-dioate (6)** A solution of dimethyl 2-acetyl-3-benzylamino-2-pentenedioate (3b) (6.2 g, 20 mmol) in THF (10 ml) was added dropwise to a suspension of 60% NaH (1.68 g, 42 mmol) in THF (10 ml) with ice-cooling and the mixture was stirred for 15 min. Then methyl iodide (5.68 g, 40 mmol) was added. Stirring was continued for 1 h at room temperature and then at 40°C for 1 h. After addition of water to quench the reaction, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, 1 N HCl and brine. Drying followed by evaporation and purification of the residue by silica gel chromatography gave 6 (5.0 g, 78%). mp 123.5—124°C. IR (neat): 1735, 1698 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.43 (3H, d, J = 6.9 Hz), 2.30 (3H, s), 3.61 (3H, s), 3.71 (3H, s), 3.95 (1H, q, J = 6.9 Hz), 4.49 (2H, m), 7.22—7.39 (5H, m). Anal. Caled for C₂₆H₂₅NO₂: C, 82.94; H, 6.27; N, 4.59. Found: C, 82.86; H, 6.40; N, 4.82.

**Mixture of Dimethyl (2SR,3RS,4SR)- and (2SR,3RS,4SR)-2-[1(SR)-Hydroxyethyl]-3-benzylamino-4-methylpentanediode (7a and 7b)** (Method A) A solution of 6 (15 g, 47 mmol) in AcOH (180 ml) was added dropwise to a solution of NaN₃CN (5.90 g, 44 mmol) in AcOH (180 ml) at 10°C and the mixture was stirred at the same temperature for 2 h. After removal of AcOH under reduced pressure, the oily residue was dissolved in EtOAc and washed with 5% NaHCO₃ three times and then brine. Drying followed by evaporation and purification of the residue by silica gel chromatography gave a mixture of 7a and 7b (11.7 g, 77%), 7a:7b = 3:1 by ¹H-NMR analysis. IR (neat): 3340, 1730 cm⁻¹. ¹H-NMR (CDCl₃) of 7a: δ: 1.18 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.6 Hz), 2.57 (1H, dd, J = 2.3, 4.0 Hz, 2.38) (3H, m, 4-H), 3.14 (1H, t, J = 4.6 Hz, 3-H), 2.98 (3H, m, 2-H). ¹H-NMR (CDCl₃) of 7b: δ: 2.53 (1H, dd, J = 2.6, 4.3 Hz, 2-H) 2.89 (1H, m, 4-H) 3.32 (1H, dd, J = 4.3, 6.9 Hz, 3-H).

(Method B) A 0.55% THF solution of catecholborane (0.2 ml) was added dropwise to a solution of 6 (32 mg, 0.10 mmol) in THF (0.1 ml) at ~78°C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was warmed to room temperature, then concentrated in vacuo to give 1,4-adduct (1) ¹H-NMR (CDCl₃) δ: 1.22 (3H, d, J = 7.3 Hz), 2.44 (3H, s), 2.37 (1H, m), 3.60 (3H, s), 3.69 (3H, s). The residue was dissolved in AcOH (0.1 ml), and NaBH₄CN (13 mg, 0.2 mmol) was added at 10°C. The mixture was stirred at 10°C for 1 h and at room temperature for 1.5 h. After removal of AcOH under reduced pressure, the residue was dissolved in CHCl₃ and washed with 5% NaHCO₃ three times and with brine. Drying followed by evaporation and purification of the residue by silica gel chromatography gave a mixture of 7a and 7b (25 mg, 80%), 7a:7b = 8:2 by ¹H-NMR analysis. Methyl (2SR,3RS,4SR,5RS)-Tetrahydro-2,5-dimethyl-6-oxo-4-benzyl-
amino-2H-pyrane-3-carboxylate Hydrochloride (8a) Gaseous hydrogen chloride was passed through a solution of the 3:1 mixture 7a and 7b (5.90 g, 18.3 mmol) in CH₂Cl₂ (50 mL) for 1 h at room temperature and the mixture was stirred for 1 h. After the reaction was complete, the residue was crystallized from Et₂O to give 8a as crystals (3.89 g, 65%). mp 159.5–161°C (dec.). IR (neat): 1728 cm⁻¹. ¹H-NMR (CDCl₃) δ: 8.14 (3H, d, J = 6.6 Hz), 1.43 (3H, d, J = 6.6 Hz), 2.38 (1H, m), 2.81 (1H, dd, J = 2.0, 3.0 Hz), 3.02 (1H, dd, J = 2.0, 6.3 Hz), 3.73 (1H, s), 3.80 (2H, ABq), 4.74 (1H, d, J = 3.0, 6.6 Hz), 7.24–7.37 (5H, m). Anal. Caled for C₁₇H₁₄N₂O₂Cl: C, 58.6; H, 6.7; N, 4.27. Found: C, 58.4; H, 6.75; N, 4.35.

(2RS,3RS,4RS,5SR)-2-Methyl-3-benzyliamino-4-methyl-2-hydroxy-1-butanol (7d) A suspension of 7c (123 mg, 0.31 mmol) and 10% Pd-C (23 mg) in MeOH (10 mL) was stirred under a hydrogen atmosphere for 2.5 h. The catalyst was filtered off and the filtrate in vacuo to give 7d (68 mg, quantitative). IR (neat): 3300, 1722 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.30 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 2.42 (3H, s), 3.00 (1H, m), 3.73 (3H, s), 4.11 (1H, m), 4.90 (1H, brs). (3RS,4SR)-3-[1H]-Ethyl-2-azetidinone (12) DCC (40 mg, 0.19 mmol) was added to a solution of 7d (40 mg, 0.18 mmol) in CH₂Cl₂ (2.0 mL) and the mixture was stirred for 3 h at 60°C, then diluted with EtOAc, and the insoluble material was removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC to give 12 (26 mg, 60%). IR (neat): 3140, 1704 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.26 (3H, d, J = 7.3 Hz), 1.33 (3H, d, J = 6.3 Hz), 2.67 (1H, m), 3.06 (1H, dd, J = 2.3, 5.9 Hz), 3.69 (1H, d, J = 2.3 Hz), 3.71 (3H, s), 4.11 (3H, m, 6.11 (H, br s))

References and Notes
7) Efficient syntheses of the racemic and optically active δ-lactones have been reported by several groups, after our study was completed and a patent concerning this work was filed.  